Scientific Methodology Protocol for Public Comment
Alcohol Intake and Health Study

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach will be utilized to assess how alcohol impacts health (Guyatt et al., 2011a, Guyatt et al., 2011b, Guyatt et al., 2008). The project will assess the health impacts caused by ethanol in alcoholic beverages, and, therefore, will not distinguish between harms caused by different types of alcohol-containing products (e.g., beer, wine, spirits, and other alcoholic beverages). Harms caused by beer, wine, spirits, and other alcoholic beverages are based mainly on ethanol content, regardless of the form in which the ethanol is consumed, with the exception of alcohol poisonings which are caused predominately by the consumption of spirits (Rehm et al., 2017) and some other forms of unintentional injury where there is evidence of a higher risk due to the consumption of spirits (Rehm and Hasan, 2020). A systematic review of existing guidelines on alcohol and health as well as individual modelling projects will be performed to generate estimates of risk on (i) weekly thresholds to minimize long-term and short-term risks of morbidity and mortality, (ii) per occasion thresholds to minimize the short-term risks of injury or acute illness due to per occasion drinking, (iii) alcohol use among vulnerable populations, and (iv) situations and individual circumstances that are hazardous.

Systematic review of previous guidelines on alcohol and health

Although a 2016 systematic review highlighted differences in alcohol guidelines across 37 countries (Kalinowski and Humphreys, 2016), this review did not assess the scientific quality or the methodologies used to produce the various guidelines. Thus, this review is of limited value for the development of future guidelines. Accordingly, a systematic literature search of country-level guidance on alcohol and health will be performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and will be preregistered with PROSPERO (Moher et al., 2009b, Schiavo, 2019). Guidance on alcohol and health will be identified through websites of countries' health ministries using an internet search (i.e., '[country] AND health ministry'), and/or using the World Health Organization's Global Information System on Alcohol and Health (World Health Organization, 2019). A list of all country names will be

obtained from the World Health Organization (https://www.who.int/countries). In addition to searching websites of countries' health ministries, a peer-reviewed literature search for guidance documents will be performed. Articles will be identified through a systematic search of PubMed, PsycInfo, and Web of Science based on keywords and subject headings. As an example, the search strategy for PubMed is outlined in Table 1.

Table 1. Keyword search strategies for PubMed

Systematic Review	Key word category	Keywords
Guidance on alcohol and health		
	Study design	"Systematic review" OR "meta-analysis"
	Exposure	"alcohol" OR "ethanol"

Searches will be piloted and refined with the aid of a research librarian. No publication year or language restrictions will be applied. References contained in the articles included will be examined for relevant publications. The processes used for the screening of articles, data extraction, and standardization are outlined below.

Screening of articles

Titles and abstracts of articles will screened for inclusion by two independent reviewers and will be retained for full text review if they are deemed to have relevant information. Articles will be included if they meet the inclusion criteria outlined in Table 2. Inter-rater reliability of search results and data extraction will be cross-examined using Fleiss's weighted Kappa (McHugh, 2012, Hallgren, 2012, Landis and Koch, 1977). Assessment of full-text articles that are deemed to have uncertain eligibility for inclusion in the study will be conducted in duplicate and independently. Investigators will discuss differences in data extraction to reach a consensus.

Table 2. Inclusion and exclusion criteria

Inclusion criteria	
1	Systematic review and meta-analysis
2	Study was published on January 1, 2010 or afterwards
3	Exposure of interest is average alcohol use
4	The study reports an odds ratio, risk ratio, relative risk, or hazards ratio
5	The confounders taken into account in the underlying observational studies are reported
Exclusion criteria	
1	Study was beverage specific (wine, beer or spirits only) and not focused on total alcohol use
2	Study was focused on patterns of alcohol use and not total alcohol use

Data extraction

Data will be extracted (see Table A3) by two independent reviewers. In cases where there is not enough information presented in the article, corresponding authors will be contacted.

Table 3. Data extraction

Extracted data	
1	General information: authors' names, year of publication
2	Conflicts of interest
3	Funding sources
4	Study objective(s)
4	Systematic review registration
5	Inclusion criteria
6	Exclusion criteria
7	Definition of the outcome of interest
8	Definition of exposure of interest
9	Reference group used for the relative risk estimations
10	Databases searched
11	Search dates
12	Search terms
13	Total number of studies included in the quantitative synthesis
14	Data characteristics: number of cases, number of person years, attrition rates, estimates of effect and association (odds ratios, relative risks, hazards ratios) and their error (standard error or confidence intervals), and adjustment factors.
15	Alcohol exposure measurement: When standard drinks are the unit of measurement, standard conversion factors will be used to standardize alcohol consumption to grams per day of pure alcohol.
16	Methods used for the meta-analysis
17	Tests for publication bias
18	Tests for heterogeneity
19	Analyses will be performed, if possible, by sex, age, and race (i.e., Black, White, Hispanic, Pacific islander, Asian, Other)

Each guideline on alcohol and health will be evaluated according to its methodological rigor; the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument is the most commonly used guideline appraisal and consistency evaluation tool in the GRADE protocol and will be used here (Goldet and Howick, 2013, Hoffmann-Eßer et al., 2018). The review will summarize advice on (i) weekly thresholds to minimize long-term and short-term risks of morbidity and mortality, (ii) daily thresholds to minimize the short-term risks of injury or acute illness due to per occasion drinking, (iii) vulnerable populations, and (iv) situations and individual circumstances that are hazardous.

Collecting and generating evidence on weekly thresholds to minimize health risks

Two methods can be used to generate evidence on weekly thresholds to minimize health risks associated with different levels of average alcohol consumption: (i) the examination of all-cause absolute risk curves

from cohort studies (which include deaths from all causes, including conditions from which a causal relationship with alcohol use has not been determined), and (ii) the modelling of lifetime all-cause absolute alcohol-attributable mortality and morbidity risk curves by combining data on cause-specific relative risks with corresponding data on absolute mortality risks for lifetime abstainers. Based on the positives and negatives of each method, it was decided to proceed with the modelling of lifetime all-cause absolute alcohol-attributable mortality and morbidity risk curves (i.e., method (ii)) to align with the current practices of the Centers for Disease Control and Prevention, the World Health Organization, and the Institute for Health Metrics and Evaluation for estimating the burden of disease attributable to alcohol use (World Health Organization, 2018a, World Health Organization, 2018b, Rumgay et al., 2021, Griswold et al., 2018), and with other recently released guidance documents on alcohol and health (Department of Health [United Kingdom], 2016, Santé publique France, 2019, Alcohol Guidelines Project Team, 2020, Canadian Centre on Substance Use and Addiction, 2023).

Mathematical modelling will be used to estimate the lifetime risk of death and disability for different levels of average alcohol consumption. The risk curves generated will be based on the average amount of pure alcohol (i.e., ethanol). “People who consumed alcohol” will be defined as those individuals who consumed at least one standard drink (14 grams of alcohol) in the past year. The mathematical modelling will specifically examine the following outcomes: deaths, premature deaths (i.e., deaths that occur among those <70 years of age), years of life lost (YLL), years lived with disability (YLD: a measure of disease occurrence and the disability caused by the disease), disease and injury incidence, and disability adjusted years of life lost (a combination of both YLL and YLD).

The inclusion of diseases and injuries in the modelling of alcohol-attributable deaths and disability will be based on three criteria: (i) the disease or injury has to be causally related to alcohol use, (ii) a dose-response risk function needs to be available for the risk relationship between alcohol consumption (measured in grams per day) and the disease or injury of interest, and (iii) either death or disability needs to be measured specifically for the disease or injury causally related to alcohol use. Multiple data sources will be used to establish causality for this review. Causality can be assumed in all causes of death that are solely (100%)

attributable to alcohol use (e.g., alcoholic cardiomyopathy). Furthermore, this review will use information from the World Health Organization's Global Status Report on Alcohol and Health (GSRAH) (30), the Institute for Health Metrics and Evaluation's Global Burden of Disease study (28), and the World Cancer Research Fund's (WCRF's) Continuous Update Project (World Cancer Research Fund International and American Institute for Cancer Research, 2015, World Cancer Research Fund International and American Institute for Cancer Research, 2011b, World Cancer Research Fund International and American Institute for Cancer Research, 2011a), all of which have assessed which diseases and injuries are causally related to alcohol consumption. A sensitivity analysis will be performed in which causality will be based on conditions included in the Alcohol-Related Disease Impact application of the Centers for Disease Control and Prevention (CDC, 2024).

Estimation of the risk relationship between alcohol use and injury

This project aims to quantify the relationship between chronic alcohol use and injury occurrence. While the risk of injuries is directly related to levels of intoxication and the context of alcohol use, previous meta-analyses have demonstrated a strong correlation between chronic alcohol use and injury risk. This suggests that chronic alcohol use is a marker for specific patterns and contexts of alcohol use that increase the risk of injury. This study will focus on modeling the risk relationship by age and sex using data from multiple sources.

To estimate the risk relationship, data on the proportion of injuries where there is a blood alcohol content (BAC) above 0.10 g/dL will be combined with survey data on alcohol use. The use of a BAC of 0.10 g/dL as a threshold for categorizing non-attributable and alcohol-attributable injuries is based on the current practices of the Alcohol-Related Disease Impact (ARDI) application of the Centers for Disease Control and Prevention (CDC) (CDC, 2024). The use of BAC as a marker for alcohol-attributable traffic injury deaths will be facilitated by extracting data from the Fatality Analysis Reporting System (FARS), created by the National Highway Traffic Safety Administration (NHTSA). The National Violent Death Reporting System (NVDRS) will be used to obtain BAC information on violent deaths. For all other causes of injury

deaths, the proportion of injuries with a BAC above 0.10 g/dL for the United States reported by Alpert et al. (2022) will be utilized (Alpert et al., 2022).

The risk of injuries depends on the acute consumption of alcohol and the context of this consumption. As such, this risk will differ by country (as the context of alcohol use will differ by country). Similar to the Canadian, Australian, and United Kingdom guidelines (Department of Health [United Kingdom], 2016, Alcohol Guidelines Project Team, 2020), the estimation of the relative risks for injuries in the United States is based on a two-step process. The first step is to determine the shape of the risk curve between alcohol use and the risk of injuries. The risk relationship shape will be taken from the most accurate systematic review between alcohol use and injuries.

The second step in the estimation of the relative risks for people in the United States who drink (i.e., people who consumed alcohol in the past year; RR_D) is based on the average amount of alcohol consumed per day (operationalized as x). The process used to estimate the RR_D is based on data regarding the population-attributable fractions (PAFs) of road injuries (using toxicology reports on blood alcohol content (BAC) as a proxy) and data on alcohol use. While a proportion of injuries that occur among people who have a BAC below 0.10 g/dL may also be causally associated with alcohol (in particular among people with a BAC between 0.05 to 0.10 g/dL) (Cherpitel et al., 2019), these injuries are not modelled due to a lack of certainty as to whether they are attributable to alcohol use.

The derivation of the relative risk for an alcohol-attributable injury among drinkers (RR_D) is based on the estimate of the population relative risk (compared to a counterfactual scenario of everyone in the population abstaining from alcohol for their lifetimes); such an estimation uses Formulas 1 and 2. The population relative risk can be modelled using Formula 2 based on the risk among people who drink (RR_D), prevalence of past-year drinkers (P_D), and prevalence of past-year abstainers (P_A). To solve for the RR_D in equation 3, we will transform this Formula (see Formula 4) and solve for the RR_D using the uniroot function of the statistical software package R (R Core Team, 2013).

[Formula A1]

$$PAF = (RR_{POP} - 1)/RR_{POP}$$

[Formula A2]

$$RR_{POP} = 1/(1 + PAF)$$

[Formula A3]

$$RR_{POP} = P_A + \sum_{x=1}^{xn} (P_{D_x} \cdot RR_{D_x})$$

[Formula A4]

$$0 = P_{LA} + P_{PD} + \sum_{x=1}^{xn} (P_{D_x} \cdot RR_{D_x}) - RR_{POP}$$

Systematic Review of Meta-analyses

This study also aims to conduct a systematic review of all relevant meta-analyses that have investigated diseases causally associated with alcohol use. Relative Risk (RR) estimates for each included disease category and injury will be obtained from systematic reviews identified in the evidence review process. The RRs in the reviews will have used people who are lifetime abstainers as a reference group. In cases where lifetime abstainers were not the reference group, these RRs will be rescaled so that the lifetime abstainers are the reference group.

PubMed (including MEDLINE and Life Science Journals) and Web of Science will be searched for relevant articles based on keywords and subject headings. The search strategy for MEDLINE, as an example, is outlined in Table 1. Searches will be piloted and refined with the aid of a research librarian. No language restrictions will be applied. A publication restriction of 2010 and later will be applied to ensure that only recent summaries of the epidemiological evidence are included in the review. References contained in the articles included will be examined for relevant publications. Subject matter experts will be contacted to identify relevant publications. Previous systematic reviews, the International Agency for Research on Cancer Monographs, and the WCRF's Continuous Update Project reports will be searched for relevant publications.

All systematic reviews will be evaluated for quality using the criteria from A Measurement Tool to Assess Systematic Reviews (AMSTAR 2) and from the Risk of Bias in Systematic Reviews (ROBIS) tool (Shea et al., 2017, Whiting et al., 2016). Quality assessments will consider study design and adjustments for confounding factors, among other criteria. In addition, these quality assessments will take into account factors specific to alcohol epidemiological studies. For example, biases in exposure and outcome measurements, such as the use of current abstainers instead of lifetime abstainers as the risk reference group (i.e., allowing the misclassification of former drinkers as lifetime abstainers), and how representative the cohorts are of the US general population (Rehm et al., 2008a).

The systematic review will be pre-registered with PROSPERO, and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009a).

Selection of Meta-analyses

Meta-analyses used in the modelling process will be selected by panels of nominal group interview experts in the distinct areas of (i) cancer, (ii) cardiovascular diseases, (iii) digestive conditions, (iv) neurological disorders, (v) infectious diseases, and (vi) injuries who will be consulted to determine the RR estimates for each condition considered to be causally related to alcohol use. The sampling frame of experts will be decided based on the authors who have published the largest number of first and last author publications concerning the above-noted disease areas (as determined by performing a PubMed Search) in the past 10 years. These authors will be asked to participate in the nominal group interview panels. Quota sampling will also be used to establish nominal group interview panels which ensure diversity and representation based on geographic location, sex, race and ethnicity, which will be reported by the potential participants before they are included in the nominal group interview panels. Specifically, the following parameters will be established: (i) a minimum of 90% of the experts will be United States-based, (ii) a minimum of 40% of the experts will identify as female, with a goal of 50%, and (iii) no more than 80% of the experts will be non-Hispanic White, with a goal of no more than 60% of participants being non-Hispanic White. Experts will be required to have no potential conflicts of interest.

To evaluate whether conflicts of interest (COI) could compromise the impartiality of information provided by nominal group members both actual conflicts and the perception of conflicts of interest will be assessed. The project will utilize the definition of a COI as outlined by the International Committee of Medical Journal Editors (ICMJE). Prior to initiating contact with researchers to solicit their participation in nominal group interviews, we will conduct a review of the author's most recent article to identify any COI. Additionally, authors contacted to participate in the study will be required to complete an ICMJE disclosure form, disclosing any potential COIs relevant to this project. The assessment of COIs will be conducted independently by the statistician and a trained research analyst. Any disparities in COI assessments will be resolved by the Scientific Review Panel and Technical Review Subcommittee.

Once the panels of experts have been established, a nominal group process will be used to determine the most appropriate meta-analyses to use in the modelling study. The nominal group interview allows for the selection of meta-analyses avoiding group think (as compared to group interviews), and reduces random error in decision making by increasing the number of people whose opinions are considered (e.g., (Rehm and Gadenne, 2013)).

Selection of the most accurate meta-analyses for each condition causally related to alcohol use

To ensure the selection of the most precise relative risks for each condition causally linked to alcohol use, nominal group members will receive data extracted from systematic reviews and meta-analyses, along with the A Measurement Tool to Assess Systematic Reviews (AMSTAR 2) checklist and the Risk of Bias in Systematic Reviews (ROBIS) tool for each review (Shea et al., 2017, Whiting et al., 2016). With this information at hand, experts within each group will rank the meta-analyses and provide free-form comments on the ranking.

For the second round of reviews, all participants in the expert group will receive summary statistics of the article rankings, along with any comments from other experts. Group members will then be asked to re-rank the top 7 reviews (or all reviews if fewer than 7 systematic reviews exist). The results of this ranking exercise will be processed using a Borda count algorithm to select the most accurate systematic review (Emerson, 2013). In the event of a tie in the top-ranked systematic review, each expert group will vote to determine the most accurate systematic review among the tied systematic reviews.

All panels will also provide input on the magnitude of the underreporting of alcohol consumption in medical observation studies, as well as input on vulnerable populations and situations and individual circumstances where the consumption of alcohol is hazardous. In the first round, each expert will be provided with the results of the preregistered systematic scoping review, and will be asked to provide free-text comments on the interpretation of these studies. When necessary, experts will be contacted to clarify their answers. The scientific review committee will analyze answers to identify potential underlying patterns and prepare a draft consensus position. Each expert will also be asked the degree to which they hypothesize alcohol use to be misestimated in population surveys (what fraction is due to spillage and wastage, and what fraction is due to survey and response biases) and in cohort studies.

In the second round of interviews, based on feedback regarding the results of round 1, the consolidated information will be provided to the expert participants. During these interviews, experts will interact and clarify their positions in small group virtual meetings. At the end of the second round of interviews, all experts will be asked to complete a questionnaire which will be used to build a consensus on which meta-analyses to include in the modelling study.

In the event that this process proves too time consuming, selection of meta-analysis will be modified and streamlined. The streamlined approach will involve selecting the meta-analysis for modelling based on its performance on the AMSTAR 2 and ROBIS tools, prioritizing the study with the least potential risk of bias.

Data sources: Mortality and Alcohol Exposure

A comparative risk method (i.e., the systematic evaluation of changes in population health that would be avoided in the absence of a risk factor) will be used to estimate the alcohol-attributable burden of disease. For this method, the reference group of lifetime abstainers will be utilized – thus determining the number of deaths and the burden of disability that would not occur if alcohol consumption was eliminated (see: (Shield et al., 2017, Department of Health [United Kingdom], 2016, Santé publique France, 2019, Alcohol Guidelines Project Team, 2020)). Lifetime risk curves will be based on an exposure of average grams of pure alcohol (i.e., ethanol) consumed per week.

Data on the number of deaths that occurred in the United States by age, sex, and cause will be obtained from the National Vital Statistics System (Ahmad et al., 2022, Ahmad et al., 2023). Data on population by age and sex will be obtained from the Census Bureau of the United States (United States Census Bureau, 2023). Data on disease incidence and YLD will be obtained from the Institute for Health Metrics and Evaluation's Global Burden of Disease study (Institute of Health Metrics and Evaluation, 2021). Life tables by sex will be obtained from the Centers for Disease Control and Prevention, National Center for Health Statistics (Arias et al., 2022).

Estimating the burden of disease in the United States in 2022 attributable to alcohol use

The key component of population-attributable fractions (PAF) allows us to express the proportion of the risk of death due to alcohol consumption. These attributable fractions will be generated using a Levin-based method that pools data on alcohol exposure with the associated relative risk estimates from the identified systematic reviews (Levin, 1953a, Rehm et al., 2008a).

The number of alcohol-attributable deaths will be calculated using the corresponding PAF applied to the death estimates by sex, age, and cause. Next, the risk of death for lifetime abstainers for specific health conditions and age will be calculated by taking the total alcohol-attributable deaths and subtracting that number from the total number of deaths, which is then divided by the total population of United States. All such calculations will be completed by age and sex.

This study aims to estimate the burden of disease 2022 in the United States attributable to alcohol use using the relative risks obtained from a systematic review. Mortality estimates will be obtained from the National Center for Health Statistics (NCHS) National Vital Statistics System, while exposure data will be obtained from various sources such as the National Alcohol Survey, NSDUH, NHIS, NESARC-III, and BRFSS.

A comparative risk assessment methodology will be utilized to estimate the burden of disease in 2022 attributable to alcohol use. These estimations will be based on the theoretical minimum risk exposure level (TMREL) of lifetime abstention (LA) from alcohol use. LA will be utilized as a TMREL based on historical

precedent; however, no assumption will be made about the exposure to alcohol which resulted in the lowest risk of overall health loss (GBD 2016 Alcohol Collaborators, 2018). The alcohol-attributable health burden estimations will be based on alcohol consumption statistics from 2012 for cancer, and from 2022 for all other diseases causally associated with alcohol use. For diseases which were 100% attributable to alcohol, the population-attributable fraction (PAF) will be assumed to be 1.

To obtain data on alcohol exposure in the United States, we will extract information from a collective re-analysis of population surveys, including the National Alcohol Survey, NSDUH, NHIS, NESARC-III, and BRFSS. These surveys provide comprehensive data on alcohol consumption patterns and allow us to estimate the prevalence of different levels of alcohol use in the population. To correct these surveys for undercoverage of alcohol use, data on adult *per capita* consumption will be obtained from the NIAAA (Slater and Alpert, 2021) using the methods of Rehm et al., 2010 and Kehoe et al., 2012 (Kehoe et al., 2012, Rehm et al., 2010).

The correction factor to account for (i) alcohol that was not consumed, and (ii) the underreporting of alcohol consumption in medical observation studies from which the relative risk estimates used in this study will be obtained will be applied to alcohol use data. The correction factor will be determined through the nominal group study. A study by Stockwell and colleagues found that cohort studies of the relationship between alcohol consumption and all-cause mortality had a coverage rate (when compared to *per capita* consumption) of 61.7% (ranging from 29.2% for Russia to 96.5% for Japan) (Stockwell et al., 2018). The method used to model alcohol consumption among people who drink assumes that the undercoverage of alcohol consumption is constant by age and sex.

Mortality data by age, sex, race, cause, will be obtained from the National Vital Statistics System (Arias and Xu, 2022, Xu et al., 2018). Morbidity data will be obtained from the Institute for Health Metrics and Evaluation Global Burden of Disease study (Murray et al., 2020). Population data will be obtained for 2022 by age, sex, and race from the United States Census Bureau.

The PAF for alcohol use is estimated based on a Levin-based method which combines data on alcohol exposure (the prevalence of lifetime abstainers (P_{LA}), prevalence of past year abstainers (i.e., previous drinkers) (P_{PD}), and prevalence of drinkers (P_D) with corresponding relative risk estimates (Levin, 1953b, Rehm et al., 2008b) (see Formula A5).

[Formula A5]

$$PAF = \frac{P_{LA} + P_{PD}RR_{PD} + \int_{0.037\ g/day}^{250\ g/day} P_D(x) \cdot RR_D(x)dx - 1}{P_{LA} + P_{PD}RR_{PD} + \int_{0.037\ g/day}^{250\ g/day} P_D(x) \cdot RR_D(x)dx}$$

The number of alcohol-attributable deaths (AA_Deaths) and alcohol-attributable years live with disability (YLD) (AA_YLD) will be estimated by applying the PAFs to corresponding deaths and YLD estimates by sex, age, and cause of death or disability. The risk of death for people who engaged in lifetime abstention (Risk_D_LA) for a given cause of death (c) and age (a) will be estimated by subtracting the total number of alcohol-attributable deaths (AA_Deaths) from the total number of deaths and dividing this number by the population (Pop in the formulas below) (See Formula A6). Similarly, the risk of disability for people who engaged in lifetime abstention (Risk_D_YLD) for a given cause of disability (c) and age (a) will be estimated by subtracting the total number of alcohol-attributable YLD (AA_YLD) from the total number of YLD and dividing this number by the total population of ther United States (See Formula A7).

[Formula A6]

$$Risk\_D\_LA_{a,s,c} = \left[Deaths_{a,s,c} - AA\_Deaths_{a,s,c}\right]/Pop_{a,s}$$

[Formula A7]

$$Risk\_YLD\_LA_{a,s,c} = \left[YLD_{a,s,c} - AA\_YLD_{a,s,c}\right]/Pop_{a,s}$$

Relative risks from the systematic review of meta-analyses will be combined with estimates of the risk of mortality and morbidity for lifetime abstainers to estimate lifetime risk curves. A comparative risk assessment methodology will be used to estimate the risk of mortality and morbidity for lifetime abstainers. Lifetime risk curves will be calculated by estimating alcohol-attributable mortality and morbidity risk by cause, age, and sex. The life-year specific alcohol-attributable mortality risks will be multiplied by the YLL for each cause of death. The lifetime risk curves will also account for competing causes of death (i.e., deaths which occur that are not attributable to alcohol use).

Lifetime risks of alcohol-attributable mortality and morbidity

The lifetime risks of experiencing alcohol-attributable mortality and morbidity will be estimated based on a cause-specific approach. The lifetime risks of experiencing alcohol-attributable mortality and morbidity represent absolute risks. The first step in this approach is the estimation of age-, sex- and cause-specific alcohol-attributable mortality and morbidity risks. Cause-specific alcohol-attributable mortality risk (Risk_D_AA) for a given life year will be estimated by multiplying Risk_D_LA by the corresponding relative risk given an age, sex, cause, and average daily alcohol consumption amount (see Formula A8). Cause-specific alcohol-attributable morbidity (measured in YLD) risk will be estimated by multiplying Risk_YLD_LA by the corresponding relative risk given an age, sex, cause, and average daily alcohol consumption amount (see Formula A9).

[Formula A8]

$$Risk\_D\_AA_{a,s,c,x} = Risk\_D\_LA_{a,s,c} \cdot (RR_{a,s,c}(x) - 1)$$

[Formula A9]

$$Risk\_YLD\_AA_{a,s,c,x} = Risk\_YLD\_LA_{a,s,c} \cdot (RR_{a,s,c}(x) - 1)$$

Total alcohol-attributable mortality risk and morbidity risk for a given life year will be estimated by summing all cause-specific alcohol-attributable mortality risk and morbidity risk for a given life year, respectively (see Formulas A10 and A11).

[Formula A10]

$$Risk\_D\_AA_{a,s,x} = \sum_{c=ci}^{cn} Risk\_D\_AA_{a,s,c,x}$$

[Formula A11]

$$Risk\_YLD\_AA_{a,s,x} = \sum_{c=ci}^{cn} Risk\_YLD\_AA_{a,s,c,x}$$

Estimates of lifetime risks of alcohol-attributable mortality and morbidity will account for competing causes of death (i.e., deaths which are not attributable to alcohol use); to account for competing causes of death, the probability of survival for a given life year will be estimated based on a person's sex and on average daily alcohol consumption. The age-specific mortality risk will be estimated as the sum of the risk of an alcohol-attributable death and the risk of a non-alcohol attributable death. Based on age -specific mortality risk, we will estimate the probability of being alive at a given life course age (see Formula A12).

[Formula A12]

$$Alive_{a,s,x} = Alive_{a-1,s,x} \cdot \left[1 - (Risk\_D\_AA_{a,s,x} + Risk\_D\_LA_{a,s})\right]$$

The total lifetime risk of an alcohol-attributable death will then be estimated by summing the one year age-specific alcohol-attributable mortality risks multiplied by the proportion of people alive in the population at the end of a given life year based on their sex and on average daily alcohol consumption (see Formula A13). The life risk of alcohol-attributable YLL will then be estimated by summing the life year-specific alcohol-attributable mortality risks multiplied by the years of life lost for that death and the proportion of people alive in the population at the end of a given age based on their sex and on average daily alcohol consumption (see Formula A14). The life risk of alcohol-attributable YLD will then be estimated by summing the life year-specific alcohol-attributable YLD risks multiplied by the proportion of people alive in the population at the end of a given life year based on their sex and on average daily alcohol consumption (see Formula A15). The life risk of disability-adjusted life years (DALYs) lost will be estimated by summing the lifetime risks of alcohol YLL and YLD (see Formula A16).

[Formula A13]

$$Lifetime\_R\_Death_{s,x} = \left[\sum_{a=0}^{n} Alive_{a,s,x} \cdot Risk\_D\_AA_{a,s,x}\right]$$

[Formula A14]

$$Lifetime\_R\_YLL_{s,x} = \left[\sum_{a=0}^{n} Alive_{a,s,x} \cdot Risk\_D\_AA_{a,s,x} \cdot YLL_{a,s}\right]$$

[Formula A15]

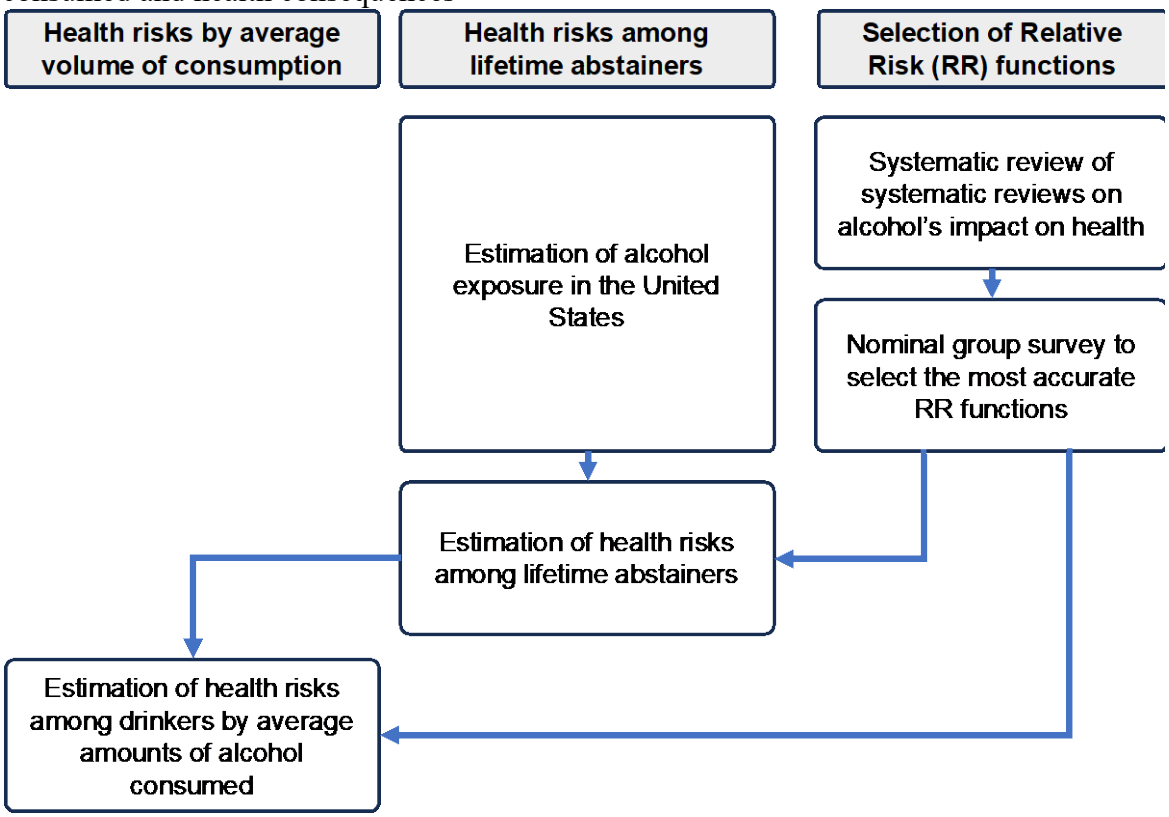
$$Lifetime\_R\_YLD_{s,x} = \left[\sum_{a=0}^{n} Alive_{a,s,x} \cdot Risk\_YLD\_AA_{a,s,x}\right]$$

[Formula A16]

$$Lifetime\_R\_DALYs_{s,x} = Lifetime\_R\_YLL_{s,x} + Lifetime\_R\_YLD_{s,x}$$

The lifetime risk curves for alcohol-attributable mortality and morbidity risks will be provided to members of all nominal group interview panels. We will then use the nominal group interview process, including all members from all panels, to establish data on weekly and/or daily alcohol use thresholds.

