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BELGIAN NATIONAL BURDEN OF DISEASE STUDY

Guidelines for the calculation of risk factor attributable burden

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Authors

Sarah NAYANI

•

Leonor GUARIGUATA

•

Sarah CROES

•

Arno PAUWELS

•

Masja SCHMIDT

•

Vanessa GORASSO

•

Brecht DEVLEESSCHAUWER

Contact • burden@sciensano.be

Visit our website: https://burden.sciensano.be

Sponsors

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Updates to the protocol

Version 2025	• Initial version (risk factor-specific methods for tobacco and alcohol use)

ABBREVIATIONS

AB	Attributable Burden
AAF	Alcohol Attributable Fraction
APC	Alcohol Per Capita Consumption
BEBOD	Belgian National Burden of Disease Study
BHIS	Belgian Health Interview Survey
BOD	Burden of Disease
COD	Cause of Death
CRA	Comparative Risk Assessment
DALY	Disability-Adjusted Life Year
EU	European Union
GBD	Global Burden of Disease
GLM	Generalised Linear Models
INLA	Integrated Nested Laplace Approximations
NCD	Non-Communicable Disease
PAF	Population Attributable Fraction
PHE	Public Health England
RCT	Randomized Controlled Trial
RR	Relative Risk
TMRED	Theoretical Minimum Risk Exposure Distribution
TMREL	Theoretical Minimum Risk Exposure Level
WAIC	Watanabe-Akaike Information Criterion
WHO	World Health Organization
YLD	Years Lived with Disability
YLL	Years of Life Lost

CONTENTS

1. General Outline

1.1 INTRODUCTION

To promote population health and set relevant decisions and priorities, the use of comprehensive information on the health status of the population is important. Beyond just the presence/absence of specific diseases and conditions, burden of disease (BoD) methods provide a comprehensive and comparable quantification of the physical and psychosocial health impact of diseases, injuries, and risk factors (Devleesschauwer et al., 2014). A key aspect of many BoD assessments is the attribution of disease burden to risk factors, as it gives an understanding to what extend these factors contribute to disease burden. Indeed, identifying key risk factors is crucial for reducing disease burden and enhancing future health by setting new priorities but also assessing the effectiveness of prevention efforts (Murray et al., 2003).

In the 2021 Global Burden of Disease (GBD) study, non-communicable diseases (NCDs) accounted for approximately 1.73 billion Disability-Adjusted Life Years (DALYs), representing 59.9% of the total global DALYs, which were approximately 2.88 billion. Behavioral risks contributed significantly to the attributable burden, with 763 million DALYs (26.5% of total DALYs) associated with behavioral risks, followed by metabolic risks at 476 million DALYs (16.5%) and environmental/occupational risks at 416 million DALYs (14.4%). Collectively, all GBD 2021 risk factors accounted for 41.4% of the total global DALYs in 2021 (Brauer et al., 2024; Institute for Health Metrics and Evaluation, 2024).These risk factors are organized into four hierarchical levels, as shown in Table 1. Level 1 represents the overarching categories (behavioural, environmental and occupational, and metabolic); Level 2 contains both single risks and risk clusters (such as child and maternal malnutrition); Level 3 contains the disaggregated single risks from within Level 2 risk clusters (such as low birthweight and short gestation); and Level 4 details risks with the most granular disaggregation, such as for specific occupational carcinogens, the subcomponents of child growth failure (stunting, wasting, underweight), and suboptimal breastfeeding (discontinued and non-exclusive breastfeeding) (Murray et al., 2020).

Table 1. Risk factors as defined by the Global Burden of Disease Study by risk factor groups

Levels	Risk groups		
Level 1	**Behavioural risk factors**	**Metabolic risk factors**	**Environmental/Occupational risks**
Level 2	**1. Dietary Risks**	**1. High fasting plasma glucose**	**1. Air Pollution**
Level 3	Low fruit intake		Ambient particulate matter pollution
	Low legume intake		Ambient ozone pollution

Low whole grain intake High sodium intake High red meat intake Low fiber intake High trans-fat intake Low nuts and seeds intake Low vegetable intake High processed meat intake Low polyunsaturated fatty acid intake Low omega-3 intake High sugar-sweetened beverage intake Low milk intake Low calcium intake		Household air pollution from solid fuels
2. Tobacco Use Smoking tobacco Secondhand smoke exposure Chewing tobacco	**2. High systolic blood pressure**	**2. Occupational Risks** Occupational carcinogens Occupational particulate matter, gases, and fumes Occupational ergonomic factors Occupational noise Occupational injuries
3. Alcohol Use	**3. High body mass index (BMI)**	**3. Water, Sanitation, and Hygiene (WaSH)** Unsafe water source Unsafe sanitation No accessibility to handwashing facilities
4. Drug Use	**4. High total cholesterol**	**4. Other environmental risks** Residential Radon Lead exposure
5. Unsafe Sex	**5. Low glomerular filtration rate (GFR)**	**5. Non-optimal temperature** High temperature Low temperature
6. High Body Mass Index (BMI) **7. Low Physical Activity** **8. Childhood Sexual Abuse** **9. Child and Maternal nutrition** Child stunting Child wasting Child underweight Child overweight Child micronutrient deficiency Maternal anemia	**6. Low bone mineral density**	

The most recent iteration of the GBD study (Brauer et al., 2024) examined 88 risk factors in 204 countries and territories. Although the GBD now provides results for all World Health Organisation (WHO) member states, including Belgium, (sub)national studies still have

advantages, including ownership of the results. National BOD studies also promote sustainability, as they can be regularly updated and adapted over time. Most importantly, they allow for tailored estimates at both the national and regional levels, using the best available national data (De Pauw et al., 2023). Initially, the Belgian National Burden of Disease study (BeBOD) estimated years of life lost, years lived with disability, and DALY for key diseases. In a second phase, the BeBOD study has been extended to include the burden of disease attributable to risk factors. The current document describes the methodological framework for risk factor attributable burden developed and applied by BeBOD.

2. Methodological overview

While there are several ways of presenting the relative impact of different risk factors on diseases, one of the more established methods that allows for direct comparison is Comparative Risk Assessment (CRA). This framework, elaborated by the GBD in the 1990s, compares a current harmful risk factor in the population against a “counterfactual” exposure situation, where the selected risk factor is reduced to the so-called Theoretical Minimum Risk Exposure Level (TMREL) (Murray et al., 2003; Plass et al., 2022). This allows us to estimate the proportion of the disease attributable to that risk factor, the Population-Attributable Fraction (PAF). BeBOD aims to present risk factor attributable burden from 2013 to the most recent reference year (2021, at the time of writing this), by region, sex, and age group, using a time series of data and present yearly estimates of risk-attributable burden. A methodology tailored to specific risk factors will be developed sequentially, prioritizing them based on population health significance, policy relevance, and data availability.

The CRA method uses a step-wise approach to arrive at attributable burden estimates. Typically, estimating the fraction of disease attributable to a risk factor involves five consecutive steps where steps 1 and 2 are complementary, as illustrated in Figure 1 (Murray et al., 2003; Plass et al., 2022).

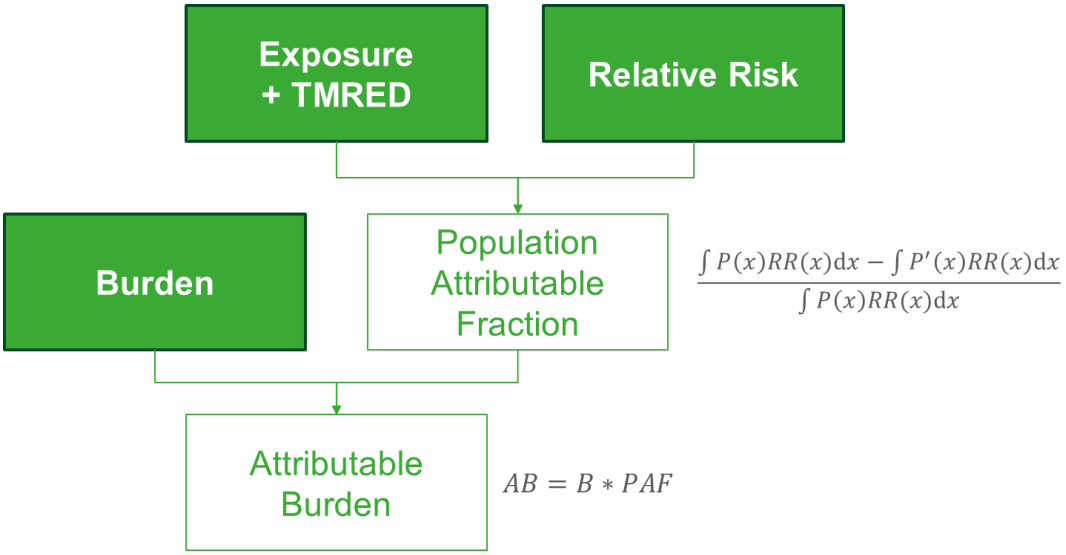

Figure 1: Stepwise approach for calculating the attributable burden of disease through comparative risk assessment

2.1 IDENTIFICATION AND QUANTIFICATION OF RISK-OUTCOME-PAIRS ASSOCIATION

Which health outcomes are caused by the risk factors? What is the risk of developing the outcome in function of exposure?

A fundamental step in estimating the burden of disease attributable to risk factors is identifying the health outcomes causally linked to specific exposures. Establishing these risk-outcome associations is essential for ensuring the validity and robustness of CRA results (Zheng et al., 2022). Risk-outcome pairs must be based on strong causal evidence to ensure that the estimated burden accurately represents true public health impacts rather than false associations (Plass et al., 2022).

This section will explain the process of identifying and quantifying risk-outcome associations, using evidence standards that support this step.

