WHAT IS THE RELATIONSHIP BETWEEN ALCOHOL CONSUMPTION AND RISK OF CARDIOVASCULAR DISEASE?: SYSTEMATIC REVIEW PROTOCOL

This document describes the protocol for a systematic review to answer the following question: What is the relationship between alcohol consumption and risk of cardiovascular disease?

The 2020 Dietary Guidelines Advisory Committee, Beverages and Added Sugars Subcommittee, will be answering this question by conducting a systematic review with support from USDA’s Nutrition Evidence Systematic Review (NESR).

NESR methodology for answering a systematic review question involves:
- searching for and selecting articles,
- extracting data and assessing the risk of bias of results from each included article,
- synthesizing the evidence,
- developing a conclusion statement,
- grading the evidence underlying the conclusion statement, and
- recommending future research.

More information about NESR’s systematic review methodology is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews.

This document describes the protocol, or plan, for how the systematic review will be conducted. The protocol provides:
- The analytic framework (p. 2) illustrates the overall scope of the question, including the population, the interventions and/or exposures, comparators, and outcomes of interest.
- The literature search and screening plan (p. 2) details the electronic databases and inclusion and exclusion criteria (p. 3) that will be used to search for, screen, and select articles to be included in the systematic review.
- The literature search and screening results (p. 6) includes a list of included articles, and a list of excluded articles with the rationale for exclusion.

This protocol is up-to-date as of: 03/10/2020
ANALYTIC FRAMEWORK

The analytic framework (Figure 1) illustrates the overall scope of the systematic review, including the population, the interventions and/or exposures, comparators, and outcomes of interest. It also includes definitions of key terms and identifies key confounders considered in the systematic review. The inclusion and exclusion criteria that follow provide additional information about how parts of the analytic framework will be defined and operationalized for the review.

Figure 1: Analytic framework

<table>
<thead>
<tr>
<th>Intervention/exposure</th>
<th>Comparator</th>
<th>Endpoint outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average consumption of alcoholic beverages</td>
<td>Primary Different average alcohol consumption or pattern of alcohol consumption among current drinkers</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>Pattern of consumption of alcoholic beverages (i.e., number of drinks per drinking day or drinks per drinking occasion)</td>
<td>Secondary Never drinkers</td>
<td>Myocardial infarction, coronary heart disease, coronary artery disease, Stroke (ischemic &amp; hemorrhagic separated when possible) Cardiovascular disease-related mortality</td>
</tr>
</tbody>
</table>

Population: Primarily adults 21y and older

Key Confounders: Sex, age, race/ethnicity, SES (income, education, health insurance, preventive health care access), eating pattern or diet quality, physical activity, smoking
Exposure-specific key confounders:
Key confounder for average consumption exposure: Pattern of consumption
Key confounder for pattern of consumption exposure: Average consumption
Other factors to be considered: Total energy intake (ideally without alcohol), age distribution of the study sample, menopausal status, medications, supplements, family history of CVD, beverage type (e.g., beer, wine, spirits), cholesterol (total cholesterol (TC), LDL, HDL, TC:HDL ratio, LDL:HDL ratio), triglycerides, blood pressure, glucose, insulin, diabetes status, anthropometry

Legend

The relationship of interest in the systematic review
Factors that may impact the relationship of interest in the systematic review

LITERATURE SEARCH AND SCREENING PLAN

Electronic databases

Listed below are the databases that will be searched to identify all potentially relevant articles that have been published to address the systematic review question. Additional details regarding the search strategy will be published upon completion of the review, and are available upon request prior to publication.

- Pubmed
- Cochrane
- Embase

Question: What is the relationship between alcohol consumption and risk of cardiovascular disease?
Inclusion and exclusion criteria

This table provides the inclusion and exclusion criteria for the systematic review. The inclusion and exclusion criteria are a set of characteristics used to determine which articles identified in the literature search will be included or excluded in the systematic review.

Table 1. Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>• Randomized controlled trials</td>
<td>• Uncontrolled trials</td>
</tr>
<tr>
<td></td>
<td>• Mendelian randomization studies</td>
<td>• Case-control studies</td>
</tr>
<tr>
<td></td>
<td>• Non-randomized controlled trials including quasi-experimental and controlled before-and-after studies</td>
<td>• Cross-sectional studies</td>
</tr>
<tr>
<td></td>
<td>• Prospective cohort studies</td>
<td>• Uncontrolled before-and-after studies</td>
</tr>
<tr>
<td></td>
<td>• Retrospective cohort studies</td>
<td>• Narrative reviews</td>
</tr>
<tr>
<td></td>
<td>• Nested case-control studies</td>
<td>• Systematic reviews</td>
</tr>
<tr>
<td></td>
<td>• Uncontrolled trials</td>
<td>• Meta-analyses</td>
</tr>
<tr>
<td>Study duration</td>
<td>• 4-week minimum for experimental studies</td>
<td>• Experimental studies &lt;4wk in duration</td>
</tr>
<tr>
<td></td>
<td>• No cutoff for observational studies</td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>• Observational studies enrolling &gt;1,000 participants</td>
<td>• Observational studies enrolling &lt;1,000 participants</td>
</tr>
<tr>
<td>Intervention/exposure</td>
<td>Average consumption of alcoholic beverages</td>
<td>• Data on ‘non-drinker’ groups where never and former drinkers are combined</td>
</tr>
<tr>
<td></td>
<td>Pattern of consumption of alcoholic beverages (i.e., number of drinks per day or drinks per drinking occasion)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Information on type of beverage (e.g., beer, wine, spirits) will be collected if available</td>
<td></td>
</tr>
<tr>
<td>Comparator</td>
<td>Primary</td>
<td>• No comparator</td>
</tr>
<tr>
<td></td>
<td>• Comparisons across different average alcohol consumption or pattern of alcohol consumption among current drinkers</td>
<td>• Comparisons with never and former drinkers as a combined ‘non-drinker’ group</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Comparisons between never drinkers and current drinkers</td>
<td></td>
</tr>
</tbody>
</table>
### Outcomes

**Health outcomes:**
- Cardiovascular disease
  - Myocardial infarction, coronary heart disease, coronary artery disease
- Stroke (separating ischemic & hemorrhagic when possible)
- Cardiovascular disease-related mortality

### Date of publication

- January 2010 – January 2020 (Building on 2010 DGAC review)
- Articles published prior to January 2010

### Publication status

- Articles published in peer-reviewed journals
- Articles not published in peer-reviewed journals, including unpublished data, manuscripts, reports, abstracts, pre-prints, and conference proceedings

### Language of publication

- Articles published in English
- Articles published in languages other than English

### Country

- Studies conducted in Very High or High Human Development Countries
- Studies conducted in Medium or lower Human Development Countries

### Study participants

- Human participants
- Males
- Females
- Animal subjects
- Hospitalized samples

### Age of study participants

- Primarily adults 21y and older
- Studies that enroll *some* participants under 21 years old
- Studies that *exclusively* enroll participants under 21 years old
<table>
<thead>
<tr>
<th>Category</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health status of study participants</td>
<td>• Studies that enroll participants who are healthy and/or at risk for chronic disease, including those with obesity</td>
<td>• Studies that exclusively enroll participants diagnosed with a disease, or hospitalized with an illness or injury. (For this criterion, studies that exclusively enroll participants with obesity will not be excluded).</td>
</tr>
<tr>
<td></td>
<td>• Studies that enroll some participants diagnosed with a disease</td>
<td>• Studies that exclusively enroll participants with high blood pressure or high cholesterol and are evaluating cardiovascular disease endpoint outcomes (i.e., studies that aim to prevent cardiovascular disease in participants who are at high risk</td>
</tr>
<tr>
<td></td>
<td>• Studies that exclusively enroll participants with high blood pressure or high cholesterol and are evaluating cardiovascular disease endpoint outcomes (i.e., studies that aim to prevent cardiovascular disease in participants who are at high risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Studies that enroll some participants with endpoint outcomes of cardiovascular disease</td>
<td></td>
</tr>
</tbody>
</table>

1 The Human Development classification was based on the Human Development Index (HDI) ranking from the year the study intervention occurred or data was collected. If the study did not report the year in which the intervention occurred or data were collected, the HDI classification for the year of publication was applied. HDI values are available from 1980, and then from 1990 to present. If a study was conducted prior to 1990, the HDI classification from 1990 was applied. When a country was not included in the HDI ranking, the current country classification from the World Bank is used instead.
LITERATURE SEARCH AND SCREENING RESULTS

This protocol will be updated with the literature search and screening results after the search and screening plan has been finalized and implemented.

The flow chart (Figure 2) below illustrates the literature search and screening results for articles examining the systematic review question. The results of the electronic database searches, after removal of duplicates, were screened independently by two NESR analysts using a step-wise process by reviewing titles, abstracts, and full-texts to determine which articles met the inclusion criteria. A manual search was done to find articles that were not identified when searching the electronic databases; all manually identified articles are also screened to determine whether they meet criteria for inclusion.

Figure 2: Flow chart of literature search and screening results (To be added)

Included Articles (To be added)

1. Ref

Excluded Articles (To be added)

The table below lists the articles excluded after full-text screening. At least one reason for exclusion is provided for each article, which may not reflect all possible reasons. Information about articles excluded after title and abstract screening is available upon request.

Table 2. Excluded articles

<table>
<thead>
<tr>
<th>Citation</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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</tbody>
</table>