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Review of Evidence on Alcohol and Health

Bruce N. Calonge and
Katrina Baum Stone, *Editors*

Committee on Review of Evidence on Alcohol and Health

Food and Nutrition Board

Health and Medicine Division

Consensus Study Report

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This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We thank the following individuals for their review of this report:

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report nor did they see the final draft before its release. The review of this report was overseen by **ALFRED O. BERG,** University of Washington, and **CATHERINE E. WOTEKI,** Iowa State University. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

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[1]Appendixes E through J are available online at https://nap.nationalacademies.org/catalog/28582.

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BOXES

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Acronyms and Abbreviations

ALDH	acetaldehyde dehydrogenase
AMSTAR	A Measurement Tool to Assess Systematic Reviews
AND	Academy of Nutrition and Dietetics
ASD	autism spectrum disorder
AUD	alcohol use disorder
AUDIT	Alcohol Use Disorders Identification Test
BAC	blood alcohol concentration
BMI	body mass index
CARDIA	Coronary Artery Risk Development in Young Adults
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
DGA	*Dietary Guidelines for Americans*
DGAC	Dietary Guidelines Advisory Committee
DNA	deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
DXA	dual x-ray absorptiometry
$GABA_A$	γ-aminobutyric acid

HDL	high density lipoprotein
HHS	U.S. Department of Health and Human Services
HR	hazard ratio
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
kcal	kilocalorie
kg	kilogram
LDL	low density lipoprotein
MI	myocardial infarction
MACE	major adverse cardiovascular event
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NESR	Nutrition Evidence Systematic Review
NHANES	National Health and Nutrition Examination Survey
NLM	National Library of Medicine
NIAAA	National Institute on Alcohol Abuse and Alcoholism
OR	odds ratio
oz	ounce
PedsQL	Pediatric Quality of Life Inventory
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analyses
RCT	randomized controlled trial
RR	relative risk
SR	systematic review
USDA	U.S. Department of Agriculture
WC	waist circumference
WHI	Women's Health Initiative
WHO	World Health Organization

Preface

The United States has a long and complex societal relationship with alcohol consumption. According to the National Institute of Alcohol Abuse and Alcoholism, well over half of Americans consume at least some alcohol every year, and more people over age 12 have used alcohol in the past year than any other drug or tobacco product. The acceptability of alcohol consumption by nonpregnant adults at levels deemed to be "moderate" or "responsible" is fairly ubiquitous, although there are faiths and cultures, even in the United States, in which total abstinence is supported and practiced. There were even two separate amendments to the U.S. Constitution related to alcohol for beverage purposes: one to prohibit the manufacture, sale, transportation, import, and export of alcohol and the other to repeal the first. For many, drinking alcoholic beverages is part of daily life and in many social scenarios, including watching sporting events, celebrating important life events and achievements, convening socially, as part of meals, and accompanying other activities pursued for entertainment and enjoyment. There is also a major economy revolving around alcoholic beverages, ranging from farming to provide ingredients, industry for manufacturing and packaging, distribution, sales, and marketing efforts that support consumer access, and the service industry that provides public and social settings for consumption.

Why do people drink alcohol? Many alcohol-containing beverages provide flavors and sensations that people enjoy—fine wine, craft beer, or distinct distilled spirits, which may be mixed with other flavored, often sweet ingredients. Alcohol has other characteristics that likely impact the decision to consume it, specifically the effect on how we act and respond in

social situations based on how alcohol may affect self-confidence, inhibition, stress/anxiety, mood, pleasure and enjoyment. Furthermore, there is a cultural sense of alcohol consumption as a rite of passage or a sign of adulthood that likely influences the decision to drink alcoholic beverages.

While very small doses of alcohol may not have noticeable effects, higher doses of alcohol can impact judgement, and the line between the two can be fine and not appreciated by the individual at a given moment. The harms of acute intoxication and habitual heavy drinking are well known, and, as with other drugs that are addictive, use at low levels carries a risk of increasing and excess use. Based on the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), over 20 percent of those who consume alcohol will develop an alcohol use disorder (AUD) sometime during their lifetime. AUD is the most common substance use disorder in the United States according to the National Institute on Drug Abuse, although this progression is likely dependent on drinking patterns and individual characteristics including ancestry/genetics.

Looking at the evidence for lower consumption levels, the health effects of alcohol are inconsistent with a mixture of both potential health benefits and health harms. There is a significant body of evidence that examines the health effects of moderate drinking, generally defined as daily consumption of less than or up to 1–2 drinks, each containing about 14 grams of alcohol. There are underlying physiologic reasons for both increased and decreased risk of disease at these levels. Beyond physiology, though, there may be other impacts that are more difficult to measure, but may also be associated with health outcomes, such as social connectivity. Joining others to interact "over a drink" in private and public settings is a common behavior that may well provide measurable social connectivity benefits. However, there are also potential harms related to alcohol and social connectivity. Evidence for this occurred during the COVID-19 epidemic when, along with increased stress, there was increased isolation that accompanied social distancing interventions. This perfect storm was temporally related to increased drinking, with alcohol sales increasing by almost 3 percent in the United States and research reports of increases in consumption.

Research on the health effects of moderate drinking is challenging. Currently there are no published clinical trials for most important health outcomes, so even the substantial evidence base noted above is challenged by threats of bias inherent in observational studies, especially residual confounding. Exposure measurement is challenged by the inherent bias of the under-reporting of alcohol consumption as well as by the lack of standardized cutoffs for exposure categories. There is variation due to drinking patterns, including binge drinking, and to different types of alcohol consumed such as wine, beer, and spirits. Finally, the comparison group used in alcohol studies has been identified as a major source of bias. This

is because categories of "nondrinkers" often include former drinkers, who may have stopped drinking for health reasons including AUD and whose past consumption levels and associated health issues may well exceed those included in moderate drinking exposure levels.

It is with this background and these challenges that the committee convened by the National Academies of Sciences, Engineering, and Medicine undertook this review of the evidence on alcohol and health to inform the next edition of the *Dietary Guidelines for Americans* (DGA). This evidence review is based on the more recent evidence published over the past 5 to 15 years and is intended to be considered in the context of previous reviews. We believe the result of this report will help inform the DGA and support the expansion of and improvements in research of the health effects of moderate drinking.

Ned Calonge, *Chair*
Committee on Review of Evidence on Alcohol and Health

Summary

The *Dietary Guidelines for Americans* (DGA), a joint publication of the U.S. Department of Agriculture (USDA) and the U.S. Department of Health and Human Services (HHS), provide guidance to Americans to help them maintain health, achieve nutrient sufficiency, and help prevent diet-related chronic diseases through healthful dietary patterns. Included in the DGA recommendations is guidance for adults who consume beverages containing alcohol. This DGA guidance on alcohol is included because it is a source of energy for those who consume it and consider it part of their diet, and thus should be taken into consideration as a contributor to total caloric intake. Consumption of alcohol has been linked to a range of health outcomes, including those that are potentially detrimental to health. Thus, the DGA recommend that individuals should not start drinking for any reason and that drinking less is better for health than drinking more. For those who do consume alcohol, the DGA recommend drinking in moderation by limiting intake to two drinks or fewer in a day for men and one drink or fewer in a day for women on days alcohol is consumed. Further, alcohol should not be consumed by some individuals, including for example, those under the legal drinking age or those who are pregnant or lactating. The DGA recommendations are informed by systematic reviews conducted by the Dietary Guidelines Advisory Committee (DGAC) with support from the Nutrition Evidence Systematic Review (NESR) group within USDA.

THE COMMITTEE'S TASK

In 2023, Congress asked USDA to contract with the National Academies of Sciences, Engineering, and Medicine (the National Academies) to undertake an independent review of the evidence on the relationship between alcohol consumption and eight health outcomes previously published by USDA and HHS and reviewed by NESR. The review was limited to the eight questions related to alcohol consumption and health outcomes listed in the statement of task (Box S-1). Additionally, the National Academies was asked to prioritize the evidence and determine whether it was sufficient to support a systematic review that could be used to answer each question. In response to this congressional request, the National Academies empaneled a committee of 14 experts in the areas covering the eight areas of health as specified in the statement of task, as well as systematic reviews, previous experience with the DGA, and public health.

APPROACH TO THE TASK

To approach its task, the committee convened two public information-gathering sessions, including a public comment session. Based on the eight questions from the statement of task, the committee developed search strategies to support evidence scans of the published literature from multiple databases. Because there were sparse publications for the three questions related to lactation, the committee decided these questions should not have a systematic review.

The committee determined that the evidence for each of the other five health outcomes (i.e., weight, cancer, cardiovascular disease, neurocognition, all-cause mortality) was sufficient to conduct a *de novo* systematic review. An important requirement was to have a comparison group that did not combine never drinkers with former drinkers because of the resulting "abstainer bias" that would occur; therefore, results in this report are not directly comparable to past evidence that does include such abstainer bias. These systematic reviews were registered in the PROSPERO international database for systematic reviews and carried out by the Academy of Nutrition and Dietetics Evidence Practice Center at the request of the committee.

In assessing the evidence, the committee interpreted its task as requiring a focus on data related to moderate alcohol consumption. Although individual studies used terminology variations such as light-to-moderate, the committee adopted the term *moderate*, which it defined as:

> Consuming alcoholic beverages up to the limit defined by the *Dietary Guidelines for Americans*, i.e., two drinks or 28 grams of alcohol in a day for men and one drink or 14 grams of alcohol in a day for women.

BOX S-1
Statement of Task

The National Academies of Sciences, Engineering, and Medicine will convene a committee of experts to undertake a review of the current scientific evidence on the relationship between consumption of alcohol and health outcomes. The committee will carry out an assessment and prioritization process for reviewing the current literature to determine whether the quality and availability of peer-reviewed published evidence is sufficient to conduct a full systematic review. When a systematic review is warranted, the committee will determine whether an existing systematic review can be updated or a new review is needed. The committee will consider the following questions, previously published by USDA and HHS as the focus of the review:

1. What is the relationship between alcohol consumption and growth, size, body composition, and risk of overweight and obesity?
2. What is the relationship between alcohol consumption and risk of certain types of cancer?
3. What is the relationship between alcohol consumption and risk of cardiovascular disease?
4. What is the relationship between alcohol consumption and neurocognitive health?
5. What is the relationship between alcohol consumption and risk of all-cause mortality?
6. What is the relationship between alcohol consumption during lactation and postpartum weight loss?
7. What is the relationship between alcohol consumption during lactation and human milk composition and quantity?
8. What is the relationship between alcohol consumption during lactation and infant developmental milestones, including neurocognitive development?

The committee will produce a report that summarizes the evidence in conclusion statements that have been graded to indicate the strength of the evidence but do not include dietary guidance statements, recommendations, or advice.

Evidence that met this definition of *moderate* served as the upper threshold of alcohol consumption that the committee considered when developing its findings and conclusions.

To determine the certainty of its conclusions, the committee used a framework based on the following methods from the U.S. Preventive Services Task Force:

- *High certainty*: Evidence includes consistent results from good-quality studies in relevant populations assessing effects on health outcomes; the conclusion is unlikely to be affected by future studies. (Note that it is unlikely to be rated as high certainty without a randomized controlled trial).
- *Moderate certainty*: Evidence is sufficient to determine effects on health outcomes but is constrained by issues raised in the quality assessment of the evidence; additional information from future studies could change the conclusion.
- *Low certainty*: Evidence is insufficient to assess effects on health outcomes; additional information from future studies may allow for assessment.

Low certainty was concluded when the results of eligible studies were inconsistent or when the data were too sparse. When the level of certainty could not be assigned, the committee determined that no conclusion could be drawn. This determination was made when there was a statistically non-significant meta-analysis result or there were no eligible studies.

SYSTEMATIC REVIEWS

With a goal of completing this report in time to inform the 2025–2030 DGA, the committee decided to undertake *de novo* systematic reviews rather than perform updates and reanalysis of past reviews. To determine whether to request a systematic review of studies published since the last DGA, the committee established a process whereby the committee reviewed articles published within the search time frames.

All-Cause Mortality

According to the Centers for Disease Control and Prevention, heart disease, cancer, accidents, and stroke are the leading causes of death in the United States. Previous research studies have demonstrated that modifiable lifestyle factors, including alcohol consumption, are associated with these causes of death. With respect to alcohol consumption, there is strong evidence that *heavy drinking* has adverse effects on the risk of these leading

causes of death. However, the association of moderate alcohol consumption with all-cause mortality is less clear.

A NESR systematic review on all-cause mortality was conducted for the DGA 2020–2025; therefore, the search dates for this report were January 2019 to September 2023. Of the 27 included studies, 12 had sufficient data to assess the association of moderate alcohol consumption with all-cause mortality, and 8 of those 12 studies contributed to the overall estimate quantified in a meta-analysis. Risk-of-bias assessment showed concerns attributable to confounding and/or exposure assessment.

Findings

Finding 3-1: On the basis of a meta-analysis of eight eligible studies, there was a 16 percent lower risk of all-cause mortality among those who consumed moderate levels of alcohol compared with those who never consumed alcohol (RR = 0.84, 95%CI [0.81, 0.87]).

Finding 3-2: On the basis of a meta-analysis of three eligible studies, a 23 percent lower risk of all-cause mortality was found among females who consumed moderate amounts of alcohol compared with females who never consumed alcohol (RR = 0.77, 95%CI [0.6, 0.97]). An assessment of four studies showed a 16 percent lower risk of all-cause mortality among males who consumed moderate amounts of alcohol compared with males who never consumed alcohol (RR = 0.84, 95%CI [0.81, 0.88]). The committee found no evidence for a difference in the effect size by sex, as reflected in the p-value of 0.56 for the test for heterogeneity between the sexes.

Finding 3-3: On the basis of a meta-analysis of two eligible studies, a 20 percent lower risk of all-cause mortality was found among persons less than 60 years of age who consumed moderate amounts of alcohol compared with persons less than 60 years of age who never consumed alcohol (RR = 0.80, 95%CI [0.74, 0.86]). An assessment of four eligible studies found an 18 percent lower risk of all-cause mortality among persons 60 years of age or older who consumed moderate amounts of alcohol compared with persons 60 years of age or older who never consumed alcohol (RR = 0.82, 95%CI [0.77, 0.87]). The committee found no evidence for a difference in the effect size by age, as reflected in the p-value of 0.61 for the test for heterogeneity between the age groups. This comparison was not graded for certainty of the evidence.

Finding 3-4: On the basis of a meta-analysis of five studies published between 2019 and 2023, the committee found that, among moderate

alcohol consumers, higher versus lower amounts of moderate alcohol consumption were associated with similar risks of all-cause mortality (RR = 0.96, 95%CI [0.87, 1.06]). The committee also found no evidence for a difference in this effect size by sex, as reflected in the p-value of 0.82 for the test for heterogeneity between the sexes.

Conclusion

Conclusion 3-1: Based on data from the eight eligible studies from 2019 to 2023, the committee concludes that compared with never consuming alcohol, moderate alcohol consumption is associated with lower all-cause mortality (moderate certainty).

Weight Changes

Alcohol consumption may directly or indirectly lead to changes in body weight, body composition, and body mass index (BMI) by providing energy as well as affecting metabolism, appetite, and satiety. Moderate alcohol consumption may have differential effects on weight and adiposity relative to biological sex, age, physical activity level, and other individual-level factors. Genetics also contributes to heterogenous pathophysiological responses to alcohol intake.

Databases searched from January 2010 through February 2024 identified seven eligible studies for a systematic review. A meta-analysis was not conducted due to the heterogeneity in populations, exposures, comparators, outcomes, and study designs. Three studies examined associations between different amounts of moderate alcohol consumption and weight, and two examined associations with BMI. Five studies examined moderate alcohol consumption, and the risk of overweight/obesity, four examined waist circumference, and one study examined waist-to-hip ratio and body fat percentage associations. Of the seven eligible studies, risk of bias was primarily caused by the measurement of alcohol consumption and attrition.

Findings

Finding 4-1: Abstainer bias was evident in all seven eligible studies published between 2010 and 2024; therefore, for weight-related outcomes (weight, BMI, risk of overweight/obesity, waist circumference) comparisons between those who consumed moderate alcohol and those who never consumed alcohol could not be made.

Finding 4-2: On the basis of three eligible studies, there was insufficient evidence to evaluate associations between the amount of moderate alcohol

consumption and changes in body weight among men. Among women, the evidence was inconsistent. There were concerns related to sparse evidence, risk of bias (mainly due to confounding), and imprecision in the studies.

Finding 4-3: On the basis of two eligible studies, higher versus lower amounts of moderate alcohol consumption among men were associated with similar changes in BMI. Among women, the evidence was inconsistent. There were concerns related to risk of bias (mainly due to confounding) and imprecision in the studies.

Finding 4-4: On the basis of four eligible studies, higher versus lower amounts of moderate alcohol consumption among men were associated with similar risks of overweight and/or obesity. Among women, the evidence was inconsistent. There were concerns related to risk of bias, mainly due to confounding, and imprecision in the studies.

Finding 4-5: On the basis of three eligible studies, the evidence for changes in waist circumference comparing higher versus lower amounts of moderate alcohol consumption was inconsistent for women and for men. There were concerns related to sparse evidence and risk of bias (mainly due to confounding).

Conclusions

Conclusion 4-1: The committee determined that there was insufficient evidence to draw a conclusion regarding the association between weight-related outcomes and moderate alcohol consumption compared with never consuming alcohol.

Conclusion 4-2: The committee determined that there was insufficient evidence to draw a conclusion regarding the association between amounts of moderate alcohol consumption and changes in weight.

Conclusion 4-3: The committee concludes that higher versus lower amounts of moderate alcohol consumption among men were associated with similar changes in BMI (low certainty). Among women the evidence was inconsistent regarding changes in BMI.

Conclusion 4-4: The committee concludes that among men who moderately consume alcohol, higher versus lower amounts of moderate alcohol consumption were associated with similar risks of overweight and/or obesity (low certainty). Among women the evidence was inconsistent regarding changes in overweight and/or obesity.

Conclusion 4-5: The committee determined that there was insufficient evidence to draw a conclusion regarding the association between amounts of moderate alcohol consumption and changes in waist circumference.

Cancer

Alcohol has been identified as a carcinogen in humans, although the mechanisms of action about the role of carcinogenesis are not completely understood. The committee identified specific cancers for systematic review—i.e., oral cavity, pharynx, esophagus, colorectum, and female breast—as outcomes of interest based on evidence from previously published reviews. The committee's systematic review focused on cancer incidence and excluded studies that exclusively examined prevalence, cancer recurrence, cancer-related mortality, or survival. As for all the analyses, studies were excluded that did not specify that only never drinkers were included in the comparison group to prevent abstainer bias.

Studies of the relationship between moderate alcohol consumption and each of bladder, endometrial, gastric, pancreas, prostate, lung, and thyroid cancer, as well as several studies that examined combined sites such as the head and neck or biliary tract and renal tract (14 studies in total), were identified in the evidence scan. A systematic review for these cancer sites was not conducted due to the small number of studies per cancer type. The committee evaluated this body of evidence and determined that there was insufficient evidence to establish certainty for an association of moderate alcohol consumption with any of these other sites.

Based on the scope of primary literature identified in the evidence scans, the committee decided to proceed with a systematic review to answer the question regarding alcohol and cancer incidence. This systematic review included studies published between January 2010 and February 2024.

Findings

Finding 5-1: A meta-analysis of four eligible studies found a 10 percent higher risk of breast cancer among persons consuming moderate amounts of alcohol compared with persons never consuming alcohol (RR = 1.10, 95%CI [1.02, 1.19]). There were some concerns related to risk of bias, mainly due to confounding and exposure assessment, in the studies contributing to this comparison.

Finding 5-2: A meta-analysis of seven eligible studies found a 5 percent higher risk of breast cancer for every 10–14 grams (0.7–1.0 U.S.

drinks) increment of higher alcohol consumption per day (RR = 1.05, 95%CI [1.04, 1.06]). On the basis of two eligible studies, consumption of higher compared to lower amounts of moderate alcohol was associated with a higher risk of breast cancer. One study reported a hazard ratio (HR) of 1.05 (95%CI [1.02, 1.09]) for women who consumed higher amounts of moderate alcohol (0.6–<1.1 drinks/day) compared with those who consumed lower amounts of moderate alcohol 0.2–0.5 drinks/day. Another study reported an HR of 1.06 (95%CI [1.01, 1.11]) for breast cancer associated with 0.4–1.1 drinks per day compared to <0.4 drinks per day. There were some concerns related to risk of bias, mainly due to confounding and exposure assessment.

Finding 5-3: On the basis of five eligible studies and a meta-analysis of three of these studies, compared with never drinkers, moderate alcohol consumption was associated with a statistically nonsignificant higher risk of colorectal cancer overall among males and females. There were some concerns with the studies related to risk of bias, mainly due to confounding and exposure assessment.

Finding 5-4: On the basis of two eligible studies, consumption of higher amounts of moderate alcohol was associated with a higher risk of colorectal cancer. One study reported an HR of 1.09 (95%CI [1.02, 1.17]) for colorectal cancer among males who consumed higher amounts of moderate alcohol (0.7–<2.1 drinks/day) compared with males who consumed lower amounts of moderate alcohol (<0.7 drinks/day). Another study reported a HR of 1.05 (95%CI [1.03, 1.07]) for colorectal cancer associated with each 15 grams (1.1 U.S. drinks) increment of higher alcohol consumption per day. There were some concerns related to risk of bias (mainly due to confounding), exposure assessment, and indirectness stemming from estimating linear trends based on alcohol consumption that may have exceeded the moderate range in some individuals in the latter study.

Finding 5-5: There was insufficient evidence to support an association between moderate alcohol consumption and risks of oral cavity, pharyngeal, esophageal, and laryngeal cancers.

Finding 5-6: Upon evaluating the body of evidence, there were several sites where there was emerging evidence that was insufficient to establish certainty for an association of moderate alcohol consumption. These sites included cancer of the head and neck, thyroid, lung, gastric, small intestine, pancreas, biliary tract, renal track, bladder, prostate, and endometrium.

Conclusions

Conclusion 5-1: The committee concludes that compared with never consuming alcohol, consuming a moderate amount of alcohol was associated with a higher risk of breast cancer (moderate certainty).

Conclusion 5-2: The committee concluded that, among moderate alcohol consumers, higher versus lower amounts of moderate alcohol consumption were associated with a higher risk of breast cancer (low certainty).

Conclusion 5-3: The committee determined that no conclusion could be drawn regarding the association between moderate alcohol consumption compared with lifetime nonconsumers and risk of colorectal cancer.

Conclusion 5-4: The committee concluded that among moderate alcohol consumers higher versus lower amounts of moderate alcohol consumption were associated with a higher risk of colorectal cancer (low certainty).

Conclusion 5-5: The committee determined that no conclusion could be drawn regarding an association between moderate alcohol consumption and oral cavity, pharyngeal, esophageal, or laryngeal cancers.

Cardiovascular Disease

Coronary heart disease and stroke, both forms of cardiovascular disease (CVD), are the first and fifth leading causes of death in the United States, respectively. It is well recognized that modifiable lifestyle factors, including alcohol consumption, may influence the risk of myocardial infarction (MI) and stroke. While heavy alcohol consumption has been associated with a higher risk of MI and hemorrhagic stroke, prior observational studies have suggested that moderate alcohol consumption is associated with a lower risk of CVD.

The evidence scan identified 19 systematic reviews. Eight of the reviews considered CVD outcomes broadly, and the remaining 11 focused on specific CVD outcomes. A subset of studies identified in the scan examined the associations of moderate alcohol consumption with particular care to include people who never consumed alcohol as the comparison group. The committee decided to proceed with a systematic review of associations of moderate alcohol consumption, compared with never consuming alcohol, on the risk of nonfatal MI, nonfatal stroke, and CVD death (referred to as major adverse cardiovascular events [MACE-3]) using studies published from January 2010 through February 2024.

Findings

Finding 6-1: A meta-analysis of two eligible studies found that among persons who consumed moderate amounts of alcohol compared with persons who never consumed alcohol, there was a 22 percent lower risk of MI (RR = 0.88, 95%CI [0.68, 0.90]). No studies reported data for males alone. One study reported a 21 percent lower risk of MI among females only; these results were consistent with the estimate for both sexes combined. There were some concerns related to risk of bias in the studies, mainly due to confounding.

Finding 6-2: A meta-analysis of seven eligible studies found an 11 percent lower risk of stroke among persons consuming moderate amounts of alcohol compared with persons never consuming alcohol (RR = 0.89, 95%CI [0.86, 0.93]). These results were driven by ischemic stroke, which showed a 12 percent lower risk (RR = 0.88, 95%CI [0.86, 0.90]). Separate examination of hemorrhagic strokes was infrequent; thus, no estimate of effect for this health outcome could be made. There were some concerns related to risk of bias among the studies, mainly due to confounding and exposure assessment.

Finding 6-3: A meta-analysis of four eligible studies found an 18 percent lower risk of CVD mortality among persons who consumed moderate amounts of alcohol compared with those who never consumed alcohol (RR = 0.82, 95%CI [0.76, 0.89]). The committee further found a 23 percent lower risk in females (RR = 0.77, 95%CI [0.70, 0.85]), and an 18 percent lower risk in males (RR = 0.82, 95%CI [0.71, 0.94]). Very limited data stratified by age were available; however, one study showed that the effect size and direction for moderate alcohol consumption compared with no alcohol consumption was consistent among persons aged less than 60 years (33 percent lower risk of CVD mortality) and among persons aged 60 years or older (19 percent lower risk of CVD mortality). There were some concerns related to risk of bias, mainly due to confounding, in the studies contributing to this comparison.

Conclusions

Conclusion 6-1: The committee concludes that compared with never consuming alcohol, consuming moderate amounts of alcohol is associated with a lower risk of nonfatal MI (low certainty).

Conclusion 6-2: The committee concludes that compared with never consuming alcohol, consuming moderate amounts of alcohol is associated with a lower risk of nonfatal stroke (low certainty).

Conclusion 6-3: The committee concludes that compared with never consuming alcohol, consuming moderate amounts of alcohol is associated with a lower risk of CVD mortality in both females and males (moderate certainty).

Neurocognition

The mainstay of research on the effects of alcohol consumption on neurocognition stems from investigations of people diagnosed with alcohol use disorder (AUD). By contrast, a paucity of research has examined *moderate drinking*, often defined by exclusion from AUD criteria. The few studies of moderate drinking that have used objective neuropsychological tests report performance advantages in some areas and impairment in others.

Dementia, Alzheimer's disease, and cognitive decline were examined longitudinally. Dementia and Alzheimer's disease were assessed separately because dementia is an umbrella diagnosis that may include Alzheimer's disease, a diagnosis determined by experts using accepted criteria for dementia. Cognitive decline was determined with quantitative measures of episodic memory, cognitive screening, or phonemic or semantic word fluency.

Findings

Finding 7-1: Four eligible studies with data from 2010 to 2024 reported that the risk of developing dementia was higher among those consuming higher amounts of moderate alcohol than lower amounts of moderate alcohol. One study reported that, when compared with long-term moderate consumers, long-term abstinence or decreasing consumption from midlife to older age was associated with higher risk of dementia. Two studies reported that moderate drinkers had a lower risk of developing dementia than never drinkers, and one study found no association between moderate consumption levels of alcohol and the development of dementia.

Finding 7-2: On the basis of six eligible studies with data from 2010 to 2024, the committee found the risk of Alzheimer's disease or dementia among those who consumed higher amounts of moderate alcohol versus lower amounts was inconsistent.

Finding 7-3: On the basis of nine eligible studies with data from 2010 to 2024, there was insufficient evidence to support an association between moderate versus never drinking or occasional drinking and the risk of cognitive decline. There were concerns with the studies related

to differences in measurement instruments, differences in comparator groups, and imprecise results.

Conclusions

Conclusion 7-1: The committee concludes there was insufficient evidence about the association between the risk of dementia for those with no alcohol consumption compared to those with moderate alcohol consumption or for those who consume higher versus lower amounts of moderate alcohol.

Conclusion 7-2: The committee concludes there was insufficient evidence regarding the association between amounts of moderate alcohol consumption and the risk of developing Alzheimer's disease.

Conclusion 7-3: The committee determined that there was insufficient evidence to draw an association between moderate alcohol consumption versus never or occasional consumption and the risk of cognitive decline.

REVIEW OF LACTATION

Human milk provides all essential and conditionally essential nutrients in amounts adequate to meet an infant's needs. It also provides a complex array of biologically active components, maternal cells, and microbes that contribute enzymatic, hormonal, and immunomodulatory functions to the developing infant. Bioactive components associated with alcohol enter milk after maternal consumption; however, their putative effects on lactation, milk composition, and infant outcomes are understudied, and research results have been inconsistent. Nonetheless, use of alcohol during breastfeeding is generally discouraged.

Because there had not been a systematic literature search by a DGAC on breastfeeding and alcohol since 2010, the committee conducted a systematic search to identify all eligible papers published between January 2010 and April 2024. Among studies identified for review, two were identified in the initial evidence scan, four additional publications were identified in a second systematic search, and one using a hand search. A systematic review with a narrative synthesis of the studies was conducted for any level of alcohol consumption (i.e., not limited to moderate) by the committee in lieu of a systematic review given the sparse literature across the three lactation-related questions in the statement of task.

Findings

No studies published since 2010 addressed the question of maternal alcohol consumption during breastfeeding and postpartum weight loss. Thus, the committee was unable to evaluate this association.

Finding 8-1: There was insufficient evidence to determine any association between maternal alcohol consumption at any level during lactation and milk composition or milk production.

Finding 8-2: There was insufficient evidence to determine an association between maternal alcohol consumption at any level during lactation and infant development.

Conclusions

Conclusion 8-1: The committee determined that no conclusion could be drawn regarding any associations between maternal alcohol consumption during lactation and milk composition or milk production.

Conclusion 8-2: The committee determined that no conclusion could be drawn regarding the association between maternal alcohol consumption during lactation and infant development.

RESEARCH GAPS

Throughout the systematic review of current literature and the preparation of this report, the committee identified a consistent set of research gaps that, when addressed, could strengthen the existing evidence on moderate alcohol consumption and health outcomes. Overarching limitations identified in the committee's review of evidence include abstainer bias; a lack of standard definitions of alcohol consumption levels and a lack of standardized cutoffs for exposure categories; underreporting of alcohol consumption by participants; lack of data stratified by smoking status, age, sex, and genetic ancestry to evaluate possible interactions between alcohol consumption and health outcomes; and limitations of observational studies. The committee urges that all studies addressing the effects of alcohol consumption on human health speak to these limitations and consider including menopausal status as well as postpartum women (both breastfeeding and nonbreastfeeding) and their infants when possible.

1

Introduction

BACKGROUND

The *Dietary Guidelines for Americans* (DGA) serve as the primary source of dietary guidance from the federal government and are used to inform food and nutrition programs and as a resource for recommendations for dietary intake and healthful dietary patterns for the U.S. population (Box 1-1). The original systematic reviews (SRs) informing DGA guidance are conducted by the Dietary Guidelines Advisory Committee (DGAC) with support from the Nutrition Evidence Systematic Review (NESR) team, which operates under the auspices of the U.S. Department of Agriculture's (USDA) Center for Nutrition Policy and Promotion. NESR, working with its collaborators, supports the conduct of systematic reviews that serve as a central resource for the federal government in making evidence-informed decisions, including development of the DGA.

Since its inception in 1980, the DGA has provided guidance that includes recommendations regarding alcoholic beverages. Previous editions, particularly the 2010–2015 DGA, have also provided guidance about the consumption of alcoholic beverages for population groups, including those who are breastfeeding (USDA and HHS, 2010). The current edition of the DGA recommends that individuals should not start drinking alcohol for any reason and further states that drinking less is better for health than drinking more (USDA and HHS, 2020). The DGA 2020–2025 also advise that some individuals should not drink alcohol at all, for example, those who are pregnant or might be pregnant, individuals under the legal age for drinking, individuals with certain medical conditions or who are taking

BOX 1-1
Overview of the Process to Develop the *Dietary Guidelines for Americans*

A Dietary Guidelines Advisory Committee (DGAC) is appointed to meet once every 5 years to examine the evidence on specific topics and scientific questions identified by the U.S. Department of Agriculture (USDA) and U.S. Department of Health and Human Services (HHS) and informed by public comments. This DGAC then develops a report outlining its science-based review and advice to the departments and submits the report to the secretaries of USDA and HHS for consideration as the departments develop the 5-year *Dietary Guidelines for Americans* (DGA). Recent DGACs answered questions to inform their advice using one of the following three approaches.

1. Data analysis,
2. Food pattern modeling, and
3. Systematic reviews.

Each of these approaches has its own rigorous, protocol-driven methodology and plays a unique complementary role in examining the science. Data analysis is a collection of methods using national data sets to understand current health and dietary intakes of Americans. Food pattern modeling is an analysis that helps identify how changes in the amounts and types of foods and beverages in a pattern might impact meeting nutrient needs across the U.S. population. The systematic reviews answer a question on diet and health by searching for, evaluating, synthesizing, and grading the strength of all relevant, peer-reviewed studies.

For systematic reviews, the DGAC creates a protocol for each question before it examines the evidence, and it includes an analytic framework, inclusion/exclusion criteria, and synthesis plans. Each protocol includes criteria for publication date, and multiple factors are considered when establishing the appropriate publication date range criteria. If the review is addressing a new question, a publication date range will be selected that ensures all relevant evidence is captured. If the review is an update to an existing review, the publication data range may capture studies published since the existing review was conducted.

certain medications that can interact with alcohol, individuals recovering from an alcohol use disorder (AUD), and individuals unable to control the amount they drink (USDA and HHS, 2020).

The DGA also carried forward a recommended limit on alcoholic beverage consumption from guidance in previous editions. Specifically, for adults of legal drinking age who choose to drink, it should be done in moderation by limiting "alcohol intake to two drinks or fewer in a day for men and one drink or fewer in a day for women" (USDA and HHS, 2020). The DGA 2020–2025 further recognized that the decision to engage in alcohol consumption at low or moderate levels reflect personal considerations that balance the potential harms against the potential benefits of alcohol (USDA and HHS, 2020).

Context of Evidence for the Development of the Next Dietary Guidelines for Americans

The DGAC is a federal advisory committee convened by USDA and HHS prior to developing updated editions of the DGA. The DGAC conducts SRs, data analyses, and food pattern modeling with support from federal staff, including NESR. Collectively, this body of work is integrated into the findings of the *Scientific Report of the Dietary Guidelines Advisory Committee* and provided to the secretaries of USDA and HHS that, along with additional input from federal agencies and comments received from the public, contribute to the development of the DGA every 5 years.

For each 5-year cycle in the DGA process, proposed scientific questions, including systematic review questions, are identified by USDA and HHS based on input from previous DGAC, federal experts, and the public. The proposed questions are prioritized based on the following criteria: relevance, importance, potential effect on federal programs, and avoiding duplication. Research availability, whether sufficient evidence exists to conduct a new review or update an existing review, is also considered. NESR estimates research availability through continuous evidence monitoring or evidence scans. The proposed questions are provided to the DGAC, who further refine and prioritize the questions based on the same criteria.

During the open session for the public on January 25, 2024 (Appendix B), USDA provided background and the most recent systematic reviews for the DGAC (Box 1-2). The 2020 DGAC conducted one systematic review on alcohol and all-cause mortality. The remaining seven questions were last examined by the 2010 DGAC.

BOX 1-2
Background on Questions in the Statement of Task

In response to the committee's request for additional information about its task, the sponsor presented the following excerpt in a public session.

Scope of Work for the Study on the Review of Evidence on Alcohol and Health 2023 Consolidated Appropriations Act outlined requirements for this study:

- USDA, in consultation with HHS, mandated to enter into an agreement with the National Academies of Sciences, Engineering, and Medicine.
- *"Conduct a study of the eight topics and scientific questions related to alcohol previously published by USDA and HHS"*
- Transparent operations
- Based on the preponderance of scientific and medical knowledge
- Timeline—in time for the 2025 *Dietary Guidelines for Americans* process to include a recommendation for alcohol.

Background on these questions:

- These eight questions were proposed by USDA and HHS to the 2020 Dietary Guidelines Advisory Committee (DGAC) for consideration in its review.
- The 2020 DGAC conducted one systematic review on alcoholic beverages: "What is the relationship between alcohol consumption and **all-cause mortality**?"
- "The [2020 DGAC] prioritized the review of alcohol and all-cause mortality because *it is arguably the most important outcome related to alcohol*, and because Dietary Guidelines Advisory Committees had not previously reviewed this topic."—*Scientific Report of the Dietary Guidelines Advisory Committee*
- The other seven questions specific to alcoholic beverages and health were last examined in the 2010 DGAC.

SOURCE: Presentation by Eve Stoody, January 25, 2024.

Overview of Alcohol and Health

The health effects of heavy drinking have been documented by a number of authoritative bodies, such as the Centers for Disease Control and Prevention (CDC) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA).[1,2] An understanding of the potential health effects of alcohol is shaped by its complex and diverse actions on physiological structures and processes, and these in turn are modified by the quantity, frequency, and pattern of intake. Alcohol exerts its pharmacologic actions through direct interactions with multiple proteins present throughout the body; ethanol's displacement of water from hydrophilic pockets alters some proteins' structure and activity (Mihic et al., 1997). This action is best understood for, but is not limited to, proteins that mediate neurotransmission, and the consequence depends on the individual protein target; for some, activity is increased (i.e., γ-aminobutryic acid A [$GABA_A$] receptors) and for others it is decreased (N-Methyl-D-aspartic acid [NMDA] receptors).

Ethanol's toxicity originates, in part, through its metabolic conversion to the chemical acetaldehyde, which can derivatize deoxyribonucleic acid (DNA) nucleotides to introduce mutations (Mizumoto et al., 2017). This metabolic conversion can also generate free radicals, which have the potential to damage cellular components including DNA, lipids, and mitochondria (Wu and Cederbaum, 2003). Alcohol also increases intestinal permeability, admitting microbial components that have proinflammatory effects in the circulation (Maccioni et al., 2023).

Alcoholic beverages contain myriad nonalcohol compounds, also known as congeners, that can have further physiological influences. Congeners range from phytochemicals present in grapes to contaminants that enter during processing, and their content varies with the type of alcoholic beverage consumed (wine versus beer versus spirits) (IARC, 1988). The complex composition of alcoholic beverages, combined with alcohol's diverse actions, have made it challenging to reach a consensus regarding the health effects of moderate drinking as defined by the DGA for low-risk drinking.

As with other pharmacologic agents, lower alcohol consumption tends to have smaller and even different effects, and intermittent consumption may not have the same overall effect as daily or near-daily intake, which can promote tolerance such that a higher amount is necessary to produce the same effect as was previously produced by a lower amount of alcohol (Elvig et al., 2021). Likewise, while it is tempting to infer a linear relationship between level of alcohol intake and risk of an outcome, alcohol may

[1] https://www.cdc.gov/alcohol/about-alcohol-use/index.html (accessed September 23, 2024).
[2] https://www.niaaa.nih.gov/alcohols-effects-health/alcohols-effects-body (accessed September 23, 2024).

have different effects at different doses, creating a *J*-shaped response curve that reflects greater or lesser effect on different health outcomes. This can reflect differences in the physiochemical properties of the proteins that alcohol interacts with, in which smaller exposures may activate protective or defensive mechanisms that repair cellular damage, enhance toxin disposal, or activate the immune system (Calabrese and Baldwin, 2001). Moreover, there is abundant evidence that individuals respond to the same alcohol dose differently with some of the differences attributable to variation in alcohol metabolism related to such factors as age, sex, and genetics, and this source of variance is discussed further in Chapter 2.

Current Drinking Patterns

Alcohol consumption is highly prevalent in the United States. According to the 2023 National Survey on Drug Use and Health, 62.5 percent of people 12 years and older reported drinking in the past year (NIAAA, 2024a). Even when excluding 11 percent of the U.S. population with a Diagnostic and Statistical Manual (DSM)-5 AUD diagnosis, about half the adult population engages in alcohol consumption. Nearly half a million visits to emergency departments annually were related to alcohol consumption. Further, CDC noted that death certificates listed chronic or acute alcohol as a factor in 178,000 deaths in 2020 and 2021, and this reflects a steady increase and tripling of numbers between 2000 and 2021, with a notable jump in prevalence in the first year of the COVID-19 pandemic (CDC, 2024). The percentage of women who consume alcohol has now caught up with the percentage of men. This convergence of proportion by sex may herald increasing alcohol-related problems in women (White, 2020). The recent increases in alcohol consumption in people aged 65 years or older similarly introduce additional health-related complications in that population (White et al., 2023). Thus, changing demographics in the populations that consume alcohol inform the importance of assessing the association between those behaviors and health outcomes.

Defining Alcohol Use, Misuse, and Abuse

There are personal, familial, and societal impacts associated with alcohol misuse, and there are important differences between *moderate drinking*, which may be considered as a term defined by exclusion, and *problem drinking*. Moderate drinking may not meet the American Psychiatric Association DSM-5 criteria for a diagnosis of AUD, which is based on presentation of symptoms rather than number of drinks consumed and is characterized on a spectrum.

In addition to considering symptoms to establish diagnosis, defined drinking patterns, notably binge drinking and heavy alcohol consumption, can be considered alcohol misuse and fall under the aegis of an AUD diagnosis. Heavy drinking is defined for men as consuming five or more drinks on any day or 15 or more per week. For women, heavy drinking means drinking four or more on any day or eight or more drinks per week.[3] According to the Substance Abuse and Mental Health Services Administration, heavy alcohol consumption can include binge drinking on five or more days in the past month.

Moderate drinking (i.e., nonproblem drinking and not to be confused with the International Classification of Diseases, 10th edition (ICD-10) nomenclature of *moderate use disorder*) can be defined as consumption within or below the NIAAA/DGA limits for *low-risk drinking* and *drinking in moderation* (NIAAA, 2024b).[4] The low-risk classification defines these limits as two drinks for men or one drink for women per day, with no more than 14 drinks for men and 7 drinks for women per week. Women who are pregnant should refrain from drinking alcohol.

According to NIAAA and CDC, one standard drink contains 14 grams (0.6 U.S. ounces) of alcohol, which is about 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of brandy or distilled spirits (NIAAA, n.d.).[5] These equivalents depend on the amount of alcohol contained in a beverage. For example, the alcohol content of table wine typically varies between 12 percent and 15 percent.

In making comparisons of health outcomes for moderate drinking compared with people who do not drink, it is important to note that categories of nondrinkers may well include former drinkers who may be persons with a former AUD or others who may have quit drinking because of health problems. Their inclusion with control or nondrinker groups may bias the health status of former regular drinker or current abstainer cohorts toward a compromised health status despite their current no-to-low level of drinking (often called abstainer bias). A further consideration is the possibility that heavy alcohol consumption during youth carries a liability for accelerated aging in older adults who are current no-to-low drinkers (Nannini et al., 2023).

[3] https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking (accessed September 23, 2024).

[4] https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking (accessed September 23, 2024).

[5] https://www.niaaa.nih.gov/alcohols-effects-health/overview-alcohol-consumption/what-standard-drink (accessed September 23, 2024).

COMMITTEE'S TASK AND APPROACH

The Consolidated Appropriations Act, 2023, section 772, requires that USDA, in consultation with the secretary of HHS, contract with the National Academies of Sciences, Engineering, and Medicine (the National Academies) to convene an *ad hoc* committee to undertake a review of the current scientific evidence on the relationship between alcohol consumption and health outcomes. The Statement of Task (Box 1-3) requests a review of evidence regarding eight questions related to alcohol consumption and health outcomes that were previously published by USDA and HHS and reviewed by NESR. The committee was asked to prioritize the evidence and determine whether it was sufficient to support a systematic review that could be used to answer each question. If enough research was available to conduct a systematic review, the committee was to determine if it should conduct an original systematic review or if a high-quality existing systematic review can be used to answer the question. The committee was then asked to produce a report summarizing the evidence in conclusion statements (graded to indicate the strength of evidence) but to not include dietary guidance statements, recommendations, or advice. In response to this congressional request, the National Academies empaneled a committee of 14 experts in the eight areas of health specified in the Statement of Task as well as experts in systematic reviews and those with previous experience with the DGA and in public.

Approach to the Task

To approach its task, the committee first convened public information gathering sessions, which included public comment sessions (see Appendix B). Based on the large body of evidence linking heavy alcohol consumption to health problems and the exclusion of binge drinking by the sponsor (Stoody, 2024), along with current dietary guidance that people should not initiate alcohol consumption to improve their health, the committee interpreted its task to focus on evidence related to moderate alcohol consumption. Although individual studies used terminology variations such as light-to-moderate, the committee adopted the term *moderate* as defined in Box 1-4. Evidence that met this definition of moderate served as the upper threshold of alcohol consumption that the committee considered when developing its findings and conclusions for this consensus study.