2.1.1 Identification of risk-outcome pairs

The process of identifying these associations relies on robust epidemiological principles, with causality assessments often guided by frameworks such as the Bradford Hill criteria (Hill, 1965):

- **Strength**: The larger the effect size, the more likely that the association is causal.
- **Consistency**: The more independent studies producing similar findings, the more likely that the association is causal.

- **Specificity**: The more specific exposure and outcome are defined, the more likely that the association is causal.
- **Temporality**: The outcome has to occur after the exposure, possibly after some delay.
- **Biological gradient**: Higher exposure should be associated with more cases of the outcome, indicative of a dose-response relationship.
- **Plausibility**: There should be a plausible mechanism between exposure and outcome.
- **Coherence**: The fewer contradictory findings in other fields of study, the more likely that the association is causal.
- **Experiment**: Do changes in exposure, for example through preventive action, have an effect on the frequency of the outcome?
- **Analogy**: A causal relationship is supported if there are similar risk-outcome pairs.

These criteria are key elements in establishing causality.

Furthermore, the GBD also performed causality assessments to decide on the inclusion of risk-outcome pairs in previous cycles (Murray et al., 2020), which are based on the grading system of the World Cancer Research Fund (Wiseman, 2008). Where they have categorize risk-outcome associations based on the strength of available evidence, from “convincing” and “probable” to “possible” or “insufficient” (Murray et al., 2020; Wiseman, 2008). Such frameworks ensure transparency and consistency in deciding which risk-outcome pairs to include in CRA analyses. These categories are defined as follows:

- **Convincing evidence**: Convincing evidence is evidence based on epidemiological studies showing consistent associations between exposure and disease and includes little or no evidence to the contrary. The available evidence is based on a substantial number of studies including prospective observational studies and, where relevant, randomized controlled trials (RCT) of sufficient size, duration, and quality that show consistent effects. The association should be biologically plausible.
- **Probable evidence**: Probable evidence is evidence based on epidemiological studies showing fairly consistent associations between exposure and disease, but for which perceived shortcomings in the available evidence exist or some evidence to the contrary precludes a more definite judgment. Shortcomings in the evidence may be any of the following: insufficient duration of trials (or studies); insufficient trials (or studies) available; inadequate sample sizes; or incomplete follow-up. Laboratory evidence is usually supportive. The association should be biologically plausible.
- **Possible evidence**: Possible evidence is evidence based mainly on findings from case-control and cross-sectional studies. Insufficient RCT, observational studies, or

non-randomized controlled trials are available. Evidence based on non-epidemiological studies, such as clinical and laboratory investigations, is supportive. More trials are needed to support the tentative associations, which should be biologically plausible.

- **Insufficient evidence**: Insufficient evidence is evidence based on findings of a few studies that are suggestive but insufficient to establish an association between exposure and disease. Little or no evidence is available from RCTs. More well-designed research is needed to support the tentative association.

In summary, the identification of risk-outcome pairs is a critical step in Comparative Risk Assessment, as it ensures that the estimated burden is based on robust and causal evidence (Plass et al., 2022; Zheng et al., 2022). Since the GBD 2021, the introduction of the burden of proof risk function methodology has further strengthened this process. This approach evaluates risk-outcome pairs using a star-rating system, where those receiving at least one star are considered for inclusion. By analyzing the relative risk (RR) estimate and its 95% uncertainty interval, the methodology ensures that risk-outcome pairs are only included if their uncertainty interval does not cross the null value of 1, even when unexplained between-study heterogeneity is not accounted for (Brauer et al., 2024; Zheng et al., 2022).

2.1.2 Selection of dose-response functions

For the selected risk-outcome pairs, a dose-response or exposure-response function is required to translate exposure to the risk factor into the relative risk for the associated health outcome. The selection of these functions is a critical step, as it directly impacts the accuracy and reliability of the burden estimates.

To ensure consistency and transparency, the following criteria can be used to evaluate epidemiological studies serving as the source of a dose-response function. These criteria also help document the rationale for selecting one function over potential alternatives:

Accessibility

Can the information be easily extracted?

- From the article text?
- From the supplementary materials?
    - Pdf
    - Document
    - Spreadsheet

In the context of BeBOD, this is essential for maintaining the study's relevance and ensuring the findings can be revised as new evidence emerges

Transparency

Are the methodology and underlying data clearly described?

- Which health data is used?
- How is the health outcome defined?
- How is exposure assessed?
- Which information is available for the study's subjects? For example:
    - Age and sex
    - Socio-economic status
    - Smoking behaviour
    - Body Mass Index
    - Physical activity level
- Is the information on subjects on the level of the individual or area-level?
- Which confounding factors are taken into account?
- In case of a systematic review and meta-analysis:
    - Is the search strategy documented?
    - What are the inclusion and exclusion criteria?
    - Which studies are included in the review?
    - Which information is extracted?

Transparency is crucial in the BeBOD study to ensure that the study findings can be verified and reproduced.

Reliability

Is the analysis methodology sound and appropriate?

- Is exposure assessment unbiased?
- Is the outcome definition appropriate?
- Are analyses performed for relevant subgroups?
- Is the relationship adjusted for all possible confounding factors?
- Are single or multiple exposure models used?
- In case of a systematic review and meta-analysis:
    - Was there publication bias detected?
    - How high is the heterogeneity of the results between the studies?

Ensuring reliability is essential to establish confidence in the estimates, as they inform decision-making by policymakers and public health stakeholders. This is a key objective of the BeBOD study.

Evidence

Is the quality and quantity of the data used in the analysis sufficient?

- What is the sample size?
- Is the sample representative of the population?
- What is the study design?
    - Systematic review
    - RCT
    - Cohort study
    - Case-control study
    - Ecological study
- In case of a systematic review and meta-analysis:
    - Are all included studies relevant?
    - Are all relevant studies included?
    - Does the review consider the most recent evidence?

In BeBOD, reliance on robust evidence ensures that the study's results are scientifically valid and can withstand scrutiny from both scientific and policy perspectives.

Relevance

Are the findings representative of the (Belgian) population and relevant?

- Do the health outcome definitions match?
- Does the definition of exposure match?
- Are the population characteristics similar?
- What is the geographical extent of the study?
- What is the observed exposure range?

For BeBOD, ensuring relevance is critical to producing estimates that accurately capture the burden of disease in Belgium and address country-specific public health priorities.

2.2 EXPOSURE ASSESSMENT

Exposure assessment is a crucial step in estimating the burden of disease , as it quantifies how much of a population is exposed to a specific risk factor and the distribution of that exposure. The methods for estimating exposure can vary widely depending on the risk factor in question and the type of data available within the relevant context (Ezzati et al ., 2002 ; Plass et al., 2022). This step requires careful consideration of the data sources, potential biases, and adjustments needed to ensure the exposure estimates are both accurate and

representative. In this section, we explore the key principles and approaches to exposure assessment (Ezzati et al., 2002).

2.2.1 Exposure definition

How can exposure to risk factors in the population be measured or modelled?

Exposure estimates vary by risk factors and available data, necessitating critical questions about exposure pathways, and the data sources for measurement. Indeed, descriptive variables for exposure to risk factors can vary considerably in data collection or processing. This variability can lead to misclassification of exposure, potentially yielding different results. The exposure variable can be continuous (e.g., body mass index, systolic blood pressure, volume of alcohol units per day) or categorical (e.g., body mass index category, smoker/non-smoker). The exposure definition sets the scene for all further steps and guides the estimation process. The selection of an indicator to describe exposure can be guided by several factors: the availability of data, the importance of aligning with estimates from other burden of disease studies to ensure comparability, and, most critically, the need to align with the relative risks identified for the risk-outcome pairs.

In practice, however, the process of defining exposure and identifying relative risks is highly interconnected. These steps often occur simultaneously, as the choice of exposure data depends on the availability of relative risks, and vice versa. While theoretical frameworks and formulas may present these steps as linear (Figure 1), the reality is that they are iterative and interdependent processes.

After selecting which exposure indicator to include, the next step is to formulate a strategy for identifying a source of information to estimate exposure across the population by year, sex, region, and age group. There are various ways to capture exposure data. For instance, a literature review provides valuable insights into how participant exposure is typically measured, which is crucial for BOD assessments relying on dose-response relationships from epidemiological studies. Consulting relevant literature allows us to align the method used to assess population exposure as closely as possible with the methodology applied to establish the dose-response relationship. Representative samples are also commonly used for this purpose. Data from surveys and questionnaires can help assess exposure, while relevant biomarkers may also provide valuable insights.

For BeBOD, a critical appraisal of national data sources is performed to identify the “best available” dataset for each risk factor/exposure. This process involves evaluating each highlighted data source against quality criteria such as:

- Frequency
- Bias assessment
- Type of data collection (e.g., population survey)
- International comparability
- Consistency over time
- Representativeness of the sample
- Level of aggregation: national, regional, provincial

2.2.2 Correcting for self-reported data

To address possible biases in self-reported data, such as the over- or under-estimation of the probability of a portion of the population being undiagnosed or exposed to certain risk factors (e.g., alcohol or tobacco consumption), adjustments can be made using correction factors. These correction factors are often derived from objectively measured data, such as biomarkers, or alternative data sources, such as sales data for alcohol or tobacco products. (e.g. high cholesterol etc.), some adjustments may be made using correction factors derived from objectively measured data or other types of data (e.g., sales).

2.2.3 Interpolation for missing data and time series

One possible data source for exposure indicators is repeated cross-sectional surveys. However, these surveys are often not conducted annually and therefore may not provide a continuous time series. When an existing time series is unavailable, methodologies can be developed to address gaps in the data and ensure a consistent representation over time. For instance, in the BeBOD study, where the goal is to present a time series of risk factor attributable estimates from 2013 to the most recent reference year, a methodology was developed to be able to fill the gaps in the years between data (De Pauw et al., 2024).

