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# Methodology used to estimate alcohol-attributable mortality in Spain, 2001-2017

## *Metodología utilizada para estimar la mortalidad atribuible a alcohol en España, 2001-2017*

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## Abstract

The objective is to describe and discuss methods and assumptions to estimate the mortality attributable to alcohol in Spain in 2001-2017. The annual mean number of deaths attributable to alcohol (DAAs) was estimated based on 19 groups of alcohol-related causes of death (18 partially attributable and one directly attributable), and 20 alcohol population-attributable fractions (PAFs), resulting from combining sex, 5 age groups, and the periods 2001-2009 and 2010-2017, for each cause group. Deaths from causes were obtained from the Spanish National Institute of Statistics. For partially attributable causes, Spain-specific PAFs were calculated using the Levin formula with alcohol exposure data from health surveys and sales statistics, and relative risks from international meta-analyses. Annual prevalences of ex-drinkers and seven levels of daily alcohol consumption were considered. The underestimation of self-reported daily average consumption with respect to the sales statistics was corrected by multiplying by a factor of 1.58-3.18, depending on the calendar year. DAA rates standardized by age and standardized proportions of general mortality attributable to alcohol, according to sex, age group, calendar period, type of drinker and autonomous community were calculated. Sensitivity analyses were performed to assess how the DAA estimates changed when changing some methodological options, such as the ex-drinker criterion or the introduction of a latency period.
***Keywords:*** alcohol, attributable mortality, Spain, methodology

## Resumen

El objetivo es describir y discutir los métodos y asunciones para estimar la mortalidad atribuible a alcohol en España en 2001-2017. Se estimó el nº medio anual de muertes atribuibles a alcohol (MAAs) basándose en 19 grupos de causas de muerte relacionadas con alcohol (18 parcialmente atribuibles y uno directamente atribuible), y 20 fracciones atribuibles poblacionales al alcohol (FAPs) para cada grupo de causas, resultantes de combinar sexo, 5 grupos de edad, y los períodos 2001-2009 y 2010-2017. Las muertes por causa se obtuvieron del Instituto Nacional de Estadística. Para las causas parcialmente atribuibles se calcularon FAPs específicas para España, usando la fórmula de Levin con datos de exposición al alcohol procedentes de encuestas de salud y estadísticas de ventas, y riesgos relativos procedentes de metanálisis internacionales. Se consideraron las prevalencias anuales de exbebedores y de siete niveles de consumo diario de alcohol. Se corrigió la subestimación del consumo medio diario autoinformado con respecto a las estadísticas de venta, multiplicando por un factor de 1,58-3,18, dependiendo del año-calendario. Se calcularon tasas de MAA y porcentajes de la mortalidad general atribuibles a alcohol estandarizados por edad, según sexo, grupo de edad, periodo-calendario, tipo de bebedor y comunidad autónoma. Se realizaron análisis de sensibilidad observando cómo cambiaban las estimaciones de MAA al hacerlo algunas opciones metodológicas, como el criterio de exbebedor o la introducción de un período de latencia.
***Palabras clave:*** alcohol, mortalidad atribuible, España, metodología

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Alcohol use is one of the main preventable risk factors for morbidity, mortality and disability in many countries (Global Burden of Disease [GBD], 2018a; Institute for Health Metrics and Evaluation [IHME], 2020). People who drink alcohol, especially high-risk drinkers or people with alcohol use disorder, have a much higher mortality risk than the general population (Roerecke & Rehm, 2013). However, alcohol use begins to raise the risk of death long before levels of consumption considered to be high risk are actually reached, or before an alcohol use disorder develops (Stockwell et al., 2016).

In estimating deaths attributable to alcohol (DAA), essential synthetic indicators are used to compare the impact of alcohol consumption across regions, periods and subgroups, to determine the need for public health interventions, to assess them and allocate resources (World Health Organization [WHO], 2009). The World Health Organization defines DAA as the algebraic sum of deaths caused and preceded by alcohol use that would not have occurred in a counterfactual scenario without historical consumption of this substance. In theory, they should be estimated by comparing the actual risk of death with the hypothetical risk in a counterfactual scenario without historical alcohol consumption (WHO, 2018a).

However, such estimates require information from multiple sources, which often have considerable gaps, so that different authors tend to make methodological choices and assumptions which do not always match, and/or turn to data that are not always possible to extrapolate from alcohol use in other times or regions. Among other aspects, methodological choices may be made based on the inclusion of alcohol-related causes of death, studies or meta-analyses providing risk functions relating the amount of alcohol consumed to mortality from each cause, whether or not risk of DAA is considered in ex-drinkers or that associated with binge drinking and the definitions of these terms, the number of subgroups for which the alcohol-related population attributable fractions (PAFs) used in the calculations are obtained, whether or not a latency period is considered between alcohol use and death, and whether or not the underestimation of average self-reported drinking in the surveys is corrected with respect to more valid sources.

For these reasons, quite dissimilar estimates are sometimes published for the same country, producing a great deal of uncertainty when the results are used in decision-making. Spain is also affected by this situation, with estimates by authors or national or international institutions of the annual number of DAA in the population aged 15 years and over ranging from 8,558 in 1999-2004 (Fierro, Ochoa, Yánez, Valderrama & Álvarez, 2008) to 37,000 in 2016 (GBD, 2018b), and the proportion of general mortality attributable to alcohol from 2.1% to 9.0%, respectively. However, the lowest estimate was only partially based on empirical consumption data obtained from Spanish surveys, and these data were not corrected for underestimation of self-reported average consumption in population-based surveys (Fierro et al., 2008). Regarding estimates by foreign or international institutions (GBD, 2018a; IHME, 2020; WHO, 2020), these use international data sources, so their data are based on the population distribution of average consumption and alcohol consumption patterns non-specific to Spain. In addition, some methodological details are opaque or difficult to comprehend, which makes it impossible to apply them to obtain different results from those published, for example, with reference to different subgroups of interest.

It therefore seems necessary that a country like Spain should have detailed procedures to allow the estimation of DAA based on data on the population distribution of alcohol consumption collected directly from the Spanish population. This would allow routine estimates of the risk of DAA to be made rapidly, including series on changes over time and inter-regional comparisons (for example, between autonomous communities) and between sociodemographic subgroups. Beyond the global estimates that may exist, many countries, especially those with an Anglo-Saxon tradition, have their own methodologies of this type for making such routine estimates.

The objective of this article is thus to describe and discuss a methodology specific to Spain with which to estimate its alcohol-attributable mortality, which will be applied in a later article to obtain estimates during the period 2001-2017.