Based on the eight questions from the Statement of Task, the committee developed search strategies to support evidence scans of the published literature from multiple databases to support its assessment and prioritization process for reviewing the current literature to determine whether the quality and availability of peer-reviewed published evidence were sufficient to conduct a systematic review. For each of the eight questions in

BOX 1-3
Statement of Task

The National Academies of Sciences, Engineering, and Medicine will convene a committee of experts to undertake a review of the current scientific evidence on the relationship between consumption of alcohol and health outcomes. The committee will carry out an assessment and prioritization process for reviewing the current literature to determine whether the quality and availability of peer-reviewed published evidence is sufficient to conduct a full systematic review. When a systematic review is warranted, the committee will determine whether an existing systematic review can be updated or a new review is needed. The committee will consider the following questions, previously published by USDA and HHS as the focus of the review:

1. What is the relationship between alcohol consumption and growth, size, body composition, and risk of overweight and obesity?
2. What is the relationship between alcohol consumption and risk of certain types of cancer?
3. What is the relationship between alcohol consumption and risk of cardiovascular disease?
4. What is the relationship between alcohol consumption and neurocognitive health?
5. What is the relationship between alcohol consumption and risk of all-cause mortality?
6. What is the relationship between alcohol consumption during lactation and postpartum weight loss?
7. What is the relationship between alcohol consumption during lactation and human milk composition and quantity?
8. What is the relationship between alcohol consumption during lactation and infant developmental milestones, including neurocognitive development?

The committee will produce a report that summarizes the evidence in conclusion statements that have been graded to indicate the strength of the evidence but do not include dietary guidance statements, recommendations, or advice.

BOX 1-4
Definition of Moderate Alcohol Consumption

In this report, *moderate alcohol consumption* is defined as consuming alcoholic beverages up to the limit defined by the *Dietary Guidelines for Americans*, meaning, two drinks or 28 grams of alcohol in a day for men and one drink or 14 grams of alcohol in a day for women.

the Statement of Task, the committee reviewed and assessed the results of the evidence scan and decided if a systematic review of more recent literature (i.e., articles published since the last systematic review used by the DGAC in developing the DGA—see Chapter 2) was needed. With a goal of completing this report in time to inform the DGA 2025–2030, the committee decided to undertake *de novo* systematic reviews rather than perform updates and reanalysis of past reviews. Protocols for these systematic reviews were registered in the PROSPERO international database for systematic reviews to avoid duplication of effort, reduce reporting bias, and promote transparency (Schiavo, 2019),[6] and the protocols were carried out by the Academy of Nutrition and Dietetics Evidence Practice Center at the request of the committee.

The approaches to the eight questions limited the population studied to nonpregnant adults of legal "drinking age" (21 years of age and older). In identifying the literature, an important requirement was to have a comparison group that did not combine never drinkers with former drinkers because of the resulting abstainer bias that would occur; therefore, results in this report are not directly comparable to past evidence that does include such abstainer bias.

Each systematic review required tailoring to its topic. For example, the committee identified many recent peer-reviewed publications (and systematic reviews) on the relationship of alcohol consumption to the health outcomes for the first five questions specified in the Statement of Task. In contrast, the committee identified little evidence for the three lactation-related questions and noted that these topics were not systematically or consistently addressed in prior versions of the DGA (Box 1-2); accordingly, the committee used a different search strategy, as described in Chapter 8, for the lactation questions. Where evidence on any topic was determined to be insufficient for a quantitative synthesis (i.e., meta-analysis), the committee performed a systematic review with a narrative synthesis of the evidence.

[6] CRD42024563137, CRD42024566062, CRD42024564414, CRD42024563189, and CRD42024545562.

In interpreting the Statement of Task term "certain cancers" (Box 1-3), the committee chose to be inclusive of all cancers for which there were studies of risk associated with moderate alcohol consumption within the search time frames described in Chapter 2. The committee asked for systematic reviews addressing the seven types of cancer for which the National Cancer Institute reports increased risks associated with moderate alcohol use: breast, oral, pharyngeal, laryngeal, esophageal, colon, and rectal (ACS, 2020; NCI, 2021). All other cancers with articles published within the search time frame were determined to have insufficient numbers of articles to warrant systematic reviews (see Chapter 4).

In reviewing the evidence for the question in the Statement of Task, "What is the relationship between alcohol consumption and growth, size, body composition, and risk of overweight and obesity?" the committee chose to exclude body composition from its review, findings, and conclusions, owing to limitations of reporting this outcome even in clinical settings (see Chapter 5).

Similarly, for the question, "What is the relationship between alcohol consumption and risk of cardiovascular disease?" the committee restricted its review, findings, and conclusions to the composite three-point major adverse cardiovascular events (3P-MACE) outcome, which consists of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death. The committee restricted neurocognition outcomes to dementia, Alzheimer's disease, and cognitive decline for the question, "What is the relationship between alcohol consumption and neurocognitive health?"

ORGANIZATION OF THE REPORT

This report is organized into nine chapters. Chapter 2 delineates the committee's approach to the task including search strategies, methodological considerations with alcohol consumption research generally, and the methods used in this report. The next five chapters present discussions and *de novo* systematic reviews for the association between moderate alcohol consumption and health for five of the questions in the Statement of Task: all-cause mortality (Chapter 3), weight changes, (Chapter 4), cancer (Chapter 5), cardiovascular disease (Chapter 6), and neurocognition (Chapter 7). Chapter 8 presents the committee's review of the three questions about lactation. Future research, including methodological considerations and research gaps regarding research on alcohol and health, is discussed in Chapter 9. Biographical sketches of the committee members are provided in Appendix A. Open session agendas are presented in Appendix B. The timeline of screening for eligibility and committee decisions are provided in Appendix C, and A Measurement Tool to Assess Systematic Reviews (AMSTAR-2) tables are in Appendix D. The search terms and results for literature searches conducted and all results for the commissioned systematic reviews conducted

by the Academy of Nutrition and Dietetics are presented in Appendixes E–I.[7] Although the three questions in the Statement of Task about maternal alcohol consumption during lactation did not result in a systematic review, the search terms are provided in Appendix J.

CONTEXTUAL ISSUES FOR THIS REPORT

As described above, every edition of the DGA is informed by different sources of information. This study was congressionally mandated to address the effect of alcohol on health for consideration by the DGAC as a part of the systematic reviews informing the DGA. Within the Statement of Task and with consideration of previous findings and conclusions of the various DGAC scientific reports, the committee adhered to the standard scientific protocols for conducting systematic reviews while recognizing the urgency of delivering this report to inform recommendations of the DGA.

Within this context, the committee sought to apply the most comprehensive and rigorous methods available in the specified time frame to inform the DGA process. This report evaluates primary research published since 2010 (and 2019 for all-cause mortality, given that it was last reviewed for the 2020–2025 DGA) and is but one piece of a multifaceted process to develop the DGA. The committee notes that there is an additional body of research published before and subsequent to (e.g., Ortolá et al., 2024) the publication search dates used for identifying evidence examined in this report. As described in the methodology in Chapter 2 and consistent with the NESR process, this report relied on evidence synthesis of primary studies and did not include results from existing systematic reviews and meta-analyses. Lastly, the committee's decision to address the effect of bias caused by including former drinkers with never drinkers in the comparison group for evaluating the health effects of moderate drinking resulted in the exclusion of several otherwise relevant studies. The committee has determined that the evidence presented herein may be useful for policy making and informing future research.

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2

Approach to the Task

This chapter describes the methods the committee used to perform systematic evidence scans based on (1) the eight questions posed in the Statement of Task (Box 1-3), (2) the committee's criteria for assessing the results of the evidence scans to determine whether there was sufficient evidence to support an updated or *de novo* systematic review of the more recent evidence, and (3) the committee's framework for assessing the certainty of conclusions as well as the process used for making conclusions. Box 2-1 provides definitions for key terminology related to systematic reviews discussed in this report.

The committee used a systematic approach to gather evidence that included evidence scans, systematic reviews (SRs) and a systematic narrative review. Additional evidence from SRs, meta-analyses, and other primary research publications were submitted to the committee for consideration. From among these, those that met the committee's defined criteria were included, while those that fell outside of the criteria were not.

EVIDENCE SCAN AND OUTCOMES

The committee developed search strategies for evidence scans based on the search terms and inclusion and exclusion criteria as outlined by the U.S. Department of Agriculture (USDA) Nutrition Evidence Systematic Review (NESR) center for the *Dietary Guidelines for Americans* (DGA). Search terms for alcohol consumption were derived from the NESR systematic review on alcohol and all-cause mortality for the DGA 2020–2025 and were applied to each of the literature searches (see Appendix E–I for search

BOX 2-1
Key Terminology Related to Systematic Reviews

AMSTAR-2: A Measurement Tool to Assess Systematic Reviews; used to assess methodological quality of systematic reviews of randomized and nonrandomized studies.[a,b]

Evidence scan: "A systematic and exploratory process used to describe the volume and characteristics of research available on a topic or question and to identify evidence gaps."[c]

GRADE: Grading of Recommendations Assessment, Development and Evaluation; an approach for assessing the certainty of evidence.[d]

Meta-analysis: The statistical analysis of a collection of analysis results from individual studies for the purpose of integrating the findings.

PICO: A formulism describing four key components of answerable research questions in systematic reviews. These include:

Population: Who is being studied, including characteristics such as age, sex, and underlying conditions.

Intervention: What is being given to the population. The intervention is what is thought to affect outcomes. In observational studies, *intervention* may be generalized to *exposure*.

Comparator: What the intervention or exposure is compared with, such as a different intervention, a placebo/no intervention, or a different amount of the intervention/exposure.

Outcome: What is thought to be affected by the intervention, such as heart disease or cancer.

terms). Except for the all-cause mortality outcome, for which a systematic review was completed for the DGA 2020–2025, inclusion and exclusion criteria for the searches for other health outcomes were derived and refined based on the criteria used in the most recent NESR reviews on dietary patterns, which included some alcohol criteria. After reviewing these search terms and inclusion/exclusion criteria, the committee made minor revisions to the search strategy by adding terms and editing criteria based on the expertise of committee members with the intent of being more inclusive of data relevant to the Statement of Task (Table 2-1).

Sometimes PICO is expanded to PICODTS to include:

Study **D**esign**:** Types of eligible study designs, such as randomized trials and cohort studies.

Timing: Duration of intervention, time-points for outcome measurement, and when the study was done or over what period.

Setting: Setting refers to where the participants experience the intervention, such as inpatient, outpatient, or community. It could also refer to rural versus suburban versus urban, or country.

Risk of bias: "The potential for study findings to systematically deviate from the truth due to methodological flaws in the design, conduct, or analysis."[e]

Scoping review: "A type of knowledge synthesis that follows a systematic approach to map evidence on a topic and identify main concepts, theories, sources, and knowledge gaps."[f]

Systematic review: "A review that uses explicit, systematic methods to collate and synthesize findings of studies that address a clearly formulated question."[g]

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[a] https://www.amstar.ca/ (accessed September 23, 2024).
[b] https://doi.org/10.1136/bmj.j4008 (accessed September 23, 2024).
[c] https://nesr.usda.gov/protein-dietary-reference-intake-evidence-scans (accessed September 23, 2024).
[d] http://www.gradeworkinggroup.org/ (accessed September 23, 2024).
[e] https://doi.org/10.1136/bmj.n160 (accessed September 23, 2024).
[f] https://community.cochrane.org/pico-search-about (accessed September 23, 2024).
[g] https://doi.org/10.7326/M18-0850 (accessed September 23, 2024).

Eligibility Criteria

The committee developed study inclusion and exclusion criteria and sought studies primarily in humans who were at least 21 years of age and at risk for chronic disease. Studies on interventions had to include at least 30 participants per arm or a power calculation, and observational studies had to include at least 1,000 individuals (comparisons with never and former drinks combined as nondrinker groups were excluded). Primary literature was used, therefore systematic reviews or meta-analyses were excluded. Table 2-1 lists the outcomes considered across the eight research questions

TABLE 2-1 Inclusion and Exclusion Criteria

Category	Inclusion Criteria	Exclusion Criteria
Population	Human participants (females, males)	Nonhuman participants (e.g., animal or *in vitro* models)
		Women during pregnancy
	Studies conducted in countries ranked as high or higher human development.	Studies conducted in countries ranked as medium or lower human development
	Age of study participants (at intervention or exposure): • Primarily adults 21 years or older • Studies that enroll *some* participants under 21 years old	Age of study participants (at intervention or exposure): • Studies that *exclusively* enroll participants under 21 years old
	Health status: • Studies that enroll participants who are healthy and/or *at risk* for chronic disease • Studies that enroll *some* participants diagnosed with a disease • Studies that enroll *some* participants diagnosed with a mild cognitive impairment, dementia, or Alzheimer's disease • Studies that enroll *some* participants who are classified with severe undernutrition, or underweight, or obese	Health status: • Studies that *exclusively* enroll participants diagnosed with a disease, or hospitalized patients with illness or injury • Studies that *exclusively* enroll participants diagnosed with a disease or illness requiring therapeutic intervention • Studies that *exclusively* enroll participants classified as obese (i.e., studies that aim to treat participants who have already been classified as obese) or who are postbariatric surgery • Interventions designed to induce weight loss or treat overweight and obesity through energy-restriction/hypocaloric diets for the purpose of treating additional or other medical conditions • Studies that *exclusively* enroll participants diagnosed with a disease (i.e., studies that aim to treat participants who have already been diagnosed with the outcome of interest)
	Size of study groups: • Interventions: 30 participants per-arm or a power calculation included • Observational studies: $N \geq 1{,}000$	Size of study groups: • Interventions: fewer than 30 participants per arm and no power calculation reported • Observational studies: $N < 1{,}000$ participants

TABLE 2-1 Continued

Category	Inclusion Criteria	Exclusion Criteria
Exposure	• Average consumption of alcoholic beverages • Pattern of alcohol consumption: Per occasion consumption of alcohol beverages (i.e., number of drinks per drinking day or drinks per drinking occasion) and drinks per meal • Information on type of beverage (e.g., beer, wine, spirits) will be collected if available	• Data on nondrinker groups where never and former drinkers are combined • Exclusive enrollment of problem drinkers (binge drinkers, alcohol use disorder, hazardous alcohol use)
Comparator	Primary • Comparisons across different average alcohol consumption or patterns of alcohol consumption among current drinkers Secondary • Comparisons between never drinkers and current drinkers	• No comparator • Comparisons with former drinkers • Comparisons with never and former drinkers as a combined nondrinker group
Outcome	**All-Cause Mortality Outcomes** All-cause mortality (i.e., total mortality): the total number of deaths from all causes during a specific time period (ideally stratified by sex)	**All-Cause Mortality Outcomes** Studies that only report cause-specific mortality (total number of deaths from a specific disease, such as cardiovascular disease or cancer)
	Weight Outcomes Weight BMI (body mass index) Waist circumference Incidence of overweight and obesity Body composition	**Weight Outcomes** Gestational weight gain
	Cancer Outcomes Breast (female), oral, pharyngeal, laryngeal, esophageal, colon, and rectal	**Cancer Outcomes** Studies that exclusively examine cancer-related mortality, prevalence, survivorship, or recurrence of cancer
	CVD Outcomes Nonfatal myocardial infarction Nonfatal stroke CVD-related mortality	**CVD Outcomes** Hypertension disorders during pregnancy and/or lactation
	Neurocognitive Outcomes Total dementia, Alzheimer's disease, Word recall, verbal fluency, MMSE	N/A

(continued)

TABLE 2-1 Continued

Category	Inclusion Criteria	Exclusion Criteria
Study Design	• Randomized controlled trials • Nonrandomized controlled trials, including quasi-experimental and controlled before-and-after studies • Prospective cohort studies • Retrospective cohort studies • Nested case-control studies • Case control studies • Mendelian randomization	• Cross-sectional studies • Uncontrolled trials • Uncontrolled before-and-after studies • Narrative reviews • Systematic reviews • Meta-analyses
	Peer-reviewed articles published in English Publication date range: 2019 to current *(all-cause mortality)* Publication date range: 2010 to current *(weight, cancer, CVD, neurocognition)*	Articles not published in peer-reviewed journals, including unpublished data, manuscripts, reports, abstracts, preprints, and conference proceedings; non-English publications

NOTES: CVD = cardiovascular disease; MMSE = Mini-Mental State Examination; *N* = number.

in the Statement of Task. Studies had to evaluate levels or patterns of alcohol consumption. The committee notes that two exclusion criteria warrant specific mention: first, studies were excluded if the exposure measurement (amount of alcohol consumption) did not allow for evaluating associations for moderate drinking distinct from greater consumption amounts (i.e., when all consumption amounts were combined as the exposure), and second, studies were excluded if persons who never consumed alcohol were combined with persons who formerly consumed alcohol to avoid the influence of abstainer bias.

Literature Search

The literature search approach was iterative based on search results and ongoing committee discussion. Databases searched included Medline, Embase, and the Cochrane Register of Controlled Trials (CENTRAL). The search comprised terms for alcohol and the eight specific outcomes. The search terms for the SRs are in Appendixes E–I.[1] Search

[1] Appendixes E through J are available online at https://nap.nationalacademies.org/catalog/28582.

terms for literature searches that did not result in an SR are provided in Appendix J.

Because the DGA were supported by a new systematic review for all-cause mortality, the search frame included studies published in January 2019 or later. The other seven questions in the Statement of Task included studies published in January 2010 (the date of the previous edition of the DGA that covered alcohol and health) or later. The search dates and periods for each topic are described in Box 2-2, and different iterations and committee discussions and decisions are provided in Appendix C. As a result of this process, two additional studies for cardiovascular disease and neurocognition were deemed to be eligible.

BOX 2-2
Search Dates, Periods, and Description

- **January 1, 2019–September 22, 2023** (*September 22, 2023, search*). Included a search for primary studies for all-cause mortality, weight changes [through December 8, 2023], cancer, cardiovascular disease, neurocognitive health, and lactation questions [through September 25, 2023].
- **January 1, 2019–February 13, 2024** (*February 13, 2024, search*). Included systematic reviews (SRs) with or without meta-analysis for all-cause mortality, weight change, cancer, cardiovascular disease, neurocognitive health, and lactation questions. The quality of the SRs was assessed using AMSTAR-2 (Appendix D).
- **January 1, 2010–January 1, 2019** (*April 9 and 11, 2024, search*). Included an SR with or without meta-analysis search for weight changes and lactation [April 9, 2024], and cancer, cardiovascular disease, and neurocognitive health [April 11, 2024]. After information was gathered during an open session with experts, the committee determined that the evidence should cover the literature from where the last primary article evidence review for alcohol used by the 2020 Dietary Guidelines Advisory Committee (DGAC) ended, which was 2010. The committee expanded its review to capture SRs published from 2010 to 2019 for all topics other than all-cause mortality, which was covered by NESR in its 2019 SR. Articles included in the SRs from this second search were screened to identify primary articles in addition to those from the previous searches.

Screening

Title and abstract screening were conducted in two phases. In the first stage, OpenAI's GPT-4.0 in the PICO Portal evidence synthesis platform removed titles and abstracts using natural language processing and machine learning based on initial screening by humans. The second stage of title/abstract screening was conducted in duplicate by independent researchers based on the eligibility criteria (Table 2-1). Subsequently, full-text articles of potentially relevant abstracts were reviewed in duplicate by independent researchers. All discrepancies were resolved by a third researcher. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow charts were created for each of the topics and are included in each chapter. The search results for the topics identified in the Statement of Task are summarized in Table 2-2.

Data Extraction

Data extraction was completed by consultants at the Academy for Nutrition and Dietetics (AND). The information extracted from each study included author(s), year of publication, country where the study was conducted, source of funding, follow-up time, sample sizes, years of data collection, description of alcohol intake and assessment tool, description of comparison group (i.e., age, sex, race/ethnicity), confounders accounted for in analysis, and results for specific analysis. One researcher extracted data from each study, where they were verified by a second researcher. Discrepancies were resolved through discussion or a third researcher.

TABLE 2-2 Search Details by Statement of Task Questions

Search question/topic	Number of articles identified by search criteria	Number of articles eligible by title and abstract screening	Number of articles eligible by full-text screening	Number of articles included in review for data extraction
All-cause mortality (2019–2023 only)	17,404	320	34	34
Weight changes	4,458	64	7	7
Cancer	20,190	382	25	25
Cardiovascular disease	20,227	423	26	26
Neurocognition	19,997	364	24	24
Lactation	4,714	17	7	0

Risk-of-Bias Assessment

All included studies were cohort studies, and risk of bias was assessed using the Risk of Bias in Nonrandomized Studies of Exposures (ROBINS-E) tool (Higgins et al., 2024). Domains evaluated had bias caused by confounding, bias arising from measurement of the exposure, bias in selection of participants, bias owing to post-exposure interventions, bias caused by missing data, bias arising from measurement of outcomes, and bias in selection of the reported result. For the five domains on bias due to confounding, important confounding variables considered were age, sex, smoking status, socioeconomic status, diet, physical activity, weight/body mass index (BMI), and comorbidities. Overall (study-level) ratings for risk of bias were as follows: low, some concerns, high, or very high (Higgins et al., 2024). Risk-of-bias assessments were conducted independently by two researchers, and discrepancies in domain-specific and/or overall assessments were resolved by a third researcher. Risk of bias was reported using a figure created in *R* using the robvis function (McGuinness and Higgins, 2021).[2]

Data Synthesis

Comparative results used mean differences for continuous outcomes, hazard ratios (HR), risk ratios (RR), or odds ratios (OR) for binary outcomes. Fully adjusted effect estimates were used when determining impact from nonrandomized studies. When studies did not report results that could be pooled, results were summarized narratively. When results from at least three studies with comparable exposures were available, meta-analysis were conducted. Two overarching meta-analyses were conducted: one with those never consuming alcohol as the comparator group, and one with those consuming alcohol. RRs were transformed to natural logs to address skewness, and studies were weighted by the inverse of the estimated variance of the natural log of the RR (Alavi et al., 2020). A restricted maximum likelihood random-effects model was used for meta-analyses. Heterogeneity was assessed using the I^2 statistic that refers to the percentage of total variability in study results caused by between-study variability. A p-value <0.05 indicated statistical significance.

When information was available, subgroup analyses were conducted according to sex, age (<60 or ≥60 years), race/ethnicity, and smoking status. A sensitivity analysis was conducted by examining results after dropping studies with high risk of bias. Another sensitivity analysis was conducted

[2] Robvis (Risk-Of-Bias-VISualization) is a tool for visualizing risk-of-bias assessments in a systematic review.

BOX 2-3
Understanding the Forest Plot

A forest plot is a visual summary of the results of a meta-analysis, which synthesizes results across multiple studies. Individual studies are represented by a horizontal row in the forest plot with their point estimate given by a square and a 95% confidence interval represented by a horizontal line around that square. The size of the square for a given study is proportional to the amount of weight the study was given in calculating the meta-analysis estimate pooling across all studies. At the bottom of the forest plot, this pooled estimate is provided as a diamond. The center of the diamond, marked by a vertical line, represents a pooled estimate, while the lefthand and righthand vertices represent the limits of its 95% confidence interval. A vertical reference line also demarcates the value corresponding to no association between outcome and exposure, located at 1 for relative measures (e.g., relative risk [RR], hazard ratio [HR]) or 0 for absolute measures (e.g., risk differences, mean differences).

using the five categories from Zhao et al. (2023) and a "one drink/day" limit for both females and males.

All meta-analyses were conducted using Stata 16 and OpenMeta.[3] Results were reported in a study characteristics table, forest plots for meta-analysis are included in Chapters 3–7 (Box 2-3), and a summary of findings tables. For analyses with at least 10 studies, publication bias was determined using visual examination of funnel plots.

Assessment of Certainty of Evidence

Certainty of evidence was rated by the AND consultants using the GRADE method, which considers study design, risk of bias, directness, inconsistency in results between studies, precision of the findings, and other factors (GRADE Working Group, 2013). Evidence certainty was initially rated as high, moderate, low, or very low by the consultants who conducted the systematic reviews (Appendixes E–I). Although these systematic reviews examined observational studies, evidence certainty started with a high rating and then downgraded because risk of bias was assessed using ROBINS-E, which is a stricter assessment of observational studies (Higgins

[3] OpenMeta is an open-sourced software platform used for meta-analyses. http://www.cebm.brown.edu/openmeta/ (accessed November 15, 2024).

et al., 2024). A GRADE table was created using GRADEPro Guideline Development Tool.[4]

Decision Process for Undertaking *De Novo* Systematic Reviews

To inform the DGA, the committee decided to undertake *de novo* systematic reviews rather than perform updates and reanalysis for past reviews. To decide whether to send a topic for a systematic review of studies published since the last review, the committee established a process based on the review of articles published in the search time frames by committee members expert in the specific topics. For all-cause mortality, this included articles published between January 2019 and September 2023. For CVD, overweight/obesity, cancer, neurocognitive health, and lactation, this included articles published between January 2010 and September 2023. Additional articles for cancers other than the seven specified as related to alcohol by the U.S. National Cancer Institute and the American Cancer Society were also reviewed (ACS, 2020; NCI, 2015).

Topics Without Systematic Reviews

Based on the low number of studies, small sample sizes, and methodological challenges related to exposure and outcome measurement, other/emerging cancer sites (see Chapter 5) and lactation (see Chapter 6) were not submitted for evidence synthesis. Conclusions for these topics were based on a review of the individual study results by the committee.

Similarly, if there were fewer than three studies meeting inclusion criteria, results from a full evidence review with meta-analysis were not conducted; rather, the committee summarized the literature, specifically evaluating whether the results were congruent with or different from previous reviews used to develop prior DGA (Table 2-3). The committee decided to base conclusions on systematic reviews and narrative synthesis of individual study results for overweight/obesity and neurocognitive health.

Process for Committee Conclusions

When there were at least three studies included in the meta-analysis, the committee included forest plots in the report to support conclusions (Box 2-3). To determine the certainty of its conclusions, the committee

[4] GRADEPro Guideline Development Tood is an evidence synthesis tool used to create summary and findings tables for Cochrane systematic reviews. https://methods.cochrane.org/gradeing/gradepro-gdt (accessed November 15, 2024).

TABLE 2-3 Dietary Guidelines Advisory Committee Links with Alcohol Sections

	2010	2015	2020
Report	2010 DGAC Report[a]	2015 DGAC Report[b]	2020 DGAC Report[c]
Methodology	2010 SR Methodology[d]	2015 SRs[e]	2020 SR Methodology[f]
Systematic Reviews	2010 SR[g]	N/A	2020 SR[h]

NOTES: DGAC = Dietary Guidelines Advisory Committee; N/A = not available; SR = systematic review.

[a] See https://www.dietaryguidelines.gov/sites/default/files/2019-05/2010DGACReport-camera-ready-Jan11-11.pdf (accessed September 19, 2024).

[b] See https://health.gov/sites/default/files/2019-09/Scientific-Report-of-the-2015-Dietary-Guidelines-Advisory-Committee.pdf (accessed September 19, 2024).

[c] See https://www.dietaryguidelines.gov/sites/default/files/2020-07/ScientificReport_of_the_2020DietaryGuidelinesAdvisoryCommittee_first-print.pdf (accessed September 19, 2024).

[d] See https://nesr.usda.gov/sites/default/files/2019-04/2010DGAC-SR-Methods.pdf (accessed October 10, 2024).

[e] See https://nesr.usda.gov/sites/default/files/2019-04/2015DGAC-SR-Methods.pdf (accessed October 10, 2024).

[f] See https://nesr.usda.gov/sites/default/files/2020-07/NESR Systematic Review Methodology for the 2020 Advisory Committee_0.pdf (accessed October 10, 2024).

[g] See https://nesr.usda.gov/sites/default/files/2019-04/2010DGAC-SR-Alcohol.pdf (accessed September 19, 2024).

[h] See https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews/beverages-and-added-sugars-subcommittee/alcohol-all-cause-mortality (accessed October 10, 2024).

used a framework based on methods from the U.S. Preventive Services Task Force (USPSTF, 2018).[5]

- *High certainty*: Evidence includes consistent results from good-quality studies in relevant populations assessing effects on health outcomes; the conclusion is unlikely to be affected by future studies. (Note that it is unlikely to be rated as high certainty without a randomized controlled trial).
- *Moderate certainty*: Evidence is sufficient to determine effects on health outcomes but is constrained by issues raised in the quality assessment of the evidence; additional information from future studies could change the conclusion.

[5] For the systematic reviews commissioned by AND that assigned "very low" certainty, the committee used the phrase "insufficient evidence" to reflect a lower level of certainty of the evidence using the USPSTF framework.

- *Low certainty*: Evidence is insufficient to assess effects on health outcomes; additional information from future studies may allow for assessment.

Low certainty was concluded when the results of eligible studies were inconsistent or the data were too sparse. When the level of certainty could not be assigned, the committee determined that no conclusion could be drawn. This determination was made when there was a statistically nonsignificant meta-analysis result or there were no eligible studies.

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Higgins, J. P. T., R. L. Morgan, A. A. Rooney, K. W. Taylor, K. A. Thayer, R. A. Silva, C. Lemeris, E. A. Akl, T. F. Bateson, N. D. Berkman, B. S. Glenn, A. Hrobjartsson, J. S. LaKind, A. McAleenan, J. J. Meerpohl, R. M. Nachman, J. E. Obbagy, A. O'Connor, E. G. Radke, J. Savovic, H. J. Schunemann, B. Shea, K. Tilling, J. Verbeek, M. Viswanathan, and J. A. C. Sterne. 2024. A tool to assess risk of bias in non-randomized follow-up studies of exposure effects (ROBINS-E). *Environment International* 186:108602.

McGuinness, L. A., and J. P. T. Higgins. 2021. Risk-of-bias VISualization (robvis): An R package and shiny web app for visualizing risk-of-bias assessments. *Research Synthesis Methods* 12(1):55-61.

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USPSTF (U.S. Preventative Services Task Force). 2018. *Grade definitions*. https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/grade-definitions (accessed September 20, 2024).

Zhao, J., T. Stockwell, T. Naimi, S. Churchill, J. Clay, and A. Sherk. 2023. Association between daily alcohol intake and risk of all-cause mortality: A systematic review and meta-analyses. *JAMA Network Open* 6(3):e236185.

3

All-Cause Mortality

According to the Centers for Disease Control and Prevention, heart disease, cancer, accidents, and stroke are leading causes of death in the United States (CDC, 2024). Previous research studies have demonstrated that modifiable lifestyle factors, including alcohol consumption, are associated with these causes of death. With respect to alcohol consumption, there is strong evidence that heavy drinking has adverse effects on the risk of these leading causes of death. However, owing to the paucity of large and well-designed studies that address the methodological challenges described in Chapter 2 (e.g., the challenges of using self-reported data to capture complexities of alcohol consumption), the association of moderate alcohol consumption with all-cause mortality is less clear. The committee sought to examine the association of moderate alcohol consumption with the risk of all-cause mortality by reviewing publications available from January 2019 through September 2023 and with the focus on moderate alcohol consumption.

CHOICE OF OUTCOMES

The outcome discussed in this chapter is all-cause mortality (i.e., total mortality), which the committee defined as the total number of deaths from all causes expressed per population at risk and calculated for a specific period of time. This outcome is of high public health relevance, and the association of alcohol intake with all-cause mortality provides an overall integration of the effects of alcohol on multiple organ systems, on intentional and unintentional injuries, and on any yet-to-be identified associations. There is strong evidence for the adverse effects of heavy drinking on the risk of the

leading causes of death, including heart disease, stroke, and cancer. While it is also important to understand the association of moderate alcohol consumption with cause-specific mortality, this chapter focuses on the association of moderate alcohol consumption and the risk of all-cause mortality.

BIOLOGICAL PLAUSIBILITY

Previous mechanistic studies have demonstrated that alcohol consumption influences serum levels of intermediary biological markers that are relevant to the incidence of heart disease and stroke. Specifically, the effects of alcohol consumption on lipids, platelet aggregation, inflammation, and endothelial function are well-documented in the literature (Camargo et al., 1985; Chiva-Blanch et al., 2015; Fragopoulou et al., 2021; Gepner et al., 2015; Masarei et al., 1986; Sierksma et al., 2002; Stote et al., 2016; Umar et al., 2005; Zhang et al., 2000). Furthermore, alcohol metabolites, including acetaldehyde, can play a role in the pathogenesis of certain cancers with downstream implication on the risk of death from cancers (Balbo et al., 2012; Ferraguti et al., 2022; Guidolin et al., 2021; Hoes et al., 2021; Mizumoto et al., 2017; Rumgay et al., 2021). The toxic effects of alcohol on several organs and the ability of alcohol to impair brain function has been well established in the literature for trauma and deaths related to alcohol intoxication (Ferragut et al., 2022; Vore and Deak, 2022). A combination of pathways is hypothesized to mediate the effects of alcohol consumption on multiple organ systems to ultimately affect all-cause mortality, including, for example, alcohol's effect on altering hemostatic factors to increase the risk of bleeding. The investigation of the association of moderate alcohol consumption with all-cause mortality provides an integrated estimate of the full effect of this level of alcohol consumption. Further consideration of cause-specific morbidity and mortality, including cancers, cardiovascular disease, and neurocognitive outcomes, are reported in Chapters 5, 6, and 7, respectively.

PRIOR DGA RECOMMENDATIONS

To contextualize the current findings on the association of alcohol consumption with all-cause mortality, the committee consulted the *Dietary Guidelines for Americans* (DGA) and the Dietary Guidelines for Americans Committee (DGAC) reports from 2010, 2015, and 2020.

2010

The 2010–2015 DGA stated, "Moderate alcohol consumption also is associated with reduced risk of all-cause mortality among middle-aged and older adults,"[1] where moderate alcohol consumption is defined as up to one

[1] 2010 *Dietary Guidelines for Americans* Report, p. 31.

drink per day for women and up to two drinks per day for men (USDA and HHS, 2010). The above statements were not referenced nor was there a systematic review of the evidence.

The 2010 DGAC report states that, compared to those who abstain, an "average daily intake of one to two alcoholic beverages is associated with the lowest all-cause mortality" (DGAC, 2010).[2] The report concluded that there was no meaningful change in the research findings compared to past reports, that no new systematic reviews were warranted, and the committee reiterated the findings of past committees. For all-cause mortality, the report cited a meta-analysis (Di Castelnuovo et al., 2006) that found an inverse association of moderate alcohol consumption and total mortality with a summary relative risk estimate of 0.80 from a *J*-shaped curve; the lowest mortality was observed in persons with an average consumption of 1–2 drinks/day.[3]

2015

The 2015–2020 DGA included an appendix on alcohol, but it did not describe or quantify the association of alcohol with all-cause mortality. The emphasis in the 2015–2020 DGA was on the consideration of the energy content (calories) from alcohol consumption, where moderate intake was defined as "up to one drink per day for women and up to two drinks per day for men" (USDA and HHS, 2015).[4] The 2015 DGAC report did not specifically address the association of alcohol intake with all-cause mortality (DGAC, 2015).

2020

The DGA included a chapter on alcohol and health. Consuming alcohol in moderation was defined as limiting intake to two drinks or less in a day for men and one drink or less in a day for women, when alcohol is consumed (USDA and HHS, 2020).[5] The DGA stated that "evidence indicates that, among those who drink, higher average alcohol consumption is associated with an increased risk of death from all causes compared with lower average alcohol consumption" (USDA and HHS, 2020).[6] The report qualified this conclusion by reiterating that cause-specific mortality may have differential associations with alcohol intake and noting that "emerging evidence suggests that even drinking within the recommended limits may increase the overall risk of death from various causes, such as from several types of cancer and some forms of cardiovascular disease" (USDA and HHS, 2020).[7]

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[2] 2010 Dietary Guidelines Advisory Committee Report, pp. 5, 559–560, 362.
[3] 2010 Dietary Guidelines Advisory Committee Report, p. 355.
[4] 2015 *Dietary Guidelines for Americans* Report, p. 93.
[5] 2020 *Dietary Guidelines for Americans* Report, pp. x, 18, 49, 129.
[6] 2020 Dietary Guidelines for Americans Report, p. 49.
[7] 2020 *Dietary Guidelines for Americans* Report, p. 49.

The 2020 DGAC report included a systematic review designed to address the question "What is the relationship between alcohol consumption and all-cause mortality?" Briefly, the 2020 systematic review included studies published between January 2010 and March 2020, Mendelian randomization studies and observational studies with more than 1,000 participants; studies of participants under 21 years of age were excluded (Mayer-Davis et al., 2020). The systematic review included 60 studies (one Mendelian randomization study, one retrospective cohort study, and 58 prospective cohort studies) with no randomized controlled trials. The primary focus of the systematic review was on risk among those who consumed alcohol, including risk of binge drinking; the findings for binge drinking are not referenced here because this exposure category is not the focus of the current report. The DGAC first addressed the association of consuming more versus less alcohol among those who consumed alcohol (DGAC, 2020). The plain language summary noted, "Moderate evidence indicates higher average volume of alcohol consumption is associated with an increased risk of all-cause mortality compared with lower average alcohol consumption among those who drink"[8] and that "Most studies found lower risk among men consuming within ranges up to two drinks per day and women consuming within ranges up to one drink per day compared to those consuming higher average amounts" (DGAC, 2020).[9] The DGAC next addressed the question of consuming alcohol at various levels compared to never consuming alcohol, concluding, "limited evidence suggests that low average alcohol consumption, particularly without binge drinking, is associated with a lower risk of all-cause mortality compared with never drinking alcohol" (DGAC, 2020). The 2020 DGAC report cautioned that the scientific and public health concerns that are associated with alcoholic beverages should involve a careful review of the evidence when comparing never drinking alcohol to low average consumption given the biases (e.g., residual confounding) known to affect observational studies.

METHODOLOGICAL CONSIDERATIONS

All-cause mortality is often used as an outcome because it is less affected by misclassification than cause-specific mortality (Weiss, 2014), which is a strength. If the exposure, in this case alcohol consumption, affects major and multiple causes of death in the same direction (i.e., uniformly increases or decreases risk), then all-cause mortality is a sensitive outcome. However, the association of alcohol consumption with all-cause mortality will be affected by confounding bias if there is a factor that affects both the likelihood of exposure and the risk of all-cause mortality. Another methodological challenge when using all-cause mortality as an outcome in alcohol research is

[8] 2020 Dietary Guidelines Advisory Committee Report, p. 11.
[9] 2020 Dietary Guidelines Advisory Committee Report, p. 11.

that it includes deaths that are attributable to factors not related to alcohol intake (e.g., natural disasters). Counting deaths that are not causally related to alcohol consumption may lead to a dilution of any true association of alcohol consumption with mortality (e.g., underestimation of true association of moderate alcohol intake with death). Studying cause-specific mortality as an outcome might mitigate some of the above issues but raises other challenges, including misclassification of cause of death and statistical power concerns for stable estimates of association when studying rare causes of deaths.

SYSTEMATIC REVIEW

Approach

An evidence scan was completed to describe the extent of the recent published literature. The scan searched for original research studies published from January 2019 to September 2023, given that the past DGAC reviewed literature through March 2020. Thirty-four studies of alcohol and all-cause mortality were identified, including 11 published from 2018 to 2020 and 23 between 2021 and 2023; the majority were prospective cohort studies (Figure 3-1). The certainty of the evidence of the studies included in the systematic review are summarized in Table 3-1. Given the number of original studies identified in the evidence scan, the committee made the subjective decision to commission a *de novo* systematic review of the relationship between alcohol consumption and the risk of all-cause mortality. The committee notes that because the commissioned systematic review was limited to studies published between January 2019 to September 2023, this is not an overall review of all the evidence on this question, given the evidence base dates back over 50 years. Also, the included studies are mainly prospective epidemiologic studies of average drinking, so there are caveats related to the methodologic concerns described in Chapter 2, including the use of self-reported data on alcohol consumption, incomplete control of confounding, and challenges in harmonizing findings across different ways of assessing and categorizing alcohol consumption (AND, 2024a).

Results

The systematic review search dates were January 1, 2019, to September 22, 2023, and the search was completed on September 22, 2023. The search focused on identifying all original research studies, using a protocol to identify exclusion/inclusion criteria. The following data were extracted from each study onto a standardized template: authors; year of publication; country where the study was conducted; source of funding; duration of follow-up; sample size; years of data collection; description of alcohol consumption and how consumption of alcohol was assessed; description

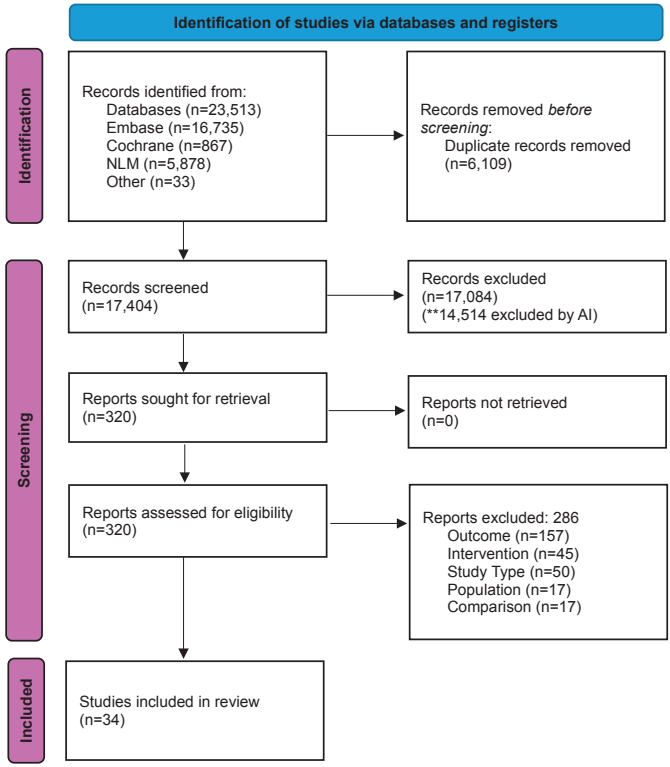


FIGURE 3-1 PRISMA flow chart for the systematic review on the association between alcohol consumption and all-cause mortality.
NOTES: The diagram shows the number of primary articles identified from the primary article search and each step of screening. The literature dates include articles with the publications between 2019 and 2023. n = number; NLM = National Library of Medicine; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
SOURCE: Figure E-1 in Appendix E, Academy of Nutrition and Dietetics, 2024.

of comparison group, age, sex, race/ethnicity; and confounders accounted for in analysis (Table E-2 of SR details specific confounders accounted for in each study [see Appendix E]). For quantitative results, hazard ratio (HR), risk ratio/relative risk (RR) or odds ratio (OR), and 95% confidence interval (CI) for the all-cause mortality outcome was extracted for each comparison of interest. The fully adjusted effect estimates were extracted, thus from models accounting for confounding factors.

Among the 27 included studies reported in 34 articles, only 12 had data available to assess this association and only eight of these studies

TABLE 3-1 Certainty of Evidence for Systematic Review Examining Associations Between Alcohol Consumption and All-Cause Mortality in Adults

Certainty Assessment							
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Relative effect (95% CI)
All-Cause Mortality: Consuming Moderate Alcohol vs. Never Consumption							
572,421 (8 nonrandomized studies)[a]	serious[b,c]	not serious[c]	not serious	not serious	none	moderate	RR 0.84 (0.81, 0.87)
All-Cause Mortality Among Moderate Alcohol Consumers: Higher vs. Lower Amounts							
28,744 (5 nonrandomized studies)[e]	serious[b]	not serious	not serious	serious[d]	none	low	RR 0.96 (0.87, 1.06)

NOTES: CI = confidence interval; RR = relative risk.
[a] Chang et al., 2020; Di Castelnuovo et al., 2022; Martínez-González et al., 2022; Muraki et al., 2023; Neumann et al., 2022; Ortolá et al., 2019; Qiu et al., 2022; Tian et al., 2023.
[b] Some concerns/high risk of bias in most included studies.
[c] High heterogeneity in results between studies.
[d] Wide confidence interval include potential benefits and harms.
[e] Daya et al., 2020, Ortolá et al., 2019, Ricci et al., 2020, Stelander et al., 2023, van de Luitgaarden et al., 2020.
SOURCE: Adapted from Table E-4 in Appendix E, Academy of Nutrition and Dietetics, 2024.

contributed to the overall estimate quantified in a meta-analysis (Table 3-2, Overall Results). Not all included studies had data on the risk of all-cause mortality for participants with moderate alcohol consumption compared to participants who never consumed alcohol. For this reason, eight studies contributed to the meta-analysis of this question. For a detailed description of all studies that met the inclusion criteria for the systematic review, please refer to Table E-2 in the systematic review. The eight studies that compared moderate alcohol consumption to never consuming alcohol primarily

TABLE 3-2 Results of Meta-Analyses with Subgroup and Sensitivity Analyses for Associations Between Alcohol Amount and All-Cause Mortality Compared to Never Consuming Alcohol

	N Studies	RR (95% CI)	I^2 (%)
Overall Results[a]			
Moderate alcohol consumption[b,c]	8	**0.84 (0.81, 0.87)**[d]	22.2
Subgroup Analyses According to Sex and Age[a]			
Sex			
Moderate alcohol consumption[b,c]			
Males	4	**0.84 (0.81, 0.88)**	0.02
Females	3	**0.77 (0.60, 0.97)**	70.3
Not Stratified	4	**0.86 (0.82, 0.89)**	0
Age			
Moderate alcohol consumption[b]			
<60 years	2	**0.80 (0.74, 0.86)**	8.5
≥60 years	4	**0.82 (0.77, 0.87)**	5.9
Not Stratified	4	**0.84 (0.78, 0.92)**	56.8

NOTES: CI = confidence interval; I^2 = heterogeneity; *N* = number; RR = relative risk.
[a] Meta-analyses of drinking categories were conducted using separate meta-analyses to avoid over-counting participants in comparison groups. Numbers in parentheses represent the range of alcohol consumption categories included in analysis.
[b] Moderate alcohol consumption is defined as: ≤1 drink/day for women and ≤2 drinks/day for men. 1 U.S. drink = 14 grams of alcohol.
[c] Alcohol consumption amount for included groups can be found in Figure E-3 and Annex E-2 in Appendix E.
[d] Results in bold are statistically significant ($p < 0.05$).
SOURCE: Adapted from Table E-3 in Appendix E, Academy of Nutrition and Dietetics, 2024.