To interpolate missing years of data, BeBOD relies on implementing a Bayesian Generalised linear models (GLM) methodology to predicts the frequency of specific exposures by making use of Integrated Nested Laplace Approximations (INLA). INLA is a method designed for approximate Bayesian inference in latent Gaussian models, which encompass a wide array of statistical models used across various scientific disciplines (Lindgren & Rue, 2015). INLA is particularly effective for models that are computationally demanding to fit using traditional Markov Chain Monte Carlo techniques due to its efficiency and speed. The method focuses on latent Gaussian models where the observed data are linked to latent Gaussian variables via a likelihood function, applicable to models like generalized linear mixed models, spatial models, and more. INLA relies on the Laplace approximation to estimate the marginal posterior distributions of the latent variables and model parameters swiftly, with less

computational overhead than conventional Bayesian methods, while also allowing for the computation of uncertainty. INLA uses a nested approach where it initially approximates the marginal posterior distributions of the hyperparameters, then, based on these approximations, computes the marginal distributions of the latent field and other parameters. The methodology includes a strategy to select the "best-fitted model" to create a time series. This model will be the best at taking into account interactions between and across independent variables (e.g. year, sex, region, and age groups). In BeBOD, estimations via INLA are done by using the R-INLA package (version 24.05.10).

General model

GLM are used to model the exposure variables in function of time and other possible covariates. Different statistical families and link functions are required to account for different types of data distributions.

Binomial model (for prevalence data):

The general model to forecast the prevalence of an exposure can be described as

$$\log\left(\frac{\pi_C}{1-\pi_C}\right) = \beta_0 + \beta_1 X_{year} + \beta_j X_j + \varepsilon,$$

Whereby π_C represents the exposure prevalence, β_0 the intercept of the model, β_1 the coefficient associated with the prevalence (π_C) and the year (X_{year}) in which the data were observed, β_i the coefficient associated with the prevalence (π_C) and a socio-demographic predictor (X_j), and ε the residual term. The term $\log\left(\frac{x}{1-x}\right)$ is the logit-link function that is implemented to model a binomial process.

Poisson or Quasi-Poisson Models (for count data):

These models are appropriate for variables representing counts or rates that are non-negative.

$$\log(\mu) = \beta_0 + \beta_1 X_{year} + \beta_j X_j + \varepsilon,$$

Where μ is the expected count (or rate). The log-link function ensures the predictions remain non-negative.

Gamma Models (for positively skewed continuous data):

Used for data that are positive and continuous, such as rates or durations.

$$\log(\mu) = \beta_0 + \beta_1 . X_{year} + \beta_j . X_j + \varepsilon$$

In BeBOD, a total of 5 different models are considered including different combinations of the independent variables year, sex, age, and region. Each model is composed of different interactions between those independent variables where the model with the higher number of interactions takes into account lower-grade interactions from the previous model.

Model 1: Fixed effects model

$$y = \beta_0 + \beta_1 * YEAR + \beta_2 * SEX + \beta_3 * AGE + \beta_4 * REGION + \varepsilon$$

Model 2: Two way interaction model with year

$$y = \beta_0 + \beta_{12} * YEAR * SEX + \beta_{12} * YEAR * SEX + \beta_{13} * YEAR * AGE + \beta_{14} * YEAR * REGION + \varepsilon$$

Model 3: Two way interaction model among all included factors

$$y = \beta_0 + \ldots + \beta_{12} * YEAR * SEX + \beta_{13} * YEAR * AGE + \beta_{14} * YEAR * REGION + \beta_{23} * SEX * AGE + \beta_{34} * AGE * REGION + \beta_{24} * SEX * REGION + \varepsilon$$

Model 4: Three way interaction model among all included factors

$$y = \beta_0 + \ldots + \beta_{123} * YEAR * SEX * AGE + \beta_{124} * YEAR * SEX * REGION + \beta_{234} * SEX * AGE * REGION + \beta_{123} * YEAR * AGE * REGION + \varepsilon$$

Model 5: Four way interaction model among all included factors

$$y = \beta_0 + \ldots + \beta_{1234} * YEAR * SEX * AGE * REGION + \varepsilon$$

The formal model-building process includes three consecutive steps. In an initial step, the different models were built and their goodness of fit values were saved into a table. The model with the best goodness-of-fit (lowest Watanabe-Akaike information criterion (WAIC), was identified as the prime candidate to construct the final model.

The most suitable model is selected based on the Watanabe–Akaike information criterion (WAIC), whereby a lower WAIC is associated with a better fit of the model to the data. Therefore, the model with the lowest WAIC is selected for the imputation. After model selection, the estimated prevalence estimates and their surrounding 95% uncertainty intervals for the years with no information on the prevalence are extracted from the posterior distribution of the Bayesian model fitted with INLA by age, sex, and region. In addition, we also use the estimated and smoothed prevalence rate derived from the most suitable model for the years in which data are available, to allow for a coherent time series.

Imputation

In BeBOD, only missingness in the response variable is considered (forecasting) given the selected final model. More specifically, projected exposure estimates are obtained by imputing the missing outcomes for unobserved years (i.e., from 2018 to 2021). Given that the distribution of the response variable is part of the model, it is possible to predict the missing values by computing their predictive distribution.

2.2.4 Normalization of categorical exposure data

For categorical exposure variables, a normalization process is applied that aims to standardize the categorical exposure values across the different categories of risk factors, ensuring that they sum to 100%. The steps below outline a general approach applicable to any risk factor.

For each risk factor, the total exposure is calculated by summing the values across all relevant categories. Each category is then normalized by dividing its value by the total exposure, ensuring that the sum of the normalized exposures equals 100%. The normalized values are verified to confirm they total 100%, ensuring the accuracy of the normalization process. Finally, these normalized values are used for the next steps.

2.3 CALCULATION OF THE ATTRIBUTABLE BURDEN OF RISK FACTORS

What is the proportion of a disease burden attributed to one or multiple risk factors?

The attributable burden quantifies the proportion of a disease burden that can be linked to one risk factor. This calculation builds on the foundations laid by Step 1 (identification of risk-outcome pairs) and Step 2 (exposure assessment), as these complementary steps provide the critical components required for the PAF equation and the resulting attributable burden (AB) estimates (Figure 1). The estimates are generated by year, age, sex, and region.

2.3.1 Theoretical Minimum Risk Exposure Level (TMREL)

To estimate the impact of the increased risk from an exposure, a baseline level of exposure must be defined as a counterfactual. This baseline, known as the TMREL, represents the exposure level that would result in the lowest possible population risk, regardless of whether it can realistically be achieved in practice (Murray et al., 2003).

To guide the choice of the TMREL, Murray et al. (2003) presented different natures of the counterfactual based on the type of risk factor:

- **Physiological Risk Factors**: These include essential physiological parameters like blood pressure. The theoretical minimum here would be a non-zero level based on empirical evidence, representing the point where risk is minimized without disrupting vital functions.

- **Behavioural Risk Factors**: For habits like smoking or alcohol use, the theoretical minimum is usually zero or the point where benefits outweigh risks, depending on the exposure-response relationship. Protective behaviours, like physical activity, also have a theoretical minimum at the highest sustainable levels of benefit.
- **Environmental Risk Factors**: These involve harmful exposures like pollution, where the theoretical minimum is the lowest achievable level, typically the natural background concentration (e.g., the lowest level of particulate matter that can be achieved in the environment).
- **Socioeconomic Risk Factors**: These factors, like income and education, have complex, context-dependent effects. The theoretical minimum varies by context and is assessed relative to policy interventions aimed at reducing disparities.

2.3.2 Population attributable fraction (PAF)

The PAF represents the proportion of a disease that can be attributed to the exposure to a specific risk factor and thus quantifies its impact on the disease burden (as a percentage). This is calculated by estimating the excess prevalence of disease in the population. This can be represented mathematically and is drawn from Murray et al. (2003). Note that different formulas exist depending on the nature of the exposure variable (i.e. binary, categorical or continuous).

For a binary exposure (presence/absence), the PAF formula is as follows:

$$PAF = \frac{P(RR-1)}{P(RR-1)+1}$$

where P is the prevalence of exposure in the population and RR is the relative risk of exposure to the outcome.

For categorical risk factors, the formula can be represented as:

$$PAF = \frac{\sum_{i=1}^{n} P_i RR_i - \sum_{i=1}^{n} P'_i RR_i}{\sum_{i=1}^{n} P_i RR_i}$$

In this equation, P_i represents the observed prevalence of exposure class *i*, P'_i refers to the counterfactual prevalence of exposure class *i*, and RR_i denotes the relative risk associated with exposure class *i*, relative to the reference class. Where $\sum_n$ is the sum of n exposure categories. Each category has its RR in this case and the TMREL is assumed to be a relative risk of 1.

For continuous risk factors, the formula can be represented as:

$$PAF = \frac{\int P(x)RR(x)dx - \int P'(x)RR(x)dx}{\int P(x)RR(x)dx}$$

Where $P(x)$ represents the observed exposure distribution, $P'(x)$ denotes the counterfactual exposure distribution, and $RR(x)$ refers to the relative risk at a specific point on the dose-response function.

Note that risk factor-specific considerations regarding PAF calculations will be addressed in their respective annexes.