## Description of methodology

### General methodological approach

Deaths caused and preceded by alcohol use that would not have occurred in a counterfactual scenario without historical use of the substance are considered DAA. To estimate the total number of DAA, the specific cause approach is used. For this purpose, a series of causes or groups of causes considered to be related to alcohol use are selected, deaths attributable to alcohol for each of these causes ($DAA_c$) are estimated and the results of all those selected are added together.

$$DAA = \sum DAA_c$$

The number of $DAA_c$ is estimated by multiplying the number of deaths from this cause ($N_c$), extracted from mortality statistics, by its corresponding PAF ($PAF_c$), which is the proportion of deaths from this cause attributable to exposure to alcohol and which could be avoided if the population stopped consuming this substance completely, and expresses the proportional contribution of alcohol use to population mortality from this cause. The PAF is obtained through an algorithm incorporating the relative risks (RR) with respect to abstainers and the population prevalences of different categories of alcohol use.

$$DAA_c = (N_c)\,(PAF_c)$$

For each cause, the process is stratified for different population subgroups of sex, age and calendar-period, with the aim of achieving a balance that allows $PAF_c$ to be obtained which are specific enough to give greater validity to the results while maintaining a reasonable level of precision. Specifically, for each cause, $PAF_c$ are obtained for the 20 subgroups based on combining both sexes, five age groups (15-24, 25-44, 45-64, 65-74 and ≥75) and two calendar periods (2001-2009 and 2010-2017). This means that independent estimates are obtained for each of the 20 subgroups and subsequently summed. The estimation applies to the population aged 15 years and over.

Thus, the total number of deaths attributable to alcohol is the sum of the deaths attributed to different causes. The process therefore involves: (1) identifying and quantifying the different related causes of death, (2) establishing an attributable fraction for each cause and population subgroup, and (3) adding the results for absolute totals and rates.

## Causes of death related to alcohol

Two types of alcohol-related causes of death are selected: 1) causes directly or completely attributable to alcohol, such as alcohol use disorder, where alcohol is always considered a necessary cause, and 2) other causes of alcohol-related death, in which alcohol is a contributing but not the sole factor; these comprise 18 groups, for example oesophageal cancer. The selection of causes is based on the most recent reviews and meta-analyses focused on assessing the risk of developing or dying from certain diseases associated with alcohol use (Corrao, Bagnardi, Zambon & Arico, 1999; Rehm et al., 2017; Samokhvalov, Irving & Rehm, 2010; Sherk, Stockwell, Rehm, Dorocicz & Shield, 2017), and in the selections made in the estimates of other countries (Connor, Kydd, Rehm & Shield, 2013; Jones & Bellis, 2013; Marmet, Rehm, Gmel, Frick & Gmel, 2014; Rey, Boniol & Jougla, 2010). Table 1 shows the codes of the International Classification of Diseases, tenth edition (ICD-10), corresponding to the 19 groups of selected causes. To avoid duplication, the codes corresponding to causes which are part of broader categories already included in a group of partially attributable causes are excluded from the list of codes for the group of causes directly attributable to alcohol. This is the case of alcoholic liver disease (K70), already included in cirrhosis/chronic liver disease, and involuntary alcohol poisoning (X45) or intentional alcohol self-poisoning (X65), included as external causes, among others (Table 1).

Not included as partially attributable causes are a broad group of diseases or health problems probably related to alcohol, such as certain cancers (for example, stomach

**Table 1**
*Groups of causes of death selected to estimate alcohol-attributable mortality in Spain 2001-2017*

| Groups of causes | ICD-10[3] codes |
|---|---|
| | **Causes partially attributable to alcohol** |
| 1. Tuberculosis | A15-A19, B90, K67.3, P37.0 |
| 2. Lower respiratory infection/pneumonia | A48.1, A70, J09-J15.8, J16, J20-J21, P23.0-P23.4 |
| 3. Cancer of the mouth and pharynx[1] | C00-C13 |
| 4. Cancer of the esophagus[1] | C15 |
| 5. Colorectal cancer[1] | C18-C21 |
| 6. Liver cancer[1] | C22 |
| 7. Laryngeal cancer[1] | C32 |
| 8. Breast cancer (women)[1] | C50 |
| 9. Diabetes mellitus | E10.0-E10.1, E10.3-E11.1, E11.3-E12.1, E12.3-E13.1, E13.3-E14.1, E14.3-E14.9, P70.0-P70.2, R73 |
| 10. Epilepsy | G40, G41 |
| 11. Hypertensive heart disease | I11 |
| 12. Ischemic heart disease | I20-I25 |
| 13. Atrial fibrillation/flutter | I48 |
| 14. Ischemic stroke | G45, I63, I67.2-I67.3, I67.5-I67.6, I69.3 |
| 15. Non-ischemic stroke | I60-I62, I69.0-I69.2, I67.0-I67.1 |
| 16. Cirrhosis/chronic liver disease | B18, I85, I98.2,K70, K71.3–K71.5, K71.7, K72.1–K74.6, K75.8–K76.0, K76.6–K76.7, K76.9 |
| 17. Pancreatitis | K85-K86 |
| 18. External cause | V01-Y98 |
| 19. Causes directly attributable to alcohol[2] | E24.4, F10, G31.2, G62.1, G72.1, I42.6, K29.2, O35.4, R78.0 |

*Note.* [1] D codes (carcinoma in situ, benign tumour, and tumours of uncertain or unknown behaviour) were not included because a fourth digit is often not available. [2] Causes of death directly attributable to alcohol part of broader categories included in groups of partially attributable causes were not considered, including alcoholic liver disease (K70), involuntary alcohol poisoning (X45), intentional alcohol self-poisoning (X65), intoxication by alcohol with undetermined intention (Y15) and evidence of involvement of alcohol (Y90-Y91). [3] ICD-10: International Statistical Classification of Diseases and Related Health Problems, tenth review.

and pancreatic cancers) since the evidence is considered insufficient to establish the causality of alcohol or to quantify the relative risk (Rehm et al., 2017; WHO, 2018b). HIV disease is excluded, although it is included in some countries (Gmel, Shield & Rehm, 2011; Marmet, Rehm & Gmel, 2016).

The number of deaths from the selected causes is sourced from the mortality register of the Spanish National Institute of Statistics [INE] (INE, 2020).

## Population fractions attributable to alcohol

The population fraction attributable to alcohol for a cause or group of causes of death ($PAF_c$) expresses the relative contribution of alcohol use to total mortality from this cause. In this way, an attributable fraction of one was applied ($PAF_c$=1) for causes of death directly attributable to alcohol, while for causes partially attributable to alcohol, specific $PAF_c$ were calculated for Spain. For the calculation, the Levin formula for categorical data was used, combining prevalence data of different levels of exposure to alcohol with the relative risks of mortality from a given cause (Rehm, Klotsche & Patra, 2007), and to which a term to include the fraction corresponding to ex-drinkers has been added. The formula is shown below:

In this formula, $P_{exd}$ is the prevalence of ex-drinkers, $P_i$ the prevalence for category *i* of the average amount of alcohol consumed daily during the last 12 months in the population, $RR_{exd}$ is the relative risk of ex-drinkers versus unexposed individuals (abstainers), $RR_i$ the relative risk of the exposed versus abstainers for this cause of death, and category *i* the amount of alcohol consumed daily. The number of categories *i* used in the calculations was seven, corresponding to the intervals ≤19, 20-39, 40-49, 50-59, 60-79, 80-99 and ≥100 grammes of pure alcohol/day. For each of the 18 groups of causes of death partially attributable to alcohol, 20 PAFs were calculated, the result of combining sex, five age groups, and the periods 2001-2009 and 2010-2017. It was decided to calculate PAFs for two multi-year periods rather than doing so for each calendar year, which would have provided more valid estimates, because the annual consumption prevalences included in the calculation formula would have been subject to greater variability due to randomness, especially considering that it would have been necessary to estimate them simultaneously by age stratum, sex and amount of alcohol consumed. The calculated PAFs are shown in Table 2.