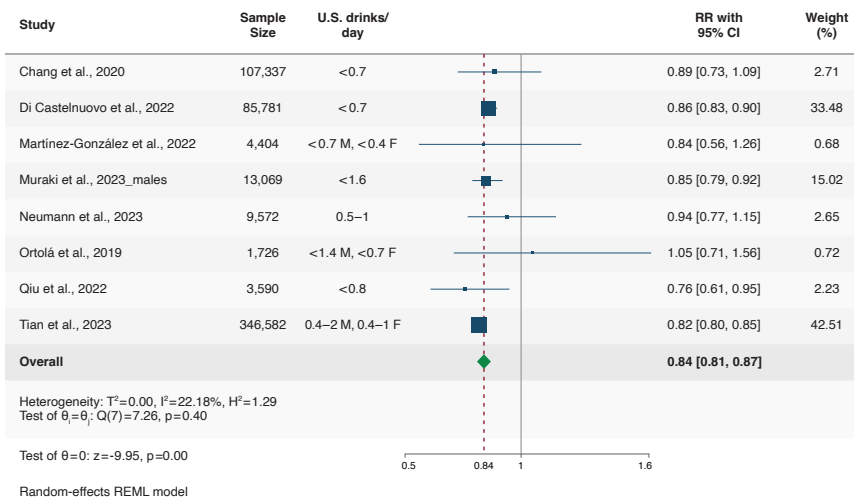


FIGURE 3-2A Meta-analysis on associations between alcohol consumption amounts that are moderate compared with never consuming alcohol on all-cause mortality.
NOTES: CI = confidence interval; I^2 = heterogeneity; REML = restricted maximum likelihood; RR = relative risk.
SOURCES: Adapted from Figure E-3 in Appendix E, Academy of Nutrition and Dietetics, 2024.

estimated the association of consuming alcohol at the lower end of moderate alcohol consumption (Figure 3-2A). For example, five of the eight studies compared an average of about 0.7 U.S. drinks/day (8.4 g/d) with never consuming alcohol. Because of how alcohol consumption was assessed and/or categorized in the included studies, there were fewer studies that contributed to an analysis of alcohol consumption at levels closer to the upper end of moderate alcohol consumption. All eight studies were assessed for risk of bias and were considered to have "some concerns" based on risk of bias due to confounding and/or exposure measurement (Table 3-3).

Among the 27 included studies, only four had data available to assess the association of moderate alcohol consumption and all-cause mortality stratified by sex (Table 3-2 and Figure 3-2B). There were three studies with data on females and males, one study with data on males only, and four studies that did not present sex-stratified analyses (note, these eight studies are the same studies in Figure 3-2A contributing to the overall estimate). All eight studies contributing data to the main question (i.e., the association of moderate consumption of alcohol compared to never consuming alcohol on the risk of all-cause mortality) adjusted for major confounders, including age, sex, socioeconomic factors, physical activity, smoking, and typically some mixture of comorbidities and body habitus. The eight included studies had serious concerns due to risk of bias (Table 3-3, primarily due

TABLE 3-3 Risk of Bias of Included Studies Examining the Association Between Alcohol Intake and All-Cause Mortality

Study	Bias Domains assessed as "some concerns" or "high"	Overall Risk of Bias
Ahlner et al., 2023	Confounding, exposure measurement, selection of participants	Some concerns
Armas Rojas et al., 2021	Confounding	Some concerns
Barbería-Latasa et al., 2022	Exposure measurement, selection of participants	High
Campanella et al., 2023	Confounding, exposure measurement	High
Chang et al., 2020	Confounding	Some concerns
Daya et al., 2020	Confounding, exposure measurement	Some concerns
Di Castelnuovo et al., 2022; Di Castelnuovo et al., 2023	Confounding, exposure measurement	Some concerns
Jankhothaew et al., 2020	Confounding, exposure measurement, missing data	Some concerns
John et al., 2021	Confounding, exposure measurement	High
Keyes et al., 2019	Confounding	Some concerns
Liu et al., 2022	Exposure measurement	Some concerns
Millwood et al., 2023	All domains low risk of bias	Low
Muraki et al., 2023	Confounding, exposure measurement	Some concerns
Neumann et al., 2022	Confounding	Some concerns
Ortolá et al., 2019	Exposure measurement	Some concerns
Patra et al., 2021	Confounding, exposure measurement	Some concerns
Peeraphatdit et al., 2020	Confounding, exposure measurement	Some concerns
Qiu et al., 2022	Confounding	Some concerns
Ricci et al., 2020	Confounding, missing data	High
Rosella et al., 2019	Confounding	Some concerns
Stelander et al., 2023	Confounding, exposure measurement	Some concerns
SUN Study • Martínez-González et al., 2022 • Schutte et al., 2020	Confounding, exposure measurement, selection of participants	Some concerns
Tevik et al., 2019	Confounding, exposure measurement, missing data	Some concerns
Tian et al., 2023	Confounding	Some concerns

TABLE 3-3 Continued

Study	Bias Domains assessed as "some concerns" or "high"	Overall Risk of Bias
UK Biobank • Jani et al., 2021 • Ma et al., 2021 • Schaefer et al., 2023 • Schatte et al., 2020 • Stamatakis et al, 2021	Confounding, exposure measurement	Some concerns
van de Luitgaarden et al., 2020	Confounding	Some concerns
Ye et al., 2021	Confounding, exposure measurement	Some concerns
Zhang et al., 2021	All domains low risk of bias	Low

NOTE: Overall risk of bias is based on seven domains: (1) confounding; (2) measurement of the exposure; (3) selection of participants into the study (or into the analysis); (4) post-exposure interventions; (5) missing data; (6) measurement of the outcome; and (7) selection of the reported results.
SOURCE: Adapted from Figure E-2 in Appendix E, Academy of Nutrition and Dietetics, 2024.

to confounding bias and/or exposure measurement bias); four studies had data available to estimate the association of moderate alcohol consumption, compared to never consuming alcohol, on all-cause mortality stratified by sex (Table 3-2 and Figure 3-2B). Limited and inconsistent data are available on the associations of beverage types and drinking patterns with risk of all-cause mortality in the context of moderate alcohol consumption, and it is unclear if such associations differ by sex and/or age.

Finding 3-1: On the basis of a meta-analysis of eight eligible studies, there was a 16 percent lower risk of all-cause mortality among those who consumed moderate levels of alcohol compared with those who never consumed alcohol (RR = 0.84, 95%CI [0.81, 0.87]).

Finding 3-2: On the basis of a meta-analysis of three eligible studies, a 23 percent lower risk of all-cause mortality was found among females who consumed moderate amounts of alcohol compared with females who never consumed alcohol (RR = 0.77, 95%CI [0.6, 0.97]). An assessment of four studies showed a 16 percent lower risk of all-cause mortality among males who consumed moderate amounts of alcohol compared with males who never consumed alcohol (RR = 0.84, 95%CI [0.81, 0.88]). The committee found no evidence for a difference in the effect size by sex, as reflected in the p-value of 0.56 for the test for heterogeneity between the sexes.

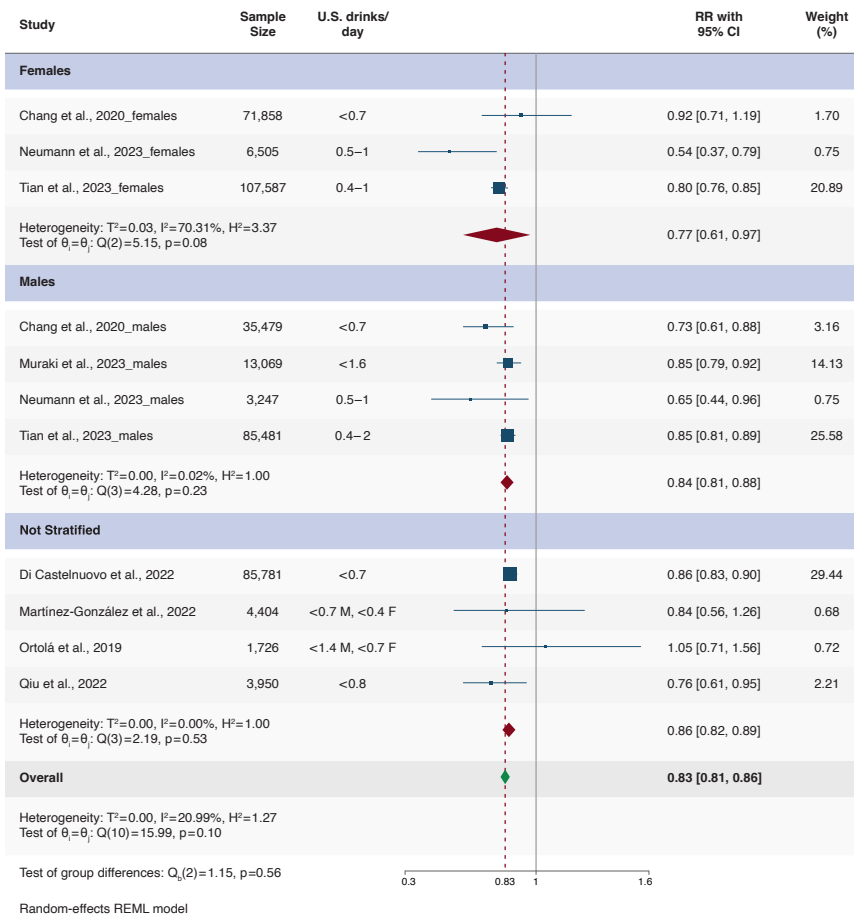


FIGURE 3-2B Meta-analysis on associations between alcohol consumption amounts that are moderate compared with never consuming alcohol on all-cause mortality according to sex.
NOTES: CI = confidence interval; I^2 = heterogeneity; REML = restricted maximum likelihood; RR = relative risk.
SOURCE: Figure E-3 in Appendix E, American Academy of Nutrition and Dietetics, 2024.

Finding 3-3: On the basis of a meta-analysis of two eligible studies, a 20 percent lower risk of all-cause mortality was found among persons less than 60 years of age who consumed moderate amounts of alcohol compared with persons less than 60 years of age who never consumed alcohol (RR = 0.80, 95%CI [0.74, 0.86]). An assessment of four eligible studies found an 18 percent lower risk of all-cause mortality among persons 60 years of age or older who consumed moderate amounts of alcohol compared with persons 60 years of age or older who never

consumed alcohol (RR = 0.82, 95%CI [0.77, 0.87]). The committee found no evidence for a difference in the effect size by age, as reflected in the *p*-value of 0.61 for the test for heterogeneity between the age groups. This comparison was not graded for certainty of the evidence.

Finding 3-4: On the basis of a meta-analysis of five studies published between 2019 and 2023, the committee found that, among moderate alcohol consumers, higher versus lower amounts of moderate alcohol consumption were associated with similar risks of all-cause mortality (RR = 0.96, 95%CI [0.87, 1.06]). The committee also found no evidence for a difference in this effect size by sex, as reflected in the p-value of 0.82 for the test for heterogeneity between the sexes.

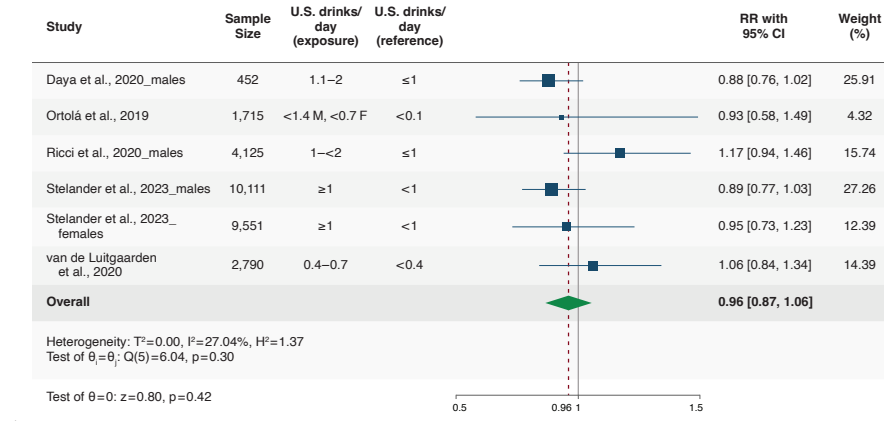
Conclusion 3-1: Based on data from the eight eligible studies from 2019 to 2023, the committee concludes that compared with never consuming alcohol, moderate alcohol consumption is associated with lower all-cause mortality (moderate certainty).

Among the 27 included studies, six studies had data available to assess the association of moderate alcohol consumption and all-cause mortality stratified by age (Table 3-2). There were two studies with data on persons less than 60 years of age, four studies with data on persons 60 years and older, and four studies that did not present stratified analyses. These studies contributed data to estimate the association of moderate alcohol consumption, compared to never consuming alcohol, on all-cause mortality stratified by age (Table 3-2).

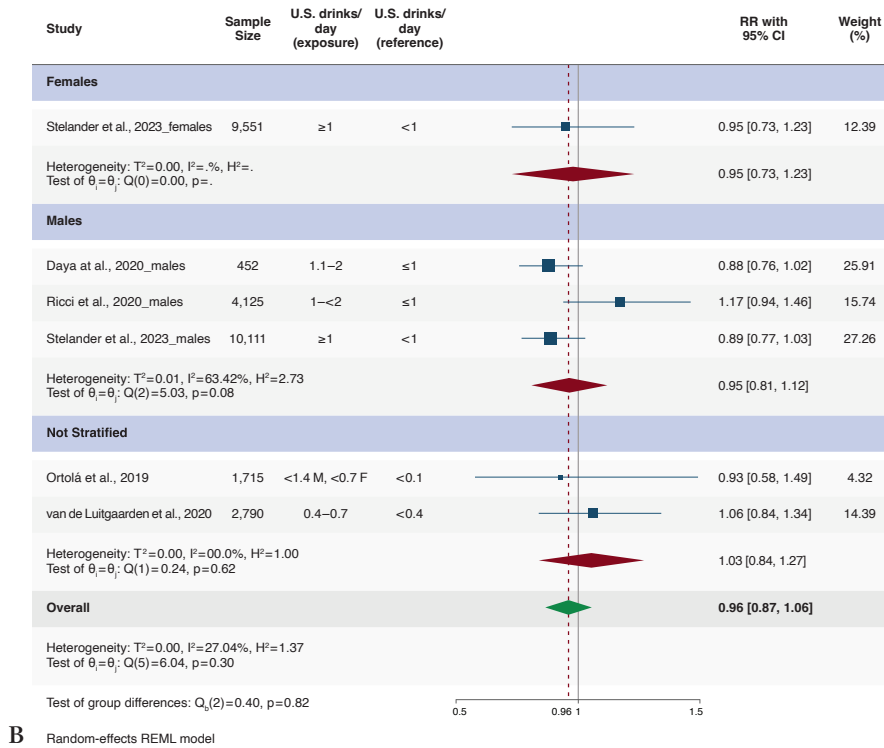
Because of how alcohol consumption was assessed and/or categorized in the eight included studies that contributed to the overall estimate of association (Table 3-2 and Figure 3-2A), the comparison mainly reflected alcohol consumption toward the lower end of the range defined as moderate consumption versus never consuming alcohol. There were five studies (with data on six comparisons) that contributed to an overall analysis of the risk of all-cause mortality comparing higher to lower categories of alcohol consumption, where all categories were within the range of moderate alcohol consumption (Figure 3-3). For example, Daya et al. (2020) compared mortality risk in males who consumed 1.1–2.0 U.S. drinks/day to those who consumed ≤1 U.S. drink/day. The five studies with data for this analysis were determined to have "some concerns" about risk of bias, primarily due to confounding, and one study was at high risk of bias due concerns about both confounding and bias due to missing data (Table 3-3).

Summary of Evidence Relative to Past DGA Guidance

Based on the results of the *de novo* systematic review, of studies published from 2019 to 2023, the committee concludes these results are consistent with prior DGAC reports, with an evidence grade of moderate



A



B

FIGURE 3-3 Meta-analysis associations between higher vs. lower alcohol consumption on all-cause mortality among moderate alcohol consumers (A) and according to sex (B).
NOTES: CI = confidence interval; I^2 = heterogeneity; REML = restricted maximum likelihood; RR = relative risk.
SOURCE: Figure E-6 in Appendix E, Academy of Nutrition and Dietetics, 2024.

certainty for the overall finding summarized in *Conclusion 3-1*. Overall, the reports from 2010, 2015, and 2020 concluded that moderate alcohol consumption, compared to never consuming alcohol, is associated with a lower risk of all-cause mortality. The SR that supported the 2020 DGAC report, which reviewed studies published from 2010 to 2020, addressed the question of consuming alcohol at various levels compared to never consuming alcohol, and concluded, "Limited evidence suggests that low average alcohol consumption, particularly without binge drinking, is associated with a lower risk of all-cause mortality compared with never drinking alcohol" (DGAC, 2020).

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4

Weight Change Related to Alcohol Intake

The incidence of overweight and obesity (Table 4-1) in the United States has steadily increased since the 1970s. This 'obesity epidemic' occurs in many high-income countries and more recently has been documented in many medium- and low-income countries. Based on 2017–2018 National Health and Nutrition Examination Survey (NHANES) data, 30.7 percent of adult men and women in the United States meet the criteria for overweight and 42.4 percent have obesity (Fryar et al., 2021).

In 2022, multiple organizations that focus on obesity, including its research, treatment, and prevention, created a consensus statement, indicating:

> Obesity is a highly prevalent chronic disease characterized by excessive fat accumulation or distribution that presents a risk to health and requires lifelong care. Virtually every system in the body is affected by obesity. Major chronic diseases associated with obesity include diabetes, heart disease, and cancer. (GWU, n.d.)

The importance of obesity as a risk factor for adverse health outcome emerges from multiple studies showing that it is an independent risk factor for chronic health conditions including dyslipidemia, hypertension, cardiovascular disease, diabetes, cancer, and arthritis, among others, and can be associated with sociological and psychological harms (Dettoni et al., 2023; Keramat et al., 2021; Pi-Sunyer, 2009).

CHOICE OF OUTCOMES

Although the Statement of Task instructed the committee to consider the association between alcohol consumption and growth, size, body composition, and risk of overweight and obesity, adults do not experience 'growth' in height; therefore, the committee focused on the remaining outcomes specified in the Statement of Task. Growth, size, body composition, and overweight or obesity risk are related but distinct outcomes. 'Size' refers to overall body dimensions, most commonly height and weight, but also includes waist circumference (WC) and various anthropometric ratios. The committee focused on three body size measurements in literature searches: body weight, body mass index (BMI), and WC. Additionally, preliminary evidence scans identified only a few articles reporting body composition; therefore, the systematic review literature search focused on the following outcomes: weight, BMI, overweight and/or obesity risk, and WC. Other weight-related outcomes that were not selected as primary outcomes but were also reported in the included studies (waist-to-hip ratio, body composition) were extracted and presented as systematic reviews with narrative synthesis. Below, the committee discusses the strengths and limitations of selected outcomes.

Body Weight (Body Mass)

The first outcome selected to reflect body size is body weight. Body weight is a measure of an individual's body mass, typically expressed in pounds (lb) or kilograms (kg). In clinical and research settings, body weight is usually measured using a calibrated scale; however, body weight may also be self-reported. Body weight can be a useful outcome to track over time to examine trends and the effects of interventions.

While an important dimension of body size, body weight alone is insufficient to assess excess adiposity and the risk of overweight or obesity because body weight is highly associated with height and does not distinguish between lean and fat mass. Body weight also varies throughout the day, and there are significant limitations to relying on self-reported body weight, as discussed below.

Body Mass Index

Another outcome selected to reflect body size is BMI, which is defined as body weight in kilograms divided by height in meters squared (kg/m^2). BMI does not measure body fat directly but is associated with body fat, and there are associations between BMI and excess adiposity having a stronger association as BMI increases. However, BMI is most useful as an outcome

when applied on a population basis—that is, assessing many people in a public health context (Cuevas and Willett, 2024).

At the individual level, BMI has limited usefulness because it does not take into consideration body composition. There are also questions regarding its interpretation with respect to different heights, frame types, and ancestries/ethnicities (Bajaj et al., 2024; Council on Science and Public Health, 2024) as well as age and sex, particularly in those with a BMI of less than 30 kg/m^2 (Frankenfield et al., 2001; Holt et al., 2023). Thus, the consensus statement also points out the following:

> The [BMI] is used to screen for obesity, but it does not displace clinical judgement. BMI is not a measure of body fat. Social determinants, race, ethnicity, and age may modify the risk associated with a given BMI. (GWU, n.d.)

Increases in BMI are primarily related to accrual of adipose tissue, whereas decreases are commonly associated with a loss of fat free mass or lean body mass as well as adipose tissue. Some of this loss in lean tissue may be mitigated by increased protein intake and/or physical activity. While increased BMI is recognized as a risk factor for metabolic dysfunction, the loss of lean tissue, particularly muscle mass or strength, is also a risk factor for cardiovascular disease (Zuo et al., 2023).

Despite these caveats, BMI is widely used and has been demonstrated to be associated with adiposity in population-based studies. Although BMI is not as granular an assessment as body composition, for large-scale observational studies, weight and height measures are reproducible when performed in a systematic manner using a calibrated scale and stadiometer and provide far more useful information than does body weight alone. Height and weight can be measured in both research and clinical settings in large numbers of individuals, and BMI is a standard component of medical records.

Although methods to estimate body composition exist, given the cost, equipment required, and time necessary to perform these measures, studies included in this chapter defined overweight and obesity using BMI because it is regularly used in large prospective cohort studies and requires minimal equipment and training; nearly all the publications reviewed here used it as a primary outcome measure.

Overweight or Obesity Classification by BMI Criteria

The most common approach to classifying people as being overweight or obese is to use BMI categories. Table 4-1 presents the most recent categories from the Centers for Disease Control and Prevention (CDC, 2024), and the categories modified for those of Asian/Pacific Islander ancestry (WHO Expert Consultation, 2004). It has been suggested that categories specific

TABLE 4-1 Centers for Disease Control and Prevention and World Health Organization Categories for Weight

Class	BMI categories (kg/m^2) CDC	WHO Asia and Pacific Islander ancestry
Underweight	<18.5	<18.5
Normal weight	18.5–24.9	18.5–22.9
Overweight	25–29.9	23–24.9
Obesity	≥30	≥25
Class I	30–34.9	N/A
Class II	35–39.9	N/A
Class III	≥40	N/A

NOTES: BMI = body mass index; CDC = Centers for Disease Control and Prevention; kg = kilogram; m = meter; N/A = not applicable; WHO = World Health Organization.
SOURCES: CDC, 2024; WHO Expert Consultation, 2004.

to other racial or ethnic groups should be developed. In an example using NHANES data, BMI values that were associated with comorbidities differed among men and women identifying as Black, Hispanic, or White (Stanford et al., 2019). At present, however, such categories are not commonly used, and the studies included in this chapter do not employ such methods.

Although dividing continuous variables such as BMI into categories may be clinically useful for ease of decision making, it raises challenges in research due to risk for misclassification. As an example, there are people in the 18.5–24.9 kg/m^2 BMI range—normal or healthy weight—who may have excess adiposity due to a lighter body frame (Sweatt et al., 2024); whereas some people with a BMI greater than or equal to 30 kg/m^2 (obesity) have high lean mass relative to their adiposity (Sweatt et al., 2024). However, as an individual's excess adiposity increases, the likelihood of classifying an individual as having excess adiposity by using BMI improves. Conversely, the usefulness of BMI for predicting negative health outcomes such as mortality similarly varies along the continuum of BMI and is particularly inconsistent in the 25.0–29.9 kg/m^2 range (classified as overweight) (Flegal et al., 2018). Pooling overweight and obesity categories together may therefore be inappropriate.

Waist Circumference

A third outcome selected to reflect body size is WC. WC is an external measurement (Borgeson et al., 2024) that improves upon BMI by capturing regional body composition, including body fat distribution. Abdominal

adiposity, particularly visceral fat, is a stronger marker for adverse health outcomes (Sweatt et al., 2024). WC measurement (cm) is performed using a flexible, inelastic measuring tape and is obtained at the iliac crest (National Institutes of Health [NIH] guidelines) or the midpoint between the last rib and iliac crest (World Health Organization [WHO] guidelines) (Ross et al., 2020). A 2020 International Atherosclerosis Society and International Chair on Cardiometabolic Risk Consensus Statement concluded that WC thresholds used to define high risk of future coronary artery events vary by ethnicity and weight category defined by BMI; for example, thresholds differ for White women of normal weight and Asian Indian women (>80 cm) and White men of normal weight and Asian Indian men (>90 cm) (Ross et al., 2020). There is a general lack of consensus among organizations including WHO and NIH regarding specific thresholds, though NHANES data and the National Cholesterol Education Program suggest >88 cm for women and >102 cm for men (Janssen et al., 2022; WHO, 2008). Waist-to-hip ratio (WHR) includes the same WC measurement (cm) divided by hip circumference (cm) to reflect upper versus lower body fat accumulation (Ross et al., 2020). Hip circumference is measured at the level of the largest lateral extension of the hips (WHO guidelines) (Jaeschke et al., 2015). Similar to WC, WHO provides guidance on WHR thresholds and suggests >0.90 for men and >0.85 for women correspond to substantially increased risk of metabolic complications (WHO, 2008).

Both WC and WHR measurements can be difficult to replicate in individuals with obesity, and two persons are often required to accurately take measurements. WC or WHR have stronger predictive values for health than weight or BMI alone and are a diagnostic component of metabolic syndrome. WC measures need only a tape measure to measure accurately (Borgeson et al., 2024; Nevill et al., 2022), yet they are seldom collected.

Body Composition

Body composition refers to defining the body by components, such as disaggregating the body based on molecules (i.e., minerals, proteins, lipids, and water) or tissues (e.g., skeletal muscle, adipose tissue, bone, blood, and other) (Wang et al., 1992). Terms describing components of body composition such as *fat mass* versus *adipose mass* may sound similar but are not necessarily equivalent: here, *fat* is used to refer to lipids, whereas *adipose* represents cells or tissues. These distinctions have potential implications for interpreting clinical relevance of changes in body composition in different compartments (Conte et al., 2024). Associations between BMI and general adiposity or fat mass were described above, as were associations between WC with central or visceral adiposity, but BMI and WC are not direct measures of body fat or adiposity.

There are various methods used to assess body composition including densitometry (using either air or water), total body water, total body potassium, dual-energy X-ray absorptiometry, and anthropometry. Because these methods are only estimates of true body composition, there are no universal reference standards and various methodologies provide different values (Fields et al., 2002; Kelly et al., 2009; Xiao et al., 2018). Factors such as age, sex, and ethnicity provide an additional source of variation using the same methodology. Lastly, updated versions of measurement devices may provide different estimates of body composition due to updates to the software used in a device (Barbour et al., 2016).

One method for estimating lean and fat mass is bioelectrical impedance analysis (BIA), which involves passing a weak current through the body. It is rapid, noninvasive, and provides better estimates of lean and fat mass than BMI (Borgeson et al., 2024). However, it has lower within-individual reproducibility and lower accuracy in persons as level of obesity increases. Acute eating and drinking can modestly affect BIA estimates (Androutsos et al., 2015), and protocols for BIA measurement include avoiding practices that may acutely alter hydration status, such as vigorous exercise or caffeine and alcohol consumption (Ritchie et al., 2005). Although other approaches for body composition estimation are available with different strengths and limitations, BIA is the only method used in any studies included in this chapter.

BIOLOGICAL PLAUSIBILITY

Alcohol consumption may directly and indirectly lead to changes in weight, body composition, and BMI by providing energy and by affecting metabolism, appetite, and satiety. Moderate alcohol consumption may have differential effects on weight and adiposity relative to biological sex, age, physical activity level, and other individual-level factors (Traversy and Chaput, 2015). Genetics also contribute to the heterogenous pathophysiological responses to alcohol intake (Suter et al., 1997). This chapter evaluates the associations between moderate alcohol consumption and the weight-related outcomes described above.

Energy and Metabolism

Alcoholic beverages primarily contain water, alcohol (ethanol), and carbohydrates, along with various congeners. Alcohol provides approximately 7 kilocalories per gram (kcal/gram) of metabolizable energy (Lieber, 2003). Total energy and nutrient content vary significantly by alcoholic beverage type (e.g., beer, wine, spirits, mixed drinks). Moderate alcohol consumption also affects the central pathways of energy metabolism and

the absorption of nutrients including glucose, glutamine, iron, and calcium (Butts et al., 2023). Ethanol is preferentially oxidized over fat and carbohydrates (Ferdouse and Clugston, 2022; Sayon-Orea et al., 2011a) to generate acetate, which either enters the tricarboxylic acid cycle for energy or is used for ketone and fatty acid synthesis. Alcohol acutely reduces lipid oxidation through direct interaction with the mitochondria, accompanied by a commensurate increase in *de novo* lipogenesis (Lu and George, 2024). It also depresses insulin signaling and may drive a partial insulin resistant state (Tatsumi et al., 2018). These metabolic effects can result in hepatic steatosis and the accumulation of excess adipose tissue (Suter et al., 1992), including in abdominal fat, which is associated with an increased risk of cardiovascular disease, metabolic syndrome, and other adverse health effects (Cigolini et al., 1996; Suter et al., 1997). However, to what extent these outcomes apply to moderate alcohol consumption remain unclear.

Alcohol is proinflammatory (Gonzalez-Reimers, 2014), and obesity is also recognized as an inflammatory disease (Wu and Ballantyne, 2020). Alcohol's inflammatory actions are driven by increases in gut permeability that facilitate the entry of microbial-derived products that promote hepatic Kupffer cell activation and cytokine production. These products, combined with repeated alcohol exposures, act in a feed-forward loop to further promote a proinflammatory state (Wang et al., 2010). To what extent these proinflammatory processes are stimulated by moderate alcohol consumption is an open question. Obesity is also considered a metabolic inflammatory state characterized by chronic, low-grade inflammation resulting from excess energy intake. There are some indications that this state of "meta-inflammation" contributes to metabolic dysfunction (Wu and Ballantyne, 2020).

Energy Balance and Ingestive Behavior

Long-term alcohol consumption without a corresponding reduction in energy intake from other foods and beverages or increased energy expenditure can lead to a chronic imbalance in energy, as is true of any other energy-containing food or beverage (Gunzerath et al., 2004). CDC reports that, based on NHANES 2007–2010 data, adults in the United States consume an average of nearly 100 kcal/day from alcoholic beverages. Men tend to consume more energy (calories) from alcoholic beverages than women (150 kcal/day versus 50 kcal/day on average) (CDC, 2012). Indeed, in moderate consumers, alcohol is often an additional source of energy, rather than displacing other energy sources (Suter, 2005). A positive energy balance that may result from moderate alcohol consumption could lead to accrual of adipose tissue over time, thus increasing the risk of obesity.

In addition to directly serving as a source of energy that may result in chronic positive energy balance over time, moderate alcohol intake has also been reported to stimulate appetite and cravings, particularly before a meal, a phenomenon known as the aperitif effect. Studies suggest that alcohol-containing beverages, but not necessarily other beverages, result in greater 24-hour energy intake (Westerterp-Plantenga and Verwegen, 1999), yet the effects do not necessarily persist in subsequent days (Caton et al., 2007). Directly elevating blood alcohol concentrations by intravenous means leads to activation of brain regions associated with food intake, thus circumventing potential social modifiers. This is accompanied by significantly greater levels of energy intake even under moderate blood alcohol concentrations with concomitant reductions in ghrelin, a hormone associated with food intake (Eiler et al., 2015). Indeed, an extensive literature has documented that many of the same neuropeptide signals modulating food intake also participate in responses to alcohol consumption with respect to intake: reward and craving (Barson and Leibowitz, 2016). Together, these studies provide mechanistic plausibility for ethanol causing acute changes in energy intake.

PRIOR DGA RECOMMENDATIONS

With respect to moderate drinking, the 2010 DGAC concluded, "Moderate evidence suggests that among free-living populations, moderate drinking is not associated with weight gain." This conclusion statement was based on a systematic review of literature published between November 1994 and May 2009 and included eight studies, one randomized controlled trial and seven prospective observational studies investigating weight and WC. The 2015 and 2020 DGACs did not examine associations between moderate alcohol consumption and weight-related outcomes. Therefore, this systematic review includes literature published between January 2010 and February 2024.

METHODOLOGICAL CONSIDERATIONS

In addition to limitations noted above for each outcome considered in this systematic review, body size measures, such as body mass and height, are sometimes self-reported. Self-reported height and weight have systematic and idiosyncratic issues that make them unreliable for assessing obesity (Flegal et al., 2018). The issue is compounded when the self-reported estimates are used to estimate BMI, which exacerbates misclassification errors in categorizing BMI categories. Different groups, including race, sex, and age, may differentially over- or under-report height and weight, making systematic corrections of BMI difficult (Banack et al., 2024; Flegal et al., 2018). Some measurement error correction techniques exist to correct self-reported

BMI (Banack et al., 2024), but the approaches do not necessarily correct the measurement error and may introduce new or different errors (Flegal et al., 2021). Conclusions based on self-reported height, weight, BMI, and obesity status should therefore be interpreted with caution.

Although self-reported consumption of alcohol is generally problematic for all the outcomes evaluated in this report, self-reported energy consumption has been identified as an invalid estimate of actual energy intake (Dhurandhar et al., 2015). Therefore, it is difficult to assess the contribution of alcohol-derived energy (calories) intake either in isolation or as a proportion of total energy, given the general challenges with reporting of alcohol intake and the specific challenges with self-reported energy intake in the context of obesity. Despite the limitations of self-reported energy consumption collected at the individual-level through methods such as 24-hour recalls, diet histories, and food frequency questionnaires, there are few validated methods that accurately measure the intake of specific nutrients. Therefore, large population-based studies continue to use self-report methods, necessitating interpretation with caution.

SYSTEMATIC REVIEW

Approach

As described in Chapter 2, databases were searched from January 2010 through February 2024 to identify articles eligible for inclusion in this systematic review. The full search strategy can be found in Appendix F. Separately, recent systematic reviews on this topic were hand searched for referenced articles that may have been missed by the database searches.

There were 4,843 unique articles identified in the database searches. The full texts of 64 articles were reviewed, and seven cohort studies were identified that met the committee's eligibility criteria and are included in this systematic review (Figure 4-1). Reasons for exclusion of studies are listed in Appendix F.

The committee focused its review on moderate alcohol consumption as defined by the DGA (≤1 drink/day for women and ≤2 drinks/day for men); a standard drink was defined as the equivalent of 14 grams of alcohol. Alcohol consumption data from individual studies were harmonized to the moderate criteria and expressed as drinks/day, as fully described in Chapter 2. None of the seven cohort studies differentiated between never drinkers and former drinkers, thus comparisons to abstainers and nondrinkers were not considered when developing conclusions to avoid abstainer bias. Therefore, all results considered in developing final conclusions compared alcohol consumption among those that consumed moderate amounts of alcohol separately in men and women when data were provided by the authors.

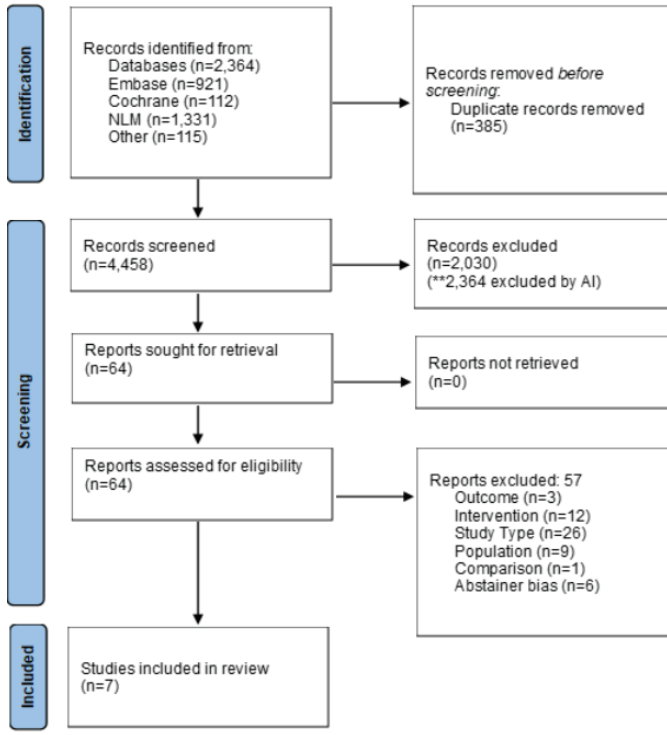

FIGURE 4-1 PRISMA flow chart for the systematic review on the association between alcohol consumption and weight change.
NOTES: The diagram shows the number of primary articles identified from the primary article and systematic review search and each step of screening. The literature dates include articles with publications between 2010 and 2024. n = number; NLM = National Library of Medicine, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
SOURCE: Figure F-1 in Appendix F, Academy of Nutrition and Dietetics, 2024.

Meta-analysis was not pursued for the seven studies due to heterogeneity in population, exposure, comparator, outcome, and design. Therefore, the studies are described narratively and summarized in a GRADE table (Table 4-2). The GRADE table was created to reflect the Academy of Nutrition and Dietetics' systematic review results that included all alcohol consumption intake levels rather than the committee's focus on comparisons among moderate alcohol consumption. Most studies adjusted for confounding variables such as age, smoking, diet, physical activity, and comorbidities (AND, 2024).

TABLE 4-2 GRADE Evidence Profile Describing Relationship Between Amount of Alcohol Intake and Weight in Adults

	Certainty Assessment					
Participants (Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Certainty of Evidence
Weight (kg) Among Consumers						
35,140 (2 studies)[g]	serious[a]	not serious	not serious	serious[b,c]	none	very[f] low
Body Mass Index Alcohol Consumption vs. Never Consuming						
4,355 (1 study)[h]	serious[a]	not serious	not serious	serious[b,d]	none	very[f] low
Body Mass Index Among Consumers						
33,419 (1 study)[i]	serious[a]	not serious	not serious	serious[b,d]	none	very[f] low
Waist Circumference Alcohol Consumption vs. Never Consuming						
4,355 (1 study)[h]	serious[a]	not serious	not serious	serious[b]	none	very[f] low
Waist Circumference Among Consumers						
74,787 (2 studies)[j]	serious[a]	not serious	not serious	serious[b]	none	low
Risk of Overweight and Obesity Among Consumers						
165,919 (3 studies)[k]	serious[a]	serious[e]	not serious	serious[b]	none	very[f] low

[a] Some concerns.
[b] No pooled effect size.
[c] No quantitative data reported.
[d] One included study.
[e] Inconsistency between study results.
[f] The committee used the phrase "insufficient evidence" to reflect a lower level of certainty of the evidence, as indicated by the assignment of "very low" in the commissioned systematic reviews by Academy of Nutrition and Dietetics.
[g] Thomson et al., 2012; Wang et al., 2010
[h] Butler et al., 2023.
[i] Inan-Eroglu et al., 2022.
[j] Choi et al., 2019; Inan-Eroglu et al., 2022.
[k] Inan-Eroglu et al., 2022; Sayon-Orea et al., 2011b; Seki et al., 2021.
SOURCE: Adapted from Table F-4 in Appendix F, Academy of Nutrition and Dietetics, 2024.

Results

Of the seven studies, six were prospective cohort studies (Butler et al., 2023; Choi et al., 2019; Inan-Eroglu et al., 2022; Sayon-Orea et al., 2011b; Thomson et al., 2012; Wang et al., 2010) and one was a retrospective cohort study (Seki et al., 2021). Three examined associations between moderate alcohol consumption and weight (Sayon-Orea et al., 2011b; Thomson et al., 2012; Wang et al., 2010), two examined associations between moderate alcohol consumption and BMI (Butler et al., 2023; Inan-Eroglu et al., 2022), five examined associations between moderate alcohol consumption and risk of overweight/obesity (Inan Eroglu et al., 2022; Sayon-Orea et al., 2011b; Seki et al., 2021; Thomson et al., 2012; Wang et al., 2010), and four examined associations between moderate alcohol consumption and WC (Butler et al., 2023; Choi et al., 2019; Inan-Eroglu et al., 2022; Seki et al., 2021). Additionally, one included article (Inan-Eroglu et al., 2022) presented results relevant to the Statement of Task (WHR and body fat percentage); these results are presented descriptively.

Two of the seven studies had low risk of bias (Sayon-Orea et al., 2011b; Thomson et al., 2012), and five studies had some concerns (Butler et al., 2023; Choi et al., 2019; Inan-Eroglu et al., 2022; Seki et al., 2021; Wang et al., 2010) (Table 4-3). Risk of bias was primarily due to measurement of alcohol consumption and attrition.

Butler et al. (2023) (moderate risk of bias) evaluated associations between 5-year changes in alcohol intake and 5-year changes in WC and BMI in the Coronary Artery Risk Development in Young Adults (CARDIA) study. The analysis included 4,355 men and women between 18 and 30 years of age at baseline and followed up at 5-year intervals over 25 years

TABLE 4-3 Risk of Bias of Included Studies Examining the Relationship Between Alcohol Intake and Weight

Study	Bias domains assessed as "some concerns" or "high"	Overall risk of bias
Butler et al., 2023	Confounding	Some concerns
Choi et al., 2019	Confounding	Some concerns
Inan-Eroglu et al., 2022	Missing data	Some concerns
Sayon-Orea et al., 2011b	All domains low risk of bias	Low
Seki et al., 2021	Confounding, missing data	Some concerns
Thomson et al., 2012	All domains low risk of bias	Low
Wang et al., 2010	Exposure measurement, missing data	Some concerns

SOURCES: CDC, 2024; WHO Expert Consultation, 2004.

to 2010–2011 (ages 43 to 55 years). Height, weight, and WC were measured during study exams using standardized protocols. Alcohol consumption was measured using the CARDIA Alcohol Use Questionnaire and was defined as nondrinker, light, moderate, or excessive (0, 0–4, 4–7, >7 drinks per week for women and 0, 0–7, 7–14, >14 drinks per week for men, respectively). Given that nondrinkers may have included former drinkers (i.e., risk of abstainer bias), only comparisons between light and moderate alcohol consumption fit the charge of this report. The authors compared changes or stability in alcohol consumption in multiple ways, including starting, stopping, increasing, decreasing, or stable intake. The committee considered "stable light/moderate" alcohol consumption versus "stop light/moderate" alcohol consumption as informative for the task. Shown in Table 4-4, in comparing point estimates and confidence intervals, changes in WC and BMI are similar among men and women who stopped light/moderate and those who maintained stable light/moderate alcohol consumption.

Choi et al. (2019) (moderate risk of bias) conducted a prospective cohort study that investigated associations between changes in alcohol consumption over 9–10 years (2004–2013) with WC from the Health Examinees-GEM study, which included 41,368 male and female participants. WC was measured during study health examinations, and alcohol

TABLE 4-4 Five-Year Changes in Waist Circumference and BMI by Moderate Alcohol Consumption Quantity Change in Young Men and Women Enrolled in the CARDIA Study

Drinking Quantity Category	*N*	Reported Data
Waist Circumference	**40,696**	**β (95% CI)**
Women Stable Moderate (0> to <0.6 drinks/day)	NR	−0.55 [−1.05, −0.04]
Women Stop Moderate (0> to <0.6 drinks/day)	NR	−0.50 [−1.01, 0.01]
Men Stable Moderate (>0 to <1 drink/day)	NR	−0.24 [−0.7, 0.22]
Men Stop Moderate (>0 to <1 drink/day)	NR	−0.04 [−0.57, 0.48]
BMI	**40,696**	**β (95% CI)**
Women Stable Moderate (0> to <0.6 drinks/day)	NR	−0.20 [−0.4, 0.02]
Women Stop Moderate (0> to <0.6 drinks/day)	NR	−0.16 [−0.38, 0.06]
Men Stable Moderate (>0 to <1 drink/day)	NR	−0.10 [−0.26, 0.06]
Men Stop Moderate (>0 to <1 drink/day)	NR	0.00 [−0.18, 0.18]

NOTES: Only groups or comparisons that met inclusion criteria are reported here. BMI = body mass index; CARDIA = Coronary Artery Risk Development in Young Adults Study; CI = confidence interval; *N* = number; NR = not reported.
SOURCES: Adapted from Tables F-6 and F-8 in Appendix F, Academy of Nutrition and Dietetics, 2024; Butler et al., 2023.

consumption was assessed via self-reported questionnaire. Alcohol consumption was defined as nondrinkers, light, moderate, and heavy separately for men and women (0, >0–1.42, 1.43–2.85, and greater than 2.85 drinks/day for men and 0, >0–0.71, 0.71–1.42, and greater than 1.43 drinks/day for women, respectively). Drink estimates were converted from grams/day to drinks/day using 14 grams per drink. The nondrinkers group did not clearly exclude former drinkers (i.e., risk of abstainer bias), and the study authors' definition of moderate slightly exceeds the moderate thresholds. With that limitation, the comparison of use to the present report is transitioning from light to moderate or moderate to light alcohol consumption. The authors pooled WC results across sexes and noted a small (~0.5 cm) statistically significant ($p < 0.01$) relative increase in WC for individuals who increased from light to moderate alcohol consumption; conversely, decreasing from moderate to light consumption was associated with a small (~0.1 cm) statistically significant decrease ($p < 0.05$) in WC. In conclusion, increasing alcohol consumption from light to moderate may be associated with a small but statistically significant increase in WC, while decreasing alcohol consumption from moderate to light may be associated with a small but statistically significant decrease in WC.