2.3.3 Estimating the attributable burden of disease

Estimating the attributable burden of disease requires estimates of that burden (e.g. DALY, YLL, YLD or number of deaths) and will be drawn from available dataset generated by the BeBOD study. For this, a PAF for YLD and a PAF for YLL are estimated and multiplied by the YLD and YLL. Mathematically this can be written as:

$$Attributable\ Burden\ (AB) PAF * BURDEN$$

The attributable burden of disease is estimated by multiplying the PAF by the burden estimate at the most disaggregated level (5-year age group, sex, region, year combination). This provides an attributable burden estimate in absolute numbers that is then aggregated to different levels (e.g., all sexes, all regions, all ages). These aggregated values are divided by the aggregate estimate of the total burden to re-estimate the PAFs for aggregate levels. This process captures the variation in burden by age and sex at the most detailed level. Rates and age-standardized rates are calculated for the attributable burden estimates after aggregation, and DALYs are calculated as the final step. Aggregated PAF estimates will be based on the attributable burden values divided by the total absolute values (not rates) and will be considered as another estimate of the metric (like rates and numbers).

3. Availability of results

The BeBOD study generates a large number of disease burden estimates by cause, age, sex, region, and year. To explore these detailed estimates, a series of interactive visualisation tools have been developed. These tools allow the creation of graphs of the relative contribution of different causes, trends over time, comparisons across regions, patterns by age, and much more. The following tools are available:

- Estimates of the mortality and years of life lost attributed to risk factors : https://burden.sciensano.be/shiny/risk
- Estimates can be downloaded from: https://zenodo.org/communities/bebod/records?q=&l=list&p=1&s=10&sort=newest

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Annex 1. Risk factors specific methods

1 CIGARETTES SMOKING

Summary

According to the GBD study, cigarette smoking contributes to the highest attributable disease burden of any risk factor across all ages for the Belgian population (Murray et al., 2020). The Belgian Health Interview Survey (BHIS) shows an overall decreasing trend in daily smoking with a greater share over time of the population reporting having quit smoking or never smoking; occasional smoking represents a relatively small proportion (around 2%) of the population with not much change over time (Figure 1).

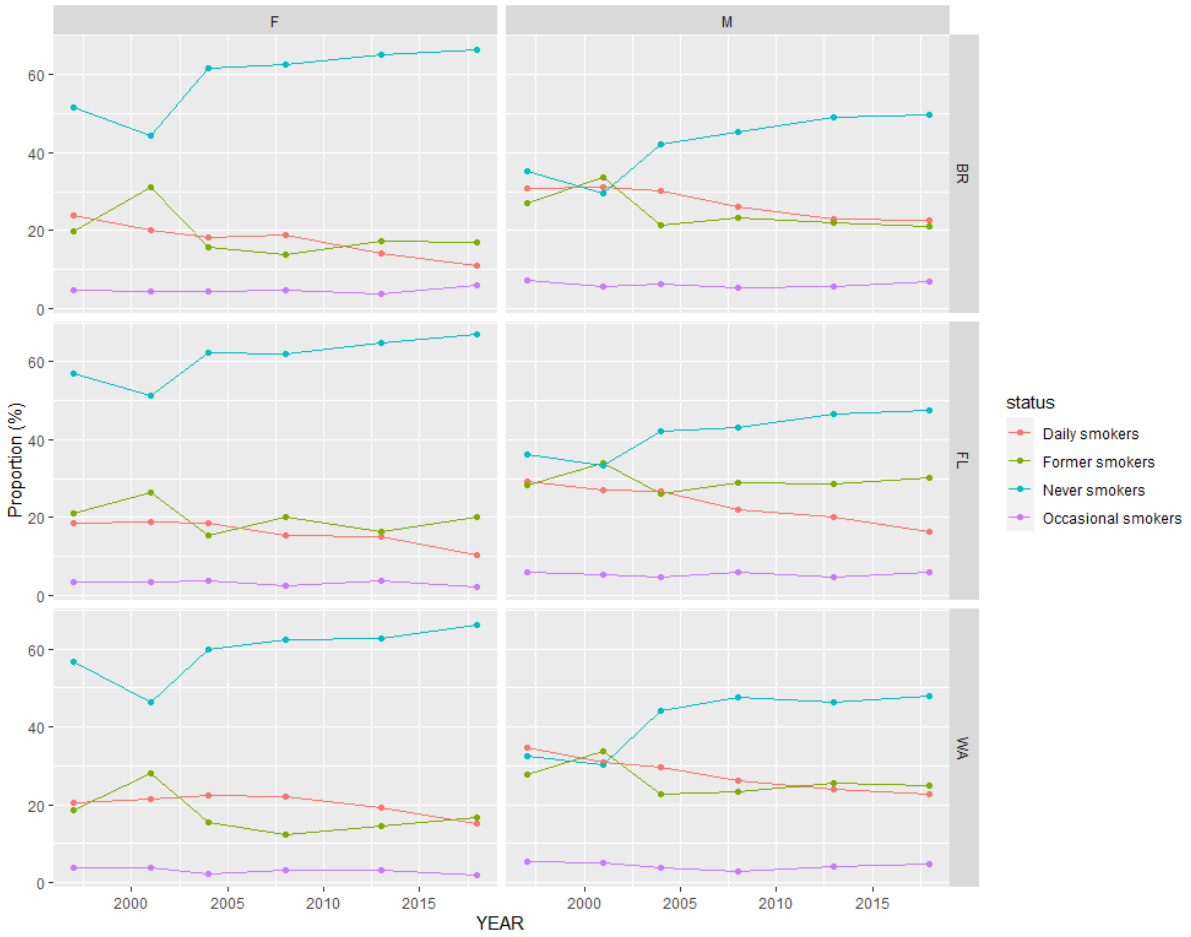

Figure 1 Trends in smoking status in Belgium as reported in the Belgian Health Interview Survey stratified by sex and region

1.1 Identification and quantification of the association of risk-outcome pairs for smoking

Comprehensive studies, such as the Global Burden of Disease (GBD) study, and national initiatives, such as Public Health England (PHE), have provided valuable insights into the

diseases attributable to cigarette smoking and the methodologies used to estimate their burden.

The GBD study relies on a variety of data sources to calculate the burden attributable to tobacco use, including epidemiological studies, national health surveys, cause-of-death registries, and hospital and clinical records: Data on admissions and outpatient visits associated with tobacco-related illnesses (GBD 2019 Risk Factors Collaborators, 2020).

At a national level, PHE has developed smoking-attributable burden estimates to inform policy and interventions in the United Kingdom. PHE's work focuses on reducing health inequalities and providing evidence-based recommendations to government bodies, local authorities, and the public. Smoking-attributable calculations were made by using hospital admissions (2019/20) and deaths (2019), focusing on individuals aged 35 and older. Data on hospital admissions come from Hospital Episode Statistics (HES), based on primary diagnoses, while mortality data are sourced from the Office for National Statistics (ONS). By analyzing and sharing this data, PHE supports targeted interventions to reduce smoking-related harm and improve public health (Public Health England, 2020b).

Table 1. Cigarette smoking outcomes included in evaluated risk-outcome pair sets

	Global Burden of Disease Study	Public Health England
Tuberculosis	X	
Lower respiratory infections	X	
Esophageal cancer	X	X
Stomach cancer	X	X
Bladder cancer	X	X
Liver cancer	X	
Larynx cancer	X	X
Tracheal, bronchus, and lung cancer	X	X
Upper respiratory sites cancer		X
Breast cancer	X	
Cervical cancer	X	X
Colon and rectum cancer	X	
Lip and oral cavity cancer	X	
Nasopharynx cancer	X	
Other pharynx cancer	X	
Pancreatic cancer	X	X
Kidney cancer	X	X
Leukemia	X	X

		(myeoloid)
Unspecified site cancer		X
Ischaemic heart disease	X	X
Stroke (includes all types of stroke)	X	X
Atrial fibrillation and flutter	X	Included in 'other heart disease category
Other heart disease		X
Other arterial disease		X
Aortic aneurysm	X	X
Atherosclerosis		X
Lower extremity peripheral arterial disease	X	
Chronic obstructive pulmonary disease	X	X
Other chronic respiratory diseases	X	
Chronic airway obstruction		X
Pneumonia, Influenza		X
Asthma	X	
Peptic ulcer disease	X	Included in 'stomach / duodenal ulcer' category
Stomach / duodenal ulcer		X
Crohn's disease		X
Periodontal disease / Periodontitis		X
Gallbladder and biliary diseases	X	
Alzheimer's disease and other dementias	X	
Parkinson's disease	X	
Multiple sclerosis	X	
Diabetes mellitus	X	
Rheumatoid arthritis	X	
Low back pain	X	
Cataract	X	X (age related)
Age-related macular degeneration	X	
Fracture	(NOT in 2021)	X (hip fracture)
Spontaneous abortion		X

Table 2. Evaluation grid for tobacco risk-outcome pair sets

	Global Burden of Disease Study	Public Health England
Accessibility	Available for download from Burden of Proof tool	Available via Appendix in 2020 report together with comparison to old RR estimates
Transparency	The methodology is described in the Appendix. Run to DisMod to get non-parametric splines. Not reproducible without their help.	Easy to reproduce. Equations and citations for each relationship.
Reliability	Evaluate risk of publication bias and quantify within and between-study heterogeneity. Uncertainty limits included.	Mainly systematic review and meta-analysis. Possible bias in selecting studies for RR curves. No uncertainty estimates. No uniform method for estimation.
Evidence	730 studies between 1970 and 2022 included, from 55 countries	Studies from 2013 onwards from selected countries
Relevance	Similar definitions for outcome and exposure. Global estimates but similar exposure ranges	Geography is limited to UK Europe, Canada, Australia, and New Zealand.

1.1.1 Discussion

The Global Burden of Proof 2021 dataset offers extensive coverage of 36 risk-outcome pairs, including fractures, and provides relative risk dose-response curves for smoking and disease outcomes. Each dose-response relationship is derived from systematic reviews of 730 studies, ensuring robust evidence. The methodology includes testing and adjusting for biases such as variation in study characteristics (e.g., population selection and study design biases) and quantifying remaining between-study heterogeneity.

Key features include bias evaluation in which publication and reporting bias are addressed using Egger's regression, as well as their outcome presentation. Results are reported using the Burden of Proof Risk Function (BPRF) alongside a score and star rating to assess the strength of evidence for each association. The GBD dataset is uniquely comprehensive due to its extensive input data, advanced bias correction methods, and quality measures. Few research institutes possess the resources to achieve this scale of analysis.

While GBD is a powerful resource, it has certain limitations such as representation issues, timeframe, biological plausibility, and evidence strength. Data spans 55 countries but does not account for subpopulations within countries, and all information is summarized into a single global estimate. The dataset uses sources from 1970 to 2021, which may smooth out recent trends. Some findings, like the reported protective effect of smoking on Parkinson's disease,

raise questions about biological reasoning. Of the 36 risk-outcome pairs, only 8 showed strong-to-very-strong evidence of association with smoking, 21 showed weak-to-moderate evidence, and 7 had no evidence of association. To address these limitations, we considered supplementing GBD with regional datasets (e.g., European or Western-European studies) to enhance the relevance of estimates for Belgian research. A rigorous assessment of data quality and reliability remains critical for ensuring suitability to our research context.

The PHE 2020 dataset also uses a systematic literature search to analyze predetermined outcomes. It reports risk factors, disease outcomes, and measures such as RR, hazard ratio (HR), or odds ratio (OR). Meta-analysis is performed to generate dose-response curves, similar to GBD. Some key differences compared to GBD are the geographic scope, study design selection, and methodological transparency. PHE focuses on Western countries (UK, Europe, Canada, Australia, and New Zealand) and includes studies published after 2013. They prioritize systematic reviews and meta-analyses, whereas GBD includes broader study designs. PHE selects the most suitable study for each purpose and provides equations and citations for reproducibility, though it lacks uncertainty limits included in GBD. PHE offers age- and sex-specific dose-response curves for some diseases (mostly 35+ years old), along with estimates for more specific causes than GBD. It excludes controversial findings, such as smoking's purported protective effect on Parkinson's disease. The PHE dataset provides only RRs for current smokers, regardless of smoking intensity (e.g., pack years or cigarettes/day), though it includes estimates for former smokers. The PHE platform lacks uncertainty measures such as those present in GBD.

After evaluating both datasets, we chose to use the GBD 2021 estimates for the following reasons:

- **Uniformity**: GBD's standardized framework is crucial for comparing results with other studies.
- **User-Friendly Tool**: The Burden of Proof framework enhances the transparency and transportability of GBD's methodology.
- **Comprehensive Bias Correction**: GBD's advanced methods for addressing biases and heterogeneity make it a more reliable option overall.

While GBD has its limitations, its global scope, bias-adjusted estimates, and robust quality measures make it the preferred choice for our study.

1.2 Exposure assessment

1.2.1 Exposure definition

Tobacco use encompasses a broader range of products and behaviors, including the use of cigarettes, cigars, pipes, and smokeless tobacco, such as chewing tobacco or snuff. In contrast, cigarette smoking specifically focuses on the consumption of manufactured or hand-rolled cigarettes. We followed the GBD 2019 study's approach to estimate the attributable burden of cigarette smoking. This involves calculating the PAF using key data inputs: prevalence of smoking categories (never, occasional, former, and daily smokers), cigarettes per day, smoking duration (to estimate pack-years), and time since quitting for former smokers.

Calculating the population attributable fraction (PAF) for smoking is based on the GBD study 2019 methods for calculating smoking-attributable burden (Murray et al., 2020) using the following formula:

$$\text{PAF} = \frac{(P_{never} + P_{former} * RR_{former} + P_{current} * RR) - 1}{P_{never} + P_{former} * RR_{reduce} + P_{current} * RR}$$

Where

P_{never} = prevalence of never-smokers

P_{former} = prevalence of former smokers

$P_{current}$ = prevalence of current smokers

RR = the relative risk to get the disease depending on the smoking intensity

RR_{former} = reduction in the relative risk among former smokers compared with current smokers.

For former smokers, the relative risk is adjusted to account for the reduction in risk over time after quitting. This is done by applying a percentage reduction ($RRreduce$) to the RR for current smokers. The RRreduce is provided as a percentage in the GBD 2021 study. The percentage is multiplied with RR for current smokers to obtain the RR for former smokers (RR_{former}).

The formula for this adjustment is:

$RR_{former} = 1 + ((RR - 1) \times RRreduce)$

This reflects a decrease in the relative risk for former smokers compared to current smokers, depending on how long it has been since they quit.

All potential data sources for estimating exposure (published or unpublished) were evaluated based on a set of quality criteria such as comparability, relevance, representativeness, currency, accuracy, validation, credibility, and accessibility in a critical appraisal published elsewhere (Nayani et al., 2023). The best-selected data source for smoking was the BHIS. Self-reported tobacco use data are available by sex, region, 5-year age group, and year from 1997 to 2018.

These variables are available in the BHIS, though not consistently across all waves (Table 3).

Table 3. Description of exposure indicators and their corresponding data sources

Exposure variable	Definition	Variables in the HIS	Years Available
Smoking status			
Daily smoker	People who report smoking every day	TA06_1	All years
Occasional smoker	People who report smoking but not every day	TA06_1	All years
Former smoker	People who report having smoked but have quit for any time	TA06_1	All years
Never smoker	People who report never having smoked	TA06_1	All years
Measures of frequency and intensity			
Cigarettes per day	Number of cigarettes per day was recorded only for those who reported daily smoking	TA07_1	2004, 2008, 2013, 2018
Duration of smoking	The number of years a person has smoked; and is estimated for daily smokers by subtracting the age at initiation from the age at the time of the survey. Age at initiation is not captured for former smokers, so a variable for the recalled duration of smoking is used.	Daily smokers: TA04_1, AGE; former smokers: TA05_1	2004, 2008, 2013, 2018
Pack-years	Calculated by multiplying duration times cigarettes per day/20 (one pack)		2008, 2013, 2018
Time since quitting	To calculate the time since quitting smoking (QUIT_TIME), we estimate the number of years that have passed since a former smoker stopped smoking. This is derived using the individual's current age, their age at smoking initiation, and the total years they smoked.	TA04_1 = is age start of daily smoking, TA05_1 = TA05_1 = number of years of daily smoking, AGE	2008, 2013, 2018

1.2.2 Correcting for self-reported data

Information on sales data were retrieved and is available annually (Nayani et al., 2023). However, sales data lack a demographical breakdown and the data includes some variability which makes it difficult to connect with individual behaviour of people on tobacco use. It is thus not useful for the estimation of disease burden but can help to describe the supply side of tobacco over time. No adjustment of consumption data using sales data will be made.

Categorical variables

The variable capturing prevalence of smoking status had a low level of missing data across all the waves (no more than 14%) with no evidence of systematic missing data. Therefore, no adjustments were made to that variable before modelling. Estimates of occasional smokers are combined with daily smokers to make up the category of current smokers.

Continuous variables

To estimate the PAF, the intensity of smoking should have to be captured for anyone in the smoking categories (i.e. daily and occasional smokers). However, the HIS only captures cigarettes per day among daily smokers. We assume that the number of cigarettes per day among occasional smokers is consistent with estimates published in (Hassmiller et al., 2003) which show that occasional smokers tend to stay in the same smoking pattern for most of their lives and using the mean number of cigarettes smoked per day (around 6) divided by the frequency of smoking asked in survey.

A similar issue arises with former smokers, for whom cigarettes per day are also not captured. Assuming the distribution of cigarettes per day for former daily smokers is similar to that of current smokers introduces a potential risk of overestimation, although this risk is mitigated by the fact that these individuals were once daily smokers. Additionally, the PAF calculation adjusts the relative risk of disease for former smokers based on the time since quitting, which should reduce the likelihood of overestimation.

Variables for continuous measures required additional calculations beyond using values directly available in the HIS. For instance, the survey directly captures the duration of smoking as TA05_1. However, upon reviewing this variable, we found inconsistencies where the reported duration of smoking exceeded the reported age at initiation. It is assumed that respondents are better at recalling their age at the initiation of daily smoking than accurately calculating their smoking duration. Therefore, we preferred using the variable TA04_1 for age

at initiation, subtracted from the respondent's age at the time of the survey, to estimate smoking duration among current smokers. For former smokers, the HIS does not capture the age at quitting, so we used TA05_1 for this group, assuming 0.5 years for two individuals who reported a duration of 0 or less. Pack-years is a calculated value and estimated directly as described in Table 3. It is a variable that is calculated for both current and former smokers.

- TA04_1 : At what age did the individuals started smoking daily (even if you have since quit)?
- TA05_1: The average number of years of daily smoking among individuals who have smoked daily for at least one year.

Time since quitting in former smokers is used to estimate a reduction in the relative risk of disease compared with current smokers. The HIS captures a categorical variable for time since quitting, but this variable does not include the level of detail that would make it possible to estimate the time series model needed for the PAF calculation. As a result, we use three variables to estimate the time since quitting. We add the age at initiation of smoking to the reported duration of smoking to estimate the ages smoked and subtract this from the current age at the time of the survey. For a few people, this calculation resulted in implausible results, in part because of the lower reliability of the recall on the duration of smoking. For these people (n=152 across all waves of the HIS), we estimated a time since quitting using the categorical variable (TA14). Those reporting a time since quitting in TA14 of :

- 1-2 years were assigned 1 year;
- for >1 month to <6 months they were assigned 0.2 years,
- for 6 to 12 months they were assigned 0.5 years,
- and for 2 to 9 years they were assigned 2 years.

Twenty-eight people across all waves had a calculated time since quitting lower than 0 and missing data for TA14; these were excluded from further analysis.

1.2.3 Interpolation for missing data and time series

The goal was to construct a time series of tobacco exposure data in Belgium from 2013 to the most recent available mortality data (2021 at the time of writing), using the BeBOD methodology to select the "best-fitted" model.

The covariates for the model for smoking categories and continuous variables include those we need for our output, namely: age, sex, region, and year.

We first estimate the mean proportion of smoking categories including the survey weighting built into the HIS using the svyby function in R.

Table 4. Model selection for categorical exposure variables

Exposure	Best-Fitted Model	WAIC Value
Current Smokers	*Current_cases* ~ 1 + YEAR * AGEGR * REGION * SEX	3683
Never Smokers	*Never_cases* ~ 1 + YEAR * AGEGR * REGION * SEX	4509
Former Smokers	*Former_cases* ~ 1 + YEAR * AGEGR + YEAR * REGION + YEAR * SEX + AGEGR * REGION + AGEGR * SEX + SEX * REGION	4247

In addition to smoking prevalence, measures of intensity of smoking must be included to calculate the PAF. The measures are selected based on the inputs used by the GBD in their calculations of attributable burden. These include cigarettes per day, pack-years (which includes duration of smoking), and the time since quitting in former smokers. Data on intensity measures was available for 2004, 2008, 2013, and 2018. The model was fitted from 1997 to 2018. As with smoking categories, a mean measure of intensity for each age, region, and sex category for each year of the HIS is computed using a svyby() function in R.

The models predicting trends in continuous variables are different from smoking prevalence in that the outcome is not a binomial. We fitted a quasi-Poisson INLA model.

Table 4. Model selection for categorical exposure variables

Exposure	Best-Fitted Model	WAIC Value
Cigarettes/Day	*CIG_DAY* ~ 1 + YEAR + SEX + AGEGR + REGION	927
Time Since Quitting	*TIME_QUIT* ~ 1 + YEAR + SEX + AGEGR + REGION	638
Pack-Years	*PACK_YEARS* ~ 1 + YEAR * AGEGR * REGION + YEAR * REGION * SEX + YEAR * SEX * AGEGR	1041

1.2.4 Normalizing smoking prevalence categories

The modelled smoking prevalence categories are computed individually using binomial models. In order to create a single estimate of smoking prevalence categories we combine these three models and normalize them. In practical terms, their sum should equal to one. Thus, current smoking prevalence is calculated to equal daily smoking prevalence divided by the sum of the current, former, and never smoking prevalence. We do a similar calculation for never smoking. Former smoking is then one minus the prevalence of daily smoking plus never smoking.

1.3 Calculation of the attributable burden to risk factors

1.3.1 Theoretical minimum risk exposure level (TMREL)

The theoretical minimum-risk exposure level is 0 (no tobacco use).

1.4 References

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2 ALCOHOL USE

Summary

Alcohol use represents a great risk to disease burden in Belgium as described by the GBD in their latest study in 2021 (Brauer et al., 2024). The BHIS has been tracking alcohol consumption since 1997, revealing trends in the prevalence of drinking status over time (Demarest et al., 2018). The survey highlights a slight decline in current alcohol consumption, while the percentage of individuals who have never consumed alcohol has risen in the Flemish and Walloon Regions. A small fraction of the population (approximately 5%) are former drinkers, showing minimal changes over the last two run of the survey. Although these patterns persist across the country, discrepancies emerge when looking at region and sex separately, as shown in Figure 2.

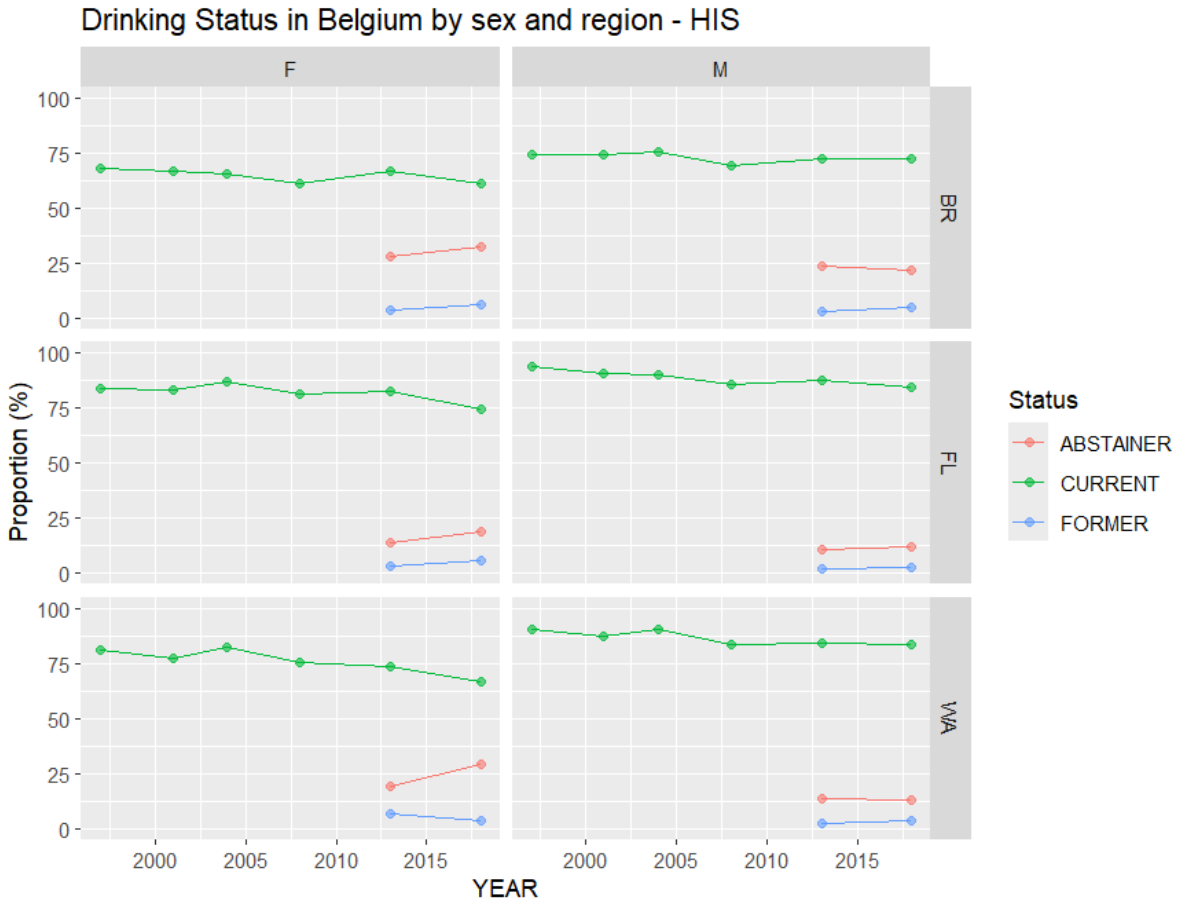

Figure 2. Trends in drinking status in Belgium as reported in the Belgian Health Interview Survey stratified by region and sex (e.g.: for age category 15-44).

2.1 Identification and quantification of the association of risk-outcome pairs for alcohol use

The GBD study is the most comprehensive effort to link risk factors to health outcomes, employing a detailed exploration of causality through the Bradford Hill criteria to identify diseases attributable to alcohol use. It also incorporates a meta-analysis to estimate relative risks associated with exposure. Additionally, the study provides insights into the burden of alcohol use across 204 countries with the latest iteration being published in 2024 (Brauer et al., 2024).

At the national level, PHE works to protect and improve population health while reducing inequalities, and providing evidence-based support to government, local authorities, and the public. Public Health England has been calculating Alcohol Attributable Fraction (AAF) since 2008. The latest report was published in 2020.

The World Health Organization (WHO) plays a pivotal role in assessing the global health impact of alcohol use and guiding evidence-based interventions to mitigate its burden. Alcohol consumption is a significant public health concern, contributing to a range of health outcomes, including injuries, chronic diseases, and premature mortality. The WHO's efforts to quantify this burden are rooted in rigorous methodologies that draw on global and country-specific data to estimate the attributable harm of alcohol use. This study highlighting the burden of alcohol use across 204 countries and territories, employed comprehensive approaches, including the GBD methodology, to evaluate the relationship between alcohol consumption and health outcomes.

The Australian Burden of Disease Study is a comprehensive effort to measure the impact of various risk factors, including alcohol use, on health outcomes in Australia. It aims to provide insights that inform public health policies and priorities. The 2011 assessment of the burden of alcohol use in Australia was published in 2018, using a combination of self-reported and corrected data to provide a more accurate picture of alcohol consumption and its effects (Australian Institute of Health and Welfare, 2019; Gao & Ogeil, 2018; Rehm, Baliunas, et al., 2010).