The above formula makes it possible to segment the numerator in order to study different groups of drinkers (Sherk et al., 2017), for example, ex-drinkers and two groups of current drinkers, with high risk and medium-low risk, defined by certain values of *i*. Ex-drinkers are those who have not consumed alcoholic beverages in the last year, but have drunk them at least 12 times in some year of their life, following the definition of the United States National Health Survey (Villarroel, Clarke & Schoenborn, 2016). People who have drunk alcohol less than 12 times in any year of their life and have not drunk in the last year are abstainers. Current high-risk drinkers are men (or women) who have consumed an average of ≥60 (or 40) g of pure alcohol/day during the last year, which corresponds to 6 (or 4) standard drink units (SDUs). This criterion was adopted following earlier studies (Marmet et al., 2014; Rehm et al., 2017; Rehm, Rehm, Shield, Gmel & Gual, 2013; Rehm, Shield, Rehm, Gmel & Frick, 2012), including high and very high-risk drinkers according to classifications by the WHO (WHO, 2000) and the European Medicines Agency [EMA] (EMA, 2010; Mann, Aubin & Witkiewitz, 2017). Other people who have drunk alcohol in the last year are considered current low-risk drinkers. When distributing DAA by type of drinker, it is assumed that all deaths directly attributable to alcohol (PAFc = 1) occur in current high-risk drinkers and that there are no deaths from external causes attributable to alcohol among former regular drinkers.

The meaning of the different parameters in the Levin formula used to calculate the PAFs and the way in which they are obtained is detailed below.

## Relative risks for different categories of population exposure to alcohol

Relative risk (RR) is a measure of association strength between alcohol exposure and death from a certain cause in a given group, place, and time compared to another group. The $RR_i$ used to calculate the $PAF_c$ can be consulted in Table 3. As reference or counterfactual scenario (RR = 1) they have abstainers, and for current drinkers they are calculated using continuous RR functions from different international meta-analyses, most of which were included in a recent review by Rehm et al. (Corrao et al., 1999; Rehm et al., 2017; Samokhvalov et al., 2010).

As a representative $RR_i$ for each exposure interval (average daily amount of alcohol consumed) for current drinkers of < 100 grams of pure alcohol/day, the figure *i* corresponding to the midpoint of each interval is used (10, 30, 45, 55, 70 and 90). For current drinkers of ≥ 100 grams of alcohol/day, however, 130 grams of pure alcohol/day is used as representative $RR_i$ , this being the median amount of alcohol consumed by the drinkers of that group included in the population health survey samples in both periods 2001-09 and 2010-17. In addition, in the case of some causes of death, sex-specific RRs were used (diabetes mellitus, hypertensive heart disease, ischemic heart disease, ischemic stroke, non-ischemic stroke, cirrhosis/chronic liver disease, and pancreatitis).

In the case of ex-drinkers, there are no published RRs for all the selected causes of death. For specific causes with available information, RRs are taken from a 2010 meta-analysis (Rehm et al., 2010a), and for those without

**Table 2**
*Population alcohol-attributable fractions for the selected causes, by sex, period and age. Spain, 2001-2017*

| | **Men** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **2001-2009** | | | | | **2010-2017** | | | | |
| | **15-24** | **25-44** | **45-64** | **65-74** | **≥75** | **15-24** | **25-44** | **45-64** | **65-74** | **≥75** |
| **Cause of death** | | | | | | | | | | |
| 1. Tuberculosis | 0.427 | 0.563 | 0.628 | 0.576 | 0.511 | 0.341 | 0.440 | 0.573 | 0.601 | 0.474 |
| 2. Lower respiratory infection/pneumonia | 0.111 | 0.157 | 0.188 | 0.171 | 0.159 | 0.084 | 0.119 | 0.167 | 0.185 | 0.155 |
| 3. Cancer of the mouth and pharynx[1] | 0.506 | 0.633 | 0.691 | 0.644 | 0.581 | 0.414 | 0.518 | 0.642 | 0.668 | 0.549 |
| 4. Cancer of the esophagus[1] | 0.529 | 0.629 | 0.677 | 0.635 | 0.579 | 0.447 | 0.540 | 0.638 | 0.658 | 0.558 |
| 5. Colorectal cancer[1] | 0.139 | 0.200 | 0.239 | 0.215 | 0.195 | 0.105 | 0.149 | 0.210 | 0.231 | 0.186 |
| 6. Liver cancer[1] | 0.369 | 0.586 | 0.670 | 0.607 | 0.528 | 0.286 | 0.394 | 0.592 | 0.631 | 0.451 |
| 7. Laryngeal cancer[1] | 0.483 | 0.497 | 0.501 | 0.493 | 0.460 | 0.240 | 0.318 | 0.418 | 0.443 | 0.348 |
| 8. Breast cancer (women)[1] | - | - | - | - | - | - | - | - | - | - |
| 9. Diabetes mellitus | -0.056 | -0.042 | -0.021 | -0.018 | -0.008 | -0.060 | -0.058 | -0.033 | -0.016 | -0.011 |
| 10. Epilepsy | 0.290 | 0.396 | 0.455 | 0.409 | 0.357 | 0.225 | 0.302 | 0.407 | 0.434 | 0.335 |
| 11. Hypertensive heart disease | 0.210 | 0.292 | 0.342 | 0.305 | 0.269 | 0.161 | 0.221 | 0.303 | 0.327 | 0.254 |
| 12. Ischemic heart disease | -0.061 | -0.044 | -0.026 | -0.026 | -0.016 | -0.049 | -0.058 | -0.036 | -0.017 | -0.016 |
| 13. Atrial fibrillation/flutter | 0.133 | 0.188 | 0.224 | 0.201 | 0.184 | 0.101 | 0.142 | 0.198 | 0.218 | 0.177 |
| 14. Ischemic stroke | -0.015 | 0.040 | 0.090 | 0.076 | 0.074 | -0.045 | -0.015 | 0.056 | 0.087 | 0.065 |
| 15. Non-ischemic stroke | 0.157 | 0.222 | 0.263 | 0.234 | 0.208 | 0.119 | 0.166 | 0.232 | 0.252 | 0.198 |
| 16. Cirrhosis/chronic liver disease | 0.666 | 0.799 | 0.844 | 0.808 | 0.755 | 0.576 | 0.680 | 0.803 | 0.824 | 0.711 |
| 17. Pancreatitis | 0.411 | 0.545 | 0.610 | 0.558 | 0.494 | 0.327 | 0.424 | 0.555 | 0.584 | 0.459 |
| 18. External cause | 0.191 | 0.256 | 0.297 | 0.267 | 0.239 | 0.144 | 0.200 | 0.267 | 0.288 | 0.233 |
| | **Women** | | | | | | | | | |
| | **2001-2009** | | | | | **2010-2017** | | | | |
| | **15-24** | **25-44** | **45-64** | **65-74** | **≥75** | **15-24** | **25-44** | **45-64** | **65-74** | **≥75** |
| **Cause of death** | | | | | | | | | | |
| 1. Tuberculosis | 0.245 | 0.251 | 0.246 | 0.197 | 0.144 | 0.220 | 0.222 | 0.257 | 0.219 | 0.158 |
| 2. Lower respiratory infection/pneumonia | 0.063 | 0.070 | 0.068 | 0.057 | 0.051 | 0.059 | 0.066 | 0.073 | 0.066 | 0.056 |
| 3. Cancer of the mouth and pharynx[1] | 0.309 | 0.315 | 0.311 | 0.250 | 0.186 | 0.282 | 0.283 | 0.324 | 0.279 | 0.204 |
| 4. Cancer of the esophagus[1] | 0.360 | 0.364 | 0.355 | 0.286 | 0.222 | 0.339 | 0.342 | 0.373 | 0.325 | 0.244 |
| 5. Colorectal cancer[1] | 0.077 | 0.085 | 0.083 | 0.069 | 0.059 | 0.072 | 0.079 | 0.088 | 0.079 | 0.065 |
| 6. Liver cancer[1] | 0.156 | 0.163 | 0.161 | 0.140 | 0.079 | 0.117 | 0.110 | 0.152 | 0.123 | 0.079 |
| 7. Laryngeal cancer[1] | 0.425 | 0.427 | 0.418 | 0.375 | 0.347 | 0.163 | 0.169 | 0.190 | 0.163 | 0.121 |
| 8. Breast cancer (women)[1] | 0.132 | 0.138 | 0.135 | 0.107 | 0.085 | 0.121 | 0.127 | 0.144 | 0.124 | 0.094 |
| 9. Diabetes mellitus | -0.243 | -0.222 | -0.177 | -0.107 | -0.070 | -0.241 | -0.230 | -0.202 | -0.136 | -0.081 |
| 10. Epilepsy | 0.163 | 0.170 | 0.166 | 0.131 | 0.101 | 0.149 | 0.154 | 0.175 | 0.150 | 0.111 |
| 11. Hypertensive heart disease | 0.191 | 0.205 | 0.219 | 0.185 | 0.122 | 0.143 | 0.143 | 0.219 | 0.192 | 0.132 |
| 12. Ischemic heart disease | -0.052 | -0.032 | -0.014 | 0.009 | 0.020 | -0.059 | -0.042 | -0.019 | 0.004 | 0.020 |
| 13. Atrial fibrillation/flutter | 0.075 | 0.082 | 0.080 | 0.066 | 0.057 | 0.070 | 0.077 | 0.086 | 0.076 | 0.062 |
| 14. Ischemic stroke | -0.154 | -0.136 | -0.095 | -0.045 | -0.044 | -0.186 | -0.183 | -0.122 | -0.081 | -0.054 |
| 15. Non-ischemic stroke | 0.191 | 0.194 | 0.190 | 0.147 | 0.105 | 0.172 | 0.172 | 0.199 | 0.167 | 0.116 |
| 16. Cirrhosis/chronic liver disease | 0.430 | 0.434 | 0.429 | 0.363 | 0.249 | 0.380 | 0.370 | 0.433 | 0.373 | 0.264 |
| 17. Pancreatitis | 0.234 | 0.240 | 0.236 | 0.189 | 0.139 | 0.211 | 0.213 | 0.246 | 0.210 | 0.152 |
| 18. External cause | 0.107 | 0.114 | 0.112 | 0.089 | 0.074 | 0.100 | 0.107 | 0.120 | 0.105 | 0.082 |