Inan-Eroglu et al. (2022) (moderate risk of bias) examined associations between baseline alcohol consumption and various measures of adiposity (BMI, body fat percentage [BF%]), WHR, WC, and incidence of overweight and obesity) at follow-up among 45,399 participants in the UK Biobank cohort, a large, population-based prospective cohort study that enrolled people 40–79 years of age between 2006 and 2010 with follow-up through 2018. Anthropometric measures were performed at baseline and follow-up using standard criteria, and BF% was estimated using BIA. Baseline alcohol consumption was assessed via self-administered questionnaire and categorized according to UK units of alcohol consumption (10 mL/unit), then converted to U.S. criteria for moderate alcohol consumption (Table 4-5). Since "non-current drinkers" included both never and former alcohol consumers, comparisons to this group were not considered in this report; the committee considered comparisons between quartiles 1, 2, and 3, which are close to moderate levels of alcohol consumption for men and women only.

Shown in Table 4-6, among men, mean differences in BMI and WC were similar in quartiles 2 or 3 compared to 1. Additionally, men in quartiles 2 and 3 had similar risk of overweight or obesity compared to men in quartile 1 (Table 4-6). Women in quartiles 2 and 3, however, had lower mean difference in BMI and WC (Table 4-5). In addition, women in quartile 2 had lower WHR ($\beta = -0.006$, 95%CI [–0.01, –0.001]) and women in quartile 3 had lower mean difference in BF% ($\beta = -0.26$, 95%CI [–0.49, –0.02]) compared to quartile 1. Shown in Table 4-6, women in quartiles 2

TABLE 4-5 Changes in BMI and Waist Circumference by Moderate Alcohol Consumption Category in Men and Women Enrolled in the UK Biobank Study[a]

Drinking Quantity Category	*N*	Reported Data
BMI	**40,517**	**β (95% CI)**
Women ≤0.10 drinks/day (Q1)	5,009	Ref [0]
Women <0.56 drinks/day (Q2)	4,841	–0.12 [–0.23, –0.02]
Women <1.15 drinks/day (Q3)	5,994	–0.17 [–0.27, –0.07]
Men ≤0.52 drinks/day (Q1)	4,712	Ref [0]
Men <1.28 drinks/day (Q2)	5,571	–0.04 [–0.12, 0.04]
Men <2.34 drinks/day (Q3)	5,708	–0.06 [–0.14, 0.02]
Waist Circumference	**40,517**	**β (95% CI)**
Women ≤0.10 drinks/day (Q1)	5,009	Ref [0]
Women <0.56 drinks/day (Q2)	4,841	–0.86 [–1.22, –0.5]
Women <1.15 drinks/day (Q3)	5,994	–0.9 [–1.25, –0.56]
Men ≤0.52 drinks/day (Q1)	4,712	Ref [0]
Men <1.28 drinks/day (Q2)	5,571	–0.28 [–0.61, 0.04]
Men <2.34 drinks/day (Q3)	5,708	–0.23 [–0.56, 0.1]

NOTES: Only groups or comparisons that met inclusion criteria are reported here. Slightly higher moderate categories are included here for completeness. BMI = body mass index; CI = confidence interval; *N* = number; Q1 = quartile 1; Q2 = quartile 2; Q3 = quartile 3.
[a] Moderate consumption: women ≤1 drink/day, men ≤2 drinks/day.
SOURCES: Adapted from Tables F-7 and F-9 in Appendix F, AND, 2024; Inan-Eroglu et al., 2022. Committee adjusted AND's quartiles.

and 3 also had lower odds of overweight and obesity compared to women in quartile 1. In conclusion, women who had alcohol consumption at the upper end of moderate alcohol consumption had smaller gains in measures of adiposity (WC, WHR, BMI, and BF%) and had lower odds of having overweight and obesity as compared to those in quartile 1, but no differences were observed for men.

Sayon-Orea et al. (2011b) (low risk of bias) examined associations between alcohol consumption and type of alcoholic beverage and yearly weight gain and risk of overweight/obesity in a Mediterranean cohort. The authors followed 9,318 healthy adults for 6.1 years as part of a prospective cohort study and collected data on dietary intake and alcohol consumption via self-reported food frequency questionnaire and self-reported weight at baseline and every 2 years during follow-up. Alcohol consumption was classified as drinks per week for men and women (0, <1, 1–<2, 2–<7, or ≥7 drinks/week) all for moderate alcohol consumption for both women

TABLE 4-6 Odds of Overweight and Obesity by Moderate Alcohol Consumption Quantity in Men and Women Enrolled in the UK Biobank Study[a]

Study and Drinking Quantity Category	*N*	Reported Data
Overweight (BMI ≥25)	**40,517**	**OR (95% CI)**
Women ≤0.10 drinks/day (Q1)	5,009	Ref [1.00]
Women <0.56 drinks/day (Q2)	4,841	0.73 [0.61, 0.87]
Women <1.15 drinks/day (Q3)	5,994	0.69 [0.58, 0.81]
Men ≤0.52 drinks/day (Q1)	4,712	Ref [1.00]
Men <1.28 drinks/day (Q2)	5,571	1.03 [0.84, 1.26]
Men <2.34 drinks/day (Q3)	5,708	0.97 [0.79, 1.20]
Obesity (BMI ≥30)	**40,517**	**OR (95% CI)**
Women ≤0.10 drinks/day (Q1)	5,009	Ref [1.00]
Women <0.56 drinks/day (Q2)	4,841	0.65 [0.53, 0.79]
Women <1.15 drinks/day (Q3)	5,994	0.57 [0.47, 0.69]
Men ≤0.52 drinks/day (Q1)	4,712	Ref [1.00]
Men <1.28 drinks/day (Q2)	5,571	0.86 [0.70, 1.06]
Men <2.34 drinks/day (Q3)	5,708	0.89 [0.72, 1.09]

NOTES: Only groups or comparisons that met inclusion criteria are reported here. Slightly higher moderate categories are included here for completeness. BMI = body mass index; CI = confidence interval; *N* = number; OR = odds ratio; Q1 = quartile 1; Q2 = quartile 2; Q3 = quartile 3.

[a] Moderate consumption: women ≤1 drink/day, men ≤2 drinks/day.

SOURCE: Inan-Eroglu et al., 2022.

and men. Comparisons to the reference group (0 drinks/week) were not considered since the study authors confirmed never and former drinkers were included in this group. All associations were adjusted for sex, baseline BMI, smoking, and other covariates.

In adjusted analyses, there was no apparent difference in weight change (Table 4-7) or risk of overweight/obesity (Table 4-8) between alcohol consumption groups within moderate consumption. Similarly, no differences were noted for weight change or risk of overweight/obesity by type of alcoholic beverage (red wine, other wines, or beer/spirits). In conclusion, change in absolute weight and risk of overweight/obesity were similar among moderate alcohol consumers including by type of alcoholic beverage consumed.

Seki et al. (2021) (moderate risk of bias) conducted a retrospective cohort study using the Japanese Ministry of Health, Labor, and Welfare large-scale health check-up (HC) database. The study included 123,182 adults receiving an HC at least once between 2008 and 2012 and a

TABLE 4-7 Changes in Weight by Moderate Alcohol Consumption Category in Men and Women Enrolled in the SUN Cohort Study[a]

Drinking Quantity Category	*N*	Reported Data β (95% CI)
<0.14 drinks/day	1,520	–2 [–67, +63]
0.14–0.29 drinks/day	1,689	+10 [–54, +74]
0.29–1 drinks/day	2,778	–8 [–67, +63]

NOTES: Only groups or comparisons that met inclusion criteria are reported here. CI = confidence interval; *N* = number; SUN = Seguimiento Universidad de Navarra.
[a] Moderate consumption: women ≤1 drink/day, men ≤2 drinks/day.
SOURCE: Sayon-Orea et al., 2011b.

follow-up HC after 5 years. BMI and WC were measured during HCs, and obesity at the fifth-year HC was defined as a BMI ≥25 kg/m^2 in accordance with Japan Society for the Study of Obesity recommendations. WC was used to define abdominal obesity. Alcohol consumption was measured via self-reported questionnaire and categorized by the amount of alcohol consumed in grams on drinking days (<20 grams, 20–40 grams, 40–60 grams, >60 grams); categories were the same for males and females. When converted to drinks per day, even the lowest category of alcohol consumption (<20 grams/day or the equivalent of <1.4 drinks/day) exceeded the *Dietary Guidelines for Americans* (DGA) recommendation for women. Therefore, since data were not stratified by sex, study results are not relevant to this report for risk of overweight/obesity since comparisons among moderate drinkers are not presented.

Thomson et al. (2012) (low risk of bias) analyzed data from 15,920 women in the Women's Health Initiative (WHI) to estimate associations between baseline alcohol intake and weight change and incident overweight or obesity in postmenopausal women over seven years. Height and weight were measured using standardized procedures at WHI clinics

TABLE 4-8 Hazard Ratios and 95% Confidence Intervals for Incident Overweight/Obesity by Moderate Alcohol Consumption Category in Men and Women Enrolled in the SUN Cohort Study

Drinking Quantity Category	*N*	Reported Data (HR and 95% CI)
<0.14 drinks/day	6,206	1.01 [0.81, 1.26]
0.14–0.29 drinks/day	6,716	1.04 [0.84, 1.29]
0.29–1 drinks/day	9,794	1.05 [0.86, 1.27]

NOTES: Only groups or comparisons that met inclusion criteria are reported. CI = confidence interval; HR = hazard ratio; *N* = number; SUN = Seguimiento Universidad de Navarra.
SOURCE: Sayon-Orea et al., 2011b.

at baseline and weight was measured annually. Alcohol consumption was assessed via semi-quantitative food frequency questionnaire at baseline and categorized into quintiles (drinks/day): Q1 = 0–<0.014, Q2 = 0.014–0.13, Q3 = 0.13–0.46, Q4 = 0.46–0.97, and Q5 = 0.97–14.07 (converted from grams/day to drinks/day using 14 grams/drink). Q1 did not clearly exclude former drinkers (i.e., risk of abstainer bias), so comparisons among Q2, Q3, and Q4 are informative for the present report.

Across all alcohol consumption quintiles, there was an inverse dose–response weight change over 7 years, with higher intake quintiles being associated with less weight gain (Q2 7-year weight change: 1.3 kg, Q3: 0.9 kg, Q4: 0.6 kg, as estimated from Figure 1 in the Thomson et al., 2012 publication). No quantitative results were reported, but the linear trend across categories was significant within each year ($p < 0.001$). Adjusted hazard ratios were estimated for incident overweight or obesity for women categorized as normal weight at baseline for total alcohol consumption quintiles (Table 4-9) and for beer, wine, and liquor. Shown in Table 4-9, women in quintiles 2, 3, and 4 had similar reductions in risk of overweight and obesity. Results of total alcohol intake across quintiles were largely similar when stratified by age (50–59 years versus 60+ years) and restricted to never smokers. In conclusion, weight gain and risk of overweight and obesity did not appear to differ among postmenopausal women at different levels of moderate alcohol consumption.

TABLE 4-9 Hazard Ratios and 95% Confidence Intervals for Incident Overweight and Obesity by Moderate Alcohol Consumption Quantity in Women Enrolled in the Women's Health Initiative Study[a]

Drinking Quantity Category	*N*	Reported Data
Incident Overweight (BMI ≥25)	**13,822**	**HR (95% CI)**
0.01–0.13 drinks/day (Q2)	2,297	0.94 [0.86, 1.02]
0.13–0.46 drinks/day (Q3)	2,285	0.88 [0.81, 0.96]
0.46–0.97 drinks/day (Q4)	2,287	0.81 [0.74, 0.90]
Incident Obesity (BMI ≥30)	**13,822**	**HR (95% CI)**
0.01–0.13 drinks/day (Q2)	2,297	0.74 [0.49, 1.12]
0.13–0.46 drinks/day (Q3)	2,285	0.54 [0.34, 0.84]
0.46–0.97 drinks/day (Q4)	2,287	0.38 [0.22, 0.64]

NOTES: Only groups or comparisons that met inclusion criteria are reported here. BMI = body mass index; CI = confidence interval; HR = hazard ratio; *N* = number; Q2 = quartile 2; Q3 = quartile 3; Q4 = quartile 4.

[a] Moderate consumption: women ≤1 drink/day.

SOURCE: Thomson et al., 2012.

Wang et al. (2010) (moderate risk of bias) conducted a prospective cohort study using data from the Women's Health Study. The analysis included 19,220 U.S. women ≥39 years of age with a BMI indicating normal weight (BMI 18.5–<25 kg/m^2) at baseline. Alcohol consumption was assessed via self-reported questionnaire at baseline and total alcohol intake was categorized as 0 grams/day, >0–<5 grams/day, 5–<15 grams/day, 15–<30 grams/day, and ≥30 grams/day. The committee focused on the following alcohol consumption categories that reflect moderate drinking according to the DGA for women: >0–<5 grams/day (>0–<0.36 drinks/day) and 5–<15 grams/day (0.36–1.1 drinks/day). Height and weight were self-reported at baseline and over 12.9 years of follow-up and used to calculate BMI to determine incidence of overweight and obesity.

Weight increased in the full sample but increased slightly less at each follow-up point in women who consumed 0.36–1.1 drinks/day compared to women who consumed >0–<0.36 drinks/day, though statistical significance was not reported. Shown in Table 4-10, women who consumed 0.36–<1.1 drinks/day had slightly lower risk of overweight/obesity (BMI ≥25) and lower risk of obesity (BMI ≥30) than women who consumed >0–<0.36 drinks/day. In conclusion, moderate drinking toward the upper versus the lower end of moderate consumption may be associated with less weight gain over time and lower risk of obesity in middle to older-aged women.

The committee reviewed seven cohort studies published between January 2010 and February 2024 in this systematic review with narrative

TABLE 4-10 Relative Risks and 95% Confidence Intervals for Incident Overweight/Obesity and Obesity by Moderate Alcohol Consumption Quantity in Middle-aged and Older Women[a]

Study and Drinking Quantity Category	*N*	Reported Data
Overweight or obesity (BMI ≥25)	**19,220**	**RR (95% CI)**
>0–<0.36 drinks/day	6,312	0.96 [0.91, 1.01]
0.36–<1.1 drinks/day	3,865	0.86 [0.80, 0.92]
Obesity (BMI ≥30)	**19,220**	**RR (95% CI)**
>0–<0.36 drinks/day	6,312	0.75 [0.63, 0.89]
0.36–<1.1 drinks/day	3,865	0.43 [0.34, 0.56]

NOTES: Only groups or comparisons that met inclusion criteria are reported here. Slightly higher moderate categories are included here for completeness. BMI = body mass index; CI = confidence interval; *N* = number; RR = relative risk.

[a] Moderate consumption: women ≤1 drink/day.

SOURCE: Wang et al., 2010.

synthesis. Data from six of these studies were included to develop the following findings and conclusions.

Findings

Finding 4-1: Abstainer bias was evident in all seven eligible studies published between 2010 and 2024; therefore, for weight-related outcomes (weight, BMI, risk of overweight/obesity, waist circumference) comparisons between those who consumed moderate alcohol and those who never consumed alcohol could not be made.

Finding 4-2: On the basis of three eligible studies, there was insufficient evidence to evaluate associations between the amount of moderate alcohol consumption and changes in body weight among men. Among women, the evidence was inconsistent. There were concerns related to sparse evidence, risk of bias (mainly due to confounding), and imprecision in the studies.

Finding 4-3: On the basis of two eligible studies, higher versus lower amounts of moderate alcohol consumption among men were associated with similar changes in BMI. Among women, the evidence was inconsistent. There were concerns related to risk of bias, mainly due to confounding, and imprecision in the studies.

Finding 4-4: On the basis of four eligible studies, higher versus lower amounts of moderate alcohol consumption among men were associated with similar risks of overweight and/or obesity. Among women, the evidence was inconsistent. There were concerns related to risk of bias, mainly due to confounding, and imprecision in the studies.

Finding 4-5: On the basis of three eligible studies, the evidence for changes in waist circumference comparing higher versus lower amounts of moderate alcohol consumption was inconsistent for women and for men. There were concerns related to sparse evidence and risk of bias, mainly due to confounding.

Conclusions

Conclusion 4-1: The committee determined that there was insufficient evidence to draw a conclusion regarding the association between weight-related outcomes and moderate alcohol consumption compared with never consuming alcohol.

Conclusion 4-2: The committee determined that there was insufficient evidence to draw a conclusion regarding the association between amounts of moderate alcohol consumption and changes in weight.

Conclusion 4-3: The committee concludes that higher versus lower amounts of moderate alcohol consumption among men were associated with similar changes in BMI (low certainty). Among women the evidence was inconsistent regarding changes in BMI.

Conclusion 4-4: The committee concludes that among men who moderately consume alcohol, higher versus lower amounts of moderate alcohol consumption were associated with similar risks of overweight and/or obesity (low certainty). Among women the evidence was inconsistent regarding changes in overweight and/or obesity.

Conclusion 4-5: The committee determined that there was insufficient evidence to draw a conclusion regarding an association between amounts of moderate alcohol consumption and changes in waist circumference.

In summary, this systematic review with narrative synthesis of studies published between January 2010 and February 2024 suggests there is insufficient evidence to draw strong conclusions on associations between moderate alcohol consumption for men and women and weight-related outcomes. Research gaps are fully described in Chapter 9.

Summary of Evidence Relative to Past DGA Guidance

Based on the results of the *de novo* SR, of studies published from 2010 to 2024, the committee concludes there was insufficient evidence to evaluate the main question of moderate alcohol consumption compared to never consuming alcohol, thus no comparison to prior versions of the DGA is possible for this question. In comparisons of lower versus higher consumption within moderate alcohol consumers the committee found little to no association of alcohol consumption with body habitus outcomes with an evidence grade of very low certainty as summarized in Conclusions 4-3, 4-4, and 4-5. This finding was consistent with the 2010 DGAC report that states that moderate alcohol consumption is not associated with weight gain. The 2015 and the 2020 DGAC reports did not evaluate the associations of moderate alcohol consumption compared to other levels of consumption in relation to weight-related outcomes.

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5

Cancer

Alcohol has been identified as a carcinogen in humans (IARC, 1988, 2010, 2012). It is metabolized to acetaldehyde, which is also a carcinogen (IARC, 2010, 2012). Although the mechanisms of carcinogenesis of alcohol and acetaldehyde for each cancer site have not been entirely determined, both human and animal studies provide evidence of their roles in carcinogenesis as detailed below. The focus here is on what is known about the effects of moderate alcohol consumption on carcinogenesis and on cancer as an outcome.

CHOICE OF OUTCOMES

For the examination of moderate intake of alcohol in relation to cancer, the following sites were systematically reviewed: cancers of the oral cavity, pharynx, esophagus (squamous cell), colorectum (as well as colon and rectum, separately), and female breast. These sites were selected because previous reviews by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) and by the World Cancer Research Fund (WCRF) Continuous Update Project identified the evidence as "sufficient" (IARC) or "convincing" that alcohol is causal in the etiology of cancer at these sites (IARC, 1988, 2010, 2012; WCRF, 2018). Studies evaluating incidence of any of these cancers as outcomes, as well as those including composites of these outcomes (i.e., head and neck cancer, oropharyngeal cancer, or colorectal cancer), were included in the systematic review of moderate intake. While liver cancer

was also identified by IARC as a cancer site with sufficient evidence of causality by alcohol consumption, it was not included in the systematic review because the association for liver cancer is with heavy alcohol consumption on the order of three or more drinks per day (WCRF, 2018), which is beyond the scope of this review.

For several other cancer sites, there is more limited evidence on the association with alcohol consumption (i.e., urinary bladder, endometrial, gastric, pancreas, prostate, and thyroid cancers); for those sites, there is discussion of that evidence here but not a systematic review (Table 5-1). For the cancer sites included, the systematic review focused on cancer incidence and excluded studies that exclusively examined prevalence, cancer recurrence, cancer-related mortality, or survival. As for all the analyses, studies were excluded that did not specify that only never drinkers were included in the referent category to prevent abstainer bias. While these exclusions are more methodologically sound, the effect of abstainer bias likely differs for cancer than it does for some other outcomes. Associations of alcohol with cancer risk are likely linear and not *J*-shaped. Inclusion of former drinkers in a nondrinker referent would lead to an underestimation of the true association. Exclusion of studies because of concerns with abstainer bias limits the number of studies that can be evaluated and therefore limits overall conclusions regarding the effect of moderate alcohol consumption.

TABLE 5-1 Types of Cancer with Emerging Evidence Regarding Moderate Alcohol Consumption by Cancer Site and Publication

Cancer Site	Publication
Head/Neck (not specified)	Hashibe et al., 2013; Im et al., 2021
Thyroid	Im et al., 2021; Sen et al., 2015
Lung	Im et al., 2021; Im et al., 2023
Gastric	Im et al., 2021; Im et al., 2023; Yoo et al., 2021
Small intestine	Boffetta et al., 2012
Pancreas	Hippisley-Cox and Coupland, 2015; Im et al., 2021; Michaud et al., 2010; Naudin et al., 2018; Yoo et al., 2021
Biliary tract	Im et al., 2021; Yoo et al., 2021
Renal tract	Im et al., 2021
Bladder	Botteri et al., 2017; Im et al., 2021
Prostate	Demoury et al., 2016; Im et al., 2021; Papa et al., 2017
Endometrium	Fedirko et al., 2013; Je et al., 2014

BIOLOGICAL PLAUSIBILITY

Direct Effects of Alcohol

Alcohol consumption has numerous biological effects, some of which can contribute to carcinogenesis, with effects depending on dose. Carcinogenic effects include production of reactive oxygen species with genotoxic effects, negative effects on folate absorption, metabolism, and excretion, with resulting effects on deoxyribonucleic acid (DNA) methylation and one-carbon metabolism, negative effects on retinoid metabolism and immune function, inflammation, alteration of the oral and intestinal microbiome, and effects on circulating steroid hormone concentrations and hormone bioavailability; the hormone-related effects are particularly important in breast carcinogenesis (Brown and Hankinson, 2015; Rumgay et al., 2021; Tin Tin et al., 2024; Toh et al., 2010). Alcohol may also serve as a solvent, increasing exposure of epithelial cells in the mouth and gastrointestinal tract to other carcinogens (Ferraguti et al., 2022; Silva et al., 2020).

Congeners in alcoholic beverages may also have biologic effects, including affecting carcinogenesis, both positively and negatively. For example, polyphenols in wine may be protective with antioxidant and anti-inflammatory effects. Additionally, carcinogens including aflatoxin and heavy metals may be found in alcoholic beverages (Okaru and Lachenmeier, 2021). However, there are few studies in humans on possible effects of congeners on carcinogenesis (Ferraguti et al., 2022; Silva et al., 2020). The preponderance of the evidence is that ethanol in alcoholic beverages is the significant active agent; there is little evidence of a difference in cancer risk by beverage type (WCRF, 2018).

Acetaldehyde

The alcohol metabolite, acetaldehyde, is a highly reactive substance with DNA-damaging properties. Acetaldehyde forms adducts with DNA resulting in deleterious effects, including effects on gene transcription, genetic mutations, single and double DNA strand breaks, and induction of DNA cross-links, all of which can contribute to carcinogenesis. Other effects include the production of reactive oxidative species with genotoxic effects, induction of changes in methylation, and other epigenetic alterations (Balbo et al., 2012; Ferraguti et al., 2022; Guidolin et al., 2021; Hoes et al., 2021; Mizumoto et al., 2017; Rumgay et al., 2021).

Acetaldehyde is metabolized to acetate by aldehyde dehydrogenases (ALDH) and is then excreted or further metabolized into ketones and fatty acids. Individuals carrying a common ALDH2 genetic variant metabolize acetaldehyde more slowly, resulting in increased exposure of tissues to

reactive acetaldehyde with the potential for greater carcinogenic effects with exposure to lower amounts of alcohol consumption. The low activity ALDH2 variant is more prevalent among those of East Asian descent (Chang et al., 2017).

Breast Cancer (Female)

Breast cancer is the leading cause of cancer among women both globally and in the United States, accounting for 32 percent of all cancer diagnoses among women in the United States. Breast cancer is second only to cancer of the lung/bronchus as a source of cancer mortality, with 15 percent of cancer deaths among women resulting from breast cancer. Breast cancer is rare among men; approximately 99 percent of cases are among women (ACS, 2024). In both the IARC (IARC, 2010, 2012) and the WCRF (WCRF, 2018) systematic reviews, the data regarding the association of alcohol with female breast cancer were determined to be strong. In the WCRF review, the available evidence for postmenopausal breast cancer risk associated with alcohol consumption was categorized as strong/convincing; for premenopausal disease, the evidence was characterized as strong/probable. The WCRF review concluded that risk was increased across intake amounts and that there was not a threshold of intake for an alcohol effect on breast cancer (WCRF, 2018).

Cumulative exposure to increased circulating steroid hormone concentrations (including estradiol, estrone, androstenedione, dehydroepiandrosterone sulfate, testosterone) increases breast cancer risk (Brown and Hankinson, 2015; Shield et al., 2016; Tin Tin et al., 2024). Alcohol consumption, including moderate intake, is associated with increases in blood steroid hormone concentrations. The increases, particularly of estrogen, are likely important as mechanisms for alcohol-associated breast carcinogenesis (Tin Tin et al., 2024). Carcinogenic effects of alcohol and acetaldehyde exposure in the breast may also contribute to carcinogenesis. Alcohol dehydrogenase, enzymatically metabolizing alcohol to acetaldehyde, is expressed in breast tissue (Wright et al., 1999).

Colorectal Cancer

Colorectal cancer is among the most diagnosed cancers in the United States, accounting for 8 percent of all cancers for men and 7 percent for women (ACS, 2024). There are 152,810 new cases and 53,010 deaths from cancer of the colon and rectum combined in the United States each year. Colon cancer is more common than rectal cancer; there are 106,590 new colon cancer cases each year in the United States. These cancers affect men and women in approximately equal numbers (ACS, 2024).

In the colon and rectum, alcohol and acetaldehyde exposure contribute to increased cell proliferation, DNA adduct formation, DNA damage, oxidative stress, and epigenetic alterations (Bishehsari et al., 2019; Johnson et al., 2021). Further, there is evidence that alcohol exposure alters the microbiome in the large intestine in terms of composition and activity with effects on intestinal permeability, inflammation, and immune suppression. Alcohol negatively effects folate metabolism, which can result in altered one-carbon metabolism with implications for epigenetic alterations in the large intestine. Acetate, formed in the metabolism of acetaldehyde, may also have deleterious effects on the colon (Johnson et al., 2021).

Cancer of the Oral Cavity, Pharynx and Larynx

In the United States each year, there are approximately 58,450 new cases of cancer of the oral cavity and pharynx and about 12,230 deaths. Tumors at these sites tend to affect men more than women; about 70 percent of the incident cases and deaths for cancer at these sites combined are for men (ACS, 2024). In systematic reviews, WCRF (2018) and IARC (2010, 2012) both concluded that there was strong evidence of alcohol increasing the risk of cancer at these sites, including evidence of a dose response. Importantly, however, most of the research used to reach this conclusion was based on higher alcohol intakes. The focus here is on moderate alcohol consumption.

There are 12,650 new laryngeal cancers diagnosed and 3,880 deaths from laryngeal cancer each year in the United States (ACS, 2024). As for cancer of the oral cavity and pharynx, these tumors are more likely to occur in men than women (ACS, 2024). The determination in the systematic reviews by IARC and WCRF was that the evidence of an association between alcohol consumption and cancer of the larynx was strong (IARC, 2010, 2012; WCRF, 2018) and that the association followed a dose-response pattern. Again, the focus here is on associations with moderate alcohol consumption.

Alcohol is metabolized in the oral cavity to acetaldehyde by the oral microbiome (Hoes et al., 2021; Nieminen and Salaspuro, 2018), and the resulting salivary acetaldehyde concentration is higher than that in the blood (Stornetta et al., 2018; Yokoyama et al., 2008). Immediately following consumption, salivary acetaldehyde concentrations vary depending on the percent alcohol in the beverage consumed (Yokoyama et al., 2008), although about 1 hour after consumption, there are no differences by beverage type (Balbo et al., 2012; Yokoyama et al., 2008). Oral acetaldehyde decreases over about 3 hours (Balbo et al., 2012). There is evidence of a marked increase in acetaldehyde DNA adducts in oral cells (Guidolin et al., 2021) within 4 hours of alcohol consumption, in a dose dependent manner (Balbo et al., 2012).

There is evidence that alcohol consumption is associated with increased risk of head and neck cancer among those carrying the low activity ALDH2 gene variant that results in greater exposure to acetaldehyde (Chang et al., 2017; Du et al., 2021).The increased risk of cancer of these sites associated with slower metabolism of acetaldehyde provides evidence of a causal role of acetaldehyde exposure in the etiology of oral cavity, pharyngeal, and laryngeal cancer (Du et al., 2021; Nieminen and Salaspuro, 2018). Additional mechanisms for carcinogenesis in the oral cavity and pharynx include increased oxidation, and alcohol as a solvent, thus increasing exposures of epithelial cells to other carcinogens, including from tobacco (WCRF, 2018). Mutational signatures related to acetaldehyde exposure have been identified in head and neck tumors (Hoes et al., 2021). Alcohol and smoking are synergistic with stronger effects of alcohol among those who also smoke and stronger effects of smoking among those who also consume alcohol (WCRF, 2018).

Esophageal Cancer (Squamous Cell)

There are approximately 22,370 new cases and 16,130 deaths from esophageal cancer in the United States each year; both incident cases and deaths are predominately (about 80 percent) among men (ACS, 2024). The major types of esophageal cancer are squamous cell and adenocarcinomas, with differences in their risk factors (Grille, 2021). In previous reviews, the association with alcohol has been found for squamous cell esophageal cancer (IARC, 2010, 2012; WCRF, 2018).

For squamous cell esophageal cancer, the mechanisms for alcohol in carcinogenesis are similar to those for oral cavity and pharyngeal cancer: production of reactive oxygen species, exposure to acetaldehyde produced in the mouth, and effects of alcohol as a solvent increasing exposure to other carcinogens (Toh et al., 2010). Mutational signatures related to acetaldehyde exposure have been identified in esophageal tumors (Hoes et al., 2021).

PRIOR DGA RECOMMENDATIONS

To contextualize current findings on the association of alcohol with certain cancers, the committee summarized the *Dietary Guidelines for Americans* (DGA) and the Scientific Reports of the Dietary Guidelines for Americans Committees (DGAC) from 2010, 2015, and 2020 as they relate to alcohol and cancer. Past DGA recommendations and DGAC reports have varied in whether and the extent to which alcohol and cancer were specifically discussed and are described below in reports issued from 2010 to the present.

2010

The 2010–2015 DGA (USDA and HHS, 2010) recommended no more than moderate alcohol consumption, noting that alcohol consumption has been associated with both health benefits and harms. Among the harms of drinking, the only association with cancer noted by the DGA is that "moderate alcohol intake . . . is associated with increased risk of breast cancer."

The 2010 DGAC report cited the WCRF/American Institute for Cancer Research (WCRF/AICR, 2007) in discussing the evidence base available relating alcohol consumption to the risk of cancer. Specifically, the report notes that there is substantial evidence of an association between alcohol consumption and risk of breast, colorectal, and liver cancer. While the association with colorectal cancer is described as demonstrating a dose-response relationship, it is designated as stronger in men than women and most notable among those consuming more than two drinks per day. The risk of liver cancer was noted as being elevated even among those consuming moderate amounts of alcohol, although the strength of this relationship appears to vary depending on smoking, diet, and underlying viral infections. There was also the suggestion that the association of alcohol with breast cancer may vary depending on folate status, with attenuation of the risk associated with alcohol among those with adequate status. Given this existing recent review and strength of the available evidence, the 2010 DGAC did not undertake a new systematic review investigating the association between alcohol consumption and cancer risk.

2015

The 2015–2020 DGA (USDA and HHS, 2015) included an appendix on alcohol with guidance consistent with the 2010–2015 DGA recommending that individuals who drink alcohol consume no more than a moderate amount. Specific health effects of alcohol, aside from the contribution of alcohol to overall caloric intake, were not discussed. The 2015 DGAC report (DGAC, 2015) did not include a separate review of evidence on the association between alcohol and health outcomes. However, the report found that, "evidence also suggests that alcoholic drinks are associated with increased risk for certain cancers." The report found an increased risk of breast cancer even at moderate intakes of alcohol.

2020

The DGA (USDA and HHS, 2020) noted that "emerging evidence suggests that even drinking within the recommended limits may increase the

overall risk of death from various causes, such as from several types of cancer" and confirms the recommendation of prior versions of the DGA of no more than moderate alcohol consumption.

The 2020 DGAC report (DGAC, 2020) included a systematic review (Mayer-Davis et al., 2020) investigating the association between all-cause mortality and alcohol consumption. While cancer was not considered as a separate outcome, the contribution of cancer-specific mortality to all-cause mortality was noted. Additionally, three Mendelian randomization studies that investigated the association between head and neck, esophageal, and colorectal cancer (Lewis and Smith, 2005; Richmond and Smith, 2022) and alcohol consumption were highlighted. The conclusions of the 2020 DGAC report note that systematic reviews and professional society guidelines extant at that time identified a likely causal relationship between alcohol consumption and cancer mortality.

METHODOLOGICAL CONSIDERATIONS

There are important methodological considerations in the evaluation of evidence regarding a causal connection between alcohol and cancer, particularly for moderate alcohol consumption. It should be noted that, unlike some other outcomes for which most of the research has focused on alcohol consumption effects among those with alcohol use disorder, most of the evidence regarding alcohol consumption in relation to cancer risk comes from cohort studies that include a broad range of the population. In those studies, most of those consuming alcohol are not heavy drinkers meaning that in these large studies there is power to examine the effects of moderate consumption.

Significantly, alcohol consumption, both drinking compared with nondrinking as well as amount and pattern of consumption, is associated with other behaviors and participant characteristics, including cancer risk factors. Importantly, an association between alcohol consumption and smoking is found consistently and in many different populations (Breslow et al., 2011; Burton et al., 2023; Gapstur et al., 2012; Romieu et al., 2015; Schuit et al., 2002). Because alcohol consumption and smoking are correlated behaviors, and because smoking is such a strong risk factor for cancer at many sites, residual confounding by smoking is an issue in the determination of risk from alcohol alone. Examination of risks associated with drinking among those who never smoke can address the issue but would not assess synergism between alcohol and smoking.

While associations of alcohol consumption with other cancer risk factors are not as consistent, there is evidence of correlations of alcohol consumption with body mass index (BMI), physical activity, diet, and education (Breslow et al., 2011; Burton et al., 2023; Gapstur et al., 2012; Joseph et al.,

2022; Romieu et al., 2015; Sayon-Orea et al., 2011; Schuit et al., 2002). Further, behavioral risk factors, including alcohol consumption, tend to cluster and to be associated with socioeconomic status (Kukreti et al., 2022). Additionally, there may be other behavioral factors that are associated with moderate drinking such as increased socializing related to consumption.

Biological interactions of alcohol with other cancer risk factors are relevant for understanding the effect of alcohol on carcinogenesis. Factors including smoking; physical activity; body weight; occupational exposures; infectious agents, such as human papillomavirus; and diet, including specific nutrients such as folate and retinol, could potentially modify the association between alcohol with cancer risk. Unaddressed interactions could alter our understanding regarding how alcohol affects cancer risk (Gapstur et al., 2022). For example, there is synergy in exposures to both alcohol and tobacco smoke. The effect of the two exposures combined is greater than the sum of their individual effects for head and neck and for squamous cell esophageal cancers (Burton et al., 2024; Prabhu et al., 2014). Further, consideration of whether alcohol is consumed with meals or not may affect the effect of consumption on cancer risk.

A further challenge in understanding the effects of moderate alcohol consumption on cancer risk is that relationships may differ for different cancer subtypes. For example, there is evidence that alcohol is associated with estrogen receptor-positive but not estrogen receptor-negative breast cancer (WCRF, 2018). Other modifying factors would include genetic variation in alcohol metabolism, particularly ALDH2, as well as other variants, such as in DNA repair genes.

Finally, the effect of abstainer bias differs for cancer compared to some other outcomes. If associations of alcohol with risk of cancer incidence are linear and not *J*-shaped, with increased risk among light and moderate drinkers, the inclusion of former drinkers compared to nondrinkers in a nondrinker referent group would lead to an underestimation of the true association. Excluding former drinkers from the nondrinker group reduces bias. The committee therefore excluded studies subject to this abstainer bias from our systematic review. However, this exclusion necessarily limits the studies that are included and potentially limits the strength of overall conclusions regarding the effects of moderate consumption.

SYSTEMATIC REVIEW

Approach

Prior systematic reviews conducted by the Nutrition Evidence Systematic Review (NESR) to inform DGAC have not considered cancer incidence as a distinct outcome. However, cancer has been considered as a component

contributing to all-cause mortality. A systematic review was conducted for the 2020 DGAC, which focused on all-cause mortality as the outcome of interest (DGAC, 2020).

An initial evidence scan was conducted to provide the committee with an overview of the literature focusing on the association between low and moderate alcohol consumption and cancer incidence to inform decision making regarding the feasibility of conducting a full systematic review. A total of 77 primary articles focusing on the relationship between moderate alcohol consumption and cancer risk published between 2019 and 2023 were identified in the initial evidence scan and went through full-text screening by members of the committee, which resulted in 25 articles that met full inclusion criteria (see Chapter 2 and Appendix G for complete details of the evidence scan). An additional evidence scan was undertaken to identify prior systematic reviews of the association between alcohol and cancer risk in the period 2010–2024 (Figure 5-1).

Based on the scope of primary literature identified in preliminary evidence scans that has not been included in prior high-quality systematic reviews, the committee decided to proceed with a systematic review to answer the question regarding alcohol and cancer incidence. This systematic review included articles published between 2010 and 2024. The committee developed a systematic review protocol including an analytic framework that described the overall scope of the review including the population, types of analyses, data sources, and definitions of key terms (see Chapter 2). Aside from specifications relating to the outcome, all elements of this protocol were standardized (AND, 2024).

Results

Breast (Female) Cancer

In the meta-analysis of breast cancer, there were five studies identified of associations between moderate alcohol consumption compared to never consuming alcohol with breast cancer risk in women: four cohort studies (Kawai et al., 2011; Klatsky et al., 2015; Li et al., 2010; White et al., 2017) and one case-control study (Zhang et al., 2011). Results from the two study designs were analyzed separately.

For the four cohort studies, compared to those who did not consume alcohol (lifetime abstainers), those who consumed moderate alcohol had higher risk of breast cancer (RR = 1.10, 95%CI [1.02, 1.19]; I^2 = 0%) (Figure 5-2).

None of the included studies reported results stratified by age, race/ethnicity, or smoking status. In sensitivity analyses of a fixed effects model instead of a random effects model, results were similar. Sensitivity analysis of

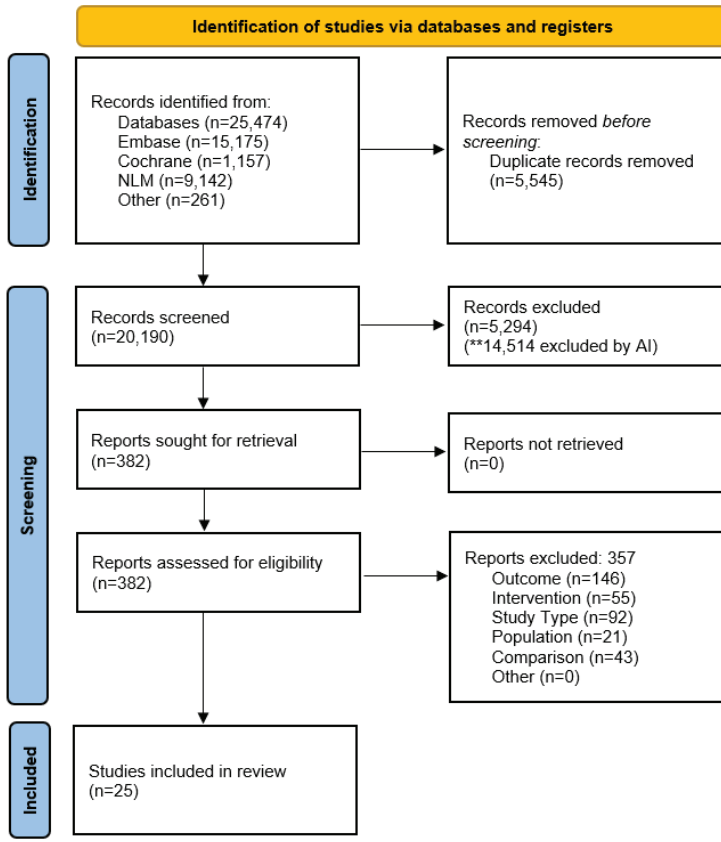

FIGURE 5-1 PRISMA flow chart for second search for the systematic review on the association between alcohol consumption and cancer incidence.
NOTES: The diagram shows the number of primary articles identified from the primary article and systematic review searches and each step of screening. The literature dates include articles with the publications between 2010 and 2024. n = number; NLM = National Library of Medicine; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
SOURCE: Annex G-3 in Appendix G, Academy of Nutrition and Dietetics, 2024.

data stratified on menopausal status was not feasible because of differences in reports of alcohol exposure groups. In two cohorts, results were provided stratified on menopausal status; there were no differences in the association of moderate alcohol with breast cancer risk by menopausal status in those studies (Kawai et al., 2011; White et al., 2017). In the study by Li et al. (2010) of postmenopausal women, results were similar to meta-analysis results.

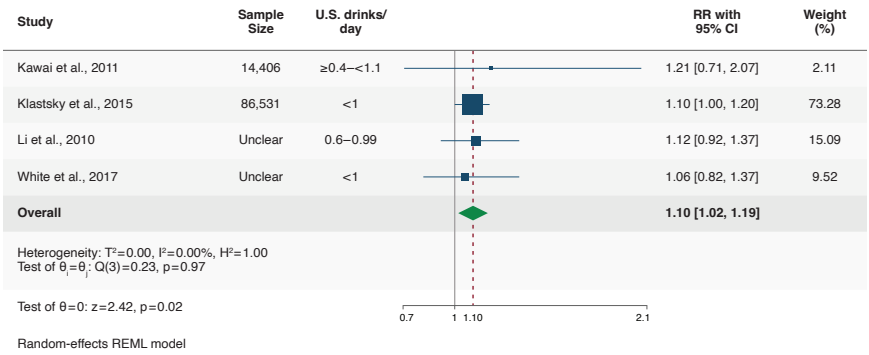

FIGURE 5-2 Associations between moderate alcohol consumption and breast cancer compared to never consuming alcohol.
NOTES: CI = confidence interval; I^2 = heterogeneity; REML = restricted maximum likelihood; RR = relative risk.
SOURCE: Figure G-1 in Appendix G, Academy of Nutrition and Dietetics, 2024.

Case-control studies were examined separately from the cohort meta-analysis. There was only one case-control study examining the association between moderate alcohol consumption and odds of breast cancer that met the inclusion criteria. Zhang et al. (2011), in a study of women in China, reported lower risk of breast cancer for those who consumed <5 grams/day (0.36 U.S. drinks/day) of alcohol compared to those who never consumed alcohol (OR = 0.56, 95%CI [0.45, 0.69]). There was no significant difference in analyses by menopausal status. For this study, there were concerns related to possible bias.

Women who consumed alcohol in moderation (≤1 U.S. drink/day) likely have a higher risk of breast cancer than women who never consumed alcohol. Evidence certainty was moderate due to some concerns of risk of bias in all included studies.

The relationship between alcohol as a continuous variable and breast cancer risk was examined in seven studies meeting the inclusion criteria. Risk was examined associated with each increase of alcohol consumption of 10–14 grams/day (Arthur et al., 2020; Heath et al., 2020; Key et al., 2019; Li et al., 2010; Park et al., 2014; Romieu et al., 2015; Suzuki et al., 2010). When these seven studies were pooled in meta-analysis, there was a higher risk of breast cancer for every 10–14 gram (0.7–1 U.S. drinks) increase in alcohol consumption per day (RR = 1.05, 95%CI [1.04, 1.06]; I^2 = 21.7%) (Figure 5-3). These studies included ones based on reports of baseline consumption such that those reporting no drinking may include former drinkers. Rainey et al. (2020) reported adjusted results as odds ratios and could not be included in meta-analysis, but results were consistent with the meta-analysis (OR = 1.09, 95%CI [1.0, 1.18]). While these

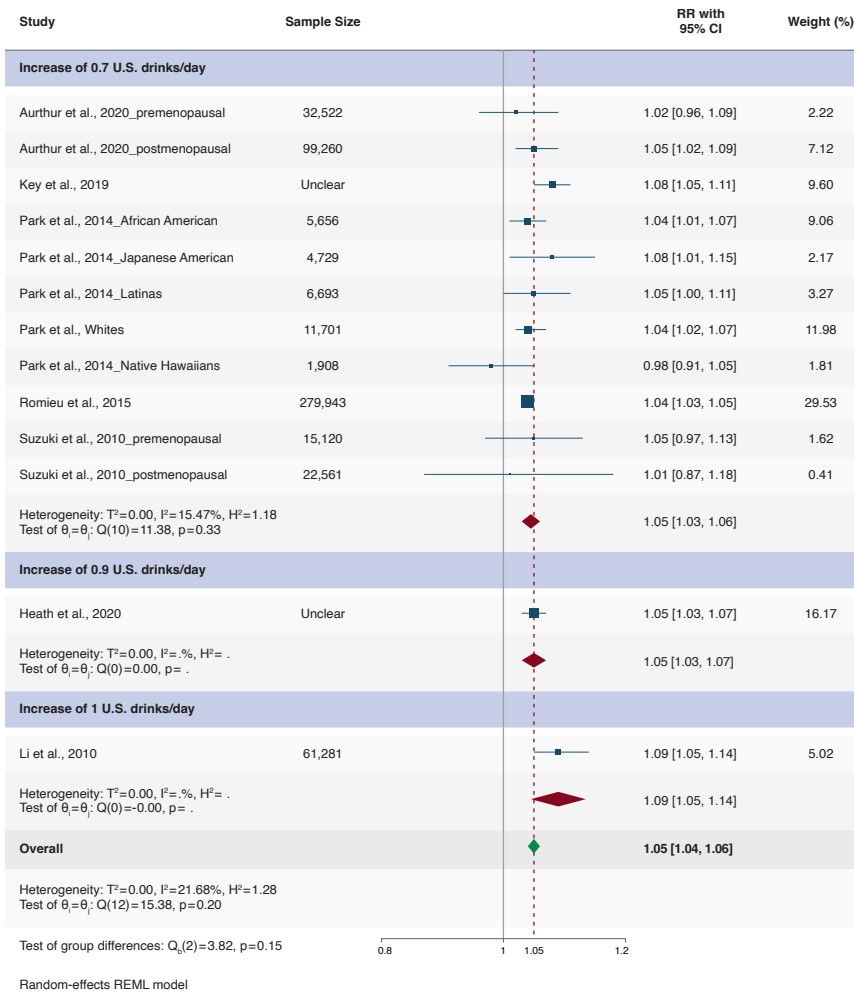

FIGURE 5-3 Meta-analysis of relationship between increasing alcohol consumption by 10–14 grams (0.7–1.0 U.S. drinks/day) and breast cancer.
NOTES: CI = confidence interval; REML = restricted maximum likelihood; RR = relative risk.
SOURCE: Figure G-7 in Appendix G, Academy of Nutrition and Dietetics, 2024.

results include intakes greater than those recommended in the DGA, they were included because they provide insight regarding the overall association of breast cancer with risk. There is no evidence of a *J*-shaped association; rather, the association appears to be linear with increased risk at all consumption amounts.

Two studies provided results stratified on menopausal status (Arthur et al., 2020; Suzuki et al., 2010). In postmenopausal women, the association between alcohol consumption as a continuous variable and breast cancer was consistent with results for all women (RR = 1.05, 95%CI [1.01, 1.08]; I^2 = 0%); in premenopausal women, the association was similar but the confidence interval included the null (RR = 1.03, 95%CI [0.98, 1.08]; I^2 = 0.04). There were some concerns regarding bias for all the included studies. Evidence certainty was moderate due to risk of bias in the included studies (Table 5-2). The certainty of the evidence of the studies included in the systematic reviews are summarized in Table 5-3.

There were two studies examining the risk of breast cancer associated with higher compared to lower intakes of alcohol among those with moderate alcohol intakes (Key et al., 2019; Romieu et al., 2015) (Figure 5-4). The committee based its conclusions on the two studies that were available, deemed to have sufficient power but downgraded the level of certainty to low.

TABLE 5-2 Risk of Bias of Included Studies Examining the Relationship Between Alcohol Intake and Breast Cancer

Study	Bias Domains assessed as "some concerns" or "high"	Overall Risk of Bias
Arthur et al., 2020	Exposure measurement	Some concerns
Heath et al., 2020	Exposure measurement	Some concerns
Kawaii et al., 2011	Exposure measurement	Some concerns
Key et al., 2019	Confounding, exposure measurement	Some concerns
Klatsky et al., 2015	Exposure measurement	Some concerns
Li et al., 2010	Confounding, exposure measurement	Some concerns
Park et al., 2014	All domains low risk of bias	Low
Rainey et al., 2020	Confounding, exposure measurement	Some concerns
Romieu et al., 2015	Confounding, exposure measurement	Some concerns
White et al., 2017	Confounding, exposure measurement	Some concerns

NOTES: Overall risk of bias is based on seven domains: (1) confounding; (2) measurement of the exposure; (3) selection of participants into the study (or into the analysis); (4) post-exposure interventions; (5) missing data; (6) measurement of the outcome; and (7) selection of the reported results.
SOURCE: Adapted from Annex G-6 in Appendix G, Academy of Nutrition and Dietetics, 2024.

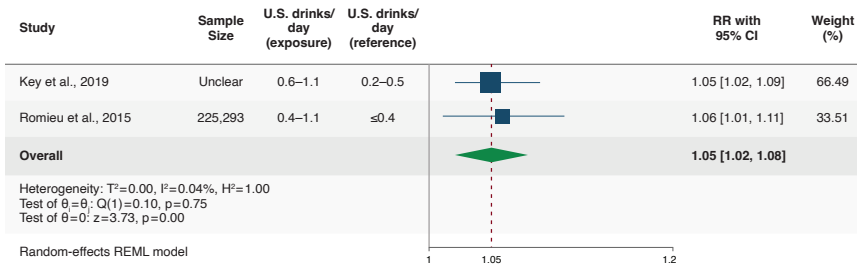

FIGURE 5-4 Meta-analysis on association between higher and lower moderate alcohol consumption and breast cancer.
NOTES: CI = confidence interval; REML = restricted maximum likelihood; RR = relative risk.
SOURCE: Figure G-4 in Appendix G, Academy of Nutrition and Dietetics, 2024.

In both studies, there was increased risk for the higher intakes among moderate consumption: in the study by Key et al. (2019), for those drinking 0.6–1.1 compared to 0.2–0.5 drinks per day, (HR = 1.05, 95%CI [1.02, 1.09]) and in the study by Romieu et al. (2015) comparing, 0.4–1.1 to ≤0.4, (HR = 1.06, 96%CI [1.01, 1.11]). The overall association was 1.05 (1.02–1.08).

Finding 5-1: A meta-analysis of four eligible studies found a 10 percent higher risk of breast cancer among persons consuming moderate amounts of alcohol compared with persons never consuming alcohol (RR = 1.10, 95%CI [1.02, 1.19]). There were some concerns related to risk of bias, mainly due to confounding and exposure assessment, in the studies contributing to this comparison.

Finding 5-2: A meta-analysis of seven eligible studies found a 5 percent higher risk of breast cancer for every 10–14 grams (0.7–1.0 U.S. drinks) increment of higher alcohol consumption per day (RR = 1.05, 95%CI [1.04, 1.06]). On the basis of two eligible studies, consumption of higher compared to lower amounts of moderate alcohol was associated with a higher risk of breast cancer. One study reported a hazard ratio (HR) of 1.05 (95%CI [1.02, 1.09]) for women who consumed higher amounts of moderate alcohol (0.6–<1.1 drinks/day) compared with those who consumed lower amounts of moderate alcohol 0.2-0.5 drinks/day. Another study reported an HR of 1.06 (95%CI [1.01, 1.11]) for breast cancer associated with 0.4–1.1 drinks per day compared to <0.4 drinks per day. There were some concerns related to risk of bias, mainly due to confounding and exposure assessment.

TABLE 5-3 Summary of Findings Table for Systematic Review on Associations Between Alcohol Consumption and Breast Cancer

	Certainty Assessment					
Participants (Studies) Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Certainty of Evidence
Breast Cancer Consuming in Moderation vs. Never Consuming						
100,937+ (4 nonrandomized studies)[b]	serious[a]	not serious	not serious	not serious	none	moderate
Breast Cancer Consuming Above Moderation vs. Never Consuming						
94,333+ (6 nonrandomized studies)[c]	serious[a]	not serious	not serious	not serious	none	moderate
Breast Cancer Consuming Higher vs. Lower Alcohol Amounts in Moderation						
225,293+ (2 nonrandomized studies)[d]	serious[a]	not serious	not serious	not serious	none	moderate
Breast Cancer Consuming Above Moderate Amounts vs. Lower Amounts in Moderation						
164,272+ (3 nonrandomized studies)[e]	serious[a]	not serious	not serious	not serious	none	moderate
Breast Cancer and Increased Alcohol Consumption of 10–14 grams/day						
409,592+ (7 nonrandomized studies)[f]	serious[a]	not serious	not serious	not serious	none	moderate

[a] Some concerns of bias in most included studies.
[b] Kawai et al., 2011; Klatsky et al., 2015; Li et al., 2010; White et al., 2017.
[c] Basset et al., 2022; Kawai et al., 2010; Klatsky et al., 2015; Li et al., 2010; Suzuki et al., 2010; White et al., 2017.
[d] Key et al., 2019; Romieu et al., 2015.
[e] Heberg et al., 2019; Key et al., 2019; Romieu et al., 2015.
[f] Arthur et al., 2020; Key et al., 2019; Park et al., 2014; Romieu et al., 2015; Suzuki et al., 2010; Heath et al, 2020; Li et al., 2010.
SOURCE: Adapted from Table G-3 in Appendix G, Academy of Nutrition and Dietetics, 2024.

Conclusion 5-1: The committee concludes that compared with never consuming alcohol, consuming a moderate amount of alcohol was associated with a higher risk of breast cancer (moderate certainty).

Conclusion 5-2: The committee concluded that, among moderate alcohol consumers, higher versus lower amounts of moderate alcohol consumption were associated with a higher risk of breast cancer (low certainty).

Colorectal Cancer

Five studies examined the relationship between alcohol consumption and colorectal cancer (Bassett et al., 2022; Cho et al., 2015; Jin et al., 2023; Klatsky et al., 2015; Murphy et al., 2019). Three studies compared moderate alcohol consumption to never consuming alcohol (Basset et al., 2022; Cho et al., 2015; Klatsky et al., 2015) (Figure 5-5). Klatsky et al. (2015) found that individuals consuming <1 drink per day had an HR of 1.10 (95%CI [0.96, 1.25]) for colorectal cancer compared to never drinkers. In an Australian study (Bassett et al., 2022) stratified by sex, men who were moderate drinkers were estimated to have an HR of 1.12 (95%CI [0.85, 1.48]). Alcohol consumption categories for women in this study did not include a category that aligns with moderate consumption. A Korean study (Cho et al., 2015) stratified by sex found that men who drank <10 grams/day (<0.7 drinks/day) had an HR of 1.28 (95%CI [0.71, 2.31]) and women had an HR of 0.82 (95%CI [0.41, 1.63]) compared to never drinkers.

Although point estimates from these studies indicate a consistent positive association between moderate alcohol consumption and risk of colorectal cancer in men, none reached statistical significance. A meta-analysis of these three studies found a nonstatistically significant positive association between moderate alcohol consumption and risk of colorectal cancer (RR = 1.09, 95%CI [0.98, 1.22]) (Figure 5-5 and Table 5-4). These studies were rated as having some concerns of risk of bias (Bassett et al., 2022; Klatsky et al., 2015) or high risk of bias (Cho et al., 2015) (Table 5-5).

Two studies examined the association between alcohol consumption and colorectal cancer risk among alcohol consumers (Jin et al., 2023; Murphy et al., 2019). The committee based its conclusions on two studies available for colorectal cancer deemed to have sufficient power but downgraded the level of certainty to low. Jin et al. (2023) examined alcohol exposure as a categorical variable and found that, after adjustment for confounding, men consuming higher amounts (0.7–<2.1 drinks/day) had higher risk of colorectal cancer compared to those consuming lower amounts (<0.7 drinks/day) (HR = 1.09, 95%CI [1.02, 1.17]) (Figure 5-5). No results for women consuming alcohol within the moderate range were reported.

TABLE 5-4 Results of Meta-Analyses with Sensitivity Analysis for Associations Between Alcohol Amount and Colorectal Cancer Compared to Never Consuming Alcohol

	N Studies	RR (95% CI)	I^2 (%)
Overall Results[a]			
Moderate Alcohol Consumption[b,c]	3	1.09 [0.98, 1.22]	0
Subgroup Analysis by Sex[a]			
Moderate Alcohol Consumption[b,c]			
Females	1	0.82 [0.41, 1.63]	N/A
Males	2	1.11 [0.89, 1.38]	0
Not Stratified	1	1.10 [0.96, 1.26]	N/A

NOTES: CI = confidence interval; I^2 = heterogeneity; *N* = number; N/A = Not Applicable; RR = relative risk.
[a] Meta-analyses of drinking categories were conducted using separate meta-analyses to avoid over-counting participants in comparison groups.
[b] Moderate levels are ≤1 drink/day for women and ≤2 drinks/day for men. 1 U.S. drink = 14 grams of alcohol.
[c] Alcohol consumption amount for included groups can be found in Figure 10 and Methods Appendix 2.
SOURCE: Adapted from Table G-8 in Appendix G, Academy of Nutrition and Dietetics, 2024.

TABLE 5-5 Risk of Bias of Included Studies Examining the Relationship Between Alcohol Intake and Colorectal Cancer

Study	Bias Domains assessed as "some concerns" or "high"	Overall Risk of Bias
Bassett et al., 2022	Exposure measurement	Some concerns
Cho et al., 2015	Confounding, exposure measurement	High
Jin et al., 2023	Confounding, exposure measurement	Some concerns
Klatsky et al., 2015	Exposure measurement	Some concerns
Murphy et al., 2019	Confounding, exposure measurement	Some concerns

NOTES: Overall risk of bias is based on seven domains: (1) confounding; (2) measurement of the exposure; (3) selection of participants into the study (or into the analysis); (4) post-exposure interventions; (5) missing data; (6) measurement of the outcome; and (7) selection of the reported results.
SOURCE: Adapted from Annex G-6 in Appendix G, Academy of Nutrition and Dietetics, 2024.

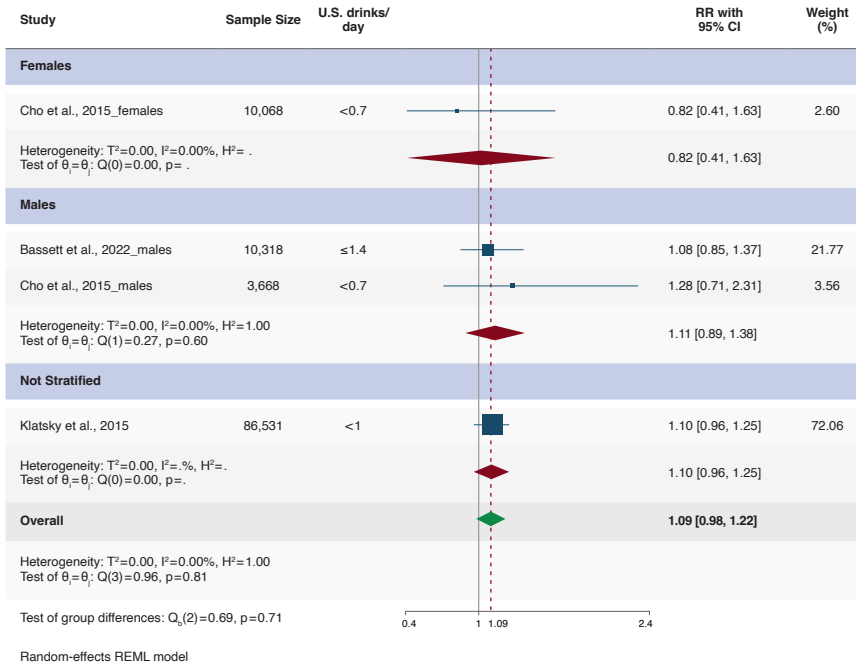

FIGURE 5-5 Meta-analysis on associations between moderate alcohol consumption and colorectal cancer compared to never consuming alcohol.
NOTES: CI = confidence interval; I^2 = heterogeneity; REML = restricted maximum likelihood; RR = relative risk.
SOURCE: Figure G-8 in Appendix G, Academy of Nutrition and Dietetics, 2024.

Murphy et al. (2019) examined alcohol consumption as a continuous variable and found that each 15 grams/day (1.1 U.S. drinks/day) higher alcohol consumption was associated with a 1.05 times higher hazard of colorectal cancer (95%CI [1.03, 1.07]). Evidence certainty was low due to risk of bias in the included studies. The certainty of the evidence of the studies included in the systematic reviews are summarized in Table 5-6.

Finding 5-3: On the basis of five eligible studies and a meta-analysis of three of these studies, compared with never drinkers, moderate alcohol consumption was associated with a statistically nonsignificant higher risk of colorectal cancer overall among males and females. There were some concerns with the studies related to risk of bias, mainly due to confounding and exposure assessment.

Finding 5-4: On the basis of two eligible studies, consumption of higher amounts of moderate alcohol was associated with a higher

TABLE 5-6 Summary of Findings for Systematic Review on Associations Between Alcohol Consumption and Colorectal Cancer

Certainty Assessment						
Participants (Studies) Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Certainty of Evidence
Colorectal Cancer Consuming Moderately vs. Never Consuming						
106,917 (3 nonrandomized studies)[d]	serious[a]	not serious	not serious	serious[b]	none	low
Colorectal Cancer Consuming Above Moderate Alcohol Consumption vs. Never Consuming						
50,894 (3 nonrandomized studies)[d]	serious[a]	not serious	not serious	not serious	none	moderate
Colorectal Cancer Consuming Higher vs. Lower Amounts Within Moderate Alcohol Consumption						
1,981,807 (1 nonrandomized study)[e]	serious[a]	not serious	serious[c]	not serious	none	low
Colorectal Cancer Consuming Above DGAs vs. Lower Amounts Within Moderate Alcohol Consumption						
1,644,833 (1 nonrandomized study)[f]	serious[a]	not serious	not serious	serious[b]	none	low

[a] Some concerns of bias in most included studies.
[b] Wide confidence interval include potential benefits and harms.
[c] Only reported alcohol consumption within *moderate alcohol consumption* for males.
[d] Bassett et al., 2022; Cho et al., 2015; Klatsky et al., 2015.
[e] Jin et al., 2023.
[f] Murphy et al., 2019.
SOURCE: Adapted from Table G-9 in Appendix G, Academy of Nutrition and Dietetics, 2024.

risk of colorectal cancer. One study reported an HR of 1.09 (95%CI [1.02, 1.17]) for colorectal cancer among males who consumed higher amounts of moderate alcohol (0.7–<2.1 drinks/day) compared with males who consumed lower amounts of moderate alcohol (<0.7 drinks/day). Another study reported a HR of 1.05 (95%CI [1.03, 1.07]) for colorectal cancer associated with each 15 grams (1.1 U.S. drinks) increment of higher alcohol consumption per day. There were some concerns related to risk of bias (mainly due to confounding), exposure assessment, and indirectness stemming from estimating linear trends based on alcohol consumption that may have exceeded the moderate range in some individuals in the latter study.

Conclusion 5-3: The committee determined that no conclusion could be drawn regarding the association between moderate alcohol consumption compared with lifetime nonconsumers and risk of colorectal cancer.

Conclusion 5-4: The committee concluded that among moderate alcohol consumers higher versus lower amounts of moderate alcohol consumption were associated with a higher risk of colorectal cancer (low certainty).

Oral Cavity, Pharyngeal, Esophageal, and Laryngeal Cancers

There were few studies identified meeting the inclusion criteria examining the association between moderate alcohol consumption compared to lifetime abstention for risk of oral, pharyngeal, esophageal, and laryngeal cancers. While four cohort studies (Im et al., 2023; Klatsky et al., 2015; Radoï et al., 2013; Steevens et al., 2010) met the inclusion criteria, there were fewer on any one of the cancer sites. Meta-analysis of evidence for these cancer sites was not conducted.

Briefly, findings from those studies were as follows. In one study of participants in a health plan in the United States, results were reported for upper airway digestive cancers as a group (Klatsky et al., 2015). They reported a nonsignificant increased risk associated with intakes of less than 1 drink per day (RR = 1.1, 95%CI [0.8, 1.6]) but increased risk associated with 1–2 drinks per day (RR = 1.5, 95%CI [1.1, 2.3]); both comparisons to lifetime abstention. Results were not stratified by sex. The study included 52 percent women; the latter category of consumption of 1–2 drinks per day would be above moderate alcohol consumption for them. In a cohort study among Chinese men examining cancers of the oral cavity and pharynx combined, intake of less than 10 drinks per week was associated with reduced risk (RR = 0.68, 95%CI [0.49, 0.93]) (Im et al., 2023).

Radoï et al. (2013) conducted a cohort study in France of cancer of the oral cavity. They reported on risk associated with consumption of individual beverages. They found no association of risk of these cancers with consumption of one or fewer drinks per day of wine, beer, spirits, or apéritif; consumption of one glass or fewer of cider was associated with reduced risk (RR = 0.6, 95%CI [0.4, 0.9]) compared to lifetime never drinkers. They also examined the interaction of smoking and alcohol. For those consuming less than or equal to two drinks per day, risk of oral cancer was increased with moderate alcohol consumption among those who had ever smoked for 30 years or longer; it was not increased among those smoking for a shorter time. The study was 80 percent males; two or more drinks per day would be above moderate alcohol consumption for women in the study (Radoï et al., 2013).

There were two studies identified that examined moderate consumption of alcohol in association with squamous cell esophageal cancer (Im et al., 2023; Steevens et al., 2010). In a cohort study in the Netherlands, neither alcohol consumption of less than 5 grams/day was associated with risk (RR = 0.85, 95%CI [0.42, 1.73]) nor was consumption of 5–15 grams/day (RR = 1.65, 95%CI [0.85, 3.17]). At intakes of approximately 1–2 drinks per day, 15–30 grams/day, alcohol consumption was associated with increased risk (RR = 2.11, 95%CI [1.09, 4.14]). This study included both men and women; intakes in the latter category would be above moderate alcohol consumption for women. In a second study of squamous cell esophageal cancer in Chinese men, Im et al. (2023) reported no association between moderate alcohol consumption of less than 10 drinks per week (RR = 0.94, 95%CI [0.79, 1.11]). In that study, they also found no association of that amount of drinking with cancer of the larynx (RR = 1.35, 95%CI [0.89, 2.07]).

Finding 5-5: There was insufficient evidence to support an association between moderate alcohol consumption and risks of oral cavity, pharyngeal, esophageal, and laryngeal cancers.

Conclusion 5-5: The committee determined that no conclusion could be drawn regarding an association between moderate alcohol consumption and oral cavity, pharyngeal, esophageal, or laryngeal cancers.

Other Types of Cancer with Emerging Evidence Regarding Alcohol Consumption

The evidence scan conducted for the committee identified several cancers for which there appears to be an emerging body of evidence regarding moderate consumption. Specifically, studies of the relationship between moderate alcohol consumption and each of bladder, endometrial, gastric,

pancreas, prostate, lung, and thyroid cancer as well as several studies that examined combined sites such as the head and neck, biliary tract, and renal tract (14 studies in total) were identified in the evidence scan (Table 5-1). A systematic review for these cancer sites was not conducted owing to the small number of studies per cancer type. The committee evaluated this body of evidence and concluded that there was insufficient evidence to establish certainty for an association of moderate alcohol consumption with any of these other sites. Additional research may provide more information for evaluation in the future.

> Finding 5-6: Upon evaluating the body of evidence, there were several sites where there was emerging evidence that was insufficient to establish certainty for an association of moderate alcohol consumption. These sites included cancer of the head and neck, thyroid, lung, gastric, small intestine, pancreas, biliary tract, renal track, bladder, prostate, and endometrium.

Summary of Evidence Relative to Past DGA Guidance

Breast Cancer

Based on the results of the *de novo* systematic review (SR), of studies published from 2010 to 2024, the committee concludes the results for breast cancer are consistent with the 2015 DGAC report that moderate alcohol consumption was associated with an increased risk of breast cancer. The committee finding, summarized in Conclusion 5-1, had an evidence grade of moderate certainty. Although the 2010 and the 2020 DGAC reports did not directly evaluate the associations between moderate alcohol consumption and cancer outcomes with a systematic review, the reports referred to extant guidelines, other publications, and a review of all-cause mortality to assert the association of alcohol consumption with the risk of cancers, including breast, colorectal, and liver cancer.

Colorectal Cancer

Based on the results of the *de novo* SR, of studies published from 2010 to 2024, the committee concludes the findings for colorectal cancer are consistent with the prior DGAC reports with an evidence grade of low certainty for the finding summarized in Conclusion 5-4. In comparisons of lower versus higher consumption of alcohol within the range of moderate alcohol consumption the committee found higher amounts of moderate alcohol consumption were associated with a higher risk of colorectal cancer, similar to findings reported in the 2010 DGAC report.

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Cardiovascular Disease

Cardiovascular disease (CVD) persists as the leading cause of death in the United States (Martin et al., 2024). CVD includes "heart attack" or myocardial infarction (MI) and stroke; these two conditions are the major CVD outcomes associated with significant levels of morbidity and mortality. Despite advances in biomedical research leading to new treatments, the societal burden of CVD remains enormous (Dunbar et al., 2018; GBD 2021 Causes of Death Collaborators, 2024; Luengo-Fernandez et al., 2023; Zhang et al., 2023), and there is a continuing need to address modifiable risk factors for CVD to mitigate its burden.

An American suffers an MI every 40 seconds, based on the American Heart Association statistics (Martin et al., 2024), with approximately 605,000 MIs per year (Martin et al., 2024). Every year, about 800,000 Americans suffer a stroke (87 percent ischemic and 10 percent hemorrhagic stroke) (Martin et al., 2024). Coronary heart disease and stroke are the first and fifth leading causes of death in the United States, respectively. It is well recognized that modifiable lifestyle factors, including alcohol consumption, may influence the risk of MI and stroke. While heavy alcohol consumption has been associated with a higher risk of MI (Song et al., 2018) and hemorrhagic stroke (Zhong et al., 2022), prior observational studies have suggested that moderate alcohol consumption is associated with a lower risk of CVD (Ding et al., 2021; Luceron-Lucas-Torres et al., 2023; Song et al., 2018). A subset of studies examined associations of moderate alcohol consumption—with the risk of MI, stroke, and CVD death—with particular care to include people who never consumed alcohol as the reference group. The commissioned systematic review studied the association of moderate

alcohol consumption, compared to never consuming alcohol, on the risk of MI, stroke, and CVD death using studies published from January 2010 through February 2024.

CHOICE OF CVD OUTCOMES

This chapter assesses the association of moderate alcohol consumption versus no alcohol consumption with the risk of experiencing a major adverse cardiovascular event (MACE-3), which includes the three primary outcomes of MI, stroke, and cardiovascular death (Ridker et al., 2005). Unlike MI and stroke, which clinicians diagnose with high accuracy, angina pectoris (another type of CVD) is a less definitive outcome given its subjective nature and the fact that revascularization to treat it may be elective. Accordingly, major randomized controlled trials (RCTs) of CVD treatments use MACE-3 as the primary outcome. While trials of CVD treatment may study a combined outcome based on the three major types of CVD events, we studied each of the three outcomes separately.

BIOLOGICAL PLAUSIBILITY

Several biologic mechanisms potentially explain how moderate alcohol consumption plays a role in reducing the risk of CVD, including the ability of alcohol to (1) increase high density lipoprotein (HDL) cholesterol and apolipoprotein A-1 (Camargo et al., 1985; Chiva-Blanch et al., 2015; Gepner et al., 2015; Masarei et al., 1986); (2) inhibit platelet aggregation (Umar et al., 2005; Zhang et al., 2000) and inflammation (Chiva-Blanch et al., 2015; Fragopoulou et al., 2021; Sierksma et al., 2002); (3) reduce fibrinogen (Chiva-Blanch et al., 2015; Sierksma et al., 2002; Stote et al., 2016) and increase plasminogen activator inhibiting factor 1 (Stote et al., 2016); and (4) favorably affect markers of glycemic control (Gepner et al., 2015), all of which are risk factors for MACE-3.

These biological mechanisms, which were originally proposed in observational studies, have also been confirmed in dozens of short-term RCTs over the past 40 years. For example, systematic reviews of RCT data have demonstrated that moderate drinking favorably affects HDL cholesterol, low density lipoprotein (LDL) cholesterol, and apolipoprotein A-1 (Brien et al., 2011; Huang et al., 2017; Spaggiari et al., 2020); fibrinogen (Brien et al., 2011; Huang et al., 2017); interleukin-6 (Huang et al., 2017); and glucose control (Schrieks et al., 2015). While each of these established effects is likely to contribute to observed reductions in risk of MI and ischemic stroke with alcohol consumption, some changes in biologic pathways (e.g., decreased clotting) also help explain how alcohol consumption may increase risk of hemorrhagic stroke.

PRIOR DGA RECOMMENDATIONS

As explained in Chapter 1 of this report, the Dietary Guidelines Advisory Committee (DGAC) reports and *Dietary Guidelines for Americans* (DGA) have sometimes addressed the association of alcohol with the risk of CVD. The past three 5-year cycles are summarized below.

In brief, the 2010–2015 DGA and 2015–2020 DGA (USDA and HHS, 2010, 2015) and the 2010 and 2015 Dietary Guidelines Advisory Committee (USDA and HHS, 2010, 2015) reports concluded that moderate alcohol consumption (defined as up to one drink per day for women and up to two drinks per day for men) is associated with lower risk of CVD, when compared to nondrinkers. The 2020 DGAC report provided a narrative synthesis of four Mendelian randomization studies and concluded that those studies did not support a lower risk of CVD at lower levels of alcohol consumption, which the report found was inconsistent with the extensive body of evidence from observational studies. It is important to note that the Mendelian randomization design has its own set of limitations (see Chapter 2).

2010

The 2010–2015 DGA (USDA and HHS, 2010) does not include much information about the specific association of alcohol consumption with CVD morbidity and/or mortality. In a general statement about the dietary factors associated with increased risk of chronic disease, the report names excess alcohol consumption as a dietary factor that increases blood pressure. The report notes: "Alcohol consumption may have beneficial effects when consumed in moderation. Strong evidence from observational studies has shown that moderate alcohol consumption is associated with a lower risk of cardiovascular disease."[1] The above statements were not linked to scientific references, and a systematic review of evidence was not conducted.

The 2010 committee addressed the question, "What is the relationship between alcohol intake and coronary heart disease?" The committee used meta-analyses and systematic reviews (SRs) published in the period since the 2005 DGAC report to answer the question. The focus was on moderate drinking, which the 2010 DGAC report defined as no more than 14 drinks a week for men and 7 drinks a week for women with no more than 4 drinks on any given day for men and no more than 3 drinks on any given day for women.[2] The 2010 DGAC report (DGAC, 2010) concluded there was no meaningful change in the research findings on alcohol and CVD risk since

[1] 2010 *Dietary Guidelines for Americans* Report, p. 31.
[2] 2010 Dietary Guidelines Advisory Committee Report, p. 354.

the 2005 report and that no new systematic reviews were warranted; the committee reiterated the findings of prior committees. The overall conclusion was: "compared to those who abstain from alcohol, regular light to moderate drinking can reduce the risk of coronary heart disease (CHD) whereas heavy irregular or binge drinking increases risk of CHD."[3]

For the risk of stroke, the report found that light to moderate alcohol consumption may be protective against total and ischemic stroke, noting that 10 prospective studies since the last report supported that finding. Furthermore, the report concluded that there is strong evidence that moderate alcohol consumption does not elevate the risk of either hypertension or stroke compared to nondrinking. The report noted that heavier alcohol intake is clearly associated with adverse cardiovascular outcomes, and evidence supports that reducing alcohol intake is an effective treatment for lowering blood pressure in persons with elevated blood pressure (DGAC, 2010).

2015

The 2015–2020 DGA include an appendix on alcohol, but it has limited information about the association of alcohol with chronic disease outcomes, including CVD endpoints (USDA and HHS, 2015). The 2015 DGAC report (DGAC, 2015) focused on dietary patterns and reached an overall conclusion that "moderate consumption of alcohol also [is] shown to be [a] component of a beneficial dietary pattern in most studies."[4] The emphasis in the 2015 report was on the need to include the energy (calories) from alcohol consumption in defining healthy eating patterns to avoid excess energy consumption and the risk of weight gain. The report concluded that there was strong evidence to indicate that some dietary patterns, for example the Mediterranean Diet, include moderate intake of alcohol and these patterns are associated with reduced risk of CVD.[5]

2020

The DGA did not specifically address the role of alcohol in cardiovascular morbidity and/or mortality (USDA and HHS, 2020). The 2020 DGAC report (DGAC, 2020) devoted a chapter to alcohol and health and conducted a systematic review designed to address the question: "What is the relationship between alcohol consumption and all-cause mortality?" The 2020 DGAC report also included a narrative synthesis of Mendelian randomization studies of alcohol and CVD because time constraints and the prioritization of all-cause mortality precluded a full systematic review for

[3] 2010 Dietary Guidelines Advisory Committee Report, p. 359.
[4] 2015 Dietary Guidelines Advisory Committee Report, p. 188.
[5] 2015 Dietary Guidelines Advisory Committee Report, p. 211.

the CVD outcome. The 2020 committee searched the literature from 2010 to 2020. The report concluded that the Mendelian randomization analysis "revealed no evidence of reduced associations for myocardial infarction or total coronary heart disease at low levels of alcohol consumption, with little overall effect of alcohol consumption on those outcomes."[6]

METHODOLOGICAL LIMITATIONS

Some of the methodological challenges associated with the use of MACE-3 as an outcome include incomplete ascertainment of CVD events, in particular silent MI; misclassification of MI or stroke depending on the rigor of diagnostic criteria; and missing averted MI or stroke in the settings of early intervention, such as percutaneous coronary intervention or early thrombolytic therapy upon onset of MI and/or stroke signs and symptoms.

SYSTEMATIC REVIEW

Approach

An evidence scan of the recent literature was conducted and searched for prior systematic reviews and original research studies published from 2020 to 2024; the screening of the search results is shown in Figure 6-1. The evidence scan identified 19 systematic reviews of which five were published in 2020, four in 2021, seven in 2022, two in 2023, and one in 2024; about half of the reviews conducted a meta-analysis. The published reviews were approximately equally distributed across AMSTAR-2[7] quality categories, thus five were high quality and nine were assessed as critically low or low quality. Eight of the 19 reviews considered CVD outcomes broadly, and the remaining 11 focused on specific CVD outcomes, including blood pressure, hypertension, heart failure, atrial fibrillation, flow mediated dilation, lipids, and metabolic markers.

The evidence scan for original research studies was conducted for the period 2010 to 2024, given that past DGACs did not review this literature. There were 109 studies of alcohol and CVD identified, including 21 published between 2010 to 2015, 45 between 2016 to 2020, and 42 between 2021 and 2024. Forty-two of these studies were noninformative due to various methodological reasons (e.g., the exposure indicator was insufficient for comparison; the comparator included subjects who consumed alcohol in the past/former drinkers; wrong study outcome). The mixed quality and the diversity of outcomes considered in past systematic reviews meant that these reviews were not adequate to support the work of this committee.

[6] 2020 Dietary Guidelines Advisory Committee Report, p. 19, 20.
[7] A Measurement Tool to Assess Systematic Reviews; see Chapter 2.

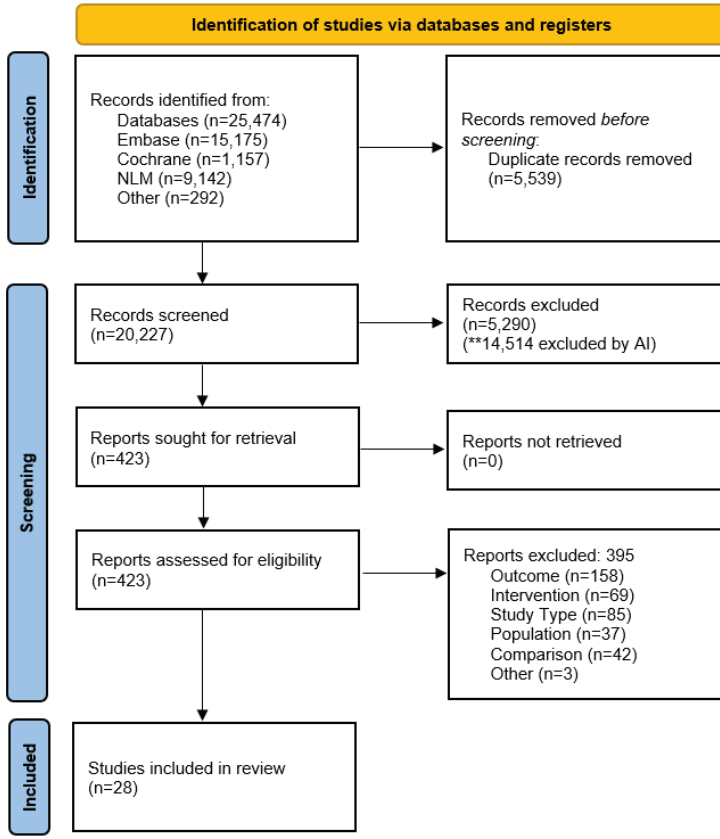

FIGURE 6-1 PRISMA flow chart for the systematic review on the association between alcohol consumption and cardiovascular disease incidence.
NOTES: The diagram shows the number of primary articles identified from the primary article and systematic review searches and each step of screening. The literature dates include articles with the publications between 2010 and 2024. n = number; NLM = National Library of Medicine; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
SOURCE: Figure H-1 in Appendix H, Academy of Nutrition and Dietetics, 2024.

Given the number of original studies identified in the evidence scan, the committee made the decision to conduct a *de novo* systematic review of the relationship between alcohol consumption and the risk of CVD; the commissioned systematic review searched for published literature from January 2010 to February 2024 (AND, 2024). The risk of bias and the certainty of the evidence of the studies included in the systematic reviews are summarized in Table 6-1 and Table 6-2, respectively.

TABLE 6-1 Risk of Bias of Included Studies Examining the Relationship Between Alcohol Consumption and Cardiovascular Outcomes

Study	Source of Bias	Overall Risk of Bias
Bell et al., 2017	Confounding, exposure assessment	Some concerns
Chang et al., 2020	Confounding	Some concerns
Chiuve et al., 2010	Confounding, exposure assessment	Some concerns
Di Castelnuovo et al., 2022	Confounding, exposure assessment	Some concerns
Duan et al., 2019	No bias identified	Low
Hernandez-Hernandez et al., 2015 (SUN Study)	Confounding, exposure assessment	Some concerns
Ilomäki et al., 2012	Confounding	Some concerns
Im et al., 2023	Confounding, exposure assessment	Some concerns
Jankhotkaew et al., 2020	Confounding, exposure assessment	Some concerns
Jeong et al., 2022	Confounding	Some concerns
Johansson et al., 2021	Exposure assessment	Some concerns
John et al., 2021	Confounding, exposure assessment	High
Jones et al., 2015	Exposure assessment	Some concerns
Kadlecová et al., 2015	Exposure assessment	Some concerns
Larsson et al., 2017	Exposure assessment	Some concerns
Liu et al., 2022	Exposure assessment	Some concerns
Liu et al., 2023	Exposure assessment, selection bias	Some concerns
Lv et al., 2017	Exposure assessment	Some concerns
Ma et al., 2021	Exposure assessment	Some concerns
Merry et al., 2011	Confounding, exposure assessment	Some concerns
Millwood et al., 2019	Confounding	Some concerns
Muraki et al., 2023	Confounding, exposure assessment	Some concerns
Ricci et al., 2020	Confounding	High
Smyth et al., 2015	Exposure assessment	Some concerns
Stamatakis et al., 2021	Exposure assessment	Some concerns
Tian et al., 2023	Confounding	Some concerns
Ye et al., 2021	Confounding, exposure assessment	Some concerns
Zhang et al., 2021	No bias identified	Low

NOTE: Overall risk of bias is based on seven domains: (1) confounding; (2) measurement of the exposure; (3) selection of participants into the study (or into the analysis); (4) post-exposure interventions; (5) missing data; (6) measurement of the outcome; and (7) selection of the reported results.
SOURCE: Adapted from Figure H-2 in Appendix H, Academy of Nutrition and Dietetics, 2024.

TABLE 6-2 GRADE Summary of Findings Table for Systematic Review Examining Associations Between Alcohol Consumption and All Cardiovascular Outcomes

	Certainty Assessment					
Participants (Studies) Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Certainty of evidence
CVD Mortality for Moderate Consumption vs. Never Consuming						
329,772 (4 nonrandomized studies)[b]	serious[a]	not serious	not serious	not serious	none	moderate
CVD Mortality Consuming Higher vs. Lower Moderate Alcohol Consumption						
14,920 (1 nonrandomized study)[i]	very serious[d]	not serious	not serious	serious[c]	none	very[f] low
MI for Moderate Alcohol Consumption vs. Never Consuming						
139,317 (2 nonrandomized studies)[j]	serious[a]	not serious	not serious	not serious	none	moderate
MI Consuming Higher vs. Lower Alcohol Amounts Within Moderate Alcohol Consumption						
38,751 (2 nonrandomized studies)[k]	serious[a]	serious[b]	not serious	serious[e]	none	very[f] low
Stroke for Moderate Alcohol Consumption vs. Never Consuming						
3,129,600 (7 nonrandomized studies)[l]	serious[a]	not serious	not serious	not serious	none	low[g]
Stroke Consuming Higher vs. Lower Alcohol Amounts Within Moderate Alcohol Consumption						
7,277 (1 nonrandomized study)[m]	serious[a]	not serious	not serious	serious[c]	none	low

[a] Some concerns of bias in most included studies.
[b] High heterogeneity in results between studies.
[c] Wide confidence interval include potential benefit and harms.
[d] One study with high risk of bias.
[e] Meta-analysis was not possible, as Ilomäki et al. (2012) compared lower to higher consumption, and Larsson et al. (2017) compared higher to lower consumption.
[f] The committee used the phrase "insufficient evidence" to reflect a lower level of certainty of the evidence, as indicated by the assignment of "very low" in the commissioned systematic reviews by the Academy of Nutrition and Dietetics.
[g] Jeong et al. (2022) met inclusion criteria by the Academy of Nutrition and Dietetics. Because it was unclear how never drinkers were classified, the Academy of Nutrition and Dietetics' categorization was retained, but the committee downgraded the certainty from "moderate" to "low" certainty.
[h] Chiuve et al., 2010; Di Castelnuovo et al., 2022; Muraki et al., 2023; Tian et al., 2023.
[i] Ricci et al., 2020.
[j] Chiuve et al., 2010; Smyth et al., 2015.
[k] Larsson et al., 2017; Zhang et al., 2021.
[l] Chang et al., 2020; Duan et al., 2019; Jeong et al., 2022 Jones et al., 2015; Liu et al., 2023; Lv et al., 2017; Smyth et al., 2015.
[m] Johansson et al., 2021.
SOURCE: Adapted from Table H-4 in Appendix H, Academy of Nutrition and Dietetics, 2024.

Results

Myocardial Infarction

While 26 cohort studies that examined the associations between alcohol consumption and cardiovascular outcomes of interest were included in the systematic review, only eight studies reported findings for the outcome of myocardial infarction (MI). Of these eight studies, only two studies had comparisons that could be included in summarizing the association of moderate alcohol consumption, compared to never consuming alcohol, and the risk of MI. The committee based its conclusions on two studies available for MI deemed to have sufficient power but downgraded the level of certainty to low. The findings are summarized in Table 6-3 and Figure 6-2.

> Finding 6-1: A meta-analysis of two eligible studies found that among persons who consumed moderate amounts of alcohol compared with persons who never consumed alcohol, there was a 22 percent lower risk of MI (RR = 0.88, 95%CI [0.68, 0.90]). No studies reported data for males alone. One study reported a 21 percent lower risk of MI among females only; these results were consistent with the estimate for both sexes combined. There were some concerns related to risk of bias in the studies, mainly due to confounding.

TABLE 6-3 Subgroup and Sensitivity Analyses for Associations Between Moderate Alcohol Amount and Myocardial Infarction Compared to Never Consuming Alcohol

	N Studies	RR (95% CI)	I^2 (%)
Main Analysis[a]			
Moderate Alcohol Consumption	2	0.78 [0.68, 0.90]	25.9
Subgroup Analyses[a]			
Moderate Alcohol Consumption			
Males	–	–	
Females	1	0.79 [0.69, 0.91]	N/A
Both	1	0.77 [0.63, 0.94]	N/A

NOTES: A dash indicates that there were no studies available for this comparison. CI = confidence interval; I^2 = heterogeneity; MI = myocardial infarction; *N* = number; N/A = not applicable; RR = relative risk.

[a] Meta-analyses of drinking categories were conducted using separate meta-analyses to avoid over-counting participants in comparison groups.

SOURCE: Adapted from Table H-3 in Appendix H, Academy of Nutrition and Dietetics, 2024.

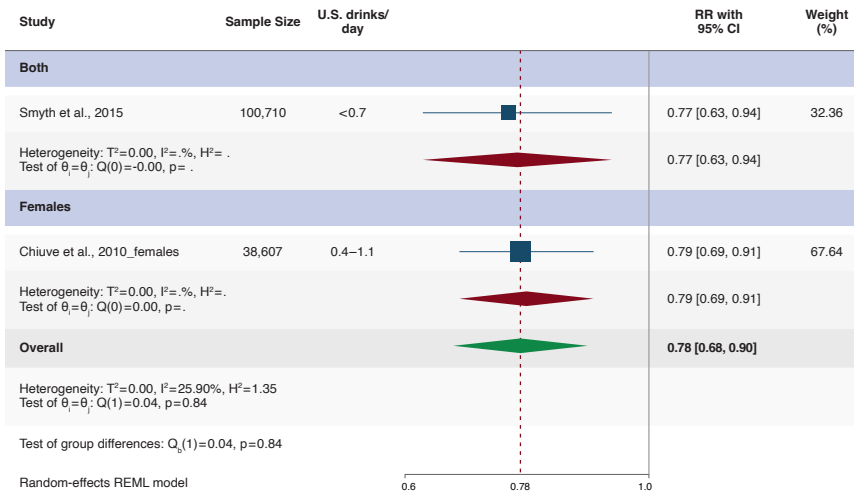

FIGURE 6-2 Meta-analysis of association between moderate alcohol consumption compared with never consuming alcohol and myocardial infarction according to sex.
NOTES: CI = confidence interval; REML = restricted maximum likelihood; RR = relative risk.
SOURCE: Figure H-3 in Appendix H, American Academy of Nutrition and Dietetics, 2024.

Conclusion 6-1: The committee concludes that compared with never consuming alcohol, consuming moderate amounts of alcohol is associated with a lower risk of nonfatal MI (low certainty).

Stroke

Of the 26 cohort studies included in the review, 13 cohort studies examined the association of alcohol consumption on the risk of stroke; seven of these studies compared alcohol consumption to never consuming alcohol. Results from included studies were extracted for total stroke when available and ischemic stroke when total stroke was not reported, given ischemic stroke comprises most stroke cases (Table 6-4 and Figure 6-3).

Finding 6-2: A meta-analysis of seven eligible studies found an 11 percent lower risk of stroke among persons consuming moderate amounts of alcohol compared with persons never consuming alcohol (RR = 0.89, 95%CI [0.86, 0.93]). These results were driven by ischemic stroke, which showed a 12 percent lower risk (RR = 0.88, 95%CI [0.86, 0.90]).

TABLE 6-4 Subgroup Analyses for Associations Between Alcohol Amount and Stroke Compared to Never Consuming Alcohol

	N Studies	RR (95% CI)	I^2 (%)
Main Analysis[a]			
Moderate Alcohol Consumption[b]	7	**0.89 [0.86, 0.93]**[c]	7.3
Subgroup Analyses[a]			
Moderate Alcohol Consumption			
Males	3	1.02 [0.70, 1.49]	77.0
Females	2	0.86 [0.51, 1.44]	8.9
Both	4	**0.88 [0.86, 0.90]**	0.01

NOTES: CI = confidence interval; *N* = number; I^2 = heterogeneity; RR = relative risk.
[a] Meta-analyses of drinking categories were conducted using separate meta-analyses to avoid over-counting participants in comparison groups.
[b] Moderate consumption levels are ≤1 drink/day for women and ≤2 drinks/day for men. 1 U.S. drink = 14 grams of alcohol.
[c] Results in bold are statistically significant ($p < 0.05$).
SOURCE: Adapted from Table H-6 in Appendix H, Academy of Nutrition and Dietetics, 2024.

Separate examination of hemorrhagic strokes was infrequent; thus, no estimate of effect for this health outcome could be made. There were some concerns related to risk of bias among the studies, mainly due to confounding and exposure assessment.

Conclusion 6-2: The committee concludes that compared with never consuming alcohol, consuming moderate amounts of alcohol is associated with a lower risk of nonfatal stroke (low certainty).

CVD Mortality

While 13 studies investigated the association of alcohol consumption with CVD mortality, only seven of those used never drinkers as the comparison group; among those seven studies, only four were informative for estimating the association of moderate alcohol consumption compared to never consuming alcohol on the risk of CVD mortality. These four studies were meta-analyzed as shown in Table 6-5 and Figure 6-4.

Finding 6-3: A meta-analysis of four eligible studies found an 18 percent lower risk of CVD mortality among persons who consumed moderate amounts of alcohol compared with those who never consumed alcohol

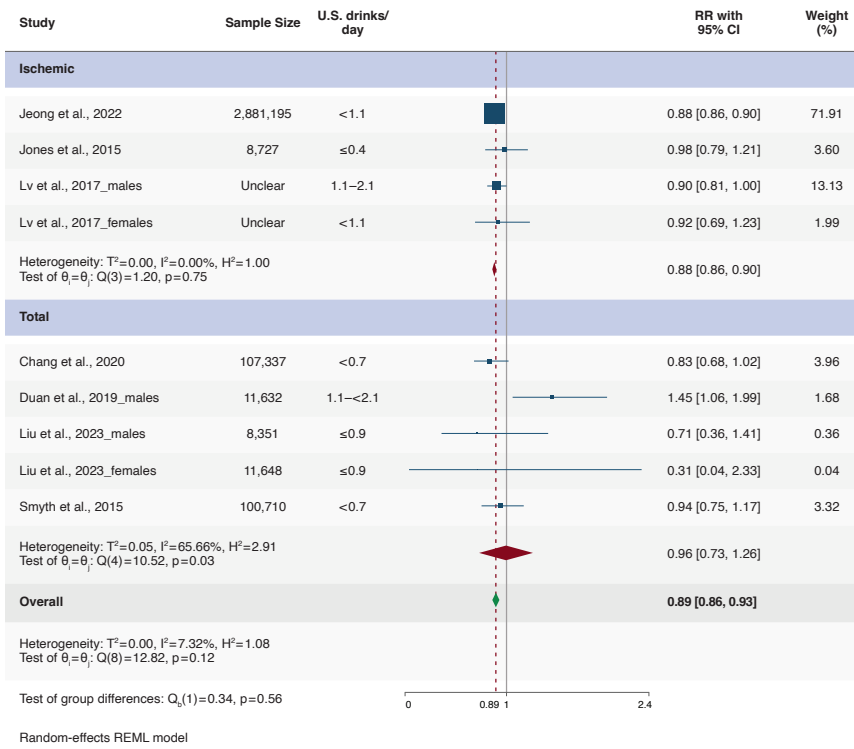

FIGURE 6-3 Meta-analysis of association between moderate consumption of alcohol compared with never consuming alcohol on stroke according to stroke type.
NOTES: CI = confidence interval; REML = restricted maximum likelihood; RR = relative risk.
SOURCE: Figure H-6 in Appendix H, American Academy of Nutrition and Dietetics, 2024.

(RR = 0.82, 95%CI [0.76, 0.89]). The committee further found a 23 percent lower risk in females (RR = 0.77, 95%CI [0.70, 0.85]), and an 18 percent lower risk in males (RR = 0.82, 95%CI [0.71, 0.94]). Very limited data stratified by age were available; however, one study showed that the effect size and direction for moderate alcohol consumption compared with no alcohol consumption was consistent among persons aged less than 60 years (33 percent lower risk of CVD mortality) and among persons aged 60 years or older (19 percent lower risk of CVD mortality). There were some concerns related to risk of bias, mainly due to confounding, in the studies contributing to this comparison.

TABLE 6-5 Subgroup Analyses for Associations Between Moderate Alcohol Amounts and Cardiovascular Disease Mortality Compared to Never Consuming Alcohol

	N Studies	RR (95% CI)	I^2 (%)
Main Analysis[a]			
Moderate Alcohol Consumption[b]	4	**0.82 [0.76, 0.89]**[c]	63.0
Subgroup Analyses[a]			
Moderate Alcohol Consumption			
Males	2	**0.82 [0.71, 0.94]**	68.1
Females	2	**0.77 [0.70, 0.85]**	0
Not stratified	1	**0.90 [0.83, 0.97]**	N/A
Moderate Alcohol Consumption			
<60 years	1	**0.67 [0.59, 0.76]**	N/A
≥60 years	1	**0.81 [0.75, 0.87]**	N/A
Not stratified	3	**0.89 [0.83, 0.95]**	0.03

NOTES: CI = confidence interval; I^2 = heterogeneity; *N* = number; N/A = Not Applicable; RR = relative risk.

[a] Meta-analyses of drinking categories were conducted using separate meta-analyses to avoid over-counting participants in comparison groups.

[b] Moderate amounts are ≤1 drink/day for women and ≤2 drinks/day for men. 1 U.S. drink = 14 grams of alcohol.

[c] Results in bold are statistically significant ($p < 0.05$).

SOURCE: Adapted from Table H-8 in Appendix H, Academy of Nutrition and Dietetics, 2024.

Conclusion 6-3: The committee concludes that compared with never consuming alcohol, consuming moderate amounts of alcohol is associated with a lower risk of CVD mortality in both females and males (moderate certainty).

Summary of Evidence Relative to Past DGA Guidance

Based on the results of the *de novo* SR using data from 2010 to 2024, the committee concludes these results are consistent with prior DGAC reports that moderate alcohol consumption, compared to never drinking, is associated with a lower risk of MI, total stroke, and CVD mortality with evidence grades of low certainty, low certainty, and moderate certainty for findings summarized in Conclusions 6-1, 6-2, and 6-3, respectively.

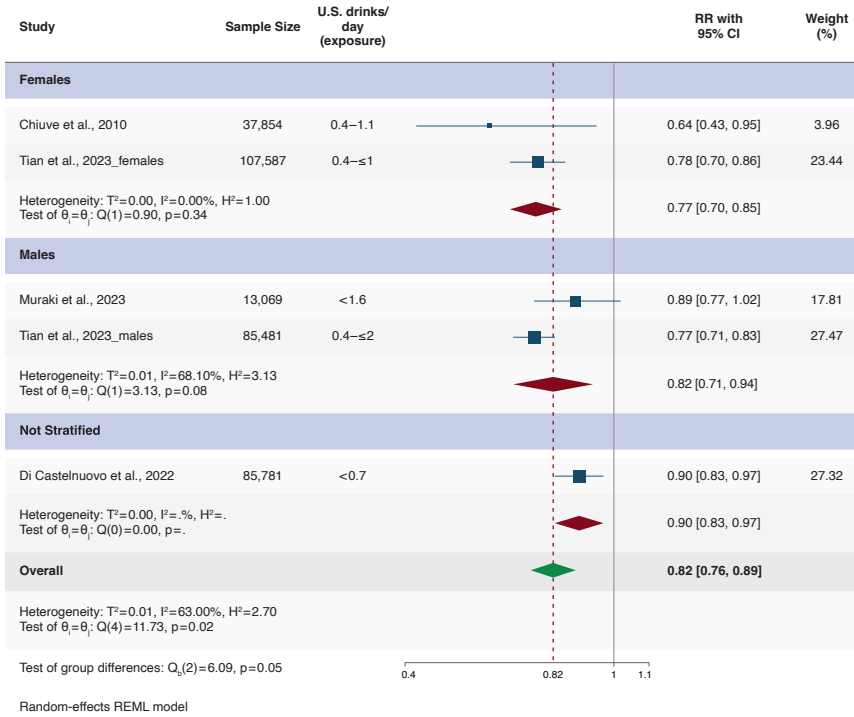

FIGURE 6-4 Meta-analysis on associations between moderate consumption of alcohol compared with never consuming alcohol on cardiovascular disease (CVD) mortality according to sex.
NOTES: CI = confidence interval; REML = restricted maximum likelihood; RR = relative risk.
SOURCE: Figure H-9 in Appendix H, Academy of Nutrition and Dietetics, 2024.

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7

Neurocognition

Analyses of whether moderate alcohol consumption is positively or negatively associated with cognitive abilities or development of dementia was guided by a 75-year history of rigorous peer-reviewed studies on the effects of alcohol use (Adams and Victor; 1989; Oscar-Berman et al., 2014; Parsons and Nixon, 1993; Sullivan et al., 2023). The mainstay of this work has focused on alcohol dependence, which is now called alcohol use disorder (AUD). Mild, moderate, severe, or profound impairments associated with AUD are detectable with objective quantitative testing conducted after the acutely consumed alcohol has been fully metabolized and is no longer active in the system. Acute alcohol consumption commonly impairs motor control, resulting in postural instability, slurred speech, and eye-to-hand discoordination affecting activities such as driving; memory consolidation for events experienced during intoxication; emotional lability evidenced as unprovoked crying or physical aggression; and poor judgment, for example, deciding to drive while intoxicated. Areas of impairment that persist after acute intoxication and accompanying chronic AUD include specific component processes of memory, such as verbal and spatial working memory, and select cognitive functions, such as problem solving, decision making, and spatial construction.

Myriad demographic, environmental, family history, and genetic factors can influence the course of AUD. For example, high risk for the development of AUD is associated with early initiation of drinking during young adolescence, family history of AUD, poor inhibitory control, binge drinking, history of blackouts, and access to alcoholic beverages. Whether AUD initiated at any age accelerates age-related health declines remains an open question.

Relative to AUD, far less research has been devoted to objective studies of moderate drinking, which is often defined by exclusion from AUD criteria. The few studies of moderate drinking, sometimes referred to as *social drinking*, that have used objective neuropsychological tests, report performance advantages in some areas, including executive functioning (Hogenkamp et al., 2014), episodic memory (Downer et al., 2015), and working memory (Boissoneault et al., 2016). Along with the apparently positive effects of moderate drinking are cautions, including lifestyle factors that can co-occur with alcohol consumption that are either positive, such as healthful nutrition, regular exercise, and good sleep habits, or negative, such as smoking or interference with medication functions. Other positive lifestyle factors potentially intersect with moderate drinking, such as presenting opportunities for socialization and family interaction.

In addition to studies focused on the cognitive and motor effects of drinking within the limits of low risk, moderate drinkers are characteristically the no-to-low drinking control groups for AUD study groups (Nixon and Lewis, 2019). It must be emphasized that none of these observations, even when an adequate comparison group is examined or with longitudinal assessment, can provide conclusions about causality. Lack of cognitive decline, cognitive improvement, or absence of development of dementia observed in low to moderate drinkers does not mean that these desirable outcomes occurred because of drinking.

Simply focusing on one to a dozen variables as potential moderators of cognitive decline, impairment, or dementia may be inadequate to determine with confidence a direct correlation between current drinking amount by category and cognitive outcome. This includes a consideration of genetic influences that in themselves affect the risk for developing dementia-related disorders. Comorbidities are also common concomitants of drinking. For example, some people may use alcohol to self-medicate against certain psychiatric symptoms, notably depression, anxiety, obsessive-compulsiveness, traumatic stress, learned helplessness, and more. Other comorbidities include infections, such as HIV or hepatitis C, nonalcohol illicit drug use, and misuse of tobacco and cannabis, which is legal in many U.S. states. Aging, sex, race and ethnicity, and socioeconomic status are also leading factors that have been shown to influence cognitive status (Delker et al., 2016; Sullivan et al., 2023).

CHOICE OF OUTCOMES

Outcomes selected for the consideration of alcohol and neurocognitive relations were limited by data available in peer-reviewed publications and the committee's inclusion and exclusion criteria. In addition, results were restricted to moderate alcohol consumption with reference group outcomes in people who reported never or occasional alcohol consumption. Studies

were excluded if the no-alcohol consumption comparison group included former heavy drinkers; an exception was made when the analyses were stratified such that low-to-light consumption could be directly compared with moderate consumption.

Outcomes were of two types: dementia (total dementia and Alzheimer's disease) and cognitive decline. Dementia and Alzheimer's disease were assessed separately because dementia is an umbrella diagnosis that may include Alzheimer's disease. All considered studies were based on objective, longitudinal measurements that could yield decline, which is necessary evidence for determining dementia generically or categorized as Alzheimer's disease based on diagnosis by experts, such as clinical neurologists or other clinician diagnosticians using *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV or DSM-5 criteria or *International Classification of Diseases* (ICD)-9 or -10 criteria for dementia. Determination of dementia could be made from medical charts, nursing home records, or death certificates with the assumption or notation that experienced clinicians made the diagnosis; studies that did not use these criteria were excluded from the analysis.

Cognitive decline was determined with quantitative measures of episodic memory, cognitive screening, or phonemic or semantic word fluency and did not consider dementia as an outcome in longitudinal study. At least two cognitive assessments needed to be made at times separated by several years so a change in cognitive performance could be captured. Too few studies of cognitive decline were available to conduct meta-analyses; rather, findings are based on systematic review with consideration of study quality.

None of the available studies provided adequate evidence to determine causation between drinking and dementia or cognitive outcome. Studies could potentially support conclusions of faster or slower decline associated with moderate alcohol consumption relative to a matched nondrinking group, but absence of association would not necessarily indicate harm or protection from cognitive decline related to moderate alcohol consumption.

BIOLOGICAL PLAUSIBILITY

High alcohol consumption has multiple consequences that may promote or accelerate age-related neurocognitive decline or dementia. A leading speculation is that these disorders feature a chronic inflammatory state that promotes the formation of the amyloid plaques and neurofibrillary tangles associated with neurodegeneration and dementia (Kinney et al., 2018; Sudduth et al., 2013). This inflammation is driven, in part, by the persistent activation of brain microglia that continuously release cytokines that act in a feed-forward loop to further drive inflammation (Pascoal et al., 2021). Alcohol's proinflammatory properties would preclude the resolution of those signals and further promote this cascade (Wang et al.,

2010). High alcohol intakes also disrupt the blood–brain barrier integrity to enhance neuronal damage (Vore and Deak, 2022) and elevate circulating cholesterol to increase cerebrovascular damage (De Oliveira et al., 2000). Finally, excessive alcohol use combined with inadequate nutrition can culminate in the severe cognitive impairment marking the neurodegenerative disorder Wernicke–Korsakoff syndrome, which is caused by depletion of the essential vitamin thiamine (vitamin B1) (Adams and Victor, 1989). Alcohol-related seizures and withdrawal symptoms can also result in cognitive decline, which may not be fully reversible especially following repeated heavy drinking episodes interspersed with alcohol abstinence.

With advancing age, metabolism of alcohol slows with declining activity of acetaldehyde dehydrogenase, extending the time that this toxic form of alcohol lingers in the older person's system. Further, with normal aging, blood flow declines (Brodkey and Dugdale, 2022; Mouches et al., 2022) and bodily water distribution lessens (Lu et al., 2023), each contributing to increasing the concentration of consumed alcohol. These factors may heighten risks of moderate drinking in older age not necessarily associated with younger age. Further compounding these concerns are certain drugs, which may be prescribed with higher prevalence in older people. The effects of moderate drinking in older (i.e., 55 years and older) men and women are newly emerging and indicate negative, synergistic effects on cognitive and psychomotor skills relevant to reaction time, working memory, and driving safety (Lewis et al., 2019).

Conversely, moderate alcohol consumption has been posited to reduce the risk for cognitive disorders. At lower levels of consumption, its milder proinflammatory properties might stimulate microglia and enhance their clearance of amyloid and neurofibrillary depositions (Doens and Fernandez, 2014), in a mechanism called hormesis (Calabrese and Baldwin, 2001). Its cardiovascular effects with respect to elevated high density lipoprotein may help to limit cerebrovascular damage (De Oliveira et al., 2000). Moderate consumption levels have been also associated with reduced risk for type 2 diabetes, hyperlipidemia, and obesity, all of which are independent risk factors for cognitive decline and dementia (Neto et al., 2023; Willette et al., 2015). However, associations of moderate drinking with the Mediterranean diet are confounded by the influences of its higher-quality diet, which itself reduces risk factors for cognitive decline and dementia (Charbit et al., 2024). Similarly, the higher socioeconomic status associated with moderate drinking is also associated with a higher-quality diet, access to health care, and higher education; the latter is associated with a greater cognitive reserve that serves as a protective buffer against cognitive decline (Cheng, 2016). Finally, congeners present in some alcohol-containing beverages, most notably phytochemicals such as quercetin and resveratrol, may have antioxidant properties to attenuate neuronal damage (Grabska-Kobylecka et al., 2023). Whether the content in those beverages is sufficient to achieve biological relevance remains in question.

PRIOR DGA RECOMMENDATIONS

2010

The 2010 Dietary Guidelines for Americans (DGA) Subcommittee on Alcohol investigated the question, "What is the relationship between alcohol intake and cognitive decline with age?" This included a systematic review with narrative synthesis of eight publications dating from 1995 to June 2009, seven primary research studies, plus a meta-analysis of 23 studies; 29 additional publications were excluded. Both heavy/binge drinking, and moderate alcohol consumption were evaluated, and the subcommittee defined moderate alcohol consumption using the same definition used in the current analysis. Their evidence summary concluded that "individuals who consume alcohol moderately have a slower cognitive decline with age," as compared with nonconsumers of alcohol, with a grade of study quality of moderate.

In the meta-analysis that was discussed (Peters et al., 2008), moderate alcohol intake was associated with lower risk for dementia (RR = 0.63, 95%CI [0.53, 0.75]) and Alzheimer's disease (RR = 0.57, 95%CI [0.44, 0.74]) relative to current nonconsumers but was not significantly associated with risk for vascular dementia (RR = 0.82, 95%CI [0.50, 1.35]) or the risk for cognitive decline (RR = 0.89, 95%CI [0.67, 1.17]). The outcomes of studies discussed in the review were inconsistent. For example, some studies reported a negative association between low-to-moderate intake of wine and lower risk of developing dementia but a positive association between low-to-moderate intake of beer and higher risk of developing dementia. The different outcomes for wine and beer raise the possibility that the association was not with alcohol per se, but with congeners in the alcohol beverage or with lifestyle behaviors that are associated with moderate alcoholic beverage consumption. Additional studies found no associations at low-to-moderate intakes. A significant limitation of most studies from this time period is that the nondrinkers reference group often comprised both never-consumers and former alcohol consumers, and the latter group can introduce substantial bias, as decisions to avoid alcohol consumption may reflect compromised health status.

The 2010 DGAC also investigated the question, "What is the relationship between heavy alcohol intake or binge drinking and cognitive decline with age?" This analysis also included an assessment of moderate alcohol consumption. The analysis concluded that "evidence suggests that heavy or binge drinking is detrimental to age-related cognitive decline," with a grade of study quality as limited. With respect to low-to-moderate alcohol consumption, studies in the accompanying systematic review with narrative synthesis found greater, lower, or no associations with cognitive decline. Nonconsumers were again the reference group, and the limitations

discussed above were also relevant for these analyses. Another limitation emphasized in the meta-analysis was the heterogeneity within and across studies that contributes to inconsistency of outcomes.

2015

The 2015 DGAC report did not specifically address a potential relationship between neurocognitive decline and alcohol. It notes that a healthier dietary pattern that is associated with reduced risk for neurocognitive disorders, such as a Mediterranean diet, may also be moderate in alcohol; however, this postulated association was not systematically evaluated.

2020

The 2020 DGAC report contains a chapter focused on alcoholic beverages and health. However, this chapter did not consider questions regarding potential associations between alcohol and neurocognitive health and disease. The 2020 report also examined the relationship between dietary patterns and neurocognitive health. Whereas alcohol was not a specific focus of that systematic analysis, it noted the dietary patterns associated with better neurocognitive health did not consistently include alcoholic beverages, and the protective association was not reduced when alcoholic beverages, notably red wine, were included. Conversely, the protective association of those diets was still present when alcohol consumption was excluded from the analysis.

METHODOLOGICAL CONSIDERATIONS

To understand moderate alcohol consumption and neurocognitive health, the committee sought to define alcohol consumption variables as antecedent or associative factors as they influence or correlate with positive or negative cognitive health outcomes. Given the vast number of potential and known moderating factors influencing alcohol and neurocognitive relations, it was practical to reduce the moderators considered, define alcohol consumption parameters, define how cognitive health is measured, narrow the age range considered, and limit reports to those based on longitudinal assessment.

Despite their power, even longitudinal studies of adults (i.e., people ages 21 years and older) have limitations in that they seldom have prospective assessment initiated before the onset of heavy drinking. Further, they are limited in their usefulness without contemporaneously assessed low-to-no drinking control participants to establish normal cognitive trajectories of change with aging against which trajectories of drinkers at identified levels can be compared.

SYSTEMATIC REVIEW

Approach

An evidence scan was completed to describe the extent of the published literature, searching for prior systematic reviews and primary research studies published between 2010 and 2024, and following the last assessment of this topic in the 2010–2015 DGA. Of the 19,997 peer-reviewed papers that were published between 2010 and 2024 and were identified using the search terms noted in Appendix I, 364 articles were reviewed, and 24 articles met the eligibility criteria and were included in the review (Figure 7-1). Of these 24, all were primary research studies; 23 were prospective cohorts, and one was a retrospective cohort (see Appendix I). As defined by the ROBINS-E[1] tool, one study had low risk of bias, 16 had some concerns, and seven were at high risk of bias (Table 7-1).

Review criteria strictly applied moderate alcohol consumption as defined as ≤1 drink/day for women and ≤2 drinks/day for men, wherein one drink was equivalent to 14 grams of alcohol. The alcohol intakes for studies outside the United States were harmonized to the U.S. DGA criteria and expressed as 14 grams/day (AND, 2024; Appendix I). Most studies adjusted for confounding variables, including age, smoking, diet, physical activity, or comorbidities. The certainty of the evidence of the studies included in the systematic reviews for dementia and Alzheimer's disease (AD) are summarized in Table 7-2.

Results

Dementia

Eight studies were reviewed as part of this systematic review and narrative review of dementia. Six cohort studies examined the associations between moderate alcohol consumption and dementia risk, stratified by lower or higher intakes of moderate alcohol consumption (Handing et al., 2015; Jeon et al., 2023; Koch et al., 2019; Langballe et al., 2015; Sabia et al., 2018; Shimizu et al., 2023). Four of these studies found that intakes at the higher range of moderate alcohol consumption had greater risk for developing dementia. Handling et al. (2015) found that men consuming 0.7–2.1 drinks/day had a hazard ratio (HR) of 1.09 ($p = 0.01$) for developing dementia compared with those consuming >0–0.7 drinks/day. Jeon et al. (2023) evaluated changes in alcohol consumption patterns among adults aged 40 years and older and found that individuals who increased their alcohol

[1] Risk Of Bias In Non-randomized Studies - of Exposures.

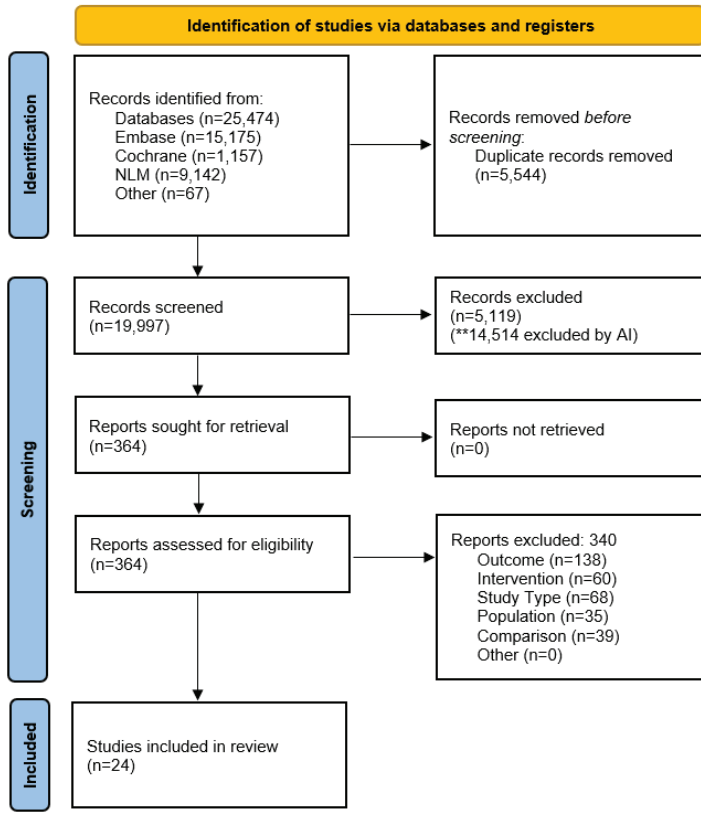

FIGURE 7-1 PRISMA flow chart for the systematic review on the association between alcohol consumption and neurocognitive health.
NOTES: The diagram shows the number of primary articles identified from the primary article and systematic review searches and each step of screening. The literature dates include articles with the publications between 2010 and 2024. n = number; NLM = National Library of Medicine; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
SOURCE: Annex I-3 in Appendix I, Academy of Nutrition and Dietetics, 2024.

consumption to moderate drinking (15–29 grams/day or 1.07–2.07 U.S. drinks/day) compared with those who sustained mild drinking (<15 grams/day or <1.07 U.S. drinks/day) exhibited greater risk of all-cause dementia: HR = 1.09, 95%CI [1.03, 1.15] (Table 7-3). The results endured after stratifying by age, sex, and smoking status. Langballe et al. (2015) evaluated the association between alcohol consumption patterns and risk of dementia in Norwegian adults. Results indicated that individuals who consumed alcohol frequently (≥5 times in last 2 weeks) had higher dementia risk than

TABLE 7-1 Risk of Bias of Included Studies Examining the Relationship Between Alcohol Consumption and Neurocognition

Study	Bias Domains assessed as "some concerns" or "high"	Overall Risk of Bias
Cheng et al., 2023	Confounding, missing data, outcome measurement	High
Garduno et al., 2023	Confounding	Some concerns
Han et al., 2021; Han et al., 2022	Confounding, exposure measurement, missing data	High
Handling et al., 2015	Confounding, exposure measurement, missing data	High
Horvat et al., 2015	Confounding, missing data, outcome measurement	Some concerns
Jeon et al., 2023	Confounding	Some concerns
Kawakami et al., 2023	Confounding, exposure measurement	Some concerns
Koch et al., 2019	Confounding, exposure measurement, selection of participants	Some concerns
Langbelle et al., 2015	Confounding, outcome measurement	Some concerns
Larsson and Wolk, 2018	Exposure measurement	Some concerns
Lee et al., 2022	Confounding, exposure measurement, missing data, outcome measurement, selection of reported results	Some concerns
Love et al., 2020	Missing data, outcome measurement, selection of reported results	High
Nooyens et al., 2014	Selection of participants, missing data, outcome measurement	High
Sabia et al., 2014	Confounding	Some concerns
Sabia et al., 2018	All domains low risk of bias	Low
Salvador et al., 2022	Confounding, exposure measurement	Some concerns
Schaefer et al., 2022	Confounding, exposure measurement, missing data	Some concerns
Shimizu et al., 2023	Confounding	Some concerns
Tian et al., 2022	Confounding, exposure measurement, missing data	Some concerns
Tian et al., 2023	Confounding	Some concerns
Vasiliadis et al., 2019	Confounding, exposure measurement	Some concerns
Zhang et al., 2020	Confounding, exposure measurement, selection of participants, missing data, outcome measurement	Some concerns
Zhou et al., 2014	Confounding, exposure measurement, selection of participants	High

NOTE: Overall risk of bias is based on seven domains: (1) confounding; (2) measurement of the exposure; (3) selection of participants into the study (or into the analysis); (4) post-exposure interventions; (5) missing data; (6) measurement of the outcome; and (7) selection of the reported results.
SOURCE: Adapted from Annex I-6 in Appendix I, Academy of Nutrition and Dietetics, 2024.

TABLE 7-2 GRADE Summary of Findings for Systematic Review on Associations Between Alcohol Consumption and Total Dementia and Alzheimer's Disease

	Certainty Assessment					
Participants (Studies) Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Certainty of Evidence
Dementia Moderate Alcohol Consumption vs. Never Consuming Alcohol—not reported						
NR	NR	NR	NR	NR	NR	NR
Dementia Above Moderate Alcohol Consumption vs. Never Consuming Alcohol						
6,798 (1 nonrandomized study)[e]	serious[a]	not serious	not serious	very serious[c]	none	very[d] low
Dementia Consuming Higher vs. Lower Amounts of Moderate Alcohol Consumption						
9,122 (2 nonrandomized studies)[f]	serious[a]	not serious	not serious	serious[c]	none	low
Dementia Consuming Alcohol Above Moderate vs. Lower Amounts of Moderate Alcohol Consumption						
6,742 (2 nonrandomized studies)[g]	serious[a]	serious[b]	not serious	serious[c]	none	very[d] low
Alzheimer's Disease Moderate Alcohol Consumption vs. Never Consuming						
193,068 (2 nonrandomized studies)[b]	serious[a]	not serious	not serious	serious[c]	none	low
Alzheimer's Disease Above Moderate Alcohol Consumption vs. Never Consuming						
146,288 (2 nonrandomized studies)[b]	serious[a]	not serious	not serious	serious[c]	none	low
Alzheimer's Disease Among Alcohol Consumers						
291,200 (2 nonrandomized studies)[b]	serious[a]	serious[d]	not serious	serious[e]	none	very[d] low

NOTE: NR = not reported.
[a] Some concerns/high risk of bias in most included studies.
[b] High heterogeneity in results between studies.
[c] Wide confidence interval include potential benefits and harms.
[d] The committee used the phrase "insufficient evidence" to reflect a lower level of certainty of the evidence, as indicated by the assignment of "very low" in the commissioned systematic reviews by the Academy of Nutrition and Dietetics.
[e] Kawakami et al., 2023.
[f] Handing et al., 2015; Koch et al., 2019.
[g] Koch et al., 2019; Shimizu et al., 2023.
[b] Larsson and Wolk, 2018; Tian et al., 2023.
SOURCE: Adapted from Table I-2 in Appendix I, Academy of Nutrition and Dietetics, 2024.

TABLE 7-3 Results of Included Studies Examining the Relationship of Drinking Frequency or Patterns of Alcohol Consumption and Risk of Dementia Among Current Drinkers

Study and Drinking Frequency Category	Events/ Total Sample	Reported Data HR (95% CI)
Jeon et al., 2023		
Stopped drinking	6,153/25,3643	1.27 [1.23, 1.32]
Sustained mild drinking (<15 g/d)	6,690/625,723	1.00 [reference]
Increased to moderate drinking (15.0–29.9 g/d)	1,471/130,116	1.09 [1.03, 1.15]
Increased to heavy (≥30 g/d)	767/39,096	1.37 [1.27, 1.47]
Koch et al., 2019		
<1 drink/week	36/274	1.00 [reference]
1–6 drinks/week, 1 drink/d	24/215	0.93 [0.55, 1.57]
1–6 drinks/week, ≥2 drinks/d	14/85	1.54 [0.82, 2.90]
7 drinks/week, 1 drink/d	23/240	0.69 [0.40, 1.19]
7 drinks/week, ≥2 drinks/d	28/255	1.03 [0.61, 1.71]
Langballe et al., 2015		
Occasional (drinking 0× in last 2 weeks, no abstainers)	529/18,900	1.12 [0.95, 1.32]
Drinking 1–4× in last 2 weeks	242/11,182	1.00 [reference]
Drinking ≥5× in last 2 weeks	69/2,400	1.40 [1.07, 1.84]
Sabia et al., 2018		
Long-term abstinence	74/837	1.67 [1.26, 2.23]
Decreased consumption	36/500	1.50 [1.04, 2.16]
Increased consumption	28/1,004	0.85 [0.57, 1.26]
Long-term consumption 1–14 units/week	207/5,304	1.00 [reference]
Long-term consumption >14 units/week	51/1,282	1.36 [0.99, 1.88]
Shimizu et al., 2023		
Long-term abstinence	2,319/18,102	1.61 [1.28, 20.3]
Regular drinking over time, <75 g/week	77/1,381	1.00 [reference]
Regular drinking over time, 75–150 g/week	150/1,973	1.34 [1.02, 1.77]
Regular drinking over time, 150–300 g/week	314/3,782	1.37 [1.06, 1.76]
Regular drinking over time, 300–450 g/week	227/2,938	1.41 [1.08, 1.84]
Regular drinking over time, ≥450 g/week	174/2,142	1.96 [1.49, 2.59]

TABLE 7-3 Continued

Study and Drinking Frequency Category	Events/ Total Sample	Reported Data HR (95% CI)
Zhou et al., 2014		
Occasional drinking	91/765	NR
Monthly drinking	51/491	NR
Weekly drinking	41/402	NR
Daily drinking	174/1,301	NR

NOTES: CI = confidence interval; d = day; g = grams; HR = hazard ratio; NR = not reported.
SOURCE: Table I-4 in Appendix I, American Academy of Nutrition and Dietetics, 2024.

the reference group, which comprised participants who reported drinking alcohol 1–4 times in the last 2 weeks (HR = 1.4, 95%CI [1.07, 1.84]) even after adjusting for age, sex, education, obesity, smoking, and symptoms of depression.

Shimizu et al. (2023) examined alcohol consumption patterns among Japanese adults aged 54–84 years old and found a linear association of weekly regular alcohol consumption with risk for developing dementia. Specifically, regular weekly alcohol consumption of >75–150 grams (5.3–10.7 U.S. drinks/week; (HR = 1.34, 95%CI [1.02, 1.77]) and 150–200 grams (10.7–14.3 U.S. drinks/week; (HR = 1.37, 95%CI [1.06, 1.76]), 300–450 grams (14.3–32.1 U.S. drinks/week; (HR = 1.41, 95%CI [1.08, 1.84]), and ≥450 grams (>32.1 U.S. drinks/week; (HR = 1.96, 95%CI [1.49, 2.59]) were all associated with higher risk for incidence of dementia compared with the reference group who regularly consumed <75 grams alcohol/week (<5.3 U.S. drinks/week). Because their consumption levels were not determined on a per day basis, it is uncertain how these intakes correspond to the DGA recommendations.

By contrast, Sabia et al. (2018) examined alcohol consumption changes from midlife (mean 44.8 years of age) to early old age (mean 61.2 years of age) and its association with dementia risk and found that individuals who maintained long-term abstinence (HR = 1.67, 95%CI [1.26, 2.23]) or decreased their alcohol consumption (HR = 1.50, 95%CI [1.04, 2.16]) had a higher risk of dementia compared to individuals who maintained long-term moderate consumption of 1–14 units/week (0.08–1.14 U.S. drinks/day). The reasons for decreasing alcohol consumption were not provided and could be related to issues related to health or activities of daily living.

Koch et al. (2019) observed a nonsignificant nonlinear relationship (quadratic trend $p = 0.07$) between greater alcohol consumption and higher dementia risk in people who consumed alcohol. Among those without mild cognitive impairment at baseline, the lowest risk was associated with 1.4 U.S. drinks/day.

Zhao et al. (2023) used sensitivity analysis to compare moderate alcohol consumption of 0.09–1.7 U.S. drinks/day to low alcohol consumption <0.09 U.S. drinks/day and found a greater risk of dementia in the moderate drinking group (HR = 1.10, 95%CI [1.02, 1.18]).

Finally, Kawakami et al. (2023) followed people (age 40 to 70 years for 8 years) who never consumed alcohol (reference) and those who drank moderately. Compared with never drinkers, people who drank at moderate levels (1.0–21.2 grams/day, >0–1.5 U.S. drinks/day) had a lower risk of expressing dementia (HR = 0.69, 95%CI [0.49, 0.98]). Given the consumption ranges for the total group of men and women, it is unclear whether the women's consumption was moderate (Table 7-4).

Finding 7-1: Four eligible studies with data from 2010 to 2024 reported that the risk of developing dementia was higher among those consuming higher amounts of moderate alcohol than lower amounts of

TABLE 7-4 Subgroup Analyses for Associations Between Alcohol Amount and Total Dementia Among Adults Consuming Alcohol

	N Studies	RR (95% CI)	I^2 (%)
Main Analysis[a]			
Moderate Alcohol Consumption[b]	2	0.98 [0.92, 1.04]	0
Above Moderate Alcohol Consumption	2	1.18 [0.83, 1.69]	53.4
Sensitivity Analyses with Different Alcohol Intake Categories[a]			
Five Categories (U.S. drinks/day)			
<0.09	–	0	0
0.09–1.7 (0.1–1.7 vs. <0.8 U.S. drinks/day)	3	**1.10 [1.02, 1.18]**[c]	0.01
1.7–3.1 (1.5–3.1 vs. <0.8 U.S. drinks/day)	1	1.01 [0.85, 1.20]	N/A
3.2–4.6 (3.1–4.6 vs. <0.77 U.S. drinks/day)	1	1.13 [0.95, 1.35]	N/A
>4.6 (≥4.6 vs. 0.8 U.S. drinks/day)	1	**1.34 [1.12, 1.60]**	N/A
1 U.S. Drink/Day (Males and Females)			
≤1 drink/day (0.14–1.0 vs. <0.1)	2	0.98 [0.92, 1.04]	0
>1 drink/day (>1.14 vs. <1.14)	4	**1.18 [1.05, 1.34]**	20.2

NOTES: A dash indicates that there were no studies available for this comparison. Results in bold are statistically significant ($p < 0.05$). CI = confidence interval; I^2 = heterogeneity; *N* = number; N/A = not available; RR = relative risk.

[a] Meta-analyses of drinking categories were conducted using separate meta-analyses to avoid over-counting participants in comparison groups.

[b] Moderate alcohol consumption levels are ≤1 drink/day for women and ≤2 drinks/day for men. 1 U.S. drink = 14 grams of alcohol.

[c] Results in bold are statistically significant ($p < 0.05$).

SOURCE: Adapted from Table I-3 in Appendix I, Academy of Nutrition and Dietetics, 2024.

moderate alcohol. One study reported that, when compared with long-term moderate consumers, long-term abstinence or decreasing consumption from midlife to older age was associated with higher risk of dementia. Two studies reported that moderate drinkers had a lower risk of developing dementia than never drinkers, and one study found no association between moderate consumption levels of alcohol and the development of dementia.

Conclusion 7-1: The committee concludes there was insufficient evidence about the association between the risk of dementia for those with no alcohol consumption compared to those with moderate alcohol consumption or for those who consume higher versus lower amounts of moderate alcohol.

Alzheimer's Disease

Three cohort studies reported on associations between moderate alcohol consumption versus never drinking and the development of Alzheimer's disease (AD) (Koch et al., 2019; Larsson and Wolk, 2018; Tian et al., 2023) (Table 7-5). Tian et al. (2023) reviewed death certificates that indicated AD as a contributing cause of death but did not find a significantly greater risk of AD in moderate drinkers than nondrinkers even after stratifying by sex, age, or smoking. One exception was for white women (0.4 to ≤1.0 U.S. drink/day) whose risk of developing AD was lower in moderate drinkers than in nondrinkers (HR = 0.77, 95%CI [0.64, 0.93]). In contrast to the Tian study, Larsson and Wolk (2018) failed to find significant associations between risk for AD and moderate alcohol consumption. Forest plots (Figure 7-2) indicated high heterogeneity in the two studies and the absence of robust risk ratios linking AD with moderate drinking. Koch et al. (2019) assessed cognitive status and risk for AD in older adults using the Alzheimer's Disease Assessment Scale (ADAS). This study found no difference in risk of AD in people who consumed 1–6 drinks/week and no more than 1.0 U.S. drinks/day (HR = 0.95, 95%CI [0.57, 1.58]) or 7 drinks/week at no more than 1.0 U.S. drinks/day (HR = 0.93, 95%CI [0.58, 1.51]), as compared with those consuming <1 drink/week (reference group). However, these confidence intervals are quite wide.

Three additional cohort studies examined the association of alcohol consumption stratified as higher or lower level of moderate alcohol consumption and the risk of developing AD (Jeon et al., 2023, Langballe et al., 2015; Zhou et al., 2014) (Table 7-6). Jeon et al. (2023) evaluated changes in alcohol consumption patterns among adults aged 40 years and older residing in Korea. Results indicated that individuals who increased their alcohol consumption to moderate drinking (15–29 grams/day or

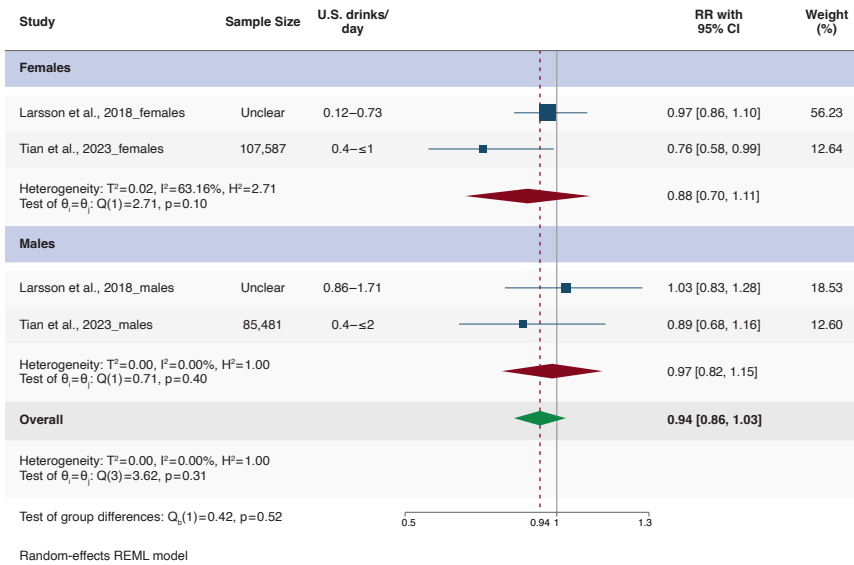

FIGURE 7-2 Associations between moderate alcohol consumption and Alzheimer's disease compared to never consuming alcohol.
NOTES: CI = confidence interval; REML = restricted maximum likelihood; RR = relative risk.
SOURCE: Figure I-4 in Appendix I, American Academy of Nutrition and Dietetics, 2024.

1.07–2.07 U.S. drinks/day; (HR = 1.10, 95%CI [1.03, 1.18]) or heavy drinking (≥30 grams/day or 2.14 U.S. drinks/day; (HR = 1.37, 95%CI [1.25, 1.49]) compared to those who sustained mild drinking (<15 grams/day or <1.07 U.S. drinks/day; reference) over time exhibited higher risk of AD (Table 7-5). Stratified analysis by age, sex, and smoking status were consistent with the above findings.

Langballe et al. (2015) evaluated the association between alcohol consumption patterns and risk of dementia in Norwegian adults enrolled in the HUNT1 cohort. In contrast to individuals who refrained from drinking or drank rarely and did not have a significant AD risk, individuals who consumed alcohol frequently (≥5 times in last 2 weeks) had a significant AD risk (HR = 1.47, 95%CI [1.00, 2.16]) even after adjusting for age, sex, education, obesity, smoking, and symptoms of depression.

Zhou et al. (2014) evaluated the association of alcohol consumption of 0.09–1.7 U.S. drinks/day to never consuming alcohol and risk of AD in China. Men who consumed alcohol daily had a higher risk of developing AD (HR = 2.25, 95%CI [1.43, 3.97]) than those who drank weekly

TABLE 7-5 Subgroup Analyses for Associations Between Alcohol Amount and Alzheimer's Disease Compared to Never Consuming Alcohol

	N Studies	RR (95% CI)	I^2 (%)
Main Analysis[a]			
Moderate Alcohol Consumption[b]	2	0.94 [0.86, 1.03]	0
Above Moderate Alcohol Consumption	2	0.77 [0.56, 1.07]	45.5
Subgroup Analyses[a]			
Moderate Alcohol Consumption			
Males	2	0.97 [0.82, 1.15]	0
Females	2	0.88 [0.70, 1.11]	63.2
Above Moderate Alcohol Consumption			
Males	2	0.82 [0.45, 1.49]	69.7
Females	2	**0.68 [0.47, 0.97]**[c]	0
Moderate Alcohol Consumption			
<60 years	1	0.87 [0.39, 1.94]	N/A
≥60 years	2	0.92 [0.80, 1.07]	54.7
Above Moderate Alcohol Consumption			
<60 years	1	0.14 [0.02, 1.01]	N/A
≥60 years	2	0.83 [0.59, 1.17]	48.4
Sensitivity Analyses with Different Alcohol Consumption Categories[a]			
Five Categories (U.S. drinks/day)			
<0.09	2	0.89 [0.66, 1.20]	90.3
0.09–1.7	2	0.93 [0.80, 1.00]	0
1.7–3.1	1	0.94 [0.74, 1.19]	N/A
3.2–4.6	–	–	–
>4.6	–	–	–
1 U.S. Drink/Day (Males and Females)			
≤1 drink/day	2	0.97 [0.89, 1.06]	0
>1 drink/day	2	1.23 [0.84, 1.80]	82.5

NOTES: A dash indicates that there were no studies available for this comparison. Results in bold are statistically significant ($p < 0.05$). CI = confidence interval; I^2 = heterogeneity; *N* = number; N/A = not available; RR = relative risk.

[a] Meta-analyses of drinking categories were conducted using separate meta-analyses to avoid over-counting participants in comparison groups.

[b] Moderate alcohol levels are ≤1 drink/day for women and ≤2 drinks/day for men. 1 U.S. drink = 14 grams of alcohol.

[c] Results in bold are statistically significant ($p < 0.05$).

SOURCE: Adapted from Table I-5 in Appendix I, Academy of Nutrition and Dietetics, 2024.

(HR = 1.31, 95%CI [0.69, 1.43]), monthly (HR = 1.03, 95%CI [0.83, 1.35]), or occasionally (Table 7-6). However, it is uncertain how these drinking patterns relate to the DGA because consumption per drinking occasion was not presented.

> Finding 7-2: On the basis of six eligible studies with data from 2010 to 2024, the committee found the risk of AD or dementia among those who consumed higher amounts of moderate alcohol versus lower amounts was inconsistent.

TABLE 7-6 Results of Included Studies Examining the Relationship of Drinking Frequency or Patterns of Alcohol Consumption and Alzheimer's Disease Among Current Drinkers

Study and Drinking Frequency Category	Events/Total Sample	Reported Data HR (95% CI)
Jeon et al., 2023		
Stopped drinking	NR	1.26 [1.20, 1.31]
Sustained mild drinking (<15 g/d)	NR	1.00 [reference]
Increased to moderate drinking (15–29.9 g/d)	NR	1.1 [1.03, 1.18]
Increased to heavy (≥30 g/d)	NR	1.37 [1.25, 1.49]
Koch et al., 2019		
<1 drink/week	38/NR	1.00 [reference]
1–6 drinks/week, 1 drink/day	26/NR	0.95 [0.57, 1.58]
1–6 drinks/week, ≥2 drinks/day	12/NR	1.04 [0.53, 2.02]
7 drinks/week, 1 drink/day	33/NR	0.93 [0.58, 1.51]
7 drinks/week, ≥2 drinks/day	29/NR	1.02 [0.62, 1.69]
Langballe et al., 2015		
Occasional (drinking 0× in last 2 weeks, no abstainers)	NR	1.2 [0.96, 1.51]
Drinking 1–4× in last 2 weeks	NR	1.00 [reference]
Drinking ≥5× in last 2 weeks	NR	1.47 [1.00, 2.16]
Zhou et al., 2014 (all men)		
Occasional drinking	38/765	1.00 [reference]
Monthly drinking	25/491	1.03 [0.83, 1.35]
Weekly drinking	18/402	1.31 [0.69, 1.43]
Daily drinking	91/1,301	2.25 [1.43, 3.97]

NOTES: CI = confidence interval; d = day; g = grams; HR = hazard ratio; NR = not reported.
SOURCE: Adapted from Table I-6 in Appendix I, American Academy of Nutrition and Dietetics, 2024.

Conclusion 7-2: The committee concludes there was insufficient evidence regarding the association between amounts of moderate alcohol consumption and the risk of developing Alzheimer's disease.

Cognitive Decline

Heterogeneity among comparison groups and lack of reported data necessary for pooled analysis precluded conducting meta-analysis for this systematic review of the outcomes on immediate and delayed word recall, verbal frequency, Mini-Mental State Examination (MMSE), or other tests of general cognitive ability. Consequently, the results are reported in tables with a narrative synthesis. Quality of studies are presented in figures, tables, and text. Many were listed as having risk of bias and low certainty of evidence (Table 7-7, Table 7-8, and Table 7-9). Unless noted, the 95% CIs for the HRs or relative risk ratios were wide and crossed below and above 1.0.

Two cohort studies (Sabia et al., 2014 and Tian et al., 2022) reported on immediate recall of words. Neither study found robust performance differences between individuals who regularly consumed alcohol within or just above moderate alcohol consumption and those who were never or occasional drinkers (Table 7-6). Sabia et al. (2014) and Horvat et al. (2015) tested differences between people who drank moderately and those who drank infrequently and at lower levels (Table 7-7). Here, the CIs were too wide to draw conclusions about group differences in recall by drinking levels. The Horvat et al. (2015) study also examined frequency of drinking moderately and found that women, but not men, who drank 1–3 times/month showed improved immediate word recall not exhibited by women who drank less than once per month (HR = 0.08, 95%CI [0.03, 0.12]).

Of the two cohort studies reporting on delayed word recall, Love et al. (2020) found no significant differences in performance between people who drank and those who did not, whereas Tian et al. (2022) found that people who drank moderately had lower scores than those who did not drink (β = –0.04, 95%CI [–0.08, –0.01]). These studies had risk of bias, not having stratified for age, smoking, or race/ethnicity. Separate analysis by sex at birth in Horvat et al. (2015) failed to reveal associations between alcohol consumption levels and delayed word recall. Lack of association was also apparent in comparisons between low and moderate drinkers.

Combining immediate and delayed recall performance did not strengthen potential relations between memory scores and drinking levels in the studies by Cheng et al. (2023) and Garduno et al. (2023). By contrast, Zhang et al. (2020) found that people drinking moderately (<1.14 drinks/day women and <2.14 drinks/day men) achieved lower recall scores than their nondrinking counterparts (OR = 0.74, 95%CI [0.69, 0.80]).

TABLE 7-7 GRADE Evidence Profile Describing Relationship Between Amount of Alcohol Intake and Memory

	Certainty Assessment					
Participants (Studies)	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Overall Certainty of Evidence**
Immediate Word Recall (Alcohol Consumers vs. Never Consumers)						
21,980 (2 studies)[f]	serious[a]	serious[b]	not serious	serious[c]	none	very[e] low
Immediate Word Recall (Among Alcohol Consumers)						
16,774 (2 studies)[g]	serious[a]	serious[b]	not serious	serious[c]	none	very[e] low
Delayed Word Recall (Alcohol Consumers vs. Never Consumers)						
7,917 (2 studies)[h]	very serious[d]	serious[b]	not serious	serious[c]	none	very[e] low
Delayed Word Recall (Among Alcohol Consumers)						
6,608 (1 study)[i]	serious[a]	not serious	not serious	serious[b]	none	low
Combined Immediate and Delayed Word Recall (Alcohol Consumers vs. Never Consumers)						
24,275 (3 studies)[j]	very serious[d]	not serious	not serious	serious[b]	none	very[e] low
Combined Immediate and Delayed Word Recall (Among Alcohol Consumers)						
165,919 (2 studies)[k]	very serious[a]	not serious	not serious	serious	none	low

[a] Some concerns.
[b] Inconsistent results between studies.
[c] Lack of pooled results.
[d] High risk of bias.
[e] The committee used the phrase "insufficient evidence" to reflect a lower level of certainty of the evidence, as indicated by the assignment of "very low" in the commissioned systematic reviews by Academy of Nutrition and Dietetics.
[f] Sabia et al., 2014; Tian et al., 2022.
[g] Horvat et al., 2015; Sabia et al., 2014.
[h] Love et al., 2020; Tian et al., 2022.
[i] Horvat et al., 2015.
[j] Cheng et al., 2023; Garduno et al., 2023; Zhang et al., 2020.
[k] Garduno et al., 2023; Nooyens et al., 2014.
SOURCE: Adapted from Table I-13 in Appendix I, Academy of Nutrition and Dietetics, 2024.

TABLE 7-8 GRADE Evidence Profile Describing Relationship Between Amount of Alcohol Intake and Verbal Fluency

	Certainty Assessment					
Participants (Studies)	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Overall Certainty of Evidence**
Verbal Fluency (Alcohol Consumers vs. Never Consumers)						
17,059 (3 studies)[e]	very serious[a]	serious[b]	not serious	serious[c]	none	very[d] low
Verbal Fluency (Among Alcohol Consumers)						
16,774 (3 studies)[f]	serious[a]	serious[b]	not serious	serious[c]	none	very[d] low

[a] Some concerns for risk of bias.
[b] Inconsistency in results.
[c] Lack of pooled results.
[d] The committee used the phrase "insufficient evidence" to reflect a lower level of certainty of the evidence, as indicated by the assignment of "very low" in the commissioned systematic reviews by Academy of Nutrition and Dietetics.
[e] Cheng et al., 2023; Garduno et al., 2023; Han and Jia, 2021.
[f] Garduno et al., 2023; Han and Jia, 2021, 2022.
SOURCE: Adapted from Table I-16 in Appendix I, Academy of Nutrition and Dietetics, 2024.

TABLE 7-9 GRADE Evidence Profile Describing Relationship Between Amount of Alcohol Intake and Mini-Mental State Examination (MMSE)

	Certainty Assessment					
Participants (Studies)	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Overall Certainty of Evidence**
Verbal Fluency (Alcohol Consumers vs. Never Consumers)						
5,367 (3 studies)[f]	very serious[a]	not serious	not serious	serious[b]	none	very[e] low
Verbal Fluency (Among Alcohol Consumers)						
4,102 (3 studies)[g]	serious[c]	serious[d]	not serious	serious[b]	none	low

[a] High risk of bias.
[b] Lack of pooled results.
[c] Some concerns.
[d] Inconsistency in results.
[e] The committee used the phrase "insufficient evidence" to reflect a lower level of certainty of the evidence, as indicated by the assignment of "very low" in the commissioned systematic reviews by Academy of Nutrition and Dietetics.
[f] Han and Jia, 2022; Lee et al., 2023; Salvador et al., 2022.
[g] Garduno et al., 2023; Han and Jia, 2021, 2022.
SOURCE: Adapted from Table I-19 in Appendix I, Academy of Nutrition and Dietetics, 2024.

Additional domains of cognitive decline beyond recall were also available to assess the association with moderate alcohol consumption. Absence of alcohol level and word fluency testing was not forthcoming in the four alcohol group comparisons (Garduno et al., 2023; Horvat et al., 2015; Love et al., 2020; Salvador et al., 2022). Three studies (Koch et al., 2019; Salvador et al., 2022; Vasiliadis et al., 2019) reported on the MMSE. None found significant associations between moderate alcohol consumption and MMSE performance.

Systematic review provided no consistent association between moderate drinking and cognitive decline in scores on episodic immediate or delayed memory tests, a test of general cognitive functioning (i.e., MMSE), or word fluency tests. With few exceptions, the findings held whether moderate drinkers were compared with no or occasional drinkers or with regular low drinkers. In general, the effect sizes were small, the confidence intervals were wide, and the quality of evidence was low.

Finding 7-3: On the basis of nine eligible studies with data from 2010 to 2024, there was insufficient evidence to support an association between moderate versus never drinking or occasional drinking and the risk of cognitive decline. There were concerns with the studies related to differences in measurement instruments, differences in comparator groups, and imprecise results.

Conclusion 7-3: The committee determined that there was insufficient evidence to draw an association between moderate alcohol consumption versus never or occasional consumption and the risk of cognitive decline.

Summary of Evidence Relative to Past DGA Guidance

Based on the results of the *de novo* systematic review using data from 2010 to 2024, the committee concludes there is insufficient evidence to evaluate the association of moderate alcohol consumption compared to never consuming alcohol for the outcomes of dementia, AD, and cognitive decline. Thus, there are no findings to compare with the 2010 DGAC report, which was the only past report to directly consider the association of moderate alcohol consumption and neurocognition.

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8

Maternal Alcohol Consumption During Lactation

This chapter discusses the last three of the eight questions in the Statement of Task (Box 8-1).

BACKGROUND

Breastfeeding and/or the feeding of human milk is the gold standard for infant nutrition for almost all healthy infants, and most expert groups recommend exclusive breastfeeding through age six months and continued breastfeeding along with appropriate complementary foods as long as mutually desired by mother and child (AAFP, 2024; ACOG, 2018; Critch et al., 2014; HHS and ODPHP, 2024; Meek and Noble, 2022; WHO and UNICEF, 2003). These recommendations reflect benefits to both maternal and infant health. Human milk provides all essential and conditionally essential nutrients in amounts adequate to meet an infant's needs. It also provides a complex array of biologically active components, maternal cells, and microbes that contribute enzymatic, hormonal, and immunomodulatory functions to the developing infant (Smilowitz et al., 2023). Although the underlying mechanisms remain unclear, exclusive breastfeeding is associated with some protection against selected illnesses such as inflammatory bowel disease, diabetes, asthma, and obesity (as reviewed by Meek and Noble, 2022). Having been breastfed may also affect neurodevelopmental outcomes such as intelligence (Horta et al., 2015; Victora et al., 2015) and risks of attention-deficit and hyperactivity disorder (Tseng et al., 2019a) and autism spectrum disorder (ASD; Tseng et al., 2019b).

BOX 8-1
Lacation Questions from the Statement of Task

6. What is the relationship between alcohol consumption during lactation and postpartum weight loss?
7. What is the relationship between alcohol consumption during lactation and human milk composition and quantity?
8. What is the relationship between alcohol consumption during lactation and infant developmental milestones, including neurocognitive development?

Breastfeeding is also associated with positive maternal outcomes, though study findings are less consistent than those for infants. Although some studies report a positive association between breastfeeding and postpartum weight loss, this relationship is complicated by the duration of breastfeeding, maternal age, maternal body mass index (BMI), and parity (Feltner et al., 2018; Jiang et al., 2018). Perhaps the most consistent evidence relates to breast cancer, such that people who have lactated have decreased risk of breast cancer compared to those who have not, and this association is even stronger with exclusive breastfeeding and longer breastfeeding durations (Chowdhury et al., 2015; Feltner et al., 2018; Unar-Munguía et al., 2017).

Breastfeeding may be contraindicated under some conditions, such as certain viral or microbial infections, when there is a risk for potentially harmful agents entering human milk (Meek and Noble, 2022). Illicit drugs such as opioids and cocaine can also pass into milk and might negatively affect infant neurodevelopment (Meek and Noble, 2022). With respect to cannabis and alcohol, which are legal in some or all U.S. states, respectively, and although their bioactive components (tetrahydrocannabinol/THC and ethanol, respectively) enter milk after maternal use, their putative effects on lactation, milk composition, and infant outcomes are understudied, and research results have been inconsistent (Castro-Navarro et al., 2024; Haastrup et al., 2014; Metz and Borgelt, 2018). Nonetheless, use of alcohol and cannabis products during breastfeeding is generally discouraged.

BIOLOGICAL PLAUSIBILITY

It is plausible that maternal alcohol consumption during lactation might be associated with changes in postpartum weight gain or loss, milk quality (composition) and quantity, and infant developmental milestones. With respect to postpartum weight change, alcohol has a high metabolizable

energy content (7 kilocalorie/gram), and thus its consumption might reduce weight loss by promoting neutral or positive energy balance. This is because ethanol can be metabolized directly for energy or converted into fatty acids and stored in adipose tissue when energy needs are met by other nutrients (Wilson and Matschinsky, 2020). Postpartum weight retention predicts obesity later in life, future cardiometabolic risk, and prepregnancy obesity in subsequent pregnancies (McKinley et al., 2018; Rooney and Schauberger, 2002; Sundaram et al., 2014). These outcomes are particularly important given current estimates from 2015 to 2018 that nearly 70 percent of U.S. women 20 years and older are overweight or obese (CDC, 2019). An established literature shows that consumed alcohol quickly distributes throughout the body, including the mammary gland. There is consistent and strong evidence that maternal alcohol consumption equivalent to 0.5–2.0 U.S. drinks/day during lactation leads to ethanol concentrations in milk that are essentially equivalent to those in the blood (Kesäniemi 1974; Lawton, 1985). The rapid appearance of ethanol in milk following maternal alcohol consumption during breastfeeding has been well established (Argote-Espinosa et al., 1992; Backstrand et al., 2004; Chien et al., 2005, 2009; da-Silva et al., 1993; Flores-Huerta et al., 1992; Kesäniemi, 1974; Lawton, 1985; Mennella, 1997; Mennella and Beauchamp, 1991, 1993). Alcohol concentrations in human milk peak at 30 to 90 minutes after alcohol consumption (as reviewed by Hutchinson et al., 2021).

Maternal alcohol consumption might also affect content of other milk constituents and/or milk production via myriad mechanisms that affect milk synthesis and letdown, including systemic (e.g., hormonal) and local (e.g., gene expression within the epithelial cell; metabolite availability) factors (Heil and Subramanian, 1998; Probyn et al., 2013; Vilaró et al., 1987). Maternal alcohol consumption may influence the presence of olfactory and other sensory molecules in human milk (Lan et al., 2021; Spahn et al., 2019), and those characteristics may negatively affect infant feeding behavior (Mennella and Beauchamp, 1991, 1993), which in turn might affect infant milk demand and thus maternal milk output (Mennella, 1997, 1999).

It is also biologically plausible that maternal alcohol consumption during lactation might affect infant development because the brain continues its exponential development during this time with substantial changes in synaptic formation and pruning along with circuitry consolidation as sensory, motor, recognition, and language skills develop. There are some differences between infant and adult brain function (e.g., the excitatory/inhibitory circuitry switch), but at the biochemical level, alcohol would be expected to interact with its protein targets and redirect their activity similarly across the lifespan, including during infancy. In other words, there is no reason to believe that infants respond differently than adults to alcohol's effects on the central nervous system and other organ systems. In fact, the

effects in infants may be magnified and more long-lasting precisely because those processes are developing and are therefore malleable.

Although it has been suggested that infant exposure may constitute "less than 2 percent of the alcohol consumed" by the mother (Hutchinson et al., 2021), mechanistic relevance is the actual alcohol concentration in the infant's circulation, as this drives the strength of alcohol's protein interactions and thus its biological impact. Additionally, the neonatal liver poorly catabolizes alcohol compared with that of adults (Pikkarainen and Räihä, 1967). As such, alcohol's effect on an infant may persist longer than an equivalent adult exposure. Finally, it should also be considered that alcohol consumption during the pre-conceptual period by both females and males may have detrimental effects across the perinatal period and beyond.

PRIOR DGA RECOMMENDATIONS

2010

The 2010 Dietary Guidelines Advisory Committee (DGAC) was the last to conduct a systematic review on the topic of breastfeeding and lactation (DGAC, 2010). The committee concluded:

> Moderate, consistent evidence shows that when a lactating mother consumes alcohol, alcohol enters the breast milk and the quantity of milk produced is reduced, leading to reduced milk consumption by the infant. Although limited, evidence suggests that alcohol consumption during lactation is associated with altered postnatal growth, sleep patterns, and/or psychomotor patterns of the offspring.

In response, the 2010–2015 DGA stated:

> Because of the substantial evidence clearly demonstrating the health benefits of breastfeeding, occasionally consuming an alcoholic drink does not warrant stopping breastfeeding. However, breastfeeding women should be very cautious about drinking alcohol, if they choose to drink at all. If the infant's breastfeeding behavior is well established, consistent, and predictable (no earlier than at 3 months of age), a mother may consume a single alcoholic drink if she then waits at least 4 hours before breastfeeding. Alternatively, she may express breast milk before consuming the drink and feed the expressed milk to her infant later. (USDA and HHS, 2010)

2015

The 2015 DGAC indirectly considered the association between alcohol consumption during breastfeeding and maternal and infant health in its review of evidence for a relationship between "dietary patterns, foods and

nutrients, and health outcomes" (DGAC, 2015). The committee's conclusion was the same as that of the 2010 DGAC. The 2015–2020 DGA stated: "Women who are breastfeeding should consult with their healthcare provider regarding alcohol consumption" (USDA and HHS, 2015).

2020

The 2020 DGAC did not review evidence regarding alcoholic beverage consumption by people who are lactating (DGAC, 2020). The 2020–2025 DGA stated:

> Not drinking alcohol also is the safest option for women who are lactating. Generally, moderate consumption of alcoholic beverages by a woman who is lactating (up to one standard drink in a day) is not known to be harmful to the infant, especially if the woman waits at least two hours after a single drink before nursing or expressing breast milk. (USDA and HHS, 2020)

REVIEW

Approach

The committee initially conducted an evidence scan as detailed in Chapter 2. This initial scan spanned January 1, 2019, to September 23, 2023, and only two papers were identified (Gibson and Porter, 2020a,b). Because there had not been a systematic literature search by any DGAC on breastfeeding and alcohol since 2010, the committee then conducted the same systematic search to identify all eligible papers published between January 1, 2010, and April 18, 2024. All search terms are provided in Appendix J. A total of 5,731 publications were initially identified (see Figure 8-1 for the PRISMA framework). Of these, 1,014 publications were removed prior to screening: 971 were found to be duplicates, and there were 43 supplemental records.

Of the 4,717 publications remaining, 4,700 were excluded: 70 by single review and 4,630 by dual review. Reasons for exclusion included being duplicates (n = 70), intervention studies not associated with alcohol (n = 858), having outcomes that were not applicable (n = 562), wrong population (n = 646), or study types that did not match the include/exclusion criteria (n = 126). An additional 2,438 studies were excluded for other reasons. The remaining 17 publications were retrieved for assessment; of these, one was excluded because it was an intervention not related to alcohol, three were excluded due to inappropriate study type, and one was excluded for other reasons. This resulted in a total of 12 publications being identified. Following removal of six papers published prior to 2010, the collection of eligible studies for review included the two identified in the initial evidence scan combined (Gibson and Porter, 2020a,b) with the four

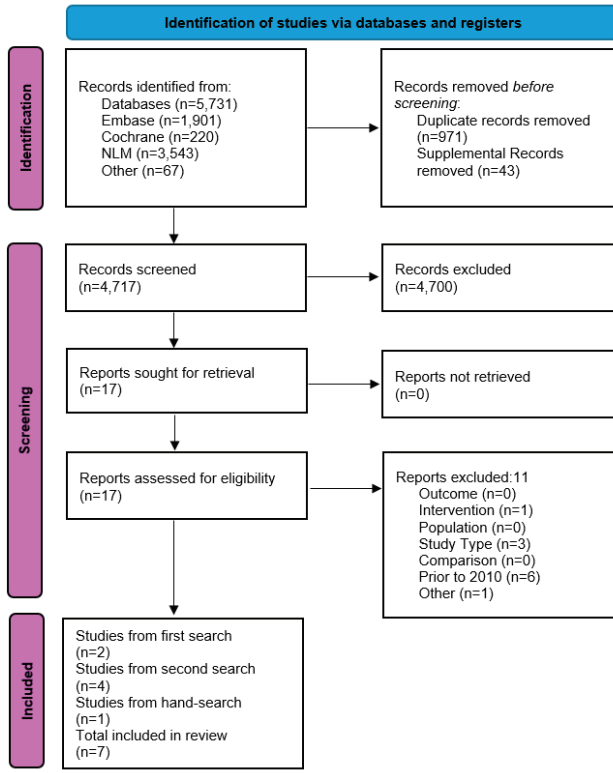

FIGURE 8-1 PRISMA flow chart for the systematic review on the association between alcohol consumption and maternal alcohol consumption during lactation. NOTES: The diagram shows the number of primary articles identified from the two primary article searches and each step of screening. The literature dates include articles with the publications between 2010 and 2024. n = number; NLM = National Library of Medicine; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

additional publications identified in the second systematic search (Gibson and Porter, 2018; Mennella and Pepino, 2010a; Schneider et al., 2013; Wilson et al., 2017).

Upon careful review of these papers and several recent reviews on the topic, committee members determined that the search strategy may not have identified all eligible studies and began handsearching the literature for additional pertinent studies. These included reviews of the references cited in the previously retrieved studies and several recent reviews on the topic. PubMed was also searched for papers that referenced all these studies. This

process identified one additional paper (Mennella and Pepino, 2010b). In sum, the committee identified a total of seven studies published since 2010 (two from the initial scan, four from the second systematic search, and one from handsearching) that could be used to address the three questions posed in the Statement of Task.

Because the systematic searches identified so few relevant studies, the committee concluded that there were insufficient publications to warrant meta-analyses (including grading of evidence) for any of the questions posed in the Statement of Task, particularly publications evaluating the impact of chronic, moderate maternal alcohol consumption. All the identified studies related to milk composition and milk production were small-scale intervention studies evaluating the effects of acute alcohol consumption—though sometimes at levels above what is considered to be "moderate consumption" (one drink/day). Because of the relative dearth of data published since 2010, it was determined that all seven studies should be included in this chapter and not just those focused on moderate alcohol consumption. Consequently, this chapter is a systematic review with narrative synthesis of the studies identified from the literature searches for each health outcome.

Results

Lactation and Postpartum Weight Loss

No studies published since 2010 addressed the question of maternal alcohol consumption during breastfeeding and postpartum weight loss. Thus, the committee was unable to evaluate this association.

Lactation and Human Milk Composition and Quantity

The committee did not identify any reports since 2010 that provided information on potential changes to milk components other than ethanol after maternal alcohol consumption, although one publication found that when people who are breastfeeding consume small amounts of alcohol, ethanol appears in the milk they produce (Schneider et al., 2013). These researchers investigated the effect of nonalcoholic beer on the ethanol concentration of human milk. Nonalcoholic beverages are of interest because some people who are lactating consume them to avoid alcohol consumption. However, nonalcoholic beverages may still contain small amounts (~0.5–1.2 percent volume) of ethanol. The researchers enrolled 15 breastfeeding women who abstained from alcohol consumption for at least five days and then consumed 1.5 liters of nonalcoholic beer containing 0.42 percent ethanol within a period

of one hour. Complete breast expressions were obtained prior to drinking the nonalcoholic beer (left breast only), from both breasts immediately following beer consumption, and again one and three hours later. Only two of the 105 milk samples collected immediately after beverage consumption had detectable ethanol concentrations, and only one of these had a quantifiable concentration (0.21 milligram/deciliter).

Closely related to the effect of maternal alcohol consumption on milk *composition* is the impact on milk *quantity*, which includes milk synthesis, output, and infant milk consumption. These outcomes are distinct and difficult to assess, and thus researchers often rely on proxy measurements (e.g., breastfeeding patterns or duration) and/or circulating levels or effects of lactation-related hormones (e.g., prolactin, oxytocin). The committee identified two papers relevant to this question (Mennella and Pepino, 2010a,b). Mennella and Pepino (2010a) studied 28 exclusively breastfeeding women, seven of whom had a family history of alcoholism; none had alcohol dependence or practiced lifetime alcohol abstinence. Women were randomized to consume 0.4 gram/kilogram body weight of alcohol in orange juice or an equal volume of orange juice in two sessions one week apart. Thirty-five minutes thereafter, the women expressed milk using an electronic pump, and this was reported as "milk yield." Blood prolactin concentrations were analyzed ~10 minutes before and multiple times after beverage consumption. Participants also recorded how often and at what times of day they nursed their infants. Alcohol consumption magnified the prolactin response to breast pumping regardless of family history of alcoholism. However, compared to those without such a history, women with a family history of alcoholism had a blunted circulating prolactin response to milk expression after consuming both the control and alcohol-containing beverages. There were no associations of family history group or alcohol consumption with amount of milk pumped. Women with family histories of alcoholism reported nursing their infants more frequently than those who did not—particularly in the late afternoon and early morning. Using this same alcohol consumption model, these investigators (Mennella and Pepino, 2010b) also examined the effect of milk expression using a breast pump on ethanol pharmacokinetics and reported that pumping before maternal alcohol consumption reduced breath alcohol concentrations, and pumping after alcohol consumption altered the time curve of breath alcohol concentrations. The data suggest that the act of breastfeeding (or expressing milk) may affect alcohol pharmacokinetics.

Finding 8-1: There was insufficient evidence to determine any association between maternal alcohol consumption at any level during lactation and milk composition or milk production.

Conclusion 8-1: The committee determined that no conclusion could be drawn regarding any associations between maternal alcohol consumption during lactation and milk composition or milk production.

Infant Development

At sufficient levels, alcohol can damage the developing brain through multiple mechanisms including alterations in axonogenesis, synaptogenesis, neuronal expansion and survival, myelination, and neuroinflammation. These changes redirect the brain's developmental trajectory and cause permanent deficits in multiple behavioral and cognitive domains. However, it is unknown whether quantities of alcohol in human milk can reach a threshold to alter infant brain development. Determining the answer is challenging because the dosage for that threshold is unknown for humans and is likely individualized due to variation in genetics, nutritional status, and external socioeconomic factors. Another challenge is that many people (13.5 percent, Gosdin et al., 2022) consume alcohol during pregnancy as well as during lactation, and it is difficult to disentangle the consequences of prenatal versus lactational alcohol exposure.

The committee identified one study (Wilson et al., 2017) that assessed the effect of maternal alcohol consumption during breastfeeding on infant sleep, which is critical for brain development and represents a time of active synaptogenesis and pruning to create and stabilize neurocircuitries. In a longitudinal survey of Australian women (Wilson et al., 2017), self-reported alcohol use during lactation was not associated with differences in maternally reported measures of infant sleep, including frequency or duration.

Four studies were identified that addressed the association between maternal alcohol consumption during lactation and offspring cognition and behavior (Gibson and Porter, 2018, 2020a,b; Wilson et al., 2017). Wilson et al. (2017) also assessed child development at eight weeks and 12 months of age using a parental report tool, the Ages and Stages Questionnaire (ASQ-3), and the ASQ Social-Emotional. Compared to children born to mothers who abstained, the investigators found no associations between maternal alcohol use during lactation and infant outcomes at eight weeks of age, including gross and fine motor skills, problem solving, personal-social interactions, and communication skills. At 12 months of age, there was an association only with personal-social interactions and these scores were improved in the abstainers(OR_{adj} = 2.43, 95%CI [1.43, 4.13]; p = 0.001).

Gibson and Porter (2018) assessed cognitive measures at six to seven years of age in an Australian cohort (Longitudinal Study of Australian Children) recruited during infancy. Maternal alcohol consumption in the year prior to recruitment was assessed using the Alcohol Use Disorders Identification

Test-Concise (AUDIT-C) tool. Although an association was found between maternal AUDIT-C scores and nonverbal reasoning at six to seven years of age for children whose mothers had never breastfed, this association did not hold up at age 10 years nor was it found for children whose mothers reported alcohol consumption at the time of first assessment during lactation. There were no associations with vocabulary or early literacy and numeracy. Moreover, the study design did not distinguish between maternal alcohol consumption during pregnancy versus during lactation. In contrast, a follow-up study (Gibson and Porter, 2020a) of this cohort found no association between maternal alcohol consumption and measures of physical, emotional, and social functioning at 6 to 7 years or 10 to 11 years of age, as assessed using the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales.

An additional follow-up study (Gibson and Porter 2020b) evaluated academic performance during school in third and fifth grades. No associations were found between maternal alcohol consumption and academic outcomes. Nonetheless, for mothers who had breastfed at any time, their AUDIT-C scores were negatively associated with the offsprings' scores with respect to third grade writing ($\beta = -1.56$, 95%CI [–2.52, –0.60]; $p_{adj} = 0.01$), spelling ($\beta = -2.06$, 95%CI [–3.31, –0.81]; $p_{adj} < 0.0001$), and grammar/punctuation ($\beta = -2.11$, 95%CI [–3.59, –0.64]; $p_{adj} = 0.01$), and spelling in fifth grade ($\beta = -1.58$, 95%CI [–2.74, –0.43]; $p_{adj} = 0.03$). The authors concluded that these reductions in scores were likely attributed to maternal alcohol consumption during breastfeeding, as associations were not observed when considering number of drinking days per pregnancy trimester nor were associations observed in children who were never breastfed. A limitation of these studies is that the infants were recruited from birth to one year, and the AUDIT-C tool assesses alcohol consumption in the entire past year. In addition, Gibson and Porter (2020b) relied on retrospective recall. Thus, the infant's alcohol exposure during pregnancy and lactation was not differentiated.

One study found no association between alcohol use during lactation and infant sleep as assessed using maternal report. Several observational studies found inconsistent findings on the association between maternal alcohol consumption during lactation and infant and child developmental milestones.

Finding 8-2: There was insufficient evidence to determine an association between maternal alcohol consumption at any level during lactation and infant development.

Conclusion 8-2: The committee determined that no conclusion could be drawn regarding the association between maternal alcohol consumption during lactation and infant development.

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9

Future Directions

As the committee discussed its approach to the Statement of Task, it deliberated on and outlined its methodology, reviewed papers and obtained additional support for the systematic reviews of current literature. In the course of drafting and finalizing its findings and conclusions the committee identified additional methodological considerations as well as a consistent set of research issues that could strengthen the existing evidence on moderate alcohol consumption and health outcomes. This culminated in development of a list of specific research gaps for consideration for future studies looking at the questions in the Statement of Task. These future directions are discussed below.

METHODOLOGICAL CONSIDERATIONS

Exposure Measurement

A common challenge for studies examining the effects of alcohol on health is a lack of standard definitions of alcohol consumption levels and a lack of standardized limits for exposure categories. As discussed in Chapter 1, not all studies define exposure subgroups with reference to the U.S. *Dietary Guidelines for Americans* (DGA). Additionally, within the boundaries of moderate alcohol consumption there is a paucity of data on how variations in the volume, beverage type, frequency, and pattern of moderate alcohol consumption (i.e., low versus higher moderate intake) affect the associations of moderate alcohol consumption with health outcomes.

Standard Drink Sizes

In the United States, the Centers for Disease Control and Prevention (CDC) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) define a standard drink as containing 14 grams, 19 mL, or 0.6 ounce (oz) of ethanol (CDC, 2024; NIAAA, n.d.). Fourteen grams is the approximate ethanol content of 12 oz of beer, 5 oz of wine, and 1.5 oz of spirits. Some U.S.-based researchers use 14 grams as the definition of a "standard drink" (CDC, 2024; NIAAA, n.d.). Uniformity is further complicated by the fact that the definition of standard drink size varies by country and ranges from, for example, 8 grams in Korea to 10 grams in the United Kingdom to 8 grams in Sweden. When investigators use different definitions (e.g., 14 grams versus 10 grams), alcohol intake quantification must be adjusted accordingly to facilitate comparisons. The variation in the definition of a standard drink also complicates the categorization of moderate drinking that make evidence synthesis efforts more difficult.

Type of Alcoholic Beverage

Alcohol beverage type is typically divided into predominantly wine, predominantly beer, or predominantly spirits. Some individuals will consume only one beverage type while others consume multiple types of beverages and will thus be categorized into a mixed beverage group. If the health effects of alcohol (ethanol) are due solely to alcohol, comparable quantity, frequency, and pattern of intake should provide similar health effects across those beverage types; however, there are certainly opinions regarding differential benefits associated with specific types. This additional detail of exposure measurement could add important specificity to determining the health effects of moderate drinking.

Drinking Pattern

Drinking pattern refers to the number and timing of occasions where alcohol is consumed per week and may include further details, such as whether the alcohol is consumed with food. While research practice is less defined for this concept, a preferred approach for assessing the number of occasions where alcohol is consumed is to categorize consumption as frequent (e.g., ≥3 times per week) or infrequent (e.g., 1–2 times per week). In both cases, the amount of alcohol consumed must be within the limits of "low risk drinking," that is, no more than two drinks per day and 14 drinks per week for men, and half the maximum for women. With a large enough sample, it is possible to examine the interrelations of average total intake and drinking pattern. Given the pharmacologic properties of alcohol, it would be unlikely that consumption of one drink each day for one week

(average 1 drink/day) has the same health effect as seven drinks on a single night (average 1 drink/day). To improve the specificity of evidence on the health effects, future metrics for research on alcohol consumption should include these intake patterns to better evaluate health effects.

Intake Reporting

An underlying issue for assessing any alcohol intake data is that the reported amounts and patterns of intake are derived from self-reported questionnaire-based data. In longitudinal studies, the reproducibility of self-report data appears to be good, but the validity of the data is uncertain (Ravelli and Schoeller, 2020). In populations with alcohol use disorder (AUD), self-reported alcohol consumption data are inconsistent with data based on alcohol biomarkers, and the former under-reports consumption by 5.5 percent to 56.0 percent (Nielsen et al., 2021). Some studies attempt to address this issue using collateral reports from family or friends, but these also are not reliable. Biochemical markers such as phosphatidylethanol and ethyl glucuronide have high reliability, but they may have a short duration in the body depending on the tissue sampled; their quantitation incurs a significant financial cost in population-level studies (Afshar et al., 2022). Thus, self-reported data are used to assess alcohol intake, considering the underlying assumption that alcohol intake is commonly under-reported by participants (Stockwell et al., 2016).

A further challenge regarding use of self-reported data is a difference between alcohol consumption levels obtained from self-reports and data based on alcohol purchase records for geographic locations. The latter are more objective as they are derived from taxation records. When converted to per capita alcohol consumption, some studies have found that self-report consistently underestimates alcohol purchase reports by as much as 60 to 80 percent (Stockwell et al., 2018; Subbaraman et al., 2020). The committee notes that there is no consensus on how to apply this discrepancy to sub-cohorts within a population. For example, if the response error affects all respondents similarly, self-reported alcohol intake levels are "underestimated" but retain their rank-order validity. However, if the response error affects occasional, moderate, and heavy alcohol consumer sub-cohorts differently, estimates of the association of alcohol intake with outcomes could over- or underestimate the true association depending on the sub-cohort. Additionally, evidence suggests that under-reporting is greatest among those having the highest intake levels (Bhattacharya et al., 2018). Generally, response error is a potential challenge for most observational research on diet and health (Ravelli and Schoeller, 2020).

Under-reporting of alcohol consumption will continue to be a challenge, and more accurate tools to quantify alcohol exposure are needed. Additionally, alcohol consumption should be assessed at multiple time

points across the entire lifespan (i.e., adolescence, young adult, middle age, older age) because the most vulnerable periods for alcohol's impact on health outcomes are unknown. For example, are health risks (or benefits) incurred during younger or older drinking, or is alcohol's impact cumulative? Examination of the full spectrum of alcohol consumption, from never-drinker to alcohol use disorder, would enable the modeling of outcome trajectories and cut points for positive or negative health outcomes.

Comparison Groups

A limitation of many studies assessing alcohol consumption is the continued practice of using nondrinkers, including former and never drinkers, as the reference cohort. As discussed in Chapter 1, this practice introduces substantial bias because nondrinkers are a heterogenous group comprised of individuals who never consumed alcohol due to personal preferences, those who never consumed alcohol or stopped because of health problems, and former heavy alcohol consumers including individuals with AUD. These last two groups may carry a burden of illness that is absent from a moderate drinking cohort and thus possibly bias outcomes more favorably toward the moderate drinkers.

Awareness of "abstainer bias" is growing, as per the number of studies in this report that were eligible and could be analyzed. Future studies must ensure that individuals who are true abstainers are not included with former users of alcohol in reference groups. This issue is especially critical for the analysis of moderate drinking. However, because abstainers also are a heterogeneous group, as noted above, a preferred approach may be to incorporate multiple (separate) comparison groups such as lifetime abstainers, former moderate drinkers, or current infrequent drinkers. A similar finding across these groups would suggest that the choice of comparison group did not influence the results, while differences would be important to note and further understand. The committee recognizes that there has been an increased use of 'occasional drinkers' (e.g., <1 drink/week or <1 drink/month) as a reference cohort, which may further complicate conclusions regarding health effects, as well as raise the issue of the potential value of creating comparison groups that would allow assessment of the magnitude of health benefits within the definition of moderate drinking.

Analysis Issues

Confounders, Mediators, and Effect Modifiers

There are many additional biologic and behavior factors including demographic factors (e.g., age, sex, genetic ancestry, socioeconomic status),

social determinants of health, lifestyle factors (e.g., diet, physical activity, tobacco, recreational drug use), and comorbid health conditions (e.g., obesity, blood pressure, diabetes, dyslipidemias) to consider in research on the impact of alcohol consumption on health where the factors may act as confounders, effect modifier and/or mediators.

Age

Age is a major determinant of health and, more specifically, it is a predictor of the types of illness that pose the greatest risk for adverse outcomes. For example, young adults are more likely to experience trauma, while older adults are more likely to experience myocardial infarction (MI). Age can also contribute to heterogeneity and moderating factors in assessing outcomes related to alcohol intake. Conducting an analysis of moderate drinking that focuses on younger adults would emphasize trauma and minimize MI and potentially lead to a different conclusion from an analysis focused on older adults. Age itself may also modify the health effects of alcohol. For example, alcohol interacts both directly and indirectly with certain medications that could interfere with the intended action of prescribed drugs and thus affect disease risk or severity. Moreover, both alcohol metabolic rate and lean mass decline with aging and contribute to higher blood alcohol concentration (BAC) per drink equivalent and reduced alcohol clearance rates in that population (Meier and Seitz, 2008).

Sex

A person's sex (at birth) is a relevant determinant of health, and current research is limited to this binary so it is unknown how outcomes may differ for transgender individuals. Women and men differ in their alcohol pharmacokinetics. Although they metabolize alcohol at similar rates, women have lower rates of intestinal alcohol metabolism than men (5 percent in women versus 25 percent in men) and thus women absorb more alcohol into the bloodstream per drink than do men who consume an equivalent amount (Mumenthaler et al., 1999). Moreover, because alcohol is excluded from lipid compartments, the higher relative percent fat mass in women further concentrates the alcohol in their lean tissue mass (Mumenthaler et al., 1999). Thus, women experience higher BACs per drink than men, and this may increase their risk for adverse health effects, as seen in their greater risk for cirrhosis (Roerecke et al., 2019). Women and men also vary in their risk for health outcomes that may be modifiable by alcohol. For example, women are more likely than men to develop breast cancer. Lastly, perimenopause and menopausal status are important measures to include in future studies.

Genetic Ancestry

Genetic ancestry (e.g., European, East Asian) is also an important effect modifier for alcohol-related outcomes. For example, genetic variants in the enzymes that metabolize alcohol affect peak BAC and ethanol clearance, and thus modify the extent of an alcohol exposure. Another example—an enzyme variant that rapidly converts ethanol to acetaldehyde would reduce ethanol exposure but prolong acetaldehyde exposure (Edenberg, 2007). Additionally, the proteins that ethanol interacts with have genetic variants that further modify alcohol-related outcomes. For instance, variants that affect the expression or activity of proteins mediating neurotransmission can modify the risk for AUD (Gameiro-Ros et al., 2023; Zhou and Gelernter, 2024).

Additional Factors

Factors such as race and ethnicity can be confounded with socioeconomic status, health disparities, and educational differences and be further influenced by genetic variants that can modify outcomes. Race and ethnicity differences can exert additional influences on alcohol-related health outcomes. Studies must also consider socioeconomic status, as higher affluence correlates with both moderate alcohol use and factors that are protective for health, including educational attainment, better health care access, and nutritional adequacy; conversely, abstention is associated with risk factors for worsened health status including low income, reduced healthcare access, poor nutrition, and low educational attainment. Additionally, alcohol is often consumed in the context of diet, e.g., as part of the Mediterranean Diet. The committee encourages further research on how the dietary context influences the relation of moderate drinking to health.

Mediators

Analytic strategies initially should not include factors in the model that could act as mediators of a causal link between alcohol intake and outcome because this may mask or lessen the true effects of alcohol. Controlling for mediators, for example, is likely to obscure the potential "benefit" of moderate alcohol intake on an outcome. Thus, controlling for potential mediators should be used in the final analyses to assess the extent to which a measured variable explains any observed association between alcohol intake and a particular health outcome.

Causal Inference Study Designs

As noted earlier, most evidence regarding the health effects of moderate drinking is based on observational data from cohort studies. While there are

many smaller, short-term randomized controlled trials (RCT) designed to evaluate the effect of moderate drinking on intermediate outcomes—such as high density lipoprotein, low density lipoprotein, and apolipoprotein A-1 (Brien et al., 2011; Huang et al., 2017; Spaggiari et al., 2020); fibrinogen (Brien et al., 2011; Huang et al., 2017); interleukin-6 (Huang et al., 2017); and glucose control (Schrieks et al., 2015)—large RCTs evaluating actual clinical outcomes are lacking. Although large RCTs would be ideal, their design and implementation present major challenges. From a logistical standpoint, an RCT on the effect of moderate drinking, versus abstention, on risk of MI, for example, would require a large sample and long study duration. Moreover, it would require provision of alcohol to study participants, who, ideally, would be blinded to their randomly assigned group.

Ethics boards would likely be concerned about the potential health risks of assigning any abstainers to drinking for years, and there would be substantial challenges convincing abstainers to begin drinking. The alternative to asking current moderate drinkers to stop drinking for years also may be unrealistic and, over time, as the "abstention" group resumed drinking, might eventually result in a trial of moderate drinking versus moderate drinking and a spurious conclusion that moderate drinking had no impact on health. Focusing the trial on small changes in intake (e.g., asking daily drinkers to drink a little more or a little less) would tend to bias results toward null due to the small contrast between the randomly assigned groups. In short, such major challenges make it unlikely that there will be large RCTs on this important topic.

Mendelian randomization is a technique to study causal effects of modifiable exposures (e.g., moderate drinking) on health and other outcomes using genetic variants that are associated with exposures of interest (Burgess et al., 2019). However, moderate alcohol drinking is a complex and time-varying phenomenon, and currently identified gene(s) do not adequately capture individual differences in level of alcohol intake and/or drinking pattern. If the chosen genes cannot distinguish drinkers in the moderate range (e.g., 0.5 versus 1.5 drink per day), the results of Mendelian randomization studies on the health effects of moderate drinking will be biased toward the null.

RESEARCH GAPS BY TYPE OF HEALTH OUTCOME

For studies of *all-cause mortality* and moderate alcohol consumption, additional studies are needed to further elucidate the all-cause findings, especially because the direction of association may differ across outcomes. For example, many studies suggest that moderate drinking is associated with lower risk of myocardial infarction but higher risk of breast cancer. How do these disparate health findings affect overall (all-cause) mortality

in different socioeconomic groups? In the assessment of *cardiovascular disease*, studies of the association between moderate alcohol consumption and risk of major adverse cardiovascular events (MACE-3) (composite outcome) would be helpful. Moreover, there is a need for more studies that focus on the relationship of moderate drinking to other types of cardiovascular disease (e.g., heart failure, specific arrhythmias, and stroke).

With respect to *weight changes*, studies should include validated measures of adiposity, such as body composition measured via bioelectrical impedance analysis (BIA), with appropriate adjustment for factors such as hydration, or dual energy x-ray absorptiometry (DXA) instead of focusing on measures with established limitations like body weight, body mass index (BMI), and weight categories such as overweight and obesity defined by BMI. This is also relevant for studies of weight changes for women who are lactating because postpartum shifts in fluid balance similarly confound assessments that rely on body weight and BMI instead of body composition. In resource-poor settings or very large cohort studies where BIA and/or DXA) are unavailable, waist circumference and waist-to-hip ratio measures may still be better options than BMI. Further, self-reported measures of body size including weight and height are less desirable than relying on standardized, validated measures obtained by trained staff. Finally, studies assessing impacts of moderate alcohol consumption on weight-related outcomes should also assess dietary intake (e.g., energy-yielding nutrients, kcal/d), and measures of activity, sleep, and energy expenditure.

Several research gaps were identified for *cancer* of various sites. For breast cancer, further examination of moderate alcohol consumption by menopausal status is needed to determine if there are differences in those strata, particularly to determine risk associated with moderate alcohol consumption for premenopausal breast cancer and tumor type. Further examination of moderate alcohol consumption and colorectal cancer is warranted. The finding of a modest risk but with confidence intervals that include the null, merits additional consideration to determine if, with larger numbers of study participants and with greater power, a significant association would be identified. While current evidence is suggestive of a dose-response relationship, studies focusing on the dose-response relationship within the moderate consumption range are also needed with careful attention to abstainer bias.

Examination of moderate alcohol consumption with risk of cancer for the other sites identified as being associated with overall alcohol consumption is needed: oral, pharyngeal, laryngeal, esophageal, and liver. Examination of moderate alcohol consumption is needed with risk of other cancer sites such as gastric, pancreas, prostate, bladder, renal, and endometrium. Lastly, research is needed for moderate alcohol consumption with cancer

risk within strata of smoking status, especially for those cancer sites with smoking as a strong risk factor.

When considering *neurocognition*, diagnoses of dementia or Alzheimer's disease must be made by medical professionals and follow established guidelines, such as *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-5 or *International Classification of Diseases* (ICD)-10. Cognitive assessments should use standardized tests that are well-accepted to assess cognitive capacity (e.g., Montreal Cognitive Assessment [MoCA]; Mini-Mental State Examination [MMSE]) and should be performed, at a minimum, at two distinct ages to capture potential differences in cognitive performance and change in drinking patterns. Abstainers of alcohol to low drinking comparison groups are essential to account for test practice effects, also known as testing experience, that can endure over decades and under-estimate disease-related impairments. Additionally, focusing on one to a dozen variables as potential moderators of cognitive decline, impairment, or dementia may be inadequate to determine with confidence a direct correlation between current drinking amount by category and cognitive outcome. This includes a consideration of genetic influences that in themselves affect the risk for developing dementia-related disorders. Comorbidities are also common concomitants of drinking. For example, some people may use alcohol to self-medicate against certain psychiatric symptoms, notably depression, anxiety, obsessive-compulsiveness, traumatic stress, learned helplessness, and more. Other comorbidities include infections such as HIV or hepatitis C, nonalcohol illicit drug use, and misuse of tobacco and cannabis, which is legal in many U.S. states. Aging, sex, race and ethnicity, and socioeconomic status are also leading factors that have been shown to influence cognitive status (Delker et al., 2016; Sullivan et al., 2023).

With respect to alcohol consumption during *lactation*, studies are needed to evaluate the impact of acute and chronic maternal alcohol consumption on holistic milk composition and infant milk consumption. Milk composition varies within and among individuals, and factors affecting this variability (e.g., time of day, time within feed, time postpartum, maternal diet, physical activity, and body composition) should be accounted for, and controlled for if possible, using optimized and standardized collection methodology. For instance, complete breast expressions should be obtained when assessing milk composition, and infant milk consumption should be estimated using validated methods (e.g., test weighing or use of stable isotopes). Otherwise, research findings related to the potential impact of maternal alcohol consumption during lactation on milk composition or production are not useful. With respect to infant outcomes, future studies must control for confounding variables such as the influence of prenatal versus postnatal maternal alcohol use and the extent and duration of breastfeeding. A non-breastfeeding (formula feeding) cohort should be included as a reference

group. Finally, the committee concurs that the lack of research on alcohol consumption during lactation reflects the overall lack of alcohol research involving women (NASEM, 2024). Although logistic and experimental challenges certainly exist, the committee urges all studies that address the impact of alcohol consumption on human health to include postpartum women (both breastfeeding and non-breastfeeding) and their infants when possible.

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Appendix A

Committee Member Biosketches

Bruce N. Calonge, M.D., M.P.H. (*Chair*), is the associate dean for public health practice and professor of epidemiology at the Colorado School of Public Health and is the chief medical officer for the Colorado Department of Public Health and Environment. He is a professor of family medicine at the University of Colorado School of Medicine. Nationally, Dr. Calonge chairs the Health Resources and Services Administration's Advisory Committee on Heritable Disorders of Newborns and Children and the Board on Population Health and Public Health Practice for the National Academies of Sciences, Engineering, and Medicine's Health and Medicine Division, for whom he has served and chaired several study committees on topics including health equity, genetic testing in clinical care, the quality and safety of abortion services, evidence-based public health emergency preparedness and response, per- and polyfluoroalkyl substances environmental exposure, and the Department of Veterans Affairs' Presumption Decision Process. He is a past chair of the Board on Population Health and Public Health Practice for the National Academies of Sciences, Engineering, and Medicine's Health and Medicine Division, for which he has served on and chaired several study committees on topics including health equity, genetic testing in clinical care, the quality and safety of abortion services, evidence-based public health emergency preparedness and response, PFAS environmental exposure, and the Department of Veterans Affairs' Presumption Decision Process. He is also past chair of the Centers for Disease Control and Prevention's Community Services Task Force and the Agency for Healthcare and Research Quality U.S. Preventive Services Task Force. Dr. Calonge has an M.D. from the University of Colorado School of Medicine and an M.P.H.

in epidemiology from the University of Washington School of Public and Community Medicine. He was elected to the National Academy of Medicine in 2011.

Andrew W. Brown, Ph.D., is associate professor in the department of biostatistics at the University of Arkansas for Medical Sciences and director of biostatistics for Arkansas Children's Research Institute. He is currently a scientific advisor for the Soy Nutrition Institute Global, associate editor of the *International Journal of Obesity*, Statistical Review Board member for the four American Society for Nutrition journals, and an unpaid public assembly member for the International Food Information Council. He has conducted research using simulation, in vitro, ex vivo, animal, and human observational and interventional models. He conducts "research on research" through qualitative and quantitative research summaries, characterizing reporting practices that perpetuate scientific misinformation, and evaluating methodological and statistical choices that may lead to misinterpreted research. He has received local, regional, and national recognition, including the Mead Johnson Award from the American Society for Nutrition for work accomplished within 10 years of postgraduate training, and he has served in leadership roles with the American Society for Nutrition, The Obesity Society, and the American Public Health Association, Dr. Brown received his B.S. and M.S. in biochemistry from Iowa State University with a graduate minor in statistics, his Ph.D. from the University of Nebraska–Lincoln in the Interdepartmental Nutrition Program with a minor in statistics, and his postdoctoral training with the University of Alabama at Birmingham's Nutrition Obesity Research Center.

Carlos A. Camargo, Jr., M.D., Dr.PH., is a professor of emergency medicine, medicine, and epidemiology at Harvard University, and the Conn Chair in Emergency Medicine at Massachusetts General Hospital. He founded and currently leads the Emergency Medicine Network (EMNet), an international research collaboration with about 250 hospitals. EMNet focuses on respiratory/allergy emergencies, health services research in emergency care, and social determinants of health. Dr. Camargo also works on the role of nutrition in respiratory/allergy disorders, both in large cohort studies (e.g., the Nurses' Health Studies) and in large randomized controlled trials. For over 25 years, he actively worked on the health effects of moderate alcohol consumption; he chaired the Alcohol Committee for the 2005 U.S. Dietary Guidelines Advisory Committee. Dr. Camargo received his M.D. from the University of California, San Francisco, and his Dr.P.H. from Harvard School of Public Health.

Patricia A. Cassano, Ph.D., M.P.H., is the Alan D. Mathios Professor in the Division of Nutritional Sciences at Cornell University. Dr. Cassano

directs the Pan American Health Organization/World Health Organization Collaborating Centre on Nutrition and Health Research at Cornell and the Cochrane US Network Associate Center on Nutrition at Cornell. Dr. Cassano leads the annual World Health Organization/Cochrane/Cornell Summer Institute on Systematic Reviews in Nutrition for Global Policymaking. She co-directs the Cornell University Center for Precision Nutrition and Health and is a co-investigator for the Research Coordinating Center of the National Institutes of Health Common Fund's Nutrition for Precision Health, powered by the *All of Us* Research Program. Her research focuses on nutritional genomics of chronic disease to elucidate disease causation, with the overall goal to improve population health. Dr. Cassano has expertise in clinical trials, longitudinal study design and analysis, biological markers, genetic epidemiology including gene expression, Genome-Wide Association Study (GWAS), epigenome Wide Association Study (eWAS), and pathway and network studies. Dr. Cassano received her M.P.H. in epidemiology from Columbia University School of Public Health and Ph.D. from the University of Washington School of Public Health, and was a T32 Research Fellow at Harvard Medical School.

Patrick M. Catalano, M.D., is professor in residence, reproductive endocrinology unit, Massachusetts General Hospital, Harvard Medical School, visiting professor at Aarhus Denmark, and a consultant for the Pennington Biomedical Research Institute at Louisiana State University on the Greaux Healthy project. Dr. Catalano is chair emeritus, Department of Reproductive Biology at Case Western Reserve University/MetroHealth Medical Center. His research interests include obesity, diabetes and metabolism in pregnancy. His research includes the longitudinal evaluation of women before, during, and after pregnancy to determine the short- and long-term effects of maternal obesity and diabetes on both the mother and her offspring. He is a member of several professional organizations including the American College of Obstetrics and Gynecology, the Society of Maternal-Fetal Medicine, Society for Reproductive Investigation, American Diabetes Association, and the Perinatal Research Society, among others. He was the previous chair of the American Diabetes Association Council on Pregnancy and Women's Health. Dr. Catalano has served as a co-chair of the National Institute of Child Health and Human Development Scientific Vision Group on Pregnancy. He was on the Institute of Medicine committee to review the weight gain in pregnancy guidelines. Awards include the Norbert Freinkel award from the American Diabetes Association, the Jorgen Pedersen award from the Diabetes in Pregnancy Study Group of the European Association for the Study of Diabetes, the Agnes Higgins award for contributions to Maternal-Fetal nutrition from the March of Dimes, and the Charles Best lecture form the University of Toronto. He has over 250 peer reviewed publications and continuous National

Institutes of Health funding since 1987. Dr. Catalano received his M.D. from the University of Vermont College Medical College, and he is certified in general obstetrics and gynecology and maternal-fetal medicine.

Kathryn E. Coakley, Ph.D., RDN, is assistant professor in the College of Population Health at the University of New Mexico Health Sciences Center and consultant for Constellation Consulting LLC. She has over 12 years of experience designing and conducting research studies and systematic reviews related to rare genetic disorders, food and nutrition security, and behavioral health. Dr. Coakley also has extensive clinical experience working with adults in recovery from alcohol use disorder and other substance use disorders as a consultant for Global Nutrition Services in Albuquerque, NM. She is a member of the Academy of Nutrition and Dietetics and the American Society for Nutrition and, in 2022, was named Outstanding Dietetics Educator for Didactic Programs in Dietetics for the state of New Mexico and the West Central Region of the United States. In 2022, she was also appointed to the Academy of Nutrition and Dietetics' Nutrition Security Strategic Advancement Group. Dr. Coakley received an M.S. in Public health nutrition and completed her dietetic internship at Case Western Reserve University, then completed a Ph.D. in nutrition and health sciences from Emory University.

Luc Djousse, M.D., D.Sc., is an associate professor of medicine at Harvard Medical School, associate professor of nutrition at T. H. Chan School of Public Health, director of research in the Division of Aging, Department of Medicine at Brigham and Women's Hospital, and chief epidemiologist, Massachusetts Veterans Epidemiology Research and Information Collaborative. He is a cardiovascular epidemiologist with a research focus on the role of dietary factors including moderate alcohol consumption on cardiovascular disease and its risk factors. Dr. Djousse has many years of research experience on modifiable factors and risk of heart failure, myocardial infarction, mortality, stroke and type 2 diabetes. He is the recipient of numerous National Institutes of Health (NIH) and non-NIH grants and received a Walter Bleifeld memorial award for his distinguished contribution to clinical research in preventive cardiology. He is also a member of the American Heart Association and the American Society of Nutrition, and uncompensated member of the International Scientific Forum on Alcohol Research. He has published his research in academic journals on topics including the role of moderate alcohol consumption on the risk of stroke, coronary artery disease, and mortality and made presentations on alcohol consumption and health. Dr. Djousse received his M.D. from the University of Saarland (Germany) and D.Sc. in epidemiology from Boston University.

Jo L. Freudenheim, Ph.D., M.S., RD, is a SUNY distinguished professor in the department of epidemiology and environmental health and associate dean for faculty affairs in the School of Public Health and Health Professions at the University at Buffalo. Her research has primarily focused on breast cancer epidemiology, seeking to use epidemiologic methods to understand carcinogenesis at the population level as well as at the individual, tissue, and molecular levels to inform improved prevention and control strategies. Her extensive research has included a focus on the effects of diet and alcohol on cancer; she was among the first to examine the interaction of folate with alcohol in relation to cancer risk. Her most recent research has focused on factors related to all-cause and breast cancer–specific mortality following a breast cancer diagnosis. This path of research has included molecular differences in breast tissues as indicators of the carcinogenic process. She is a fellow of the American Society for Nutrition and the American College of Epidemiology and received the Abraham Lilienfeld Award from the American Public Health Association Epidemiology Section. Dr. Freudenheim received her Ph.D., in nutritional sciences and her M.S. in preventive medicine (epidemiology) from the University of Wisconsin-Madison.

Rebecca A. Hubbard, Ph.D., is the Carl Kawaja and Wendy Holcombe Professor of Public Health, Professor of Biostatistics and Data Science, Brown University School of Public Health. Her research focuses on statistical methods for the analysis of observational studies of human health making secondary use of real-world data sources including electronic health records and medical claims data. This work develops and evaluates alternative methodological approaches to addressing challenges that arise due to the inconsistent and heterogeneous nature of these data sources including missing data, measurement error, and selection bias. She is an elected Fellow of the American Statistical Association and a member of the National Academy of Sciences, Engineering, and Medicine Committee on Applied and Theoretical Statistics. Dr. Hubbard has received training in both biostatistics (University of Washington, Ph.D. in biostatistics; Oxford University, M.S. in applied statistics) and epidemiology (Edinburgh University, M.S. in epidemiology).

Michelle K. McGuire, Ph.D., is professor of nutrition and director of the Margaret Ritchie School of Family and Consumer Sciences at the University of Idaho. She is also director of the National Institutes of Health Center of Biomedical Research Excellence in Nutrition and Women's Health at the University of Idaho. Her expertise relates maternal and infant nutrition with a focus on human milk and lactation. She and her group have studied a wide variety of substances in human milk including nutrients, hormones,

minerals, pesticides, and microbes (including SARS-CoV-2). Dr. McGuire was the recipient of the American Society for Nutrition's Excellence in Nutrition Education Award in 2018 and received the University of Idaho's Excellence in Research and Creative Activity Award in 2023. She previously served on the executive board for the Academic Nutrition Departments and Programs, is on the editorial board of the *Journal of Nutrition*, and is a member of the Danone Early Life Nutrition and Maternal Health Advisory Board. She served on the National Academy of Sciences Committee on Scanning for New Evidence on the Nutrient Content of Human Milk from 2019–2020. Dr. McGuire received her B.S. in biology and M.S. in nutritional sciences from the University of Illinois and her Ph.D. in human nutrition from Cornell University. She was elected to the National Academy of Medicine in 2022.

Ian J. Saldanha, Ph.D., M.B.B.S., M.P.H., is an associate professor of epidemiology (primary) and of health policy and management (joint) at the Center for Clinical Trials and Evidence Synthesis at the Johns Hopkins Bloomberg School of Public Health. He also holds an adjunct appointment as associate professor of health services, policy, and practice at the Brown University School of Public Health. He is associate director of the Johns Hopkins Evidence-based Practice Center, which is one of nine such centers funded by the Agency for Healthcare Research and Quality (AHRQ). When at Brown (2018–2022), he was assistant director of the Brown University Evidence-Based Practice Center. Dr. Saldanha has expertise conducting systematic reviews and meta-analyses, developing and advancing methods to improve them, and teaching methods for their conduct. He has also researched the use of outcomes in clinical research. Dr. Saldanha has served on three previous. National Academies of Sciences, Engineering, and Medicine's Committees on Scanning New Evidence on Nutrient Content of Human Milk, Scanning for New Evidence on Riboflavin to Support a Dietary Reference Intake Review, and the Role of Seafood Consumption on Child Growth and Development. Dr. Saldanha was the co-principal investigator (co-PI) of a National Academies contract to conduct a systematic review of public health emergency preparedness activities. He has been the PI of six AHRQ-funded systematic reviews. Additionally, he has been the PI of multiple AHRQ contracts to develop, advance, maintain, and support the Systematic Review Data Repository Plus (SRDR+). Dr. Saldanha is an elected member of the Society for Research Synthesis Methodology and currently serves as its treasurer. He is the co-editor-in-chief of the journal *Epidemiologic Reviews*. He served as the associate editor for various journals (e.g., *Trials, Systematic Reviews, Journal of Glaucoma*) and for the AHRQ Effective Healthcare Program. Dr. Saldanha has taught multiple courses and workshops related to systematic reviews, meta-analysis, clinical

trials, and epidemiology at the undergraduate, graduate, and professional levels at various universities and other venues, such as the Centers for Disease Control and Prevention. He received his M.B.B.S. (M.D. equivalent) from Grant Medical College in Mumbai, India, and his M.P.H. and Ph.D. in epidemiology from the Johns Hopkins Bloomberg School of Public Health.

Susan M. Smith, Ph.D., is the Harris-Teeter Dickson Foundation Distinguished Professor in Nutrition at the University of North Carolina (UNC) at Chapel Hill and former Deputy Director for Science at the UNC Nutrition Research Institute; she is also professor emerita of nutritional sciences at the University of Wisconsin-Madison. Dr. Smith has over 100 publications at the intersection of nutrition, alcohol, metabolism, cardiovascular function, obesity, and pregnancy. Her research studies the mechanisms by which alcohol exposure perturbs maternal-fetal development (including the brain, heart, liver, placenta, mammary gland, and metabolic syndrome) with an emphasis on nutrient-alcohol interactions and, more recently, how genetic polymorphisms modify these interactions. Her work combines untargeted omics and drill-down mechanistic approaches using a range of preclinical models, placing them back into the whole animal in the context of clinical translation. She has been the principal investigator on numerous research awards from the National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute of Environmental Health Sciences, and the National March of Dimes. Dr. Smith served on the External Advisory Board (Council) for NIAAA, chaired the Neurotoxicology & Alcohol study section, and received a 10-year MERIT award from NIAAA. She received the James Wilson Award from the Teratology Society and Future Leader in Nutrition Award from International Life Sciences Institute. Dr. Smith received her B.S. in biochemistry from Purdue University and an M.S. and Ph.D. from the University of Wisconsin-Madison, and she was a postdoctoral fellow in cellular physiology at Harvard Medical School.

Linda G. Snetselaar, Ph.D., RDN, is a professor in the Department of Epidemiology, Endowed Chair of Preventive Nutrition Education, and director of the Nutrition Center at the University of Iowa, College of Public Health, and she is secondary faculty in Internal Medicine, Endocrinology/Metabolism, the Carver College of Medicine. Dr. Snetselaar has over 300 publications focusing on dietary eating patterns and their effect on chronic disease with past funding from the National Institutes of Health (NIH) on six major dietary intervention trials focused on chronic disease prevention and treatment. She has served on numerous NIH study sections along with serving as a chair on a cancer immune therapy and diet study section. From 2019 to 2020 Dr. Snetselaar served on the U.S. Department of Agriculture Dietary Guidelines Advisory Committee, which involved policy changes

related to diet for Americans and was chair of the Dietary Fats and Seafood Subcommittee and a member of the Dietary Patterns Subcommittee. She is editor-in-chief of the *Journal of the Academy of Nutrition and Dietetics*. Dr. Snetselaar received a B.S. in nutrition and dietetics at Iowa State University, an M.S. degree in nutrition at the University of Iowa Department of Internal Medicine, and a Ph.D. in health sciences education from the University of Iowa.

Edith V. Sullivan, Ph.D., is a tenured professor in the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine. She is a neuropsychologist with expertise in magnetic resonance imaging. Together these disciplines have enabled her to identify patterns of cognitive, motor, and sensory impairment and sparing and to detect brain structural and functional substrates of performance patterns in normal aging men and women and in people with alcohol use disorder across the age span from adolescence to senescence. Dr. Sullivan has received several awards for her research, including the Research Society on Alcohol (RSA) Begleiter Award for Excellence in Research; RSA Distinguished Researcher Award; Distinguished Career Award from the International Neuropsychological Society; Mark Keller Honorary Lectureship Award from National Institute on Alcohol Abuse and Alcoholism; and Doctorate Honoris Causa, EPHE, Sorbonne, France. She is also a fellow of the American College of Neuropsychopharmacology and the American Psychological Association. Dr. Sullivan earned her B.A., M.A., and Ph.D. in experimental psychology from the University of Connecticut and conducted postdoctoral work in the Teuber and Corkin brain science laboratories at the Massachusetts Institute of Technology.

Appendix B

Public Meeting Agendas

COMMITTEE ON REVIEW OF EVIDENCE ON ALCOHOL AND HEALTH

The Keck Center, 500 Fifth Street, NW
Washington, DC 20001

JANUARY 25, 2024
ROOM 100

8:00 a.m. Breakfast available

SESSION 1—OPEN

10:00–10:10 Welcome and Introductions, Conduct of the Open Session
Ned Calonge, *Committee Chair*

10:10–10:30 Charge to the Committee
Eve Stoody, *USDA*, Nutrition Guidance and Analysis Division
Julie Obbagy, *USDA*, Nutrition Evidence Systematic Review Branch
Janet de Jesus, *HHS*, Office of Disease Prevention and Health Promotion

10:30–10:50 Related Activities at SAMHSA
Robert Vincent, *HHS*, Substance Abuse and Mental Health Services Administration

10:50–11:50 Committee Discussion

11:50 Closing Comments
Ned Calonge, *Committee Chair*

COMMITTEE ON REVIEW OF EVIDENCE ON ALCOHOL AND HEALTH

Virtual Meeting

MARCH 28, 2024

SESSION 1—OPEN

10:30–10:35 Welcome and Introductions, Conduct of the Open Session
Ned Calonge, *Committee Chair*

10:35–12:00 Public Comment Period Begins
Ned Calonge, *Moderator*, Committee Chair

12:00 Public Comment Period Ends

12:00–1:00 Break

1:00–1:50 Alcohol Consumption and Cancer
Farhad Islami, *American Cancer Society*

1:50–2:00 Break

2:00–3:20 Alcohol Consumption and Neurocognitive Development
Christina Chambers, *University of California-San Diego*, "What is known and not known about alcohol consumption during lactation, human milk and infant development"
Sara Jo Nixon, *University of Florida*, "Distilling heterogeneity in alcohol effects on neurocognitive health"
Chandra Sripada, *University of Michigan*, "Measurement of executive functions with conflict tasks: Implications for alcohol research"

3:20–3:30	Break
3:30–4:00	**Tim Stockwell,** *University of Victoria*, "The problem of selection bias in estimates of alcohol's contribution to cancer, heart disease, and all-cause mortality- and how to fix it."
4:00–4:25	**Marian Neuhouser,** *Fred Hutchinson Cancer Center*, "Alcohol assessment in free-living people: Challenges and opportunities"
4:25–4:30	Closing Comments **Ned Calonge,** *Committee Chair*
4:30	Adjourn open session

Appendix C

Timeline of Screening for Eligibility

All searches were completed by the National Academies Research Center. The literature search approach was iterative based on search results and ongoing committee discussion. Because the *Dietary Guidelines for Americans* (DGA) was supported by a new systematic review for all-cause mortality, the search frame included studies published between January 2019 and September 2023. The final search frame for other study questions included studies published between January 2010 (the date of the previous edition of the DGA that covered alcohol and health) and February 2024. These steps are described below.

Initial Search

This search included primary studies and systematic reviews between 2019 and 2023 for all-cause mortality, weight changes, cancer, cardiovascular disease, neurocognition, and lactation questions.

- Articles were screened for inclusion/exclusion by the committee.
- Studies meeting criteria for all-cause mortality were submitted for systematic review and meta-analysis.

Committee Action

The DGA 2020–2025 included only an updated systematic review for all-cause mortality, while the DGA was based on systematic reviews for all other topics other than lactation. The committee requested an additional

search to include studies published since the DGA 2010–2015 and a complete search of Embase and PubMed for lactation.

Second Search

This search included systematic reviews between 2010 and 2024 for cardiovascular disease, neurocognitive health, cancer, and overweight/obesity questions; also, a complete search of Embase and PubMed was completed for all primary articles on lactation.

- Articles included in these systematic reviews were screened for inclusion/exclusion by National Academies staff and the committee due to time constraints.
- Committee members recused themselves from screening articles if they were an author on an article.

Committee Action

During inclusion/exclusion review of the articles on cardiovascular disease, neurocognitive health, cancer, and weight changes questions identified in the first two searches, the committee chose to exclude articles for which data collection ended prior to 2010 to avoid potential bias that might be associated with older studies.

Prior to finalizing the report, the committee chose to harmonize the search strategies for consistency across the topics and alignment with best practice for study inclusion. Therefore, instead of excluding articles with data collection ending prior to 2010, the committee chose to reconsider these articles for inclusion. Articles for cardiovascular disease, neurocognitive health, cancer, and overweight/obesity questions that were excluded based on end of data collection year were re-screened for inclusion/exclusion by the committee. As a result, the committee asked for the systematic review and meta-analysis to be repeated to include two additional articles related to cardiovascular disease, one for breast cancer, one for colon cancer, and one for neurocognition. The review for the lactation questions was similarly restricted to the same search time frame and data collection time frame, and the chapter was revised accordingly. **These additional analyses did not change any of the committee's conclusions.**

Impact on Findings

When two publications on cardiovascular disease (CVD) were added, this resulted in one additional study (Liu et al., 2022) for the CVD mortality outcome. The impact of this addition (with data collection that ended prior to 2010) was relative risk difference of 0.01 and within the confidence interval, i.e., four studies (RR = **0.81** [0.73, 0.89] versus three studies (RR = **0.82** [0.76, 0.89]).

Appendix D

AMSTAR-2 Tables

TABLE D-1 AMSTAR-2 Evaluation for All-Cause Mortality Systematic Reviews with or without Meta-Analyses Published between 2019 and 2024

	Study (Author, Year)					
AMSTAR Question	**van de Luitgaarden et al., 2022**	**Zhao et al., 2023**	**Estruch and Hendriks 2022**	**Boushey et al., 2020**	**English et al., 2021**	**Marcos et al., 2021**
Did the research questions and inclusion criteria for the review include ALL the components of PICO?	yes	yes	yes	yes	yes	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?	yes	yes	no	yes	yes	no

(*continued*)

TABLE D-1 Continued

AMSTAR Question	Study (Author, Year)					
	van de Luitgaarden et al., 2022	Zhao et al., 2023	Estruch and Hendriks 2022	Boushey et al., 2020	English et al., 2021	Marcos et al., 2021
Did the review authors explain their selection of the study designs for inclusion in the review?	yes	yes	yes	yes	yes	yes
Did the authors use a comprehensive literature search strategy?	yes	yes	yes	yes	yes	yes
Did the review authors perform study selection in duplicate?	yes	yes	yes	yes	yes	not known
Did the review authors perform data extraction in duplicate?	yes	yes	yes	yes	yes	not known
Did the review authors provide a list of excluded studies and justify the exclusions?	partial	no	partially	yes	n/a	no
Did the review authors describe the included studies in adequate detail?	yes	yes	yes	yes	yes	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	n/a	no	yes	yes	not known
Did the review authors report on the sources of funding for the studies included in the review?	no	yes	yes	yes	yes	yes

TABLE D-1 Continued

AMSTAR Question	Study (Author, Year)					
	van de Luitgaarden et al., 2022	Zhao et al., 2023	Estruch and Hendriks 2022	Boushey et al., 2020	English et al., 2021	Marcos et al., 2021
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	n/a	yes	n/a	n/a	n/a	n/a
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	partial	yes	partially	yes	yes	no
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	yes	yes	yes	yes	yes	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?	n/a	yes	n/a	n/a	n/a	n/a
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	yes	yes	yes	yes	yes	yes
OVERALL "QUALITY"	moderate	moderate	low	high	high	critically low

NOTES: n/a = not applicable; PICO = population, intervention, comparator, outcome; RoB = risk of bias.

TABLE D-2 AMSTAR-2 Evaluation for Weight Change Systematic Reviews with or without Meta-Analyses Published Between 2019 and 2024

	Study (Author, Year)	
AMSTAR Question	**Golzarand et al., 2022**	**Siegmann et al., 2022**
Did the research questions and inclusion criteria for the review include ALL the components of PICO?	yes	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?	yes	no
Did the review authors explain their selection of the study designs for inclusion in the review?	yes	yes
Did the authors use a comprehensive literature search strategy?	yes	yes
Did the review authors perform study selection in duplicate?	yes	yes
Did the review authors perform data extraction in duplicate?	unknown	yes
Did the review authors provide a list of excluded studies and justify the exclusions?	no	yes
Did the review authors describe the included studies in adequate detail?	yes	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	yes
Did the review authors report on the sources of funding for the studies included in the review?	no	no
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	n/a	yes

TABLE D-2 Continued

AMSTAR Question	Study (Author, Year)	
	Golzarand et al., 2022	Siegmann et al., 2022
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	no	yes (but did not include RoB score for each study, just that it was accounted for)
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	yes	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	yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	yes	yes
OVERALL "QUALITY"	low	low

NOTES: n/a = not applicable; PICO = population, intervention, comparator, outcome; RoB = risk of bias.

TABLE D-3 AMSTAR-2 Evaluation for Cancer Systematic Reviews with or without Meta-Analyses Published Between 2019 and 2024

	Study (Author, Year)								
AMSTAR Question	**Breau and Ellis, 2020**	**Burton et al., 2024**	**Estruch and Hendriks, 2022**	**Fakhri et al., 2022**	**Hua et al., 2023**	**Jun et al., 2023**	**Levesque et al., 2023**	**Luceron-Lucas-Torres et al., 2023**	**McNabb et al., 2020**
Did the research questions and inclusion criteria for the review include ALL the components of PICO?	yes	yes	yes	yes	yes	yes	yes	yes	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 mention of protocol	yes	yes	no mention of protocol	yes	yes	yes	yes	no mention of protocol
Did the review authors explain their selection of the study designs for inclusion in the review?	yes	yes	yes	yes	yes	yes	yes	yes	yes
Did the authors use a comprehensive literature search strategy?	yes	yes	yes	no	yes	yes	yes	yes	n/a

Did the review authors perform study selection in duplicate?	yes	yes	yes	not stated	yes	yes	yes	yes	n/a
Did the review authors perform data extraction in duplicate?	yes	No	yes	not stated	yes	yes	yes	yes	n/a
Did the review authors provide a list of excluded studies and justify the exclusions?	Partial	Yes	partial	no	partial	partial	partial	yes	n/a
Did the review authors describe the included studies in adequate detail?	yes	yes	yes	yes	yes	yes	yes	yes	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	yes	no	no	yes	yes	yes	yes	not stated
Did the review authors report on the sources of funding for the studies included in the review?	No	No	no	no	no	no	no	no	no
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	yes	yes	n/a	n/a	yes	yes	n/a	yes	yes

(*continued*)

TABLE D-3 Continued

AMSTAR Question	Study (Author, Year)								
	Breau and Ellis, 2020	Burton et al., 2024	Estruch and Hendriks, 2022	Fakhri et al., 2022	Hua et al., 2023	Jun et al., 2023	Levesque et al., 2023	Luceron-Lucas-Torres et al., 2023	McNabb et al., 2020
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	yes	yes	yes	no	yes	yes	yes	yes	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?	No	Yes	n/a	n/a	yes	yes	n/a	yes	n/a
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	yes	yes	yes	yes	yes	yes	yes	yes	yes
OVERALL "QUALITY"	critically low	high	low	critically low	high	moderate	moderate	high	unknown

NOTES: n/a = not applicable; PICO = population, intervention, comparator, outcome; RoB = risk of bias.

TABLE D-3 Continued

AMSTAR Question	Study (Author, Year)							
	Papadimitriou et al., 2021	Poorolajal et al., 2021	Shin et al., 2023	Sun et al., 2023	Veettil et al., 2021	Wiggs et al., 2021	Xu et al., 2019	Zhong et al., 2022
Did the research questions and inclusion criteria for the review include ALL the components of PICO?	yes	yes	yes	yes	yes	yes	yes	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 mention of protocol	yes	yes	yes	yes	no mention of protocol	yes	yes
Did the review authors explain their selection of the study designs for inclusion in the review?	yes	yes	yes	yes	yes	yes	yes	yes
Did the authors use a comprehensive literature search strategy?	yes	yes	yes	yes	yes	yes	yes	yes
Did the review authors perform study selection in duplicate?	yes	yes	yes	yes	yes	yes	yes	yes
Did the review authors perform data extraction in duplicate?	yes	yes	yes	yes	yes	yes	yes	yes
Did the review authors provide a list of excluded studies and justify the exclusions?	yes	partial	partial	partial	yes	partial	partial	yes
Did the review authors describe the included studies in adequate detail?	yes	yes	yes	yes	yes	yes	yes	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	yes	yes	yes	yes	no	yes	yes

(*continued*)

TABLE D-3 Continued

AMSTAR Question	Study (Author, Year)							
	Papadimitriou et al., 2021	Poorolajal et al., 2021	Shin et al., 2023	Sun et al., 2023	Veettil et al., 2021	Wiggs et al., 2021	Xu et al., 2019	Zhong et al., 2022
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	n/a	yes	yes	yes	n/a	n/a	yes	n/a
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	yes	yes	yes	yes	yes	partial	yes	yes
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	yes	yes	yes	yes	yes	yes	yes	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	yes	yes	yes	yes	n/a	yes	n/a
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	yes	yes	yes	yes	yes	yes	yes	yes
OVERALL "QUALITY"	low	moderate	moderate	high	high	critically low	high	high

NOTES: n/a = not applicable; PICO = population, intervention, comparator, outcome; RoB = risk of bias.

TABLE D-4 AMSTAR-2 Evaluation for Cardiovascular Disease Systematic Reviews with or without Meta-Analyses Published Between 2019 and 2024

	Study (Author, Year)									
AMSTAR Question	Aljuraiban et al., 2024	Arafa et al., 2023	Del Giorno et al., 2022	Giannopoulos et al., 2022	Hwang et al., 2021	Jung et al., 2020	Krittanawong et al., 2022	Levesque et al., 2023	Liu et al., 2020	Marcos et al., 2021
Did the research questions and inclusion criteria for the review include ALL the components of PICO?	yes	yes	yes	yes	yes	yes	yes	yes	yes	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?	yes	yes	yes	yes	yes	no	no	yes	no	no
Did the review authors explain their selection of the study designs for inclusion in the review?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Did the authors use a comprehensive literature search strategy?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes

(*continued*)

TABLE D-4 Continued

AMSTAR Question	Study (Author, Year)									
	Aljuraiban et al., 2024	Arafa et al., 2023	Del Giorno et al., 2022	Giannopoulos et al., 2022	Hwang et al., 2021	Jung et al., 2020	Krittanawong et al., 2022	Levesque et al., 2023	Liu et al., 2020	Marcos et al., 2021
Did the review authors perform study selection in duplicate?	yes	not stated	yes	yes	yes	yes	not stated	yes	yes	not stated
Did the review authors perform data extraction in duplicate?	yes	not stated	yes	yes	yes	yes	not stated	yes	yes	not stated
Did the review authors provide a list of excluded studies and justify the exclusions?	yes	partial	partial	partial	yes	yes	no	partial	yes	no
Did the review authors describe the included studies in adequate detail?	yes	yes	yes	yes	yes	yes	yes	yes	yes	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	yes	yes	yes	yes	yes	no	yes	yes	no

Did the review authors report on the sources of funding for the studies included in the review?	yes	no	no	no	no	no	no	no	no	yes
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	n/a	yes	n/a	yes	n/a	yes	n/a	n/a	yes	n/a
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	yes	yes	no	yes	yes	yes	no	yes	yes	no
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes

(*continued*)

TABLE D-4 Continued

AMSTAR Question	Study (Author, Year)									
	Aljuraiban et al., 2024	Arafa et al., 2023	Del Giorno et al., 2022	Giannopoulos et al., 2022	Hwang et al., 2021	Jung et al., 2020	Krittanawong et al., 2022	Levesque et al., 2023	Liu et al., 2020	Marcos et al., 2021
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?	n/a	yes	n/a	yes	n/a	yes	n/a	n/a	yes	n/a
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
OVERALL "QUALITY"	high	moderate	low	moderate	high	low	critically low	moderate	low	critically low

NOTES: n/a = not applicable; PICO = population, intervention, comparator, outcome; RoB = risk of bias.

TABLE D-4 Continued

AMSTAR Question	Study (Author, Year)								
	Siagian et al., 2023	Spaggiari et al., 2020	Tasnim et al., 2020	van de Luitgaarden et al., 2022	Wilkens et al., 2022	Yang et al., 2022	Yoon et al., 2020	Zhang et al., 2021	Zhong et al., 2022
Did the research questions and inclusion criteria for the review include ALL the components of PICO?	yes	yes	yes	yes	yes	yes	yes	yes	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?	yes	yes	yes	yes	yes	no	no	no	yes
Did the review authors explain their selection of the study designs for inclusion in the review?	yes	yes	yes	yes	yes	yes	yes	yes	yes
Did the authors use a comprehensive literature search strategy?	yes	yes	yes	yes	yes	yes	yes	yes	yes
Did the review authors perform study selection in duplicate?	yes	yes	yes	yes	yes	yes	yes	yes	yes

(*continued*)

TABLE D-4 Continued

AMSTAR Question	Study (Author, Year)								
	Siagian et al., 2023	Spaggiari et al., 2020	Tasnim et al., 2020	van de Luitgaarden et al., 2022	Wilkens et al., 2022	Yang et al., 2022	Yoon et al., 2020	Zhang et al., 2021	Zhong et al., 2022
Did the review authors perform data extraction in duplicate?	yes	yes	yes	yes	yes	yes	yes	yes	yes
Did the review authors provide a list of excluded studies and justify the exclusions?	partial	yes	yes	partial	partial	partial	partial	partial	yes
Did the review authors describe the included studies in adequate detail?	yes	yes	yes	yes	yes	yes	yes	yes	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	yes	yes	yes	yes	yes	yes	yes	yes
Did the review authors report on the sources of funding for the studies included in the review?	no	no	yes	no	no	no	no	no	no
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	yes	yes	yes	n/a	n/a	yes	yes	yes	n/a

Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	no	yes	yes	yes	yes	yes	yes	no	yes
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	yes	yes	yes	yes	yes	yes	yes	yes	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?	no	yes	yes	n/a	n/a	yes	yes	yes	yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	yes	yes	yes	yes	yes	yes	yes	yes	yes
OVERALL "QUALITY"	critically low	high	high	moderate	moderate	low	low	critically low	high

NOTES: n/a = not applicable; PICO = population, intervention, comparator, outcome; RoB = risk of bias.

TABLE D-5 AMSTAR-2 Evaluation for Neurocognitive Health Systematic Reviews with or without Meta-Analyses Published Between 2019 and 2024

	Study (Author, Year)									
AMSTAR Question	Brennan et al., 2020	Jones et al., 2024	Kilian et al., 2023	Lao et al., 2021	Luceron-Lucas-Torres et al., 2022	Porras-Garcia et al., 2023	Ran et al., 2021	Visontay et al., 2022	Wiegmann et al., 2020	Xie and Feng, 2022
Did the research questions and inclusion criteria for the review include ALL the components of PICO?	yes	yes	yes	yes	yes	yes	yes	yes	yes	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?	yes	yes	yes	yes	yes	yes	yes	yes	No	partial
Did the review authors explain their selection of the study designs for inclusion in the review?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Did the authors use a comprehensive literature search strategy?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Did the review authors perform study selection in duplicate?	yes	yes	yes	yes	yes	yes	yes	yes	not determined	yes

Did the review authors perform data extraction in duplicate?	yes	yes	yes	yes	yes	yes	yes	yes	not determined	yes
Did the review authors provide a list of excluded studies and justify the exclusions?	yes	yes	yes	yes	yes	yes	yes	yes	no	yes
Did the review authors describe the included studies in adequate detail?	yes	yes	yes	yes	yes	yes	yes	yes	yes	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	yes	yes	yes	yes	yes	yes	yes	not performed	yes
Did the review authors report on the sources of funding for the studies included in the review?	yes	no	no	no	no	no	no	no	no	no
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	n/a	n/a	n/a	yes	yes	n/a	yes	n/a	n/a	yes
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	yes	no	yes	yes	yes	yes	yes	yes	No	yes

(*continued*)

TABLE D-5 Continued

AMSTAR Question	Study (Author, Year)									
	Brennan et al., 2020	Jones et al., 2024	Kilian et al., 2023	Lao et al., 2021	Luceron-Lucas-Torres et al., 2022	Porras-Garcia et al., 2023	Ran et al., 2021	Visontay et al., 2022	Wiegmann et al., 2020	Xie and Feng, 2022
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	yes	yes	yes	yes	yes	yes	yes	yes	yes	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	n/a	n/a	Yes	yes	n/a	yes	n/a	n/a	yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
OVERALL "QUALITY"	high	low	high	high	high	high	high	high	critically low	high

NOTES: n/a = not applicable; PICO = population, intervention, comparator, outcome; RoB = risk of bias.

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