Figure 1. Flow chart for estimating the relationship between average volume of alcohol consumed and health consequences



Collecting and generating evidence on per occasion alcohol use thresholds to minimize short-term health risks

Per occasion alcohol use is based on consumption during particular times or occasions, (as compared to average consumption which is determined by dividing total consumption by time). As such, per occasion consumption is related to consumption patterns, and provides a proxy measure for blood alcohol concentrations that might be achieved based on a particular level of per occasion consumption. High per occasion consumption resulting in high blood alcohol concentrations is strongly associated with "acute" disease processes such as injuries (Cherpitel et al., 2018), but also is associated with the risk of infectious diseases (Romeo et al., 2010), breast cancer (Shield et al., 2016), ischemic heart disease and ischemic stroke (Roerecke and Rehm, 2014), diabetes (Holst et al., 2017), epilepsy (Alldredge and Lowenstein, 1993, Samokhvalov et al., 2010), and liver cirrhosis (Llamosas-Falcón et al., 2023).

Multiple sources of data will be used to assess the health impacts of per occasion alcohol use, namely: (i) results from the systematic review of meta-analyses and systematic reviews which summarize how drinking patterns affect the risk of disease and injury occurrence, (ii) results from a reanalysis of United States' emergency room case-cross-over studies which examined the relationship between alcohol use and injury occurrence (Cherpitel et al., 2018), and (iii) results from roadside survey studies where the blood alcohol content of road injury decedents was compared to that of drivers randomly selected from the same road on the same day and at the same hour as the fatal crash case (Romano et al., 2018, Kelley-Baker et al., 2013). Based on these data sources, the scientific review panel will provide statements about the risk or relative risk associated with per occasion consumption. The nominal group interviews will follow a two round structure that will also be used to determine the best RR functions to be used in the modelling of the health impacts of alcohol use.

Collecting and generating evidence on the effects of alcohol use among vulnerable populations, and situations and individual circumstances where consuming alcohol is hazardous

The planned study will build upon previous guidelines (identified through the previously noted systematic review) using nominal group interviews to provide a synthesis of the latest evidence on the effects of alcohol

use among vulnerable populations (e.g., pregnant persons, underage youth), and situations and individual circumstances where consuming alcohol is hazardous. The experts selected from the nominal group surveys will review evidence of individuals in vulnerable populations or who are subject to situations and individual circumstances where consuming alcohol is hazardous to determine if these considerations should be included in the results of the study. In addition, experts who are part of the nominal group interviews will be invited to identify vulnerable populations and situations and individual circumstances which have not been previously noted in any other guidelines, but where current research supports that these vulnerable populations and/or situations and individual circumstances should be added to alcohol and health guidance documents, as well as any relevant peer-reviewed research documents which support their addition. The structure of these nominal group interviews will follow a two round structure that will also be used to determine the best RR functions to be used in the modelling of the health impacts of alcohol use.

Collecting and generating evidence on the public's understanding and reaction to data on alcohol consumption and health

To understand how our assessment of the health impacts of alcohol use align with the alcohol consumption of the general public, we will examine alcohol use in the general population using data from the National Alcohol Survey, National Survey on Drug Use and Health (NSDUH), National Health Interview Survey (NHIS), The National Epidemiologic Survey on Alcohol and Related Conditions - III (NESARC-III), and Behavioral Risk Factor Surveillance System (BRFSS) in order to obtain data on alcohol exposure in the United States. These population surveys, which have differing sampling frames, response rates, and validation of self-reporting of alcohol use, provide comprehensive data on alcohol consumption patterns and allow estimations of the prevalences of different levels of alcohol use in the population.

To gain an understanding of the public's understanding and reaction to the risks of alcohol use on health produced by this project, we will engage in public consultations using a mixed methods (quantitative and quantitative) approach. Public consultation recruitment will be performed using a convenience sampling methodology. Specifically, the consultation process will be promoted through institutional websites, mass emails, social media, and national and regional digital news media advertisements. All residents of the

United States will be eligible to participate. Individuals who do participate will be asked categorical and open-ended questions (in English) about:

(i) their demographics, including geographic location;

(ii) their profession;

(iii) their current sources of information on health and, more specifically, on the impacts of alcohol consumption on health;

(iv) current and previous health conditions;

(v) their awareness of the *Dietary Guidelines for Americans, 2020-2025*;

(vi) their alcohol use and whether they are trying to follow the alcohol consumption guidance in the *Dietary Guidelines for Americans, 2020-2025* and their reasons for following or not following the guidelines;

(vii) their requirements for and expectations of the *Dietary Guidelines for Americans, 2026-2030*;

(viii) what information they found useful about the project's assessment on alcohol and health; and

(ix) what challenges they had in interpreting the project's assessment on alcohol and health.

Aggregate information on the demographics of participants will be examined, published and compared to United States Census data to assess whether participants in the consultation process are representative of the general population (United States Census Bureau, 2023). A thematic analysis will be performed on responses to open-ended questions to identify common themes between respondents' answers to each of the questions. As the information obtained from an analysis of the findings of the consultation process is to be used to revise and refine the research results, both a semantic and latent coding approach and analysis will be employed. Furthermore, to analyse the qualitative data, Braun and Clarke's six phases of thematic analysis approach will be utilized (Clarke and Braun, 2017).

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Appendix: Data Sources

Table A1. Methodology and data sources

Data on alcohol's impact on health	**Methodology used to reach results**	**Underlying data sources**
Weekly / daily thresholds to minimize long-term and short-term risks of morbidity and mortality	Results based on nominal group interviews	Lifetime risk of alcohol-attributable mortality and morbidity at different drinking levels
Per occasion thresholds to minimize the short-term risks of injury or acute illness due to per occasion drinking	Results based on nominal group interviews	Systematic review of meta-analyses which summarize how drinking patterns affect the risk of disease and injury occurrence
		Results from a reanalysis of United States' emergency room case-cross-over studies
		Results from roadside survey studies
Alcohol use among vulnerable populations	Results based on nominal group interviews	Systematic review of previously published guidelines
Situations and individual circumstances that are hazardous		

Table A2. Alcohol survey data

Survey name	Survey year	Sample size	Sampling method	Response rate	Sampling frame	Questions measuring alcohol use
Behavioral Risk Factor Surveillance System (BRFSS)	2022	445,132	Random-digit-dialing (RDD) of landlines and cellphones	45.0%	Noninstitutionalized adults, 18 years of age or older, residing in all 50 states, the District of Columbia (DC), Guam, the Commonwealth of Puerto Rico, and the US Virgin Islands	Quantity and frequency of past 30-day alcohol use
National Alcohol Survey (NAS)*	2014-2015	5,634	Random-digit-dialing (RDD) of landlines and cellphones	43.4%	Adults 18 years of age and older, residing in all 50 states (plus Washington, DC)	Lifetime abstention Former drinking Quantity and frequency of past year alcohol use Age of initiation
The National Epidemiologic Survey on Alcohol and Related Conditions - III (NESARC-III)	2012-2013	36,309	Face-to-face interviews	60.1%	Adults 18 years of age and older, residing in the contiguous United States, Alaska and Hawaii	Lifetime abstention Former drinking Quantity and frequency of past year alcohol use (by beverage type)
National Health Interview Survey (NHIS)	2022		Face-to-face interviews	47.7%	Noninstitutionalized U.S. adults, 18 years of age and older, residing in the 50 states and the District of Columbia living in households and noninstitutional group quarters (e.g., homeless shelters, rooming houses, and group homes)	Lifetime abstention Former drinking Quantity and frequency of alcohol use (past 30 days)
National Alcohol Survey, National Survey on	2022	71,369	Face-to-face interviews and online questionnaires	12.1%	US residents, 12 years or older, living in households (e.g., individuals living in houses or	Lifetime abstention Former drinking

Drug Use and Health (NSDUH)					townhouses, apartments, and condominiums; civilians living in housing on military bases), and individuals in noninstitutional group quarters (e.g., shelters, rooming or boarding houses, college dormitories, migratory workers' camps, halfway houses)	Quantity and frequency of alcohol use (past 30 days) Age of initiation

* oversampling of Black non-Hispanic and Hispanic groups (with interviews in Spanish for those requesting/needing this)

Table A3. Behavioral Risk Factor Surveillance System (BRFSS) questions

Domain	Question	Answers
Frequency of alcohol use (past year)	During the past 30 days, how many days per week or per month did you have at least one drink of any alcoholic beverage	_____ Days per week _____ Days in past 30 days
Quantity of alcohol use (on drinking occasions)	During the past 30 days, on the days when you drank, about how many drinks did you drink on the average?	_____ Number of drinks

Source: https://www.cdc.gov/brfss/questionnaires/pdf-ques/2022-BRFSS-Questionnaire-508.pdf

Table A4. National Alcohol Survey (NAS) questions

Domain	Question	Answers
Frequency of wine use (past year)	Thinking about the last 12 months, how often do you usually have wine? Is it:	More than once a day Once a day Nearly every day Three or four times a week Once or twice a week Two or three times a month About once a month Less than once a month but at least once a year Less than once a year
Frequency of beer use (past year)	How often do you usually have beer or malt beverages?	More than once a day Once a day Nearly every day Three or four times a week Once or twice a week Two or three times a month About once a month Less than once a month but at least once a year Less than once a year
Frequency of spirits use (past year)	And how often do you usually have drinks containing whiskey or any other liquor, including scotch, bourbon, gin, vodka, rum, and so on?	More than once a day Once a day Nearly every day Three or Four times a week Once or twice a week Two or three times a month About once a month Less than once a month but at least once a year Less than once a year
Frequency of alcohol use (past year)	Thinking of your overall drinking in the last 12 months, how often do you usually have any kind of beverage containing alcohol - whether it is wine, beer, liquor, or any other drink?	More than once a day Once a day Nearly every day Three or Four times a week Once or twice a week Two or three times a month About once a month Less than once a month but at least once a year Less than once a year
Lifetime alcohol use	Have you never had any beverage containing alcohol?	Yes No
Past year alcohol use	Think back over the last year, since (CURRENT DATE LAST YEAR). Did you have a whole drink of any alcoholic beverage like wine, beer, liquor or mixed	Yes No

Domain	Question	Answers
	drinks in these last twelve months?	
Former drinker	Have you drunk any alcohol in the past but not in the past year or currently?	Yes No
Quantity wine	Think of all the times you have had wine recently. On those days when you drink wine, how many drinks do you typically have?	_____ Number
Quantity beer	Think of all the times you have had beer or malt beverages recently. On those days when you drink beer, how many drinks do you typically have?	_____ Number
Strength beer	When you drink beer, about how much of the time do you drink higher strength beer?	Nearly every time More than half the time Less than half the time Once in a while Never
Quantity spirits	Think of all the times you have had drinks containing whiskey, liquor, or spirits recently. On those days when you drink these spirits drinks, how many drinks do you typically have?	_____ Number
Strength spirits	What spirits-based drink have you drunk the most in the last 12 months?	Strong cocktails (or those with 3 or more spirits) (ex: martini, Manhattan, Long Island iced tea) Margarita (any variation) Straight spirits (ex: shot or shooter of whiskey, gin, cognac, vodka or tequila) Spirits with ice and/or water (ex: vodka on the rocks, whiskey with water) Mixed drink with soda or juice (ex: rum and coke, gin & tonic, vodka & orange juice) Liqueurs, schnapps, or milk/cream-based spirits (ex: Bailey's, peach Schnapps, Kahlua, egg nog) Other mixed drinks (cosmopolitan, daiquiri, bloody Mary, mojito)
Age of initiation	About how old were you when you first started drinking	_____

Domain	Question	Answers
	alcoholic beverages, not including small tastes?	

Source: https://arg.org/center/national-alcohol-surveys/

Table A5. NESARC III alcohol questions

Domain	Question	Answers
Lifetime drinking	In your entire life, have you had at least 1 drink of any kind of alcohol, not counting small tastes or sips?	Yes No
Past year drinking	During the last 12 months, that is, since last (month one year ago), did you have a total of at least 12 drinks of any kind of alcohol?	Yes No
Total alcohol use	During the last 12 months, did you have at least 1 drink of any kind of alcohol?	Yes No
	During the last 12 months, about how often did you drink any kind of alcoholic beverage?	Every day Nearly every day 3 to 4 times a week 2 times a week Once a week 2 to 3 times a month Once a month 7 to 11 times in the last year 3 to 6 times in the last year 1 or 2 times in the last year
	How many drinks did you USUALLY have on days when you drank during the last 12 months?	_____ Number
Cooler consumption	During the last 12 months, did you drink any prepackaged alcoholic coolers?	Yes No
	During the last 12 months, about how often did you drink any coolers?	Every day Nearly every day 3 to 4 times a week 2 times a week Once a week 2 to 3 times a month Once a month 7 to 11 times in the last year 3 to 6 times in the last year 1 or 2 times in the last year
	What was the size of the TYPICAL bottle, can or glass of cooler that you USUALLY drank during the last 12 months?	8-ounce (small) bottle or can 12-ounce (regular) bottle or can 16-ounce (large) bottle or can 2-ounce can or bottle 3-ounce glass 4-ounce glass 5-ounce glass 6-ounce glass 7-ounce glass

Domain	Question	Answers
		8-ounce glass 9-ounce glass 12-ounce glass 15-ounce glass 18-ounce glass Other
	How many (units reported in 5c) of cooler did you USUALLY drink on days when you drank coolers?	_____ Number
	During the last 12 months, what brand of cooler, hard lemonade, hard iced tea, hard cider, alcoholic energy drink, or prepackaged cocktail did you drink the most often?	_____
Beer consumption	During the last 12 months, did you drink any beer or malt liquor? Do not count nonalcoholic beers.	Yes No
	During the last 12 months, about how often did you drink any beer or malt liquor?	Every day Nearly every day 3 to 4 times a week 2 times a week Once a week 2 to 3 times a month Once a month 7 to 11 times in the last year 3 to 6 times in the last year 1 or 2 times in the last year
	What was the size of the TYPICAL can, bottle, or glass of beer or malt liquor that you USUALLY drank during the last 12 months?	7 or 8-ounce (pony size) can, bottle or glass 10-ounce (small) can, bottle or glass 12-ounce (regular size) can, bottle or glass 16-ounce (large) can, bottle or glass 22 to 25-ounce (extra large) can, bottle or glass 40 to 45-ounce (jumbo) can or bottle Mug Pint Pitcher Other
	How many (units reported) of beer or malt liquor did you	_____ Number

Domain	Question	Answers
	USUALLY drink on days when you drank beer?	
	During the last 12 months, what brand of beer or malt liquor did you drink the most often?	_____
Wine, including champagne, sparkling wine, fortified wine consumption	During the last 12 months, did you drink any type of wine? Do not count any wine coolers you may have told me about earlier.	Yes No
	During the last 12 months, about how often did you drink any type of wine?	Yes No
	What was the size of the TYPICAL glass or bottle of wine that you USUALLY drank during the last 12 months? Please do not include the amount of any soda or ice that may have been added.	3-ounce glass 4-ounce glass 5-ounce glass 6-ounce glass 7-ounce glass 8-ounce glass 9-ounce glass 12-ounce glass 15-ounce glass 18-ounce glass 187 ml. individual serving bottle (usually sold in 4-packs) 375 ml. bottle (half bottle of wine) or ½ carafe 750 ml. bottle (regular size wine bottle) or full carafe Other – Specify
	How many (units reported) of wine did you USUALLY drink on days when you drank wine?	_____ Number
	During the last 12 months, what brand of wine, champagne, sparkling wine, fortified wine, or low-alcohol fruit-flavored wine did you drink the most often?	_____
Liquor, including mixed drinks and liqueurs consumption	During the last 12 months, did you drink any liquor, including mixed drinks and liqueurs? Do not count any liquor-based coolers or prepackaged cocktails that you may have told me about earlier.	Yes No
	During the last 12 months, about how often did you drink any liquor?	Every day Nearly every day 3 to 4 times a week 2 times a week

Domain	Question	Answers
		Once a week 2 to 3 times a month Once a month 7 to 11 times in the last year 3 to 6 times in the last year 1 or 2 times in the last year
	How much liquor did you USUALLY have in a drink? Please do not include the amount of any soda, water, ice, cola, or juice that may have been added to your drink.	1 shot or ounce 1 jigger Mini-bottle (type sold on airplanes) 1½ shots or ounces 2 shots or ounces (double) 2 jiggers 3 shots or ounces (triple) 3 jiggers 4 shots or ounces 4 jiggers ½ pint Pint Quart Fifth ½ gallon Other – Specify
	How many (drinks of this size/units reported) of liquor did you USUALLY drink on days when you drank liquor?	_____ Number
	During the last 12 months, what brand of liquor or liqueur did you drink the most often?	_____

Source: https://www.niaaa.nih.gov/sites/default/files/section%202a_Final_2_10_15.pdf

Table A6. National Health Interview Survey (NHIS) questions

Domain	Question	Answers
Lifetime alcohol use	In your ENTIRE LIFE, have you had at least 1 drink of any kind of alcohol, not counting small tastes or sips?	Yes No
Frequency of alcohol use (past year)	During the past 12 months, how many days per week, per month or per year did you drink any type of alcoholic beverage?	____ per ____
Quantity of alcohol use (on drinking occasions)	During the past 12 months, on those days that you drank alcoholic beverages, on average, how many DRINKS did you have?	_____

Source: https://ftp.cdc.gov/pub/Health_Statistics/NCHS/Survey_Questionnaires/NHIS/2022/EnglishQuest-508.pdf

Table A7. National Survey on Drug Use and Health (NSDUH) questions

Domain	Question	Answers
Lifetime drinking	Have you ever, even once, had a drink of any type of alcoholic beverage? Please do not include times when you only had a sip or two from a drink.	Yes No
Age of initiation	Think about the first time you had a drink of an alcoholic beverage. How old were you the first time you had a drink of an alcoholic beverage?	_____
Past year drinking	Did you first have a drink of an alcoholic beverage in [CURRENT YEAR - 1] or [CURRENT YEAR]?	Yes No
	How long has it been since you last drank an alcoholic beverage?	1 Within the past 30 days — that is, since [DATEFILL] 2 More than 30 days ago but within the past 12 months 3 More than 12 months ago
Frequency of alcohol use (past 30 days)	What is your best estimate of the number of days you drank alcohol during the past 30 days?	1 or 2 days 3 to 5 days 6 to 9 days 10 to 19 days 20 to 29 days All 30 days
Quantity of alcohol use (on drinking occasions)	On the days that you drank during the past 30 days, how many drinks did you usually have each day? Count as a drink a can or bottle of beer; a wine cooler or a glass of wine, champagne, or sherry; a shot of liquor or a mixed drink or cocktail.	# OF DRINKS: _____

Source: https://www.samhsa.gov/data/sites/default/files/reports/rpt39377/2022NSDUHmrbWebSpecs070822.pdf