Table 1. Alcohol outcomes included in evaluated risk-outcome pair sets

	Global Burden of Disease Study	Public Health England	World Health Organization	Australian Burden of Disease Study
HIV/AIDS			X	
Tuberculosis	X	X		X
Lower respiratory infections	X	X (Pneumonia)	X	X

Lip and oral cavity cancer	X	X (lip, oral, and pharynx cancer)		X
Pharynx and nasopharynx cancer	X	X	X (other pharynx cancer)	X
Esophageal cancer	X	X	X	X
Colon and rectum cancer	X	X	X	X
Liver cancer	X (Liver cancer due to alcohol use)	X	X	X
Larynx cancer	X	X	X	X
Breast cancer	X	X	X	X
Diabetes mellitus	X	X		X
Alcohol use disorders			X	
Epilepsy	X	X (Epilepsy and Status epilepticus)	X	X
Hypertensive heart disease	X	X	X	X
Ischaemic heart disease	X	X	X	X
Cardiomyopathy, myocarditis, endocarditis			X	
Atrial fibrillation and flutter	X	X (Cardiac arythmias)		X
Heart failure		X		
Ischaemic stroke	X	X	X	X
Hemorragic stroke	X	X	X	X
Oesophageal varices		X		
Gastro-oesophageal laceration haemorrhage syndrome		X		
Unspecified liver disease		X		
Cholelithiasis (gall stones)		X		

Cirrhosis and other chronic liver diseases	X	X	X (Cirrhosis of the liver)	X
Pancreatitis	X	X (acute and chronic)	X	X
Psoriasis		X		
Spontaneous abortion		X		
Low birth weight		X		
Unintentional injuries	X	X (Road/pedestrian traffic accidents, Poisoning, Fall injuries, Fire injuries, Drowning, other unintentional injuries)	X (Road/pedestrian traffic accidents, Poisoning, Fall injuries, Fire, heat and hot substance injuries, Drowning, Exposure to mechanical forces, other unintentional injuries)	X
Transport injuries	X	X		X
Tuberculosis	X	X		X
Cirrhosis and other chronic liver diseases	X	Included in 'other heart disease category		X
Interpersonal violence	X		X	X
Self-harm	X	X		X
Assault		X		
Event of undetermined intent		X		

Table 2. Evaluation grid for alcohol risk-outcome pair sets

	Global Burden of Disease Study	Public Health England	World Health Organization	Australian Burden of Disease Study
Accessibility	Available to download from GBD healthdata, supplementary materials GBD appendix from the Lancet publications	Available via NHS/ PHE website Appendix for RR search strategy in 2020	Appendix available via the lancet publication supplementary materials	Appendix available via the Australian Institute for Welfare and Health (AIWH) for multiple iterations. The study also relies

				on the National Drug Strategy Household Survey (NDSHS) and alcohol sales data, with adjustments outlined in publicly available reports.
Transparency	Methodology described in Appendix. Requires running DisMod to obtain non-parametric splines, and these splines cannot be reproduced without access to the GBD team's expertise. Specific adjustments for country-specific contexts (e.g., Belgium) may not be fully transparent or easily replicated.	Detailed method, easy to reproduce. Transparent with the approach and choices they made (e.g. search strings and inclusion/exclusion criteria)	The methodology, detailed in the Appendix, relies on literature reviews, self-reports, and comparisons to GBD data. It acknowledges GBD 2017 limitations, such as excluding heavy episodic drinking and risks for former drinkers. WHO's Technical Advisory Group selected relative risk estimates based on meta-analyses of alcohol-cancer dose-response relationships, adjusted for confounders and country-specific contexts.	The methodology is detailed in AIHW publications, including how self-reported survey data were adjusted using alcohol sales data and methods adapted from GBD 2013. Transparent in describing assumptions, limitations, and adjustments for the Australian context.
Reliability	The GBD model integrates data from national surveys, global reports, and studies across 190+ countries, using uncertainty analysis for confidence intervals. However, it relies on assumptions about data quality, availability, and region-specific models.	Mainly systematic review and meta-analysis, from 2013 onwards. Possible bias in selecting studies for RR curves. Latest evidence linking alcohol consumption to diseases based on new available data. Uncertainty estimates allowing for the computation of Confidence Intervals. Uniform method for	WHO's alcohol-attributable burden estimates were improved by addressing gaps in GBD 2017. The study suggests that alcohol-attributable burdens might be greater than previously thought, especially in sub-Saharan Africa and Eastern Europe regions.	Combines data from the NDSHS, epidemiological studies, and alcohol sales. Adjustments ensure better alignment between self-reported and observed data, but reliability depends on the quality of input data and assumptions used in corrections.

		estimation, same method over time but update of evidence when necessary		
Evidence	The GBD model combines extensive data from national surveys, global health reports, and studies across 190+ countries, covering decades of trends. However, variations in the quality and availability of country-level data can limit the comparability of estimates.	Studies from 2013 onwards from selected countries.	WHO reviewed publications on alcohol-related disease burden (2000–2019) from its Global Health Observatory and the IHME database. It used data from alcohol sales, drinking prevalence, self-reports, and relative risk functions. The study addresses GBD 2017 gaps and highlights a higher burden in regions like sub-Saharan Africa and Eastern Europe, though some methodological limitations persist.	Uses self-reported survey data from NDSHS (2016) adjusted with sales data and historical trends from Australian records. Relies on relative risk functions from GBD and international meta-analyses.
Relevance	The GBD model uses individual-level data for more precise estimates and provides global, standardized estimates for various risk factors. However, assumptions about certain factors may not always align with regional contexts like Belgium.	The model focuses on data from the UK, Scotland, Europe, Canada, Australia, and New Zealand. It uses individual-level data for alcohol consumption, providing detailed estimates. The burden of alcohol-related acute and chronic diseases is calculated using two separate equations, offering a comprehensive overview.	The WHO approach is global, focusing on the alcohol-attributable burden of disease across regions with varying alcohol-related health impacts. It highlights alcohol's role in both communicable and non-communicable diseases, stressing the need for regional alcohol policies. Using individual-level data allows for more precise and	Combines data from the NDSHS, epidemiological studies, and alcohol sales. Adjustments ensure better alignment between self-reported and observed data, but reliability is tailored to the Australian context and depends on the quality of input data and the assumptions used in corrections.

representative estimates.

2.1.1 Discussion

The latest GBD study estimating the attributable burden of alcohol use was published in 2024. Data on alcohol use were gathered from self-reported surveys from 63 countries. The self-reported data were corrected for underestimation using estimates of sales of alcohol in liter per capita (Brauer et al., 2024).

For GBD 2016, a systematic review was conducted to include cohort and case-control studies reporting relative risks, hazard ratios, or odds ratios for alcohol-related outcomes. Studies had to report alcohol consumption dose and uncertainty measures, with a representative population. Dose-response curves were estimated using DisMod ODE, which models non-linear relationships and handles categorical dose data, estimating relative risks for doses between 0 and 100 g/day, assuming consistent risk across ages and sexes (Brauer et al., 2024).

The GBD dataset is uniquely comprehensive due to its extensive input data, advanced bias correction methods, and quality measures. Few research institutes possess the resources to achieve this scale of analysis. Indeed, GBD contains a broad search captured studies from 1970-2019, including cohort and case-control studies reporting alcohol use, continuous dose, effect size, and relevant study details. The Fisher Scoring correction was applied for data-sparse situations, and a method for detecting publication bias was added, though bias is not yet corrected (Brauer et al., 2024).

The RRs in GBD 2016 are readily accessible and are presented by cause and consumption levels, with breaks at 12 to 72 grams per day. These levels are the same across all age groups, though they are sometimes specified by sex

The exposure indicators included are drinking category (current, abstainers), alcohol consumption in grams/day, alcohol litres per capita stock, number of tourists within a location, unrecorded alcohol stock, tourists' duration of stay. Note that the GBD study does not account for the increased risk to disease for former drinkers (Shield et al., 2020).

WHO's RR estimates for the alcohol-attributable burden of disease were selected by the WHO Technical Advisory Group on Alcohol and Drug Epidemiology. Criteria for RR selection included meta-analyses that modeled the continuous dose-response relationship, controlled for confounders, used lifetime abstainers as the reference group, and aligned with WHO-reported disease categories. For Belarus, Estonia, Latvia, Lithuania, Moldova, Russia, and

Ukraine, RRs from a Russian cohort study were used to account for regional drinking patterns and risk factors (Shield et al., 2020).

Dose-response functions are provided as mathematical expressions for current drinkers, stratified by consumption level, sex, and for some diseases, by age group. For former drinkers, only a single data point is available, which does not vary by consumption level but is stratified by sex for certain diseases (Shield et al., 2020).

Public Health England has been calculating Alcohol Attributable Fractions (AAFs) since 2008, with the most recent report released in 2020. The methodology uses exposure estimates from the 2016 Health Survey for England, adjusted for underreporting through sales data (Jaccard et al., 2020). RRs) are derived from Jones & Bellis, (2017) which synthesized data from 20 meta-analyses examining the links between alcohol use, chronic conditions, and injury risks. For the latest update, Jaccard et al. (2020) expanded on this foundation by conducting a new systematic review to identify additional sources, including studies published since 2013. To ensure transparency and replicability, the research strings, inclusion/exclusion criteria, and detailed methodology are publicly accessible. Furthermore, the dataset includes relative risks (RRs) with uncertainty intervals and source of the dose-response function offering a robust measure of reliability and transparency. These RRs are available for current drinkers, categorized by consumption levels (light, moderate, and heavy) but sometimes specific levels of consumption (continuous) as well as for former drinkers, stratified by sex (Jaccard et al., 2020). Estimates are not age-specific (Public Health England, 2020a).

The Australian Burden of Study assessed the impact of alcohol use on the burden of disease in Australia in 2011. The report was published in 2018 using exposure data of alcohol consumption in Australia from their national health survey NDSHS 2016 and covers burden estimates for 26 diseases. The self-reported data of the survey were inflated with the data of alcohol sales using the method of GBD 2013 since the amount of self-reported data does not reflect the true extent of the consumption (Australian Institute of Health and Welfare, 2019; Gao & Ogeil, 2018; Rehm, Baliunas, et al., 2010). The RR comes from the GBD 2015 and comprises 26 diseases linked with the risk factor (Gao & Ogeil, 2018). Current drinkers, lifetime abstainers, and former drinkers were used as exposure indicators for alcohol use.

Based on this appraisal, we have chosen to use the GBD 2016 RR estimates for current drinkers for the calculation of the attributable:

- **Uniformity**: GBD's standardized framework is crucial for comparing results with other studies.

- **Comprehensive Bias Correction**: GBD's advanced methods for addressing biases and heterogeneity make it a more reliable option overall.
- **Accessibility**: The GBD 2016 RR are readily available and widely documented, facilitating their use in our analysis.
- **Evidence Quality**: The estimates are underpinned by rigorous evidence, with contributing studies evaluated using established bias assessment tools to ensure reliability and validity.
- **Detailed Stratification**: These RR offer dose-response functions that are:
    - stratified by consumption levels (0,12,24,36,48,60,72)
    - categorized by sex for some diseases, but not age-groups specific
- **Global Alignment**: The GBD methodology is internationally recognized, providing a robust and standardized framework for assessing alcohol-attributable risks.

Because we acknowledge that former drinkers account for an excess risk, we will use the WHO relative risk estimates for former drinkers due to:

- **Data Availability**: WHO RR are easily retrievable, ensuring easy integration into our analysis.
- **Appropriate Risk Representation**: These estimates effectively capture the excess health risks that former drinkers face compared to lifetime abstainers, recognizing the lingering impacts of past alcohol consumption.
- **Sex-Specific Details**: While the WHO RR for former drinkers are based on a single data point, they are stratified by sex for some diseases, allowing for a more nuanced reflection of risk.

This approach ensures that both current and former drinkers are represented in our analysis, using the most accessible data sources available to calculate the attributable burden due to alcohol use.

2.2 Exposure assessment

2.2.1 Exposure definition

We followed the GBD 2016 study's approach to estimate the AB of alcohol use. This involves calculating the PAF using key data inputs: prevalence of drinking categories (former, current and lifetime abstainers) and mean consumption in grams/day among current drinkers.

To calculate population attributable fraction (PAF) to alcohol use we will use the following formula :

$$\text{PAF} = \frac{(P_{abstainers} + P_{former} * RR_{former} + P_{current} * RR_{current}) - 1}{P_{abstainers} + P_{former} * RR_{former} + P_{current} * RR_{current}}$$

Where

$P_{abstainers}$ = prevalence of lifetime abstainers

P_{former} = prevalence of former drinkers

RR_{former} = relative risk (RR) for former drinkers

$P_{current}$ = prevalence of current drinkers who consume an average daily amount (x) of alcohol

$RR_{current}$ = average daily amount of alcohol consumed by current drinkers

All potential data sources for estimating exposure (published or unpublished) were evaluated based on a set of quality criteria such as comparability, relevance, representativeness, currency, accuracy, validation, credibility, and accessibility in a critical appraisal published elsewhere (Nayani et al., 2024). The best-selected data source for drinking status was the BHIS. Self-reported alcohol use data are available by sex, region, 5-year age group, and year from 1997 to 2018. Note that for former drinkers and lifetime abstainers, data were only available for 2 time points: 2013 and 2018 and the mean consumption in drinks per day was available from 2008-2018.

Table 3 Description of exposure indicators and their corresponding data sources

Exposure variable	Definition	Variables in the HIS	Years available
Current drinkers	Proportion of individuals who have consumed at least one alcoholic beverage (or some approximation) in 12 months.	AL01_1	All years
Former smoker	People who report having smoked but have quit for any time	AL01	2013, 2018
Lifetime abstainers	Proportion of individuals who have never consumed an alcoholic beverage	AL01	2013,2018
Measures of intensity			
Average number of drinks per day among weekly drinkers	Number of drinks per day recorded only for those who report weekly drinking	AL_7	2008, 2013, 2018

2.2.2 Correcting for self-reported data

Categorical variables

No adjustments to the categorical variable of drinking status (i.e. former, abstainers, current drinkers) was made.

Continuous variables

To calculate the harm caused by alcohol use, accurate data on current alcohol consumption is essential. This is typically gathered in surveys like the BHIS, which provides information on alcohol use in Belgium, broken down by year, age, sex, and region.

Variables for continuous measures required some additional calculation than just using values directly available in the BHIS. We need data on the average number of drinks per day for current drinkers to calculate the PAF equation. Currently, data on the average number of drinks per day is available in the BHIS for weekly drinkers (AL_7). The method to obtain data on current drinkers, was derived from the average number of drinks per week among weekly drinkers (AL_7). This variable is obtained by combining the number of days of consumption by the number of drinks usually consumed on those days and then adding up the products obtained for the weekdays (AL02 - AL03) and for the weekend (AL04 - AL05).

- AL.02. From Monday to Thursday, on how many of these 4 days do you typically consume alcoholic beverages? (From 1= all 4 days to 5= none of these 4 days).
- AL.03. From Monday to Thursday, when you consume alcoholic beverages, how many do you usually drink on an average day? (From 1= 16+ glasses per day to 7= 1 glass per day).
- AL.04. From Friday to Sunday, on how many of these 3 days do you typically consume alcoholic beverages? (From 1= all 3 days to 4= none of these 3 days).
- AL.05. From Friday to Sunday, when you consume alcoholic beverages, how many do you usually drink on an average day? (From 1= 16+ glasses per day to 7= 1 glass per day).

We started by identifying the number of drinking days for both weekly and non-weekly drinkers. The dataset includes information on drinking days for weekly drinkers, but non-weekly drinkers (= those who drink less than once a month) do not have this information directly.

To estimate the drinking behaviour of non-weekly drinkers, we assume that the number of drinks consumed per drinking day is similar between weekly and non-weekly drinkers. This assumption allows us to use the drinking habits of weekly drinkers to estimate consumption for non-weekly drinkers.

For weekly drinkers, we directly use their data for AL7, which is calculated based on the total drinking days (both weekdays and weekends) and the number of drinks per day. For non-weekly drinkers (those who drink less than weekly), we adjust the calculation by estimating the total number of drinking days for the month and applying the average number of drinks per drinking day observed among weekly drinkers.

For instance, if a non-weekly drinker drinks 2-3 times a month, we multiply the average drinks per day by 2.5 (an average between 2 and 3 days) and then adjust this figure to a weekly value. Similarly, for those who drink once a month, we multiply the drinks per day by 1 and adjust for the week. For drinkers who consume less than once a month, we use a value of 0.5 times the average drinks per day.

By merging the drinking patterns of weekly drinkers with the estimated consumption for non-weekly drinkers, we generate a new AL7 value for non-weekly drinkers, giving an estimate of their weekly alcohol consumption. This allows us to have a complete dataset with AL7 values for all current drinkers, regardless of how frequently they drink. This process gives us the average number of drinks per day among current drinkers for a given year.

However, survey data have bias and limitations, including underreporting of alcohol use, non-responses from heavier drinkers (non-response bias), non-recall bias (omission of heavy drinking episodes), and a tendency for individuals to portray themselves as moderate drinkers (Kilian et al., 2020). As a result, relying solely on survey data likely underestimates the true burden of alcohol use. Indeed, underreporting in surveys is well-documented, with estimates suggesting that survey data capture only 30-40% of actual alcohol sales (Stockwell et al., 2018).

To address this challenge, a method integrating sales data with survey information has been developed. Sales data, such as Total Alcohol Per Capita (APC) for Belgium, was obtained from the WHO Global Health Observatory dashboard and was available from 2000-2019 (5 data points). These data are derived from the production and sales of both recorded and unrecorded alcohol, adjusted for tourism, and reflect the overall volume of alcohol consumed in a given year per capita (Manthey et al., 2023; Poznyak et al., 2014; World Health Organization, 2022).

Note that APC data lacks demographic breakdowns such as age, sex, and region (Kehoe et al., 2012; Kilian et al., 2020). To address this gap, we applied a method developed by Rehm et al. (2007) that calculates the proportion of alcohol consumption for each year, age group, and region from survey data . This proportion, based on the ratio of individual to total consumption, is used to refine the APC estimates, allowing for APC estimates, broken down by age group, sex, and region. The amount of pure alcohol was converted into grams per day

using a conversion factor of 789 g/L. This variable will be called mean consumption in grams/day in further steps.

2.2.3 Interpolation for missing data and time series

The goal was to construct a time series of alcohol exposure data in Belgium from 2013 to the most recent available mortality data (2021 at the time of writing), using the BeBOD methodology to select the "best-fitted" model.

The covariates for the model for drinking categories and continuous variables include those we need for our output, namely: age, sex, region, and year.

We first estimate the mean proportion of drinking categories including the survey weighting built into the HIS using the svyby function in R.

Table 4. Model selection for categorical exposure variables

Exposure	Best-Fitted Model	WAIC Value
Current Drinkers	Current_cases ~ 1 + YEAR * AGEGR * REGION + YEAR * REGION * SEX + YEAR * SEX * AGEGR	1041
Former Drinkers	Former_cases ~ 1 + YEAR * AGEGR * REGION * SEX	272
Lifetime Abstainers	Abstainers_cases ~ 1 + YEAR * AGEGR * REGION + YEAR * REGION * SEX + YEAR * SEX * AGEGR	276

The models predicting trends in continuous variables are different from drinking prevalence in as the outcome is not a binomial. We applied a gamma INLA model instead. Indeed, a gamma distribution is often used in the literature to present the continuous distribution of alcohol consumption the best based on its flexibility. This model is usually used to model alcohol consumption for its flexibility and ability to take into account heavy drinkers, as the tail of the distribution is long (Kehoe et al., 2012; Rehm, Kehoe, et al., 2010).

Table 5. Model selection for continous exposure variables

Exposure	Best-Fitted Model	WAIC Value
Mean Consumption (grams/day)	up_g_day ~ 1 + YEAR * AGEGR * REGION + YEAR * REGION * SEX + YEAR * SEX * AGEGR	276

2.3 Calculation of the attributable burden to risk factors

2.3.1 Theorical minimum risk exposure level (TMREL)

The theoretical minimum-risk exposure level is 0 (no alcohol use).

2.3.2 Population attributable fraction

One specificity in the calculation of the attributable burden for alcohol use is that alcohol use disorders was considered fully attributable to alcohol consumption, with a PAF of 100%.

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