

# THE LANCET

## Supplementary appendix 1

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

**This online publication has been corrected. The corrected version first appeared at [thelancet.com](https://www.thelancet.com) on July 19, 2022**

Supplement to: GBD 2020 Alcohol Collaborators. Population-level risks of alcohol consumption by amount, geography, age, sex, and year: a systematic analysis for the Global Burden of Disease Study 2020. *Lancet* 2022; **400**: 185–235.

## **Supplementary Methods**

### **Risks of alcohol consumption by geography, age, sex, and year: a systematic analysis from the Global Burden of Disease Study 2020**

GBD 2020 Alcohol Use Collaborators

## Table of Contents

<b><i>Geographies Estimated</i></b>	<b>3</b>
Geographic Hierarchy	3
<b><i>Demographics</i></b>	<b>13</b>
<b><i>Relative Risks</i></b>	<b>14</b>
Systematic Review	14
Estimating Dose-Response Relative Risk Curves	14
<b><i>Theoretical Minimum Risk Exposure and Non-Drinker Equivalence Levels</i></b>	<b>16</b>
Computing aggregate relative risks	16
Theoretical Minimum Risk Exposure Level	16
Non-drinker Equivalence Level	17
<b><i>Population Attributable Fractions</i></b>	<b>17</b>
<b><i>Sensitivity Analyses</i></b>	<b>17</b>
<b><i>Search Strings and PRISMA Diagrams</i></b>	<b>18</b>
<b><i>Diabetes Mellitus</i></b>	<b>18</b>
<b><i>Intracerebral Hemorrhage</i></b>	<b>23</b>
<b><i>Ischemic Stroke</i></b>	<b>27</b>
<b><i>Ischemic heart disease</i></b>	<b>32</b>
<b><i>Tuberculosis</i></b>	<b>40</b>
<b><i>Modeled Relative Risk Curves</i></b>	<b>42</b>
<b><i>GATHER Checklist</i></b>	<b>47</b>
<b><i>Contributions</i></b>	<b>49</b>
Managing the overall research enterprise	49
Writing the first draft of the manuscript	49
Primary responsibility for applying analytical methods to produce estimates	49
Primary responsibility for seeking, cataloguing, extracting, or cleaning data; designing or coding figures and tables	49
Providing data or critical feedback on data sources	49
Developing methods or computational machinery	50
Providing critical feedback on methods or results	50
Drafting the work or revising it critically for important intellectual content	53
Managing the estimation or publications process	54

## Geographies Estimated

This study utilized the standard geographical hierarchy for the Global Burden of Diseases, Injuries, and Risk Factors Study 2020 (GBD 2020). The 204 countries and territories included in this analysis are nested in 21 aggregate regions and seven aggregate super-regions (Table SM1). The regions and super-regions in the GBD are defined based on a combination of epidemiologic patterns and spatial distance.

### *Geographic Hierarchy*

<b>Location</b>	<b>Super-Region</b>	<b>Region</b>
<b>Armenia</b>	Central Europe, Eastern Europe, and Central Asia	Central Asia
<b>Azerbaijan</b>	Central Europe, Eastern Europe, and Central Asia	Central Asia
<b>Georgia</b>	Central Europe, Eastern Europe, and Central Asia	Central Asia
<b>Kazakhstan</b>	Central Europe, Eastern Europe, and Central Asia	Central Asia
<b>Kyrgyzstan</b>	Central Europe, Eastern Europe, and Central Asia	Central Asia
<b>Mongolia</b>	Central Europe, Eastern Europe, and Central Asia	Central Asia
<b>Tajikistan</b>	Central Europe, Eastern Europe, and Central Asia	Central Asia
<b>Turkmenistan</b>	Central Europe, Eastern Europe, and Central Asia	Central Asia
<b>Uzbekistan</b>	Central Europe, Eastern Europe, and Central Asia	Central Asia
<b>Albania</b>	Central Europe, Eastern Europe, and Central Asia	Central Europe
<b>Bosnia and Herzegovina</b>	Central Europe, Eastern Europe, and Central Asia	Central Europe
<b>Bulgaria</b>	Central Europe, Eastern Europe, and Central Asia	Central Europe
<b>Croatia</b>	Central Europe, Eastern Europe, and Central Asia	Central Europe
<b>Czechia</b>	Central Europe, Eastern Europe, and Central Asia	Central Europe
<b>Hungary</b>	Central Europe, Eastern Europe, and Central Asia	Central Europe
<b>Montenegro</b>	Central Europe, Eastern Europe, and Central Asia	Central Europe
<b>North Macedonia</b>	Central Europe, Eastern Europe, and Central Asia	Central Europe
<b>Poland</b>	Central Europe, Eastern Europe, and Central Asia	Central Europe

<b>Romania</b>	Central Europe, Eastern Europe, and Central Asia	Central Europe
<b>Serbia</b>	Central Europe, Eastern Europe, and Central Asia	Central Europe
<b>Slovakia</b>	Central Europe, Eastern Europe, and Central Asia	Central Europe
<b>Slovenia</b>	Central Europe, Eastern Europe, and Central Asia	Central Europe
<b>Belarus</b>	Central Europe, Eastern Europe, and Central Asia	Eastern Europe
<b>Estonia</b>	Central Europe, Eastern Europe, and Central Asia	Eastern Europe
<b>Latvia</b>	Central Europe, Eastern Europe, and Central Asia	Eastern Europe
<b>Lithuania</b>	Central Europe, Eastern Europe, and Central Asia	Eastern Europe
<b>Republic of Moldova</b>	Central Europe, Eastern Europe, and Central Asia	Eastern Europe
<b>Russia</b>	Central Europe, Eastern Europe, and Central Asia	Eastern Europe
<b>Ukraine</b>	Central Europe, Eastern Europe, and Central Asia	Eastern Europe
<b>Australia</b>	High-income	Australasia
<b>New Zealand</b>	High-income	Australasia
<b>Brunei Darussalam</b>	High-income	High-income Asia Pacific
<b>Japan</b>	High-income	High-income Asia Pacific
<b>Republic of Korea</b>	High-income	High-income Asia Pacific
<b>Singapore</b>	High-income	High-income Asia Pacific
<b>Canada</b>	High-income	High-income North America
<b>Greenland</b>	High-income	High-income North America
<b>United States of America</b>	High-income	High-income North America
<b>Argentina</b>	High-income	Southern Latin America
<b>Chile</b>	High-income	Southern Latin America
<b>Uruguay</b>	High-income	Southern Latin America

<b>Andorra</b>	High-income	Western Europe
<b>Austria</b>	High-income	Western Europe
<b>Belgium</b>	High-income	Western Europe
<b>Cyprus</b>	High-income	Western Europe
<b>Denmark</b>	High-income	Western Europe
<b>Finland</b>	High-income	Western Europe
<b>France</b>	High-income	Western Europe
<b>Germany</b>	High-income	Western Europe
<b>Greece</b>	High-income	Western Europe
<b>Iceland</b>	High-income	Western Europe
<b>Ireland</b>	High-income	Western Europe
<b>Israel</b>	High-income	Western Europe
<b>Italy</b>	High-income	Western Europe
<b>Luxembourg</b>	High-income	Western Europe
<b>Malta</b>	High-income	Western Europe
<b>Monaco</b>	High-income	Western Europe
<b>Netherlands</b>	High-income	Western Europe
<b>Norway</b>	High-income	Western Europe
<b>Portugal</b>	High-income	Western Europe
<b>San Marino</b>	High-income	Western Europe
<b>Spain</b>	High-income	Western Europe
<b>Sweden</b>	High-income	Western Europe
<b>Switzerland</b>	High-income	Western Europe

<b>United Kingdom</b>	High-income	Western Europe
<b>Bolivia (Plurinational State of)</b>	Latin America and Caribbean	Andean Latin America
<b>Ecuador</b>	Latin America and Caribbean	Andean Latin America
<b>Peru</b>	Latin America and Caribbean	Andean Latin America
<b>Antigua and Barbuda</b>	Latin America and Caribbean	Caribbean
<b>Bahamas</b>	Latin America and Caribbean	Caribbean
<b>Barbados</b>	Latin America and Caribbean	Caribbean
<b>Belize</b>	Latin America and Caribbean	Caribbean
<b>Bermuda</b>	Latin America and Caribbean	Caribbean
<b>Cuba</b>	Latin America and Caribbean	Caribbean
<b>Dominica</b>	Latin America and Caribbean	Caribbean
<b>Dominican Republic</b>	Latin America and Caribbean	Caribbean
<b>Grenada</b>	Latin America and Caribbean	Caribbean
<b>Guyana</b>	Latin America and Caribbean	Caribbean
<b>Haiti</b>	Latin America and Caribbean	Caribbean
<b>Jamaica</b>	Latin America and Caribbean	Caribbean
<b>Puerto Rico</b>	Latin America and Caribbean	Caribbean
<b>Saint Kitts and Nevis</b>	Latin America and Caribbean	Caribbean
<b>Saint Lucia</b>	Latin America and Caribbean	Caribbean
<b>Saint Vincent and the Grenadines</b>	Latin America and Caribbean	Caribbean
<b>Suriname</b>	Latin America and Caribbean	Caribbean
<b>Trinidad and Tobago</b>	Latin America and Caribbean	Caribbean
<b>United States Virgin Islands</b>	Latin America and Caribbean	Caribbean

<b>Colombia</b>	Latin America and Caribbean	Central Latin America
<b>Costa Rica</b>	Latin America and Caribbean	Central Latin America
<b>El Salvador</b>	Latin America and Caribbean	Central Latin America
<b>Guatemala</b>	Latin America and Caribbean	Central Latin America
<b>Honduras</b>	Latin America and Caribbean	Central Latin America
<b>Mexico</b>	Latin America and Caribbean	Central Latin America
<b>Nicaragua</b>	Latin America and Caribbean	Central Latin America
<b>Panama</b>	Latin America and Caribbean	Central Latin America
<b>Venezuela (Bolivarian Republic of)</b>	Latin America and Caribbean	Central Latin America
<b>Brazil</b>	Latin America and Caribbean	Tropical Latin America
<b>Paraguay</b>	Latin America and Caribbean	Tropical Latin America
<b>Afghanistan</b>	North Africa and Middle East	North Africa and Middle East
<b>Algeria</b>	North Africa and Middle East	North Africa and Middle East
<b>Bahrain</b>	North Africa and Middle East	North Africa and Middle East
<b>Egypt</b>	North Africa and Middle East	North Africa and Middle East
<b>Iran (Islamic Republic of)</b>	North Africa and Middle East	North Africa and Middle East
<b>Iraq</b>	North Africa and Middle East	North Africa and Middle East
<b>Jordan</b>	North Africa and Middle East	North Africa and Middle East
<b>Kuwait</b>	North Africa and Middle East	North Africa and Middle East
<b>Lebanon</b>	North Africa and Middle East	North Africa and Middle East
<b>Libya</b>	North Africa and Middle East	North Africa and Middle East
<b>Morocco</b>	North Africa and Middle East	North Africa and Middle East
<b>Oman</b>	North Africa and Middle East	North Africa and Middle East



<b>Palestine</b>	North Africa and Middle East	North Africa and Middle East
<b>Qatar</b>	North Africa and Middle East	North Africa and Middle East
<b>Saudi Arabia</b>	North Africa and Middle East	North Africa and Middle East
<b>Sudan</b>	North Africa and Middle East	North Africa and Middle East
<b>Syrian Arab Republic</b>	North Africa and Middle East	North Africa and Middle East
<b>Tunisia</b>	North Africa and Middle East	North Africa and Middle East
<b>Turkey</b>	North Africa and Middle East	North Africa and Middle East
<b>United Arab Emirates</b>	North Africa and Middle East	North Africa and Middle East
<b>Yemen</b>	North Africa and Middle East	North Africa and Middle East
<b>Bangladesh</b>	South Asia	South Asia
<b>Bhutan</b>	South Asia	South Asia
<b>India</b>	South Asia	South Asia
<b>Nepal</b>	South Asia	South Asia
<b>Pakistan</b>	South Asia	South Asia
<b>China</b>	Southeast Asia, East Asia, and Oceania	East Asia
<b>Democratic People's Republic of Korea</b>	Southeast Asia, East Asia, and Oceania	East Asia
<b>Taiwan (Province of China)</b>	Southeast Asia, East Asia, and Oceania	East Asia
<b>American Samoa</b>	Southeast Asia, East Asia, and Oceania	Oceania
<b>Cook Islands</b>	Southeast Asia, East Asia, and Oceania	Oceania
<b>Fiji</b>	Southeast Asia, East Asia, and Oceania	Oceania
<b>Guam</b>	Southeast Asia, East Asia, and Oceania	Oceania
<b>Kiribati</b>	Southeast Asia, East Asia, and Oceania	Oceania
<b>Marshall Islands</b>	Southeast Asia, East Asia, and Oceania	Oceania

<b>Micronesia (Federated States of)</b>	Southeast Asia, East Asia, and Oceania	Oceania
<b>Nauru</b>	Southeast Asia, East Asia, and Oceania	Oceania
<b>Niue</b>	Southeast Asia, East Asia, and Oceania	Oceania
<b>Northern Mariana Islands</b>	Southeast Asia, East Asia, and Oceania	Oceania
<b>Palau</b>	Southeast Asia, East Asia, and Oceania	Oceania
<b>Papua New Guinea</b>	Southeast Asia, East Asia, and Oceania	Oceania
<b>Samoa</b>	Southeast Asia, East Asia, and Oceania	Oceania
<b>Solomon Islands</b>	Southeast Asia, East Asia, and Oceania	Oceania
<b>Tokelau</b>	Southeast Asia, East Asia, and Oceania	Oceania
<b>Tonga</b>	Southeast Asia, East Asia, and Oceania	Oceania
<b>Tuvalu</b>	Southeast Asia, East Asia, and Oceania	Oceania
<b>Vanuatu</b>	Southeast Asia, East Asia, and Oceania	Oceania
<b>Cambodia</b>	Southeast Asia, East Asia, and Oceania	Southeast Asia
<b>Indonesia</b>	Southeast Asia, East Asia, and Oceania	Southeast Asia
<b>Lao People's Democratic Republic</b>	Southeast Asia, East Asia, and Oceania	Southeast Asia
<b>Malaysia</b>	Southeast Asia, East Asia, and Oceania	Southeast Asia
<b>Maldives</b>	Southeast Asia, East Asia, and Oceania	Southeast Asia
<b>Mauritius</b>	Southeast Asia, East Asia, and Oceania	Southeast Asia
<b>Myanmar</b>	Southeast Asia, East Asia, and Oceania	Southeast Asia
<b>Philippines</b>	Southeast Asia, East Asia, and Oceania	Southeast Asia
<b>Seychelles</b>	Southeast Asia, East Asia, and Oceania	Southeast Asia
<b>Sri Lanka</b>	Southeast Asia, East Asia, and Oceania	Southeast Asia
<b>Thailand</b>	Southeast Asia, East Asia, and Oceania	Southeast Asia

<b>Timor-Leste</b>	Southeast Asia, East Asia, and Oceania	Southeast Asia
<b>Viet Nam</b>	Southeast Asia, East Asia, and Oceania	Southeast Asia
<b>Angola</b>	Sub-Saharan Africa	Central Sub-Saharan Africa
<b>Central African Republic</b>	Sub-Saharan Africa	Central Sub-Saharan Africa
<b>Congo</b>	Sub-Saharan Africa	Central Sub-Saharan Africa
<b>Democratic Republic of the Congo</b>	Sub-Saharan Africa	Central Sub-Saharan Africa
<b>Equatorial Guinea</b>	Sub-Saharan Africa	Central Sub-Saharan Africa
<b>Gabon</b>	Sub-Saharan Africa	Central Sub-Saharan Africa
<b>Burundi</b>	Sub-Saharan Africa	Eastern Sub-Saharan Africa
<b>Comoros</b>	Sub-Saharan Africa	Eastern Sub-Saharan Africa
<b>Djibouti</b>	Sub-Saharan Africa	Eastern Sub-Saharan Africa
<b>Eritrea</b>	Sub-Saharan Africa	Eastern Sub-Saharan Africa
<b>Ethiopia</b>	Sub-Saharan Africa	Eastern Sub-Saharan Africa
<b>Kenya</b>	Sub-Saharan Africa	Eastern Sub-Saharan Africa
<b>Madagascar</b>	Sub-Saharan Africa	Eastern Sub-Saharan Africa
<b>Malawi</b>	Sub-Saharan Africa	Eastern Sub-Saharan Africa
<b>Mozambique</b>	Sub-Saharan Africa	Eastern Sub-Saharan Africa
<b>Rwanda</b>	Sub-Saharan Africa	Eastern Sub-Saharan Africa
<b>Somalia</b>	Sub-Saharan Africa	Eastern Sub-Saharan Africa
<b>South Sudan</b>	Sub-Saharan Africa	Eastern Sub-Saharan Africa
<b>Uganda</b>	Sub-Saharan Africa	Eastern Sub-Saharan Africa
<b>United Republic of Tanzania</b>	Sub-Saharan Africa	Eastern Sub-Saharan Africa
<b>Zambia</b>	Sub-Saharan Africa	Eastern Sub-Saharan Africa

<b>Botswana</b>	Sub-Saharan Africa	Southern Sub-Saharan Africa
<b>Eswatini</b>	Sub-Saharan Africa	Southern Sub-Saharan Africa
<b>Lesotho</b>	Sub-Saharan Africa	Southern Sub-Saharan Africa
<b>Namibia</b>	Sub-Saharan Africa	Southern Sub-Saharan Africa
<b>South Africa</b>	Sub-Saharan Africa	Southern Sub-Saharan Africa
<b>Zimbabwe</b>	Sub-Saharan Africa	Southern Sub-Saharan Africa
<b>Benin</b>	Sub-Saharan Africa	Western Sub-Saharan Africa
<b>Burkina Faso</b>	Sub-Saharan Africa	Western Sub-Saharan Africa
<b>Cabo Verde</b>	Sub-Saharan Africa	Western Sub-Saharan Africa
<b>Cameroon</b>	Sub-Saharan Africa	Western Sub-Saharan Africa
<b>Chad</b>	Sub-Saharan Africa	Western Sub-Saharan Africa
<b>Côte d'Ivoire</b>	Sub-Saharan Africa	Western Sub-Saharan Africa
<b>Gambia</b>	Sub-Saharan Africa	Western Sub-Saharan Africa
<b>Ghana</b>	Sub-Saharan Africa	Western Sub-Saharan Africa
<b>Guinea</b>	Sub-Saharan Africa	Western Sub-Saharan Africa
<b>Guinea-Bissau</b>	Sub-Saharan Africa	Western Sub-Saharan Africa
<b>Liberia</b>	Sub-Saharan Africa	Western Sub-Saharan Africa
<b>Mali</b>	Sub-Saharan Africa	Western Sub-Saharan Africa
<b>Mauritania</b>	Sub-Saharan Africa	Western Sub-Saharan Africa
<b>Niger</b>	Sub-Saharan Africa	Western Sub-Saharan Africa
<b>Nigeria</b>	Sub-Saharan Africa	Western Sub-Saharan Africa
<b>São Tomé and Príncipe</b>	Sub-Saharan Africa	Western Sub-Saharan Africa
<b>Senegal</b>	Sub-Saharan Africa	Western Sub-Saharan Africa

<b>Sierra Leone</b>	Sub-Saharan Africa	Western Sub-Saharan Africa
<b>Togo</b>	Sub-Saharan Africa	Western Sub-Saharan Africa

## Demographics

For the 204 countries and territories included in analysis, we produced estimates by sex and five-year age group from 1990 to 2020. Additionally, we produced estimates aggregated by age:

- All-age estimates reflect population-weighted average estimates for ages 15 and above.
- Estimates aggregated over specific age groups, for example estimates for ages 15-39, 40-64, and 65+, reflect population-weighted average estimates over the specified age range.
- Age-standardised estimates reflect weighting according to the GBD population standard.

## Relative Risks

### Systematic Review

We updated previously published systematic reviews conducted as part of the Global Burden of Disease Study for the six alcohol-attributable outcomes accounting for the largest number of global disability-adjusted life years: ischemic heart disease, ischemic stroke, intracerebral hemorrhage, diabetes mellitus type II, lower respiratory infection, and tuberculosis.

We utilized the following inclusion criteria for our review of the MEDLINE database:

- Studies published between 01/01/1970 and 12/31/2019
- Cohort and case-control studies
- Describe an association between alcohol use and a GBD outcome
- Utilize a continuous dose the exposure of alcohol consumption
- Report an effect size estimate (relative risk, hazard ratio, or odds ratio) with uncertainty

When both unadjusted and adjusted analyses were reported, we extracted the adjusted analysis. We also extracted the complete list of confounders included in each of the models, as well as metadata on study design, sample representativeness, and measurement of both exposure variables and outcomes. The set of confounders varied across the studies included in our meta-regressions, and there was substantial heterogeneity in study designs. We account for these differences in our meta-regression, with the final estimated risk curve reflecting adjusted relative risks for a general population.

Search strings and PRISMA diagrams are included in subsequent sections of the appendix.

### Estimating Dose-Response Relative Risk Curves

We utilized the meta-regression – Bayesian, regularized, trimmed (MR-BRT) meta-regression tool to update relative risk curves for the six outcomes with the largest burden. We utilized previously published relative risk curves modeled using DisMod ODE for all other health outcomes.

The MR-BRT meta-regression tool produces relative risk curves using a five-stage analysis strategy. In the first stage, a mean dose- log response curve is estimated using a B-spline. Importantly, this strategy does not assume that the log relative risk has a linear relationship with exposure, which tends to overestimate the relative risk at high exposures. This stage uses data on exposure ranges and relative risk to produce a mean dose-response relative risk curve, which is called the “signal”. The estimation of the signal imposes spline shape constraints, likelihood-based trimming to remove outliers, and ensemble knot placement. In the table below, we list each risk outcome pair that is updated in GBD 2020 along with several of the key modeling parameters.

#### MR-BRT splines and priors by type of risk

Risk-outcome	Type of risk	Spline degree, # interior knots	Priors & constraints
Ischemic heart disease	J-shaped	Quadratic, 2 I knots	No monotonicity constraint
Ischemic stroke	J-shaped	Quadratic, 3 I knots	No monotonicity constraint, right linear tail
Intracerebral hemorrhage	J-shaped	Cubic, 3 I knots	No monotonicity constraint, right linear tail
Type II diabetes mellitus	J-shaped	Cubic, 3 I knots	No monotonicity constraint, right linear tail
Tuberculosis	Harmful	Quadratic, 3 I knots	Monotonic increasing, right linear tail, Gaussian max derivative prior on the right tail (0, 0.001)
Lower Respiratory Infection	Harmful	Quadratic, 3 I knots	Monotonic increasing, right linear tail, Gaussian max derivative prior on the right tail (0, 0.001)

Stages 2 and 3 adjust for aspects of study design that contribute to potential bias in the reported relative risks. In stage 2, the signal curve is used to fit a linear mixed effects model for relative risk, to obtain a posterior variance that is used as a prior in the next step. In stage 3, a linear model is fit in which the potential bias covariates are specified as indicator variables that modify the slope of the signal curve. A generalized Lasso approach that penalizes the sum of the absolute values of the bias covariate multipliers  $\beta$  is used to select the bias covariates that are included in subsequent stages. Covariates are added to the model based on the order of their  $\beta$ s and their coefficients are tested for statistical significance. If coefficients are significant they remain in the model. As soon as any coefficient fails to be significant in the overall model, the selection process is terminated and a list of significant bias covariates is returned. The bias covariates we tested are shown in the table below:

#### Covariates tested using MR BRT Lasso Approach

Covariates	Reference Description
cv_sick_quitters	The study adequately adjusted for a sick quitter effect
cv_non_drinkers	The study reference group was non-drinkers
percent_male	The percent of the sample that was male
cv_older	The study sample represents individuals 50 years or older
cv_subpopulation	The outcome is reported for a subpopulation within a given country or territory
cv_outcome_selfreport	The outcome is self-reported
cv_exposure_study	The outcome only measured at baseline
cv_rep_geography	The study sample is geographically representative
cv_rep_prevalent_disease	The study evaluates mortality among those who have already developed a given outcome
cv_incidence	The study outcome was incidence or incidence and mortality combined. Relative risk curves represent incidence and mortality.
cv_mortality	The study outcome was mortality or incidence and mortality combined. Relative risk curves represent incidence and mortality.
cv_adjusted_1	The study was adjusted for age or sex
cv_adjusted_2	The study was adjusted for age and sex
cv_adjusted_3	The study was adjusted for age, sex, and smoking
cv_adjusted_4	The study was adjusted for age, sex, smoking, and one additional covariate
cv_adjusted_5	The study was adjusted for age, sex, smoking, and two or more additional covariates
cv_hypertension*	The study adjusts for hypertension
cv_hypercholesterolemia*	The study adjusts for hypercholesterolemia
cv_definition*	The disease outcome is identical to the GBD definition

\* covariates tested only for ischemic heart disease, ischemic stroke, and intracerebral hemorrhage curve estimation



In stage 4, the signal model is first adjusted for the bias covariates selected in stage 3. We use this adjusted model to estimate the between study heterogeneity, parameterized by  $\gamma$ . In some cases, the  $\gamma$  estimate may be 0 simply from lack of data, so we implemented the Fisher Scoring correction to  $\gamma$ , which corrects for sparse-data situations. The Fisher Scoring correction uses a quantile of  $\gamma$ , which is sensitive to the number of studies, study design, and reported uncertainty. In stage 5, we use a modified trim-and-fill method and Egger regression to test for potential publication bias. The bias covariates selected in stage 3, as well as the mean  $\gamma$  solution, are shown in the table below.

**MR-BRT parameters by risk-outcome pair**

Risk-outcome	Type of risk	Selected covariates	Mean $\gamma$ solution
Ischemic heart disease	J-shaped	cv_incidence	0.158
Ischemic stroke	J-shaped	cv_incidence	0.234
Intracerebral hemorrhage	J-shaped	cv_adjusted_2, cv_adjusted_1	0.09
Type II diabetes mellitus	J-shaped	None	0.117
Tuberculosis	Harmful	cv_sick_quitters, cv_incidence	19.488
Lower Respiratory Infection	Harmful	None	0

## Theoretical Minimum Risk Exposure and Non-Drinker Equivalence Levels

### Computing aggregate relative risks

The theoretical minimum risk exposure and non-drinker equivalence levels are based on aggregate, burden weighted relative risk curves across health outcomes associated with alcohol use. Aggregate relative risk curves were constructed by region, age group, sex, and year to reflect differing cause compositions across these dimensions. The formula for constructing the aggregate relative risk curves is:

$$\log(RR)_{w,e,l,y,a,s} = \sum_i^{\omega} \log(RR_{i,e}) * \frac{DALY_{i,l,y,a,s}}{\sum_i^{\omega} DALY_{i,l,y,a,s}}$$

Where:

$\omega$  is the set of causes associated with alcohol,  $i$  is a given cause from that set,  $e$  is a given exposure level in units of grams per day,  $l$  is a location,  $y$  is a year,  $s$  is a sex,  $a$  is an age group, DALY is a DALY rate for a given cause, and  $RR$  is the dose response curve for a given cause

DALY rates were based on results from GBD 2020.

### Theoretical Minimum Risk Exposure Level

The theoretical minimum risk exposure level of alcohol use is the minimum of this aggregate-risk curve, which will vary by region, age group, sex, and year:

$$TMREL = \operatorname{argmin} \log(RR)_{\omega,l,y,a,s}$$

The TMREL is the exposure level that minimizes the risk of suffering burden from any given cause related to alcohol. We weight the risk for a particular cause in our aggregation by the proportion of DALYs due to that cause (e.g., since more observed people die from ischaemic heart disease [IHD], we weight the risk for IHD more in the

above calculation of average risk compared to, say, diabetes, even if both have the same relative risk for a given level of consumption).

#### Non-drinker Equivalence Level

The non-drinker equivalence level is the level of consumption at which health loss is equivalent to that of non-drinkers. Consumption of alcohol in excess of this level is harmful compared to abstinence.

### Population Attributable Fractions

We calculated PAFs by setting the relative risk of alcohol consumption among abstainers and drinkers consuming alcohol below the TMREL to be 1. We then calculated PAFs for drinkers consuming alcohol in excess of the TMREL. For each location, age, sex, year, and cause, we defined the PAF as:

$$PAF(x) = \frac{P_A + \int_0^{TMREL} P(x) dx + \int_{TMREL}^{100} P(x) * RR_C(x) dx - RR_C(TMREL)}{P_A + \int_0^{TMREL} P(x) dx + \int_{TMREL}^{100} P(x) * RR_C(x) dx} \quad P(x) = P_C * \Gamma(p)$$

where:

$P_C$  is the prevalence of current drinkers,  $P_A$  is the prevalence of abstainers, and  $p$  are parameters determined by the mean and standard deviation of exposure for that location, age, sex, and year;  $RR_C$  is the global relative risk function for current drinkers for a given cause, and TMREL is the theoretical minimum exposure level for that location's region, age, sex, and year

We performed the above equation for 1000 draws of the exposure and relative risk models. We then used the complement of the estimated PAF draws to calculate risk-deleted DALY rates as alternative weights as a sensitivity analysis. .

### Sensitivity Analyses

Our weighted attributable-cause relative risk curves were based on only 22 out of 24 health outcomes since no relative risk curves could be computed for alcohol use disorder or alcoholic cardiomyopathy due to lack of studies on dose-response relative risks. To assess whether inclusion of these two outcomes could potentially impact the TMREL and NDE levels, we conducted a second sensitivity analysis in which we assumed that the risk of these outcomes was equal to a relative risk of three (scenario A), five (scenario B), and 10 (scenario C) at exposures in excess of four standard drinks per day, the lowest threshold for binge drinking found. At exposure levels lower than this, we assumed the risk increased linearly from a relative risk of 1 at zero standard drinks per day, a conservative assumption that likely overestimates risk at low-levels of alcohol consumption. We then used these hypothetical relative risk curves to re-compute a TMREL that reflects all 24 alcohol-associated outcomes.

## Search Strings and PRISMA Diagrams

### Diabetes Mellitus

**Search String:** (alcoholic beverage[MeSH Terms] OR drinking behavior[MeSH Terms] OR “alcohol”[Title/Abstract])

AND

(Diabetes Mellitus, Type 2[MeSH Terms] OR “diabetes”[Title/Abstract])

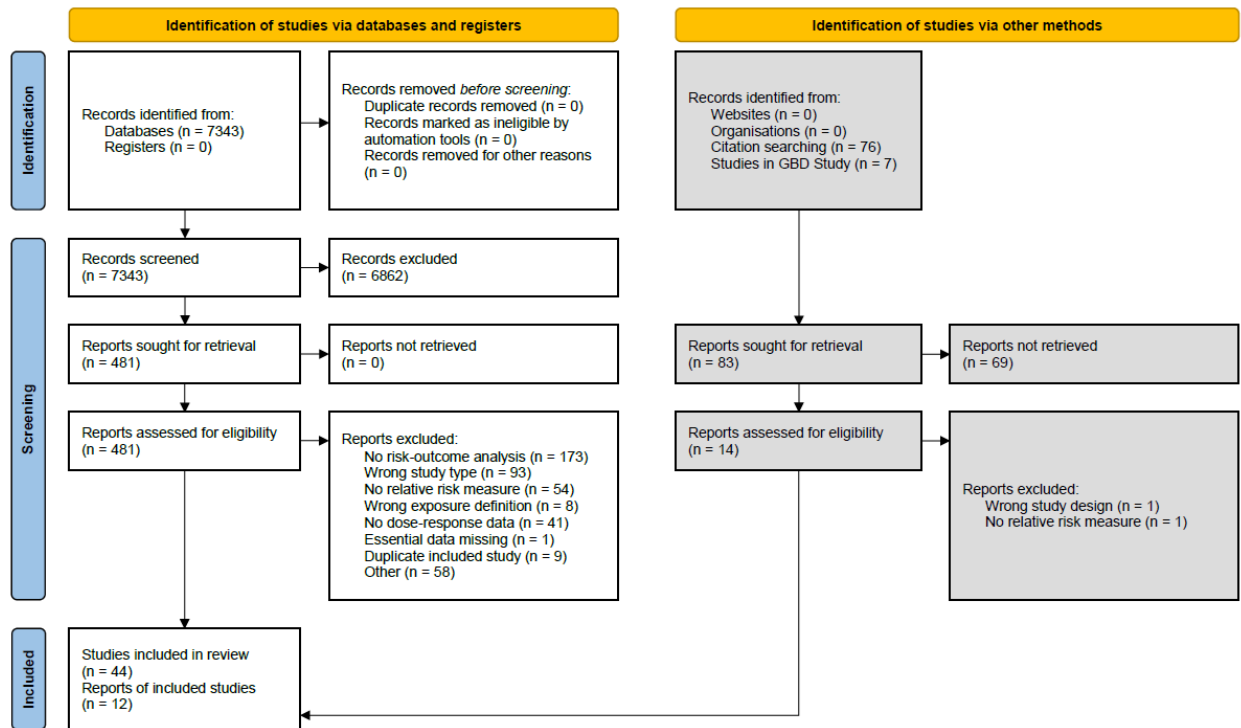
AND

(Risk[MeSH Terms] OR Odds Ratio[MeSH Terms] OR “risk”[Title/Abstract] OR “odds ratio”[Title/Abstract] OR “cross-product ratio”[Title/Abstract] OR “hazards ratio”[Title/Abstract] OR “hazard ratio”[Title/Abstract])

AND ("1970/01/01"[PDat] : "2019/12/31"[PDat])

AND (English[LA])

NOT (animals[MeSH Terms] NOT Humans[MeSH Terms])



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>

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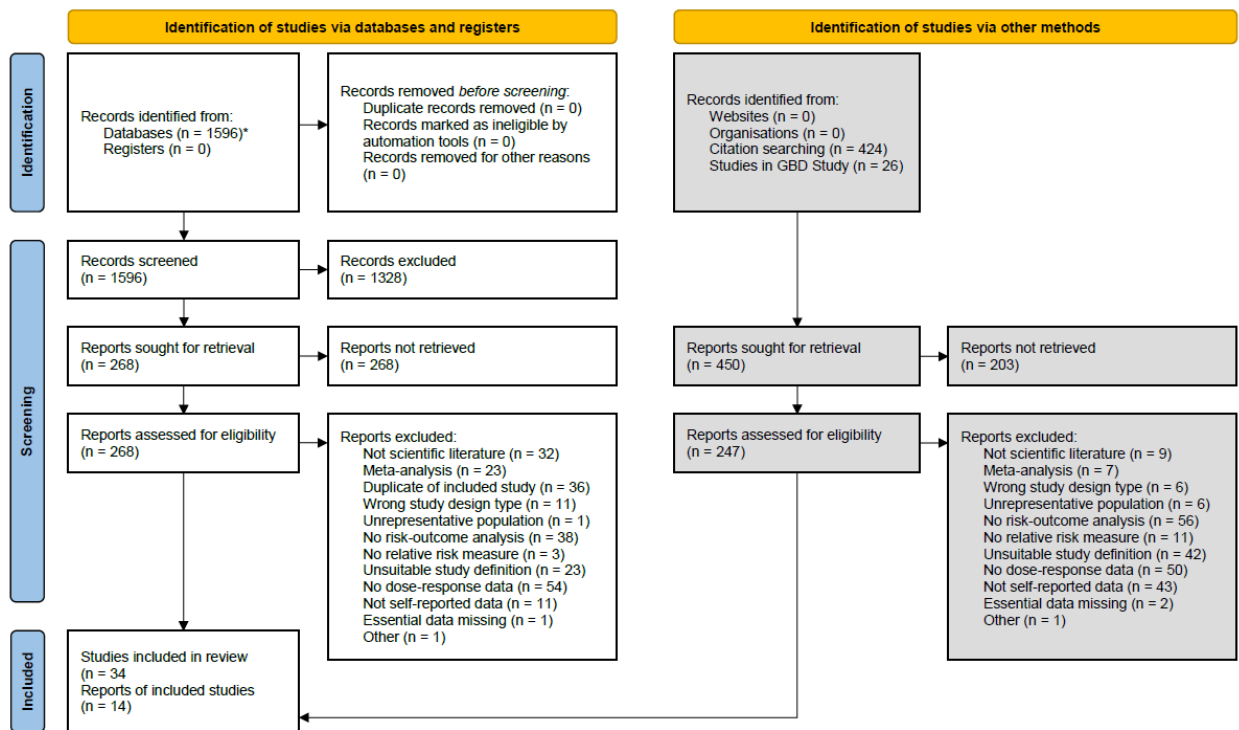
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## Intracerebral Hemorrhage

**Search String:** (alcoholic beverage[MeSH Terms] OR drinking behavior[MeSH Terms] OR "alcohol"[Title/Abstract] NOT (alcohols[MeSH Terms] NOT drinking behavior[MeSH Terms])) AND (brain infarction[MeSH Terms] OR stroke[MeSH Terms] OR intracranial hemorrhages[MeSH Terms] OR "stroke"[Title/Abstract] OR "brain infarction"[Title/Abstract] OR "cerebral infarction"[Title/Abstract] OR "intracerebral hemorrhage"[Title/Abstract] OR "intracerebral haemorrhage"[Title/Abstract] OR "subarachnoid hemorrhage"[Title/Abstract] OR "subarachnoid haemorrhage"[Title/Abstract]) AND (Case-Control Studies[MeSH Terms] OR Cross-Over Studies[MeSH Terms] OR Cohort Studies[MeSH Terms] OR Systematic Review[Publication Type] OR Meta-Analysis[Publication Type] OR "systematic review"[Title/Abstract] OR "meta-analysis"[Title/Abstract] OR "cohort"[Title/Abstract] OR "cross-over"[Title/Abstract] OR "crossover"[Title/Abstract] OR "case-control"[Title/Abstract] OR "prospective"[Title/Abstract] OR "retrospective"[Title/Abstract] OR "longitudinal"[Title/Abstract] OR "follow-up"[Title/Abstract] OR Dose-Response Relationship, Drug[MeSH Terms] OR "dose-response"[Title/Abstract]) AND (Risk[MeSH Terms] OR Odds Ratio[MeSH Terms] OR "risk"[Title/Abstract] OR "odds ratio"[Title/Abstract] OR "cross-product ratio"[Title/Abstract] OR "hazards ratio"[Title/Abstract] OR "hazard ratio"[Title/Abstract]) AND ("1970/01/01"[PDat] : "2019/12/31"[PDat]) AND (English[LA]) NOT (animals[MeSH Terms] NOT Humans[MeSH Terms])



\*A single search string was utilized to search for records containing an outcome of stroke, intracerebral hemorrhage, or ischemic stroke, but final included source counts are outcome-specific.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>



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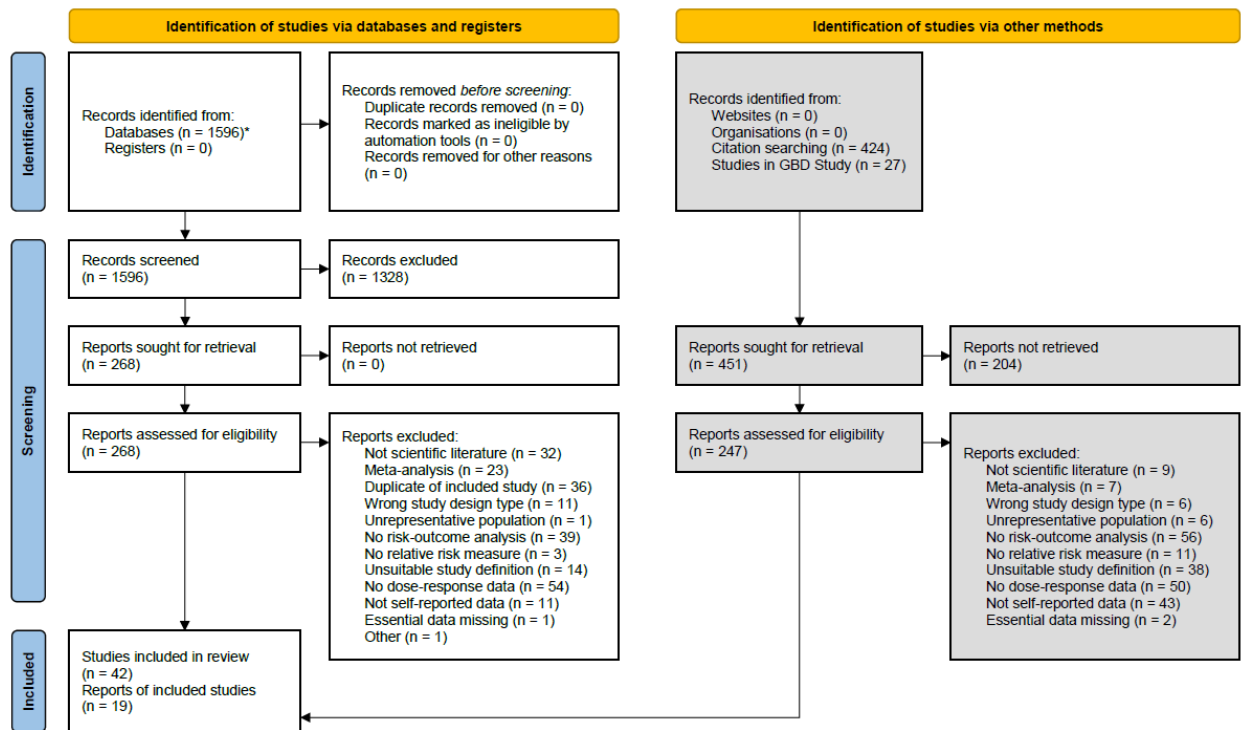
Yusuf S, Joseph P, Rangarajan S, Islam S, Mentz A, Hystad P, Brauer M, Kutty VR, Gupta R, Wielgosz A, AlHabib KF, Dans A, Lopez-Jaramillo P, Avezum A, Lanas F, Oguz A, Kruger IM, Diaz R, Yusoff K, Mony P, Chifamba J, Yeates K, Kelishadi R, Yusufali A, Khatib R, Rahman O, Zatonska K, Iqbal R, Wei L, Bo H, Rosengren A, Kaur M, Mohan V, Lear SA, Teo KK, Leong D, O'Donnell M, McKee M, Dagenais G. Modifiable risk factors, cardiovascular disease, and mortality in 155722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet*. 2019.

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Zodpey SP, Tiwari RR, Kulkarni HR. Risk factors for haemorrhagic stroke: a case-control study. *Public Health*. 2000; 114(3): 177-82.

## Ischemic Stroke

**Search String:** (alcoholic beverage[MeSH Terms] OR drinking behavior[MeSH Terms] OR "alcohol"[Title/Abstract] NOT (alcohols[MeSH Terms] NOT drinking behavior[MeSH Terms])) AND (brain infarction[MeSH Terms] OR stroke[MeSH Terms] OR intracranial hemorrhages[MeSH Terms] OR "stroke"[Title/Abstract] OR "brain infarction"[Title/Abstract] OR "cerebral infarction"[Title/Abstract] OR "intracerebral hemorrhage"[Title/Abstract] OR "intracerebral haemorrhage"[Title/Abstract] OR "subarachnoid hemorrhage"[Title/Abstract] OR "subarachnoid haemorrhage"[Title/Abstract]) AND (Case-Control Studies[MeSH Terms] OR Cross-Over Studies[MeSH Terms] OR Cohort Studies[MeSH Terms] OR Systematic Review[Publication Type] OR Meta-Analysis[Publication Type] OR "systematic review"[Title/Abstract] OR "meta-analysis"[Title/Abstract] OR "cohort"[Title/Abstract] OR "cross-over"[Title/Abstract] OR "crossover"[Title/Abstract] OR "case-control"[Title/Abstract] OR "prospective"[Title/Abstract] OR "retrospective"[Title/Abstract] OR "longitudinal"[Title/Abstract] OR "follow-up"[Title/Abstract] OR Dose-Response Relationship, Drug[MeSH Terms] OR "dose-response"[Title/Abstract]) AND (Risk[MeSH Terms] OR Odds Ratio[MeSH Terms] OR "risk"[Title/Abstract] OR "odds ratio"[Title/Abstract] OR "cross-product ratio"[Title/Abstract] OR "hazards ratio"[Title/Abstract] OR "hazard ratio"[Title/Abstract]) AND ("1970/01/01"[PDat] : "2019/12/31"[PDat]) AND (English[LA]) NOT (animals[MeSH Terms] NOT Humans[MeSH Terms])



\*A single search string was utilized to search for records containing an outcome of stroke, intracerebral hemorrhage, or ischemic stroke, but final included source counts are outcome-specific.

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drinking and overall and cause-specific mortality in China: nationally representative prospective study of 220,000 men with 15 years of follow-up. *Int J Epidemiol.* 2012; 41(4): 1101-13.

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Zhang Y, Tuomilehto J, Jousilahti P, Wang Y, Antikainen R, Hu G. Lifestyle factors on the risks of ischemic and hemorrhagic stroke. *Arch Intern Med.* 2011; 171(20): 1811-8.



## Ischemic heart disease

**Search String:** (alcoholic beverage[MeSH Terms] OR drinking behavior[MeSH Terms] OR “alcohol”[Title/Abstract])

AND

(Coronary Artery Disease[Mesh] OR Myocardial Ischemia[Mesh] OR atherosclerosis[Mesh] OR Coronary Artery Disease[TiAb] OR Myocardial Ischemia[TiAb] OR cardiac ischemia[TiAb] OR silent ischemia[TiAb] OR atherosclerosis[TiAb] OR Ischaemic heart disease[TiAb] OR Ischemic heart disease[TiAb] OR coronary heart disease[TiAb] OR myocardial infarction[TiAb] OR heart attack[TiAb] OR heart infarction[TiAb])

AND

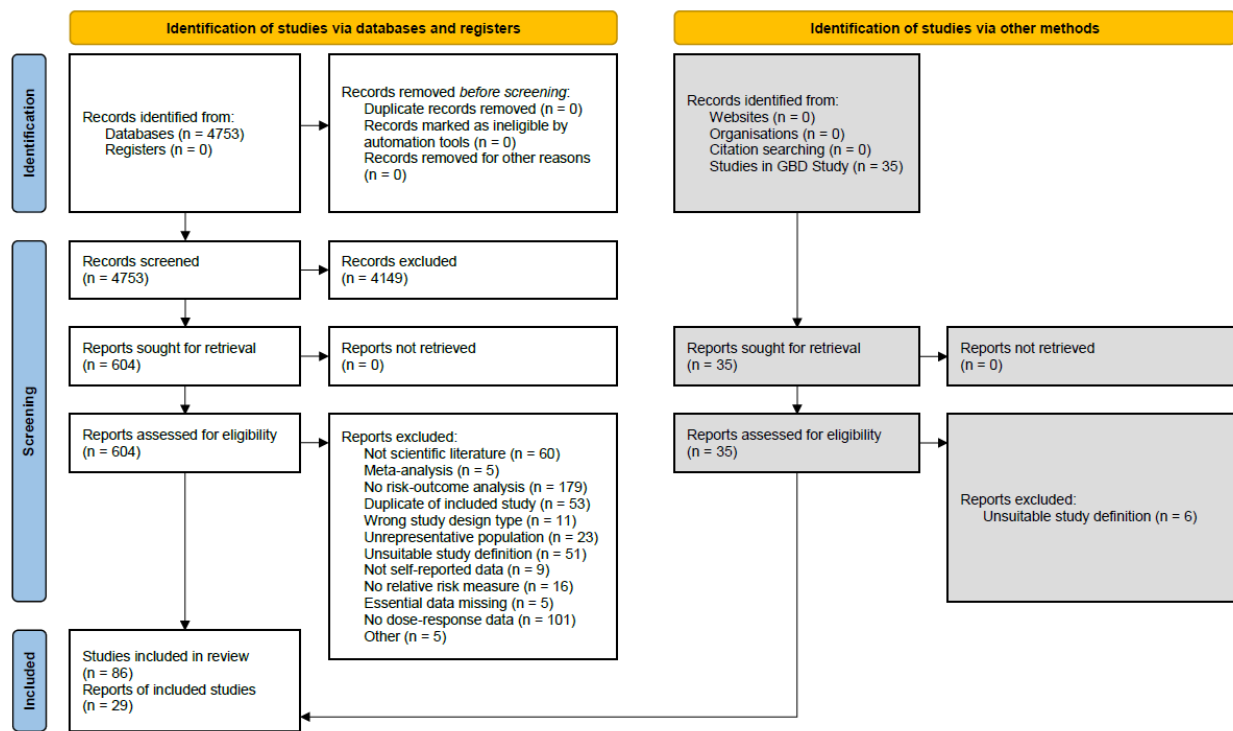
(Risk[MeSH Terms] OR Odds Ratio[MeSH Terms] OR “risk”[Title/Abstract] OR “odds ratio”[Title/Abstract] OR “cross-product ratio”[Title/Abstract] OR “hazards ratio”[Title/Abstract] OR “hazard ratio”[Title/Abstract])

AND ("1970/01/01"[PDat] : "2019/12/31"[PDat])

AND (English[LA])

NOT

(animals[MeSH Terms] NOT Humans[MeSH Terms])



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>

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## Tuberculosis

**Search String:** (alcoholic beverage[MeSH Terms] OR drinking behavior[MeSH Terms] OR “alcohol”[Title/Abstract])

AND

(tuberculosis[MeSH Terms] OR tuberculosis[Title/Abstract] OR TB[Title/Abstract] OR “Mycobacterium tuberculosis”[Title/Abstract])

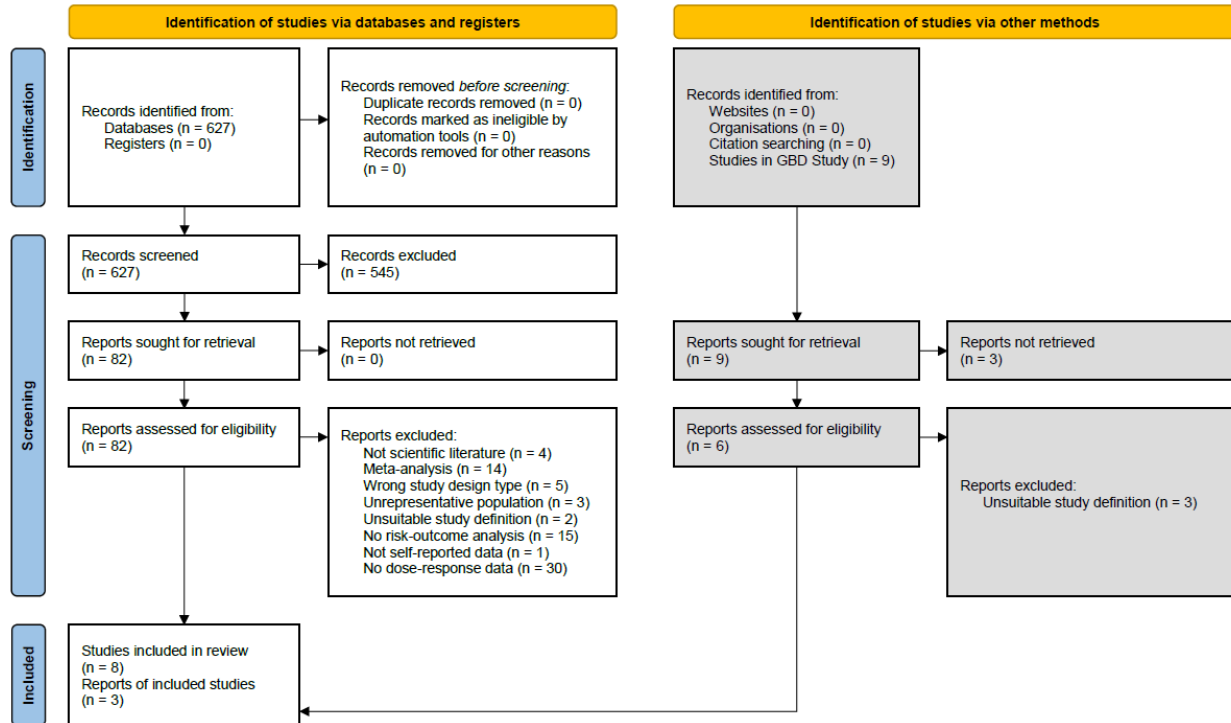
AND

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AND ("1970/01/01"[Pdat] : "2019/12/31"[Pdat])

AND (English[LA])

NOT (animals[MeSH Terms] NOT Humans[MeSH Terms])



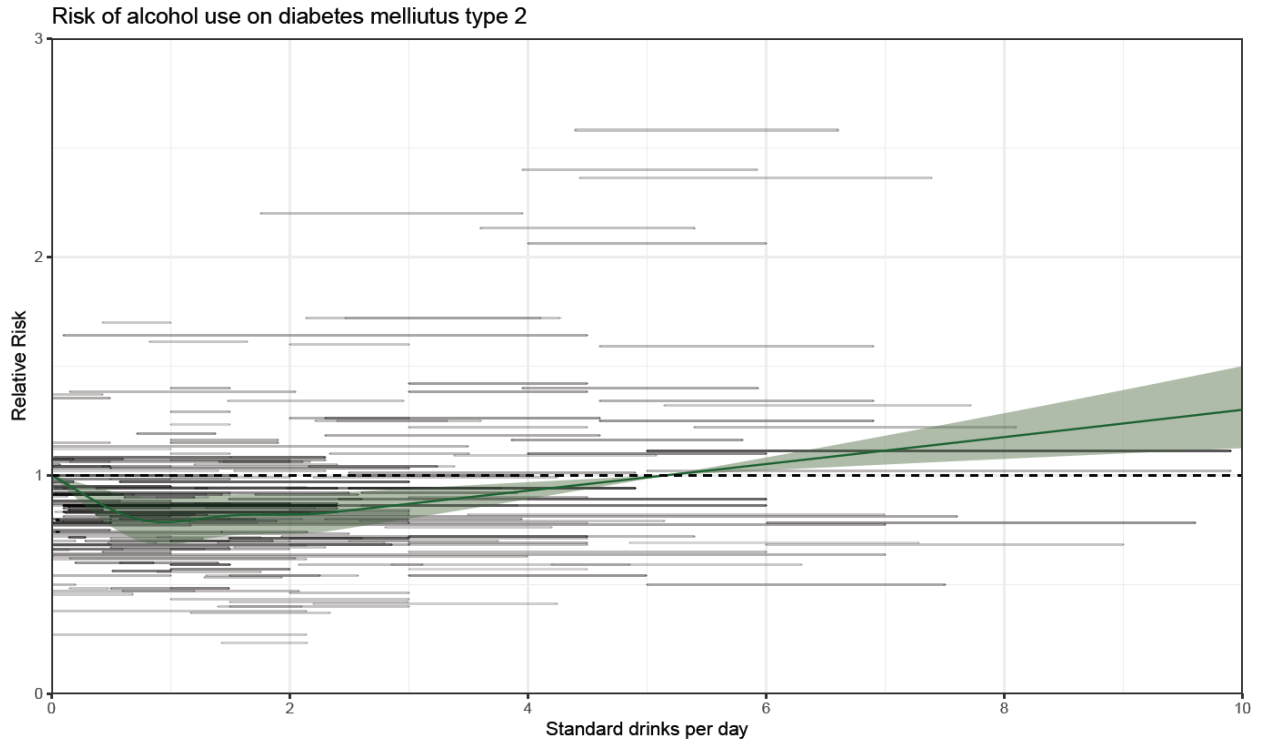
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## References for Tuberculosis

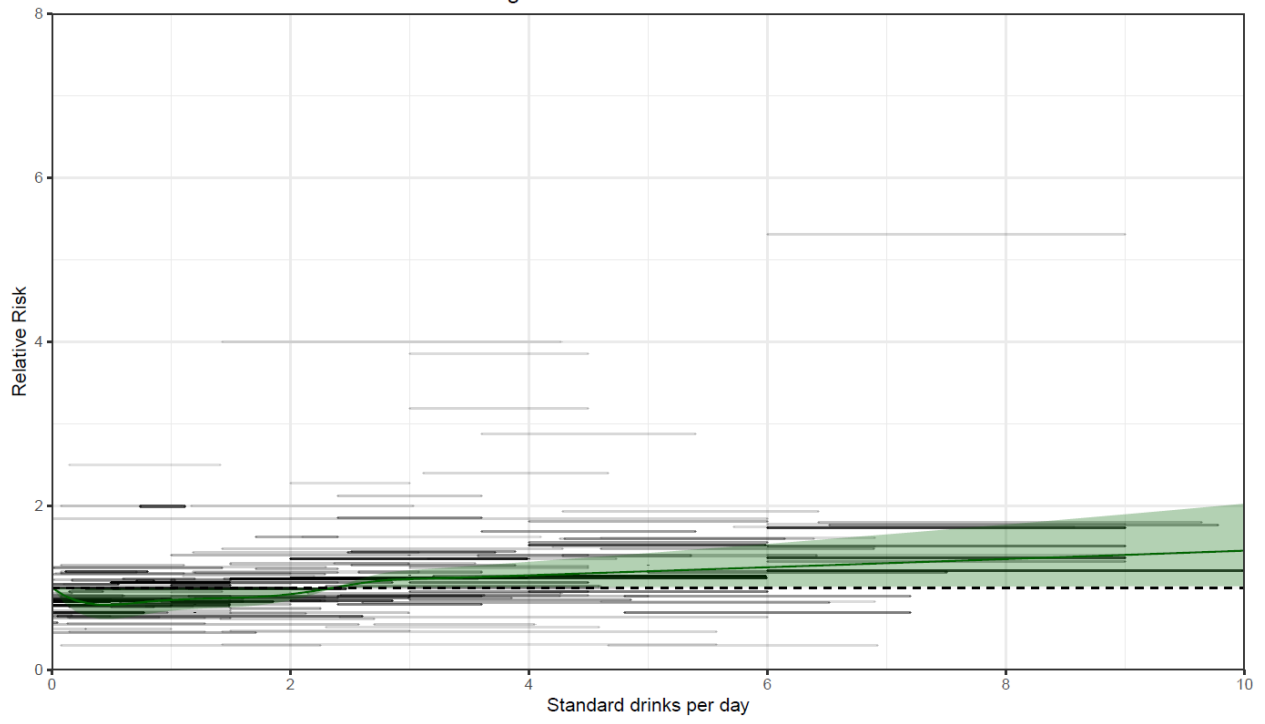
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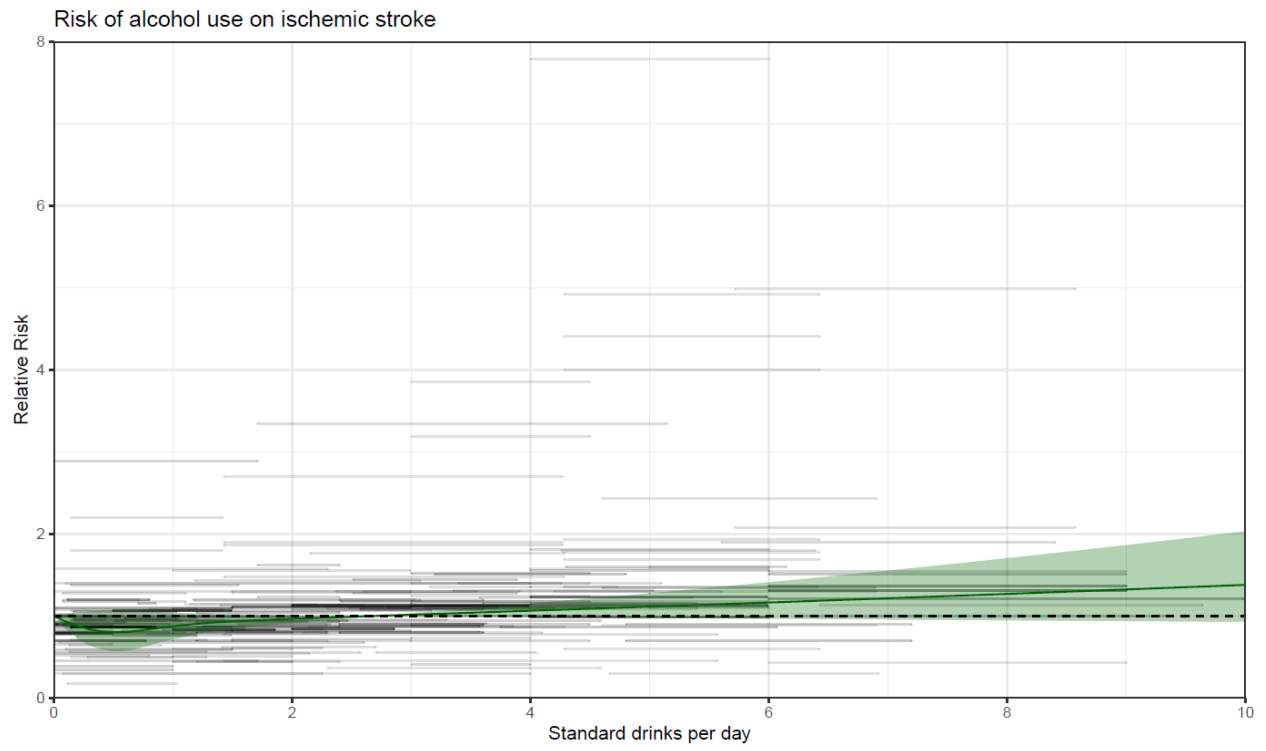
## Modeled Relative Risk Curves

The green shaded area depicts the 95% uncertainty interval of the estimates. The solid green line depicts the mean estimates. Horizontal grey lines depict study data points, the darker the points the smaller the uncertainty of the data. Horizontal lines span the exposure range reported for the data point. The horizontal dashed line highlights a relative risk of one, compared to a non-drinker reference.

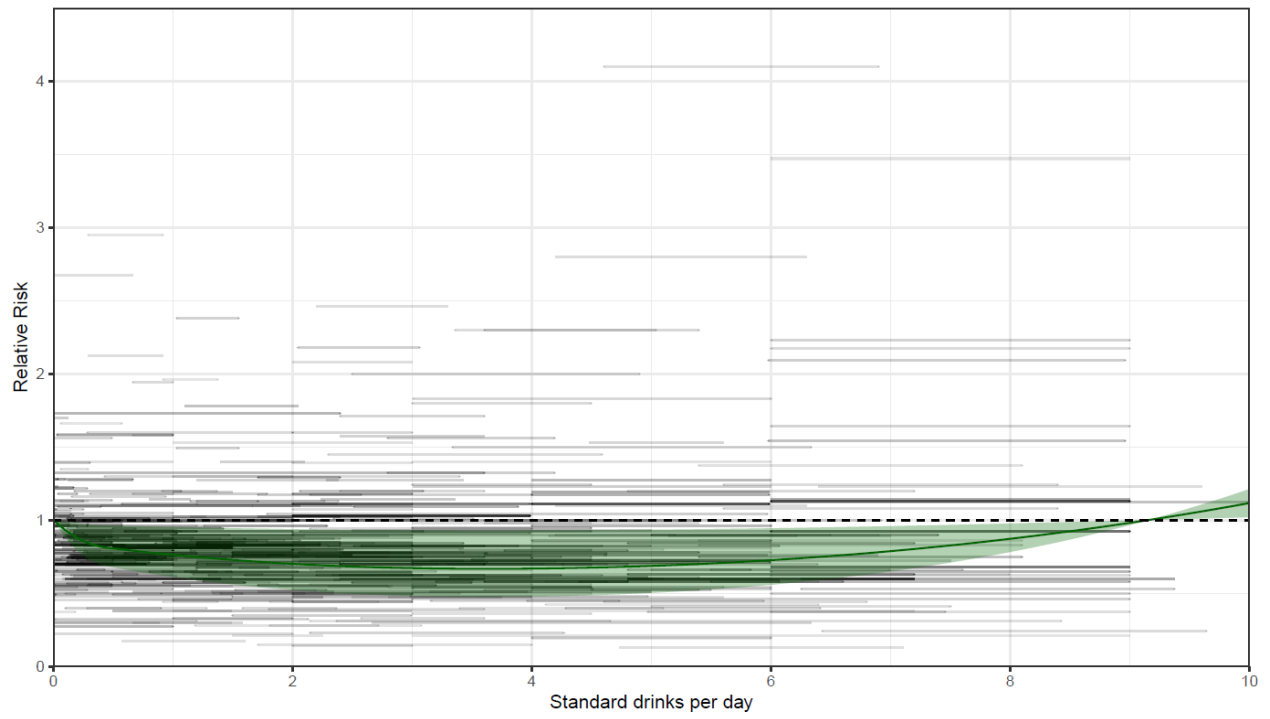


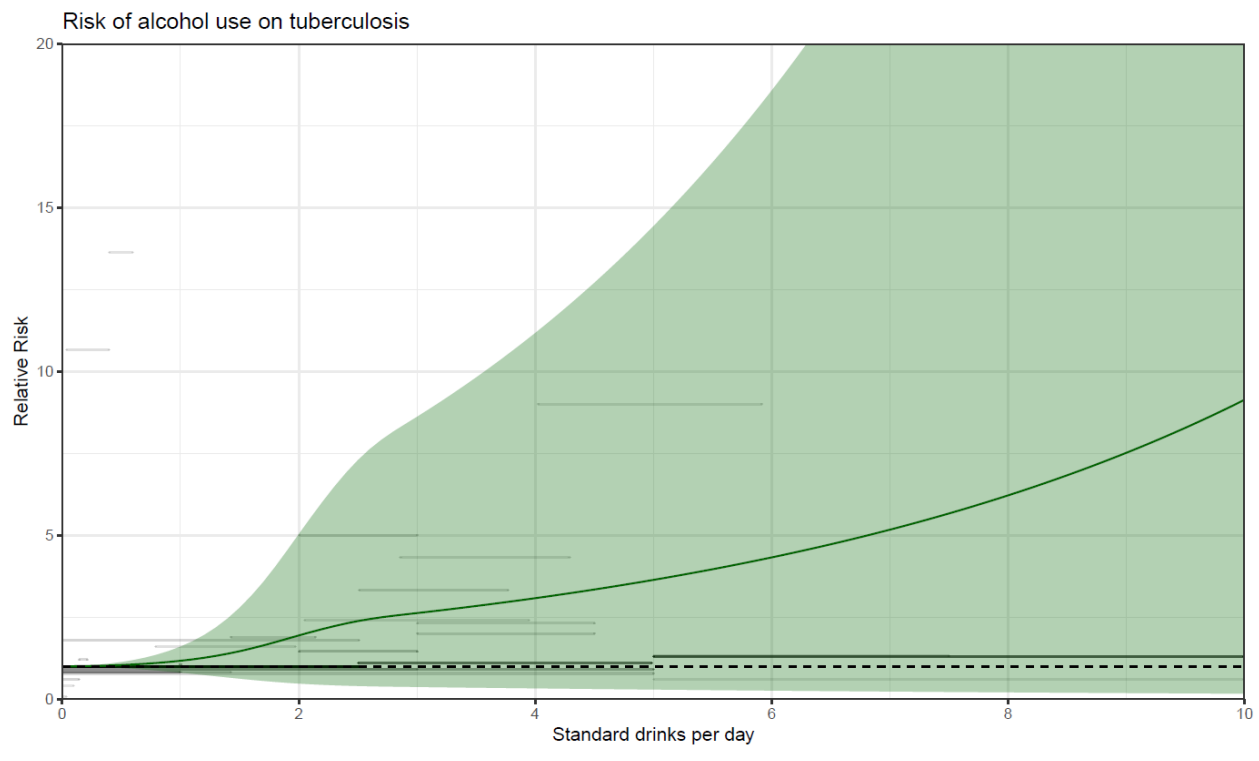
Risk of alcohol use on intracerebral hemorrhage





Risk of alcohol use on ischemic heart disease





## GATHER Checklist

This study complies with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) recommendations.

Item #	Checklist item	Reported on page #
<b>Objectives and funding</b>		
1	Define the indicator(s), populations (including age, sex, and geographic entities), and time period(s) for which estimates were made.	Main 8-12; Methods Appendix 3-9
2	List the funding sources for the work.	3
<b>Data Inputs</b>		
<i>For all data inputs from multiple sources that are synthesized as part of the study:</i>		
3	Describe how the data were identified and how the data were accessed.	Methods Appendix 10, 13-17
4	Specify the inclusion and exclusion criteria. Identify all ad-hoc exclusions.	Methods Appendix 10
5	Provide information on all included data sources and their main characteristics. For each data source used, report reference information or contact name/institution, population represented, data collection method, year(s) of data collection, sex and age range, diagnostic criteria or measurement method, and sample size, as relevant.	<a href="http://ghdx.healthdata.org/gbd-2019/data-input-sources">http://ghdx.healthdata.org/gbd-2019/data-input-sources</a>
6	Identify and describe any categories of input data that have potentially important biases (e.g., based on characteristics listed in item 5).	20
<i>For data inputs that contribute to the analysis but were not synthesized as part of the study:</i>		
7	Describe and give sources for any other data inputs.	8-12
<i>For all data inputs:</i>		
8	Provide all data inputs in a file format from which data can be efficiently extracted (e.g., a spreadsheet rather than a PDF), including all relevant meta-data listed in item 5. For any data inputs that cannot be shared because of ethical or legal reasons, such as third-party ownership, provide a contact name or the name of the institution that retains the right to the data.	<a href="http://ghdx.healthdata.org/gbd-2019/data-input-sources">http://ghdx.healthdata.org/gbd-2019/data-input-sources</a>
<b>Data analysis</b>		
9	Provide a conceptual overview of the data analysis method. A diagram may be helpful.	8; <a href="http://ghdx.healthdata.org/gbd-2019/code/risk-1">http://ghdx.healthdata.org/gbd-2019/code/risk-1</a>



<b>10</b>	Provide a detailed description of all steps of the analysis, including mathematical formulae. This description should cover, as relevant, data cleaning, data pre-processing, data adjustments and weighting of data sources, and mathematical or statistical model(s).	Main 8-12; Methods Appendix 12
<b>11</b>	Describe how candidate models were evaluated and how the final model(s) were selected.	Main 10, methods appendix 10, referenced manuscript with additional details published separately
<b>12</b>	Provide the results of an evaluation of model performance, if done, as well as the results of any relevant sensitivity analysis.	17
<b>13</b>	Describe methods for calculating uncertainty of the estimates. State which sources of uncertainty were, and were not, accounted for in the uncertainty analysis.	11
<b>14</b>	State how analytic or statistical source code used to generate estimates can be accessed.	<a href="http://ghdx.hea.lthdata.org/gbd-2019/code/risk-1">http://ghdx.hea.lthdata.org/gbd-2019/code/risk-1</a>
<b>Results and Discussion</b>		
<b>15</b>	Provide published estimates in a file format from which data can be efficiently extracted.	Will be made public through <a href="http://ghdx.hea.lthdata.org">http://ghdx.hea.lthdata.org</a> upon publication
<b>16</b>	Report a quantitative measure of the uncertainty of the estimates (e.g. uncertainty intervals).	Main 12-17; Supplemental Results;
<b>17</b>	Interpret results in light of existing evidence. If updating a previous set of estimates, describe the reasons for changes in estimates.	4-6; 19-20
<b>18</b>	Discuss limitations of the estimates. Include a discussion of any modelling assumptions or data limitations that affect interpretation of the estimates.	20

## Contributions

Managing the overall research enterprise

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Writing the first draft of the manuscript

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Primary responsibility for applying analytical methods to produce estimates

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