*Note.* The population attributable fractions (PAFs) for the group of causes of death directly attributable to alcohol are always 1 and were not included. To calculate the PAF, the corrected prevalences of consumption were used, raising the average consumption of each participant in the surveys to 80% of the average per capita consumption estimated from the sales statistics. For a more accurate calculation of deaths attributable to alcohol for a given territory or subgroup, PAFs with 5 decimal places are often required, so it is recommended to request the file from the authors.

**Table 3**
*Relative risks of death from the selected causes, by sex and level of exposure to alcohol. Spain, 2001-2017*

| | Men | | | | | | | | Women | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Average amount of alcohol consumed (g pure alcohol/day) | | | | | | | | | | | | | | | |
| Cause of death | Exd[1]. | 10 | 30 | 45 | 55 | 70 | 90 | 130 | Exd. | 10 | 30 | 45 | 55 | 70 | 90 | 130 |
| 1. Tuberculosis | 1.38 | 1.20 | 1.71 | 2.24 | 2.69 | 3.52 | 5.04 | 10.34 | 1.38 | 1.20 | 1.71 | 2.24 | 2.69 | 3.52 | 5.04 | 10.34 |
| 2. Lower respiratory infection/pneumonia | 1.38 | 1.05 | 1.15 | 1.24 | 1.30 | 1.40 | 1.54 | 1.86 | 1.38 | 1.05 | 1.15 | 1.24 | 1.30 | 1.40 | 1.54 | 1.86 |
| 3. Cancer of the mouth and pharynx[1] | 1.38 | 1.28 | 2.03 | 2.81 | 3.45 | 4.65 | 6.70 | 12.68 | 1.38 | 1.28 | 2.03 | 2.81 | 3.45 | 4.65 | 6.70 | 12.68 |
| 4. Cancer of the esophagus[1] | 1.38 | 1.46 | 2.39 | 3.21 | 3.81 | 4.80 | 6.29 | 9.76 | 1.38 | 1.46 | 2.39 | 3.21 | 3.81 | 4.80 | 6.29 | 9.76 |
| 5. Colorectal cancer[1] | 1.38 | 1.06 | 1.21 | 1.23 | 1.41 | 1.55 | 1.76 | 2.26 | 1.38 | 1.06 | 1.21 | 1.23 | 1.41 | 1.55 | 1.76 | 2.26 |
| 6. Liver cancer[1] | 1.38 | 1.01 | 1.16 | 1.40 | 1.66 | 2.29 | 3.94 | 17.55 | 1.38 | 1.01 | 1.16 | 1.40 | 1.66 | 2.29 | 3.94 | 17.55 |
| 7. Laryngeal cancer[1] | 1.38 | 1.16 | 1.52 | 1.85 | 2.10 | 2.52 | 3.17 | 4.77 | 1.38 | 1.16 | 1.52 | 1.85 | 2.10 | 2.52 | 3.17 | 4.77 |
| 8. Breast cancer (women)[1] | - | - | - | - | - | - | - | - | 1.38 | 1.11 | 1.36 | 1.58 | 1.75 | 2.04 | 2.50 | 3.76 |
| 9. Diabetes mellitus | 1.18 | 0.90 | 0.88 | 0.93 | 0.97 | 1.07 | 1.16 | 1.16 | 1.14 | 0.68 | 0.62 | 0.86 | 1.18 | 1.18 | 1.18 | 1.18 |
| 10. Epilepsy | 1.38 | 1.14 | 1.45 | 1.75 | 1.98 | 2.38 | 3.04 | 4.97 | 1.38 | 1.14 | 1.45 | 1.75 | 1.98 | 2.38 | 3.04 | 4.97 |
| 11. Hypertensive heart disease | 1.38 | 1.10 | 1.31 | 1.50 | 1.65 | 1.89 | 2.26 | 3.25 | 1.38 | 0.89 | 1.60 | 2.43 | 3.16 | 4.59 | 7.38 | 17.76 |
| 12. Ischemic heart disease | 1.25 | 0.95 | 0.84 | 0.74 | 0.67 | 1.00 | 1.00 | 1.43 | 1.54 | 0.84 | 0.99 | 1.15 | 1.26 | 1.45 | 1.74 | 2.53 |
| 13. Atrial fibrillation/flutter | 1.38 | 1.06 | 1.19 | 1.30 | 1.37 | 1.50 | 1.68 | 2.11 | 1.38 | 1.06 | 1.19 | 1.30 | 1.37 | 1.50 | 1.68 | 2.11 |
| 14. Ischemic stroke | 1.33 | 0.85 | 0.96 | 1.07 | 1.14 | 1.26 | 1.43 | 1.81 | 1.15 | 0.65 | 0.77 | 1.00 | 1.22 | 1.70 | 2.75 | 7.81 |
| 15. Non-ischemic stroke | 1.33 | 1.07 | 1.23 | 1.36 | 1.46 | 1.62 | 1.86 | 2.45 | 1.15 | 1.16 | 1.55 | 1.93 | 2.24 | 2.79 | 3.74 | 6.73 |
| 16. Cirrhosis/chronic liver disease | 1.31 | 1.33 | 2.32 | 3.53 | 4.67 | 7.10 | 12.42 | 37.95 | 6.50 | 2.82 | 5.97 | 8.90 | 11.20 | 15.24 | 21.93 | 40.87 |
| 17. Pancreatitis | 1.38 | 1.19 | 1.68 | 2.18 | 2.60 | 3.37 | 4.76 | 9.53 | 1.38 | 0.77 | 0.66 | 1.53 | 3.01 | 4.80 | 10.26 | 10.26 |
| 18. External cause | 1.38 | 1.09 | 1.30 | 1.48 | 1.62 | 1.85 | 2.21 | 2.42 | 1.38 | 1.09 | 1.30 | 1.48 | 1.62 | 1.85 | 2.21 | 2.42 |

Exd[1]: ex-drinkers.
*Note.* The references used to obtain the RRs for each cause of death are Corrao, Bagnardi, Zambon and Arico (1999); Samokhvalov, Irving and Rehm (2010), and Rehm et al. (2017), in the case of current drinkers. For ex-drinkers, references are Rehm et al. (2010a), and Stockwell et al. (2016).

information, the all-cause mortality RR of 1.38 from a Stockwell et al. meta-analysis is applied, corresponding to the joint and completely adjusted model (Stockwell et al., 2016).

## Prevalences of population exposure to alcohol

The formula for calculating PAFs involves the prevalence of ex-drinkers and the annual prevalences of different average daily amounts of alcohol consumed. These prevalences are shown in Table 4 by age, sex, and period.

Data sources and how they were obtained are described below.

### *Ex-drinker prevalences*

For the period 2010-2017, these are estimated from figures in the Spanish National Health Survey (ENS) and the European Health Survey in Spain (EESE) corresponding to the period. As the studies providing RRs for mortality in ex-drinkers most likely exclude infrequent ex-drinkers or those just trying out alcohol, it is advisable to correct the prevalences by eliminating this subgroup. To make this correction, the distribution of infrequent and regular ex-drinkers from the United States National Health Survey in the period 2011-14 (Villarroel et al., 2016) is used since there are no data for this from Spanish sources.

For the period 2001-09, the prevalence figures for ex-drinkers obtained from ENS and EESE are very low compared to 2010-17 and to those obtained from other sources for some age subgroups and were thus not considered reliable; instead, they were estimated from the 2010-17 corrected prevalences, assuming a relative change between periods similar to that observed in the Spanish Household Survey on Alcohol and Drugs (Encuesta Domiciliaria sobre Alcohol y Drogas en España, EDADES) (Delegación del Gobierno para el Plan Nacional sobre Drogas [DGPNSD], 2018).

### *Annual prevalences of average daily consumption of different amounts of alcohol*

These are obtained from the individual files of ENS 2001, 2006, 2011 and 2017, and EESE 2009 and 2014 (INE, 2019a; Ministerio de Sanidad, Consumo y Bienestar Social [MSCBS], 2019). To this end, the average self-reported daily amount of alcohol consumed by each participant during the last year is first corrected for underestimation, given the well-known fact that self-reports of alcohol use strongly underestimate real consumption (Sordo et al., 2016). The categories of consumption used for stratifying annual consumption prevalence, in grams of pure alcohol, correspond to the seven categories $i$ mentioned in the $PAF_c$ calculation. The prevalences for the intermediate years without the survey are estimated by linear interpolation.

**Table 4**

*Corrected prevalence of alcohol consumption[1] in the population aged 15 years and over[2], by age, sex, average daily amount of alcohol consumed and period (%). Spain, 2001-2017*

| | | Prevalence (%) | | | | | | | | | Sample size |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Drinker status** | | **Abstainer[3]** | **Ex-drinker[4]** | **Drinker in the previous year** | | | | | | | |
| **Grams alcohol/day[5]** | | **0** | **0** | **1-19** | **20-39** | **40-49** | **50-59** | **60-79** | **80-99** | **≥100** | |
| | | **2001-2009** | | | | | | | | | |
| **Age** | **Sex** | | | | | | | | | | |
| 15-24 | Men | 22.8 | 1.8 | 41.0 | 17.1 | 5.5 | 3.0 | 4.2 | 2.3 | 2.3 | 3368 |
| | Women | 32.2 | 2.0 | 51.6 | 9.5 | 1.8 | 0.9 | 0.7 | 0.7 | 0.7 | 3365 |
| | Total | 27.5 | 1.9 | 46.3 | 13.3 | 3.7 | 2.0 | 2.6 | 1.5 | 1.5 | 6733 |
| 25-44 | Men | 14.3 | 3.2 | 37.1 | 19.6 | 5.3 | 4.8 | 5.6 | 3.1 | 7.0 | 11240 |
| | Women | 32.4 | 4.2 | 48.8 | 9.7 | 1.3 | 1.4 | 1.2 | 0.5 | 0.7 | 13344 |
| | Total | 24.1 | 3.7 | 43.4 | 14.2 | 3.1 | 3.0 | 3.2 | 1.7 | 3.6 | 11111 |
| 45-64 | Men | 15.2 | 4.9 | 27.0 | 19.9 | 4.7 | 7.5 | 6.8 | 3.9 | 10.3 | 9033 |
| | Women | 41.4 | 4.2 | 38.0 | 10.8 | 1.0 | 2.3 | 1.2 | 0.4 | 0.7 | 11800 |
| | Total | 30.0 | 4.5 | 33.2 | 14.7 | 2.6 | 4.6 | 3.6 | 1.9 | 4.7 | 11199 |
| 65-74 | Men | 20.7 | 7.8 | 25.1 | 19.0 | 2.4 | 8.7 | 6.1 | 2.4 | 7.6 | 3614 |
| | Women | 58.6 | 5.3 | 23.4 | 9.1 | 0.4 | 1.8 | 0.7 | 0.1 | 0.6 | 5489 |
| | Total | 43.5 | 6.3 | 24.1 | 13.0 | 1.2 | 4.5 | 2.9 | 1.0 | 3.4 | 9103 |
| >=75 | Men | 26.2 | 13.2 | 20.3 | 18.7 | 1.5 | 8.8 | 3.7 | 1.6 | 5.3 | 2938 |
| | Women | 67.8 | 6.7 | 15.3 | 7.7 | 0.3 | 1.5 | 0.3 | 0.1 | 0.2 | 5104 |
| | Total | 52.6 | 9.1 | 17.1 | 11.7 | 0.7 | 4.2 | 1.5 | 0.6 | 2.1 | 8042 |
| Total | Men | 19.8 | 6.2 | 30.1 | 18.9 | 3.9 | 6.6 | 5.3 | 2.7 | 6.5 | 30193 |
| | Women | 46.5 | 4.5 | 35.4 | 9.4 | 1.0 | 1.6 | 0.8 | 0.4 | 0.6 | 39102 |
| | Total | 34.9 | 5.2 | 33.1 | 13.5 | 2.2 | 3.7 | 2.8 | 1.4 | 3.2 | 69295 |
| | | **2010-2017** | | | | | | | | | |
| **Age** | **Sex** | | | | | | | | | | |
| 15-24 | Men | 27.4 | 1.9 | 48.3 | 12.1 | 3.6 | 2.0 | 2.1 | 0.8 | 1.8 | 2195 |
| | Women | 32.8 | 2.2 | 52.8 | 8.0 | 1.6 | 1.2 | 0.7 | 0.4 | 0.4 | 2202 |
| | Total | 30.1 | 2.1 | 50.5 | 10.1 | 2.6 | 1.5 | 1.4 | 0.6 | 1.1 | 4397 |
| 25-44 | Men | 15.7 | 3.5 | 46.0 | 17.1 | 5.4 | 3.5 | 4.5 | 1.5 | 2.8 | 9749 |
| | Women | 32.0 | 4.5 | 49.9 | 9.3 | 2.1 | 0.9 | 0.9 | 0.2 | 0.3 | 10312 |
| | Total | 24.1 | 4.0 | 48.0 | 13.1 | 3.7 | 2.2 | 2.6 | 0.8 | 1.5 | 20061 |
| 45-64 | Men | 13.9 | 5.2 | 33.5 | 19.5 | 5.8 | 4.5 | 8.0 | 2.8 | 7.0 | 10753 |
| | Women | 35.4 | 4.5 | 42.3 | 11.4 | 2.3 | 1.3 | 1.9 | 0.4 | 0.5 | 11529 |
| | Total | 25.0 | 4.8 | 38.1 | 15.3 | 4.0 | 2.8 | 4.8 | 1.6 | 3.6 | 22282 |
| 65-74 | Men | 14.9 | 8.4 | 26.0 | 20.4 | 5.1 | 4.6 | 9.2 | 3.2 | 8.4 | 4051 |
| | Women | 49.5 | 5.7 | 29.1 | 10.4 | 1.6 | 1.2 | 2.0 | 0.1 | 0.3 | 5148 |
| | Total | 34.3 | 6.9 | 27.7 | 14.8 | 3.1 | 2.7 | 5.2 | 1.5 | 3.9 | 9199 |
| >=75 | Men | 24.5 | 14.9 | 19.8 | 21.8 | 4.0 | 3.8 | 6.1 | 1.7 | 3.4 | 3597 |
| | Women | 64.1 | 7.2 | 17.5 | 8.5 | 0.6 | 0.9 | 1.1 | 0.1 | 0.1 | 6546 |
| | Total | 50.1 | 9.9 | 18.3 | 13.2 | 1.8 | 1.9 | 2.9 | 0.7 | 1.3 | 10143 |
| Total | Men | 19.3 | 6.8 | 34.7 | 18.2 | 4.8 | 3.7 | 6.0 | 2.0 | 4.7 | 30345 |
| | Women | 42.8 | 4.8 | 38.3 | 9.5 | 1.6 | 1.1 | 1.3 | 0.2 | 0.3 | 35737 |
| | Total | 32.0 | 5.7 | 36.7 | 13.5 | 3.1 | 2.3 | 3.5 | 1.0 | 2.3 | 66082 |

*Note.* [1] Corrected prevalence of alcohol consumption: Prevalences obtained after correcting the underestimation of self-reported consumption in population surveys with respect to alcohol consumption sales statistics. The correction was made by applying an elevation factor to the average daily quantity consumed by each individual participant in the survey up to 80% of the average daily quantity per capita estimated from the sales statistics. [2]Population aged 15 year and older: In reality, the consumption prevalences correspond to the population aged 16 years and over, which is the reference population of the population surveys included in this study. However, the estimates of sales statistics from international organizations usually apply to the population aged 15 years and over; the fractions attributable to alcohol in the population and the estimates of attributable mortality were thus applied to the 15-and-older population. [3]Abstainer: Person who has never drunk alcoholic beverages in their life. [4]Ex-drinker: Person who has not drunk alcoholic beverages in the previous year and has drunk such beverages less than 12 times in any other year of their life. The prevalence was estimated as explained in the Methodology section. 5Alcohol consumed (g/day): Refers to the average amount of pure alcohol consumed daily in grams.

The algorithm used to correct for underestimation is detailed below. For each participant in the survey, average daily consumption in a given year in grams of pure alcohol (Ac), is obtained by multiplying the self-reported average daily consumption during the 12 months prior to the survey (As), by an elevation factor (Ef). This factor is calculated in turn by dividing the best estimate of the average daily population consumption per capita from multiple sources, mainly sales statistics (Ar), by As and multiplying the result by the degree of correction of the desired underestimation (C).

$$Ac = \mathrm{Aa}\left[\frac{Ar}{\mathrm{Aa}}C\right], \text{ donde } \left[\frac{Ar}{\mathrm{Aa}}C\right]=\mathrm{Fe}$$

According to international recommendations (Kehoe, Gmel, Shield, Gmel & Rehm, 2012; Rehm et al., 2010b; Stockwell et al., 2018), C is 0.8; that is, As is corrected up to 80% of Ar. The justification for this procedure is somewhat extensive and is included in Appendix Table 1. The estimates of As, Ar and Ef by calendar year are included in Table 5. As can be seen in this table, the Ef has increased in the most recent years, highlighting the increasing difficulty in capturing real consumption in surveys and further justifying the need to correct self-reported consumption. A specific Ef was calculated for each year with survey results and was applied to all the participants in the survey who had drunk alcohol during the last year, irrespective of their sociodemographic profile and their consumption patterns, because the annual Ar could only be estimated for the country as a whole, without the possibility of stratification by sociodemographic variables.

The methodology for estimating Ar and As has been published (Sordo et al., 2016) and is summarized below.

## Estimation of average self-reported alcohol consumption (As)

The surveys used for estimating As can be considered representative of the non-institutionalized population aged ≥ 15 years in Spain. Its characteristics can be seen in Appendix Table 2. The amount of alcohol consumed (*As*) in litres of pure alcohol (lpa) per person-year (py) is estimated following the classical approach (Dawson, 2003) with the algorithm: $As=\sum_{i-1}^{k}\frac{D_i SD_i V_i C_i}{SS}$, where the subscript *i* represents the different categories of beverages, such as wine/cava, beer/cider, aperitifs/intermediate products (drinks with alcohol content of 1.2-22% ABV, other than fermented ones such as vermouth, sherry, port and pale sherries or amontillados) and spirits/distilled beverages (including mixes made with spirits), $D_i$ is the annual number of days or times each drink is consumed, $SD_i$ the number of SDUs consumed each day or each time, $V_i$ the volume of each SDU in litres, $C_i$ the proportion of alcohol over the total volume of the drink, and *SS* the effective sample size. Given

**Table 5**
*Elevation factors used for correcting underestimated self-reported annual alcohol consumption. Spain, 2001-2017*

| | Registered alcohol consumption (Ar)[1] | Self-reported alcohol alcohol consumption (As)[2] | Elevation factor (Ef)[3] |
|---|---|---|---|
| **2001** | 12.5 | 6.3 | 1.58 |
| **2002** | 10.8 | | |
| **2003** | 11.7 | | |
| **2004** | 12.0 | | |
| **2005** | 11.3 | | |
| **2006** | 11.4 | 3.8 | 2.38 |
| **2007** | 11.1 | | |
| **2008** | 10.3 | | |
| **2009** | 9.9 | 3.0 | 2.61 |
| **2010** | 9.6 | | |
| **2011** | 9.4 | 2.6 | 2.83 |
| **2012** | 9.5 | | |
| **2013** | 9.8 | | |
| **2014** | 9.6 | 2.9 | 2.64 |
| **2015** | 9.6 | | |
| **2016** | 9.7 | | |
| **2017** | 9.6 | 2.4 | 3.18 |

*Note.* [1] Registered alcohol consumption (Ar): Average annual per capita consumption in litres of pure alcohol/year by residents in Spain aged 15 years and over, estimated from sales statistics. [2] Self-reported alcohol consumption (As): Average annual per capita consumption of pure alcohol/year in litres by residents in Spain aged 15 years and over, self-reported in population surveys. [3] Elevation factor (Fe): Ef=(Ar/As)*0.8. The multiplication factor used to correct the underestimation of self-reported alcohol use in the population statistics with respect to the estimates from sales statistics. The correction was made only up to 80% of the sales statistics consumption estimate, as recommended (Rehm et al., 2010a; Stockwell et al., 2018; Kehoe et al., 2012). It was applied to the average consumption of each individual participating in the surveys so that the population prevalences of consumption according to the average daily amount consumed could then be obtained.

the great scarcity of empirical data (Rodríguez-Martos, Gual & Llopis Llácer, 1999), the SDU volume of each drink, $V_i$, is assigned using the upper limits of the volumes reflected in some clinical and public health guidelines (Organización Médica Colegial y Ministerio de Sanidad y Consumo [OMC-MSC], 2006; Sociedad Española de Medicina de Familia y Comunitaria [SEMFYC], 2005): wine (125 ml), beer/cider (250 ml), aperitifs (100 ml), spirits (60 ml), and $C_i$ are applied to each drink on the basis of the Spanish Tax Agency guidelines (5.5%, 11.5%, 15% and 35%, respectively) (Agencia Tributaria [AT], 2015; 2019). In this way, the amounts in grams of pure alcohol per SDU of each drink are: 11.36 (wine), 10.86 (beer/cider), 11.85 (aperitifs), and 16.59 (spirits). For a vague category, such as "regional drinks", it is assumed that an SDU contains 10 g of pure alcohol.

The results of the surveys were weighted to adjust for the imbalance of the sample according to sex, age group, province, size of household, and response rate.

## Estimated average registered alcohol consumption (Ar)

The main aggregated data for estimating the average alcohol use registered per capita (Ar) refer to legal sales or supplies of drinks intended for human consumption within Spain with an alcohol content by volume (ABV) of > 1.2%. These figures are corrected to account for unregistered alcohol, consumption/purchase by international travellers, and post-sale alcoholic drink loss. The data for estimating the alcohol consumed/purchased by foreign visitors in Spain and Spanish visitors abroad are obtained from the Spanish Tourism Institute (TURESPAÑA, 2019), INE (INE, 2019b), WHO (registered per capita alcohol consumption by country) (WHO, 2020), Eurostat (Eurostat, 2019) and World Bank (World-Bank, 2019) and the scientific literature (Sordo et al., 2016). The remaining data necessary for correcting the sales statistics is obtained from the scientific literature, including the consumption of contraband beverages or those made with alcohol for other purposes, drinks from unregistered sales or production (for example, self-use), products with an alcoholic content greater than zero and ≤ 1.2% ABV, loss of alcoholic beverages (spilled, spoiled or wasted/unfinished drinks) and beverages used for cooking or for purposes other than direct human consumption (Boniface & Shelton, 2013; Landberg & Norstrom, 2011; Meier et al., 2013; Norstrom & Skog, 2001; Rehm et al., 2010b; Rehm et al., 2007; Trolldal, 2001; WHO, 2020). The characteristics of the main routine sources providing useful aggregate data for estimating per capita alcohol consumption in Spain are included in Appendix Table 3.

Alcohol quantity is expressed in litres of pure alcohol per person-year (lpa/py), using the population resident in Spain each year as the denominator. To obtain figures for the real consumption of alcohol, a multistage process was followed starting with the availability of alcohol for consumption published by the Spanish Tax Agency (TA). The TA calculates availability by adding to the alcohol from legal sales of beverages subject to excise duty on alcohol (beer, spirits and snacks) the alcohol from wine purchases which are self-reported to the Spanish Food Consumption Panel (Panel de Consumo Alimentario). This availability does not include cider, and it has been noted that self-reported wine purchases are underestimated compared to sales (as in the case of beer, where underestimation reaches 45%). A multi-source availability indicator was therefore created by replacing the wine component in TA availability with the Eurostat wine supply statistic and adding the FAO figure for cider supply. Finally, the real average per capita consumption was obtained by adding the alcohol from drinks consumed/purchased abroad by Spanish residents and the remaining unregistered alcohol, and subtracting alcohol loss and alcohol from drinks consumed/bought in Spain by foreign visitors. The specific calculation algorithms can be consulted in a previous study (Sordo et al., 2016).

## Alcohol-attributable mortality indicators

The main indicators used to express the results of alcohol-attributable mortality estimates in Spain are: absolute number of DAA and various age-standardized indicators such as DAA rate (RDAA), and the proportional contribution of alcohol to general mortality risk (CAGM), proportional contribution to the total risk of alcohol-attributable mortality of different causes of death (CMAAC), and from high-risk consumption (CMAAR).

RDAA is an indicator of the absolute risk or probability of dying from alcohol use in a given population subgroup. Population rates are expressed per 100,000 person-years (py) and standardized using the direct method with the age structure weights of the 2013 European Standard Population (Eurostat, 2013). The standardized proportional contributions are expressed as percentages and are the result of dividing the RDAA by the all-cause mortality rate (CAGM), the specific RDAA for each cause by the RDAA for all causes (CMAAC), and the RDAA in current high-risk drinkers by the sum of RDAAs in high-risk and medium-low-risk drinkers (CMAAR).

Most of the indicators were calculated by sex, age group (15-34, 35-54, 55-74 years and >= 75 years), autonomous community, calendar period (2001-09 and 2010-17) and type of drinker (ex-regular drinkers, medium-low risk drinkers and high-risk drinkers).

The populations by age group, sex, autonomous community and calendar year for the calculation of the indicators were obtained from the population figures of the Spanish National Statistics Institute (INE, 2019c). To compare the risk of DAA between groups (for example, men and women) or periods (2001-09 and 2010-17), the ratio and difference of age-standardized rates were applied, transforming the rate ratio into a percentage of change for temporal comparisons.

## Sensitivity analysis

Several sensitivity analyses were carried out to observe how the change of some methodological options affected the estimation of the total number of DAA in 2017 (Appendix Table 4). These included introducing prevalences without correction for underestimated consumption, excluding the DAA occurring in ex-drinkers from the calculations, adopting a broader definition of ex-drinker which included both "regular ex-drinkers" and "infrequent ex-drinkers", using the alcohol use prevalences of the period 2001-09 instead of 2010-2017 figures, which is equivalent to introducing a latency period of approximately 12 years with respect to 2017, and estimating the DAA in traffic accidents taking as the PAFc the proportion of drivers and pedestrians who died in such accidents with a blood alcohol level above 0.8 grams/litre during 2015-17, calculated with data extracted from the annual reports of the National Institute of Toxicology and Forensic Sciences during 2001-17 (1,870 drivers and 489 pedestrians) (Instituto Nacional de Toxicología y Ciencias Forenses [INTCF], 2019).

## Methodology discussion

This article sets out a detailed methodology for estimating alcohol-attributable mortality in Spain, following as far as possible the most common and updated international recommendations and procedures in the field (IHME, 2020; Rehm et al., 2017; Rehm et al., 2009; Sherk et al., 2017; WHO, 2000, 2018b, 2020). Its application to the period 2001-2017 has made it possible to obtain results by sex, age, calendar period, autonomous community, cause of death and type of drinker, which are quite consistent with other indicators of alcohol problems. In the future, it will in turn allow comparative results to be obtained for other subgroups of interest, such as those defined by educational level or socioeconomic position based on the mortality cohorts from the 2001 and 2011 censuses of the KharonXXI Platform for National Longitudinal Mortality Studies that is being established within the CIBERESP framework.

The two main strengths of the methodology are that the PAFs were calculated from empirical data on population exposure to alcohol from almost all Spanish sources, and that individual survey data on average self-reported alcohol use were corrected for underestimation in relation to other sources of greater validity such as statistics on the sale of alcoholic drinks, following a very painstaking process (Sordo et al., 2016). The methodology also has other strengths, such as the inclusion of DAA linked to ex-drinkers. Finally, the PAFc obtained are quite robust because the distribution of population exposure to alcohol is based on the joint analysis of surveys with a significant sample size (n = 66,082 in 2010-2017 and 69,295 in 2001-2009). This makes it possible to obtain PAFc for the 20 population subgroups mentioned above and to segment the PAFc for each cause of death by type of drinker (ex-drinker, low-risk and high-risk drinker).

Despite its strengths and the fact that great pains were taken to collect all the relevant data available, it is undoubtedly still a work in progress which will require reviewing and improving in the future. In this regard, a number of methodological options may be considered for the proposed model.

A specific cause approach was chosen in preference of all causes because it allows better control of confounding factors, as well as making it possible to estimate the relative weights of different causes or groups of causes of death in the total mortality attributable to alcohol, an aspect of interest to clinical and public health practice (Corrao, Rubbiati, Zambon & Arico, 2002). To design more appropriate prevention and treatment interventions, it is not only a matter of knowing the number of DAA but also the specific causes.

Beyond this general approach, conservative methodological strategies were adopted to avoid overestimating the number of DAA, which makes it highly likely that the figures obtained underestimate the mortality attributable to alcohol in Spain. Among these strategies, the following are worth noting: 1) Only those causes of death for which there is clear evidence linking them to alcohol use and which have valid RR estimates were included (Table 1). This excludes a broad group of diseases with a probable relationship to alcohol. 2) In calculating the amount of alcohol consumed, an alcohol content of 11.5% ABV was applied to wine, which is probably low in the current Spanish context (Alston, Lapsley, Soleas & Tumber, 2013). 3) A restrictive definition of ex-drinker was applied, including only the fraction of these individuals (regular ex-drinkers), which may offer a better fit with the profile of ex-drinkers referred to in the RRs obtained in epidemiological studies. This option, which has probably not been adopted in other studies (Rehm et al., 2010a; Stockwell et al., 2016), considerably reduces estimates of the number of DAA because ex-drinkers have RRs close to high-risk drinkers (Rehm et al., 2010a; Stockwell et al., 2016) given that many stopped drinking due to problems caused by alcohol. In any case, it must be noted that the data to make the correction came from the United States, where the epidemiological situation of alcohol use may not be equivalent to Spain's. For example, alcohol use in Spain has clearly declined during the 21st century, something that has not happened in the United States (Breslow, Castle, Chen & Graubard, 2017; Centers for Disease Control and Prevention [CDC], 2020). The effect of including only regular ex-drinkers or all ex-drinkers in the calculations can be seen in Appendix Table 4. 4) Binge drinking was not specifically addressed due to the lack of corresponding information; however, it is considered that this consumption pattern was already taken into account in the algorithm used to obtain the PAFs in a general way. Nevertheless, the changes in the estimate as a result of considering the effect of this consumption pattern can be seen in Appendix Table 4. 5) The $RR_i$ of some diseases are probably underestimated given that they are calculated in comparison with abstainers, a group that in some studies may also include former regular drinkers (Rehm et al., 2017; Rehm, Shield, Roerecke & Gmel, 2016; Stockwell et al., 2016). However, a sensitivity analysis was carried out for 2017 which considered a latency period of approximately 12 years and the estimate of the number of DAA was only 1.03 times greater than that considered valid in this study (Appendix Table 4).

In addition, there are some general limitations that affect the estimates of alcohol-attributable mortality worldwide. Among them we must mention the scarcity and low quality of the $RR_i$ estimates published for certain causes of death, age groups, sex and average daily consumption. Thus, the $RR_i$ for some severe health problems, for example, traffic accidents, can vary widely by age, so the application of the same $RR_i$ at all ages could result in an underestimation of these deaths in young people and an overestimation in older people (Jones, Bellis, Dedman, Sumnal & Tocke, 2008; Rehm, Patra & Popova, 2006). The DAA estimates for the oldest age groups and some causes of death, such as circulatory diseases, are particularly dependent on the methodological options regarding exposure to alcohol or the $RR_i$ chosen to cmeasure them (Marmet et al., 2016; Sherk, Thomas, Churchill & Stockwell, 2020; Trias-Llimós, Martikainen, Mäkelä & Janssen, 2018). Furthermore, the $RR_i$ used would most likely reflect the strength of the association between average consumption and mortality by cause in countries and time periods with different consumption patterns from those prevalent in Spain in the study period. Finally, it should be noted in this regard that when linking consumption to incidence, RRs do not normally differentiate between morbidity and mortality, so that sometimes reference is made to incidence of disease and not necessarily mortality. However, there is no alternative way to obtain these $RR_i$. A futher limitation is related to the practice of correcting for underestimation homogeneously across all participants in population surveys. If, as is likely, there are differences in the degree of underestimation according to sociodemographic factors or level of average daily alcohol use, this could bias the estimates of the total number of DAA, as well as its distribution by sociodemographic factors, cause of death and type of drinker.

As indicated, the purpose of this methodology is to serve as the basis for establishing a routine alcohol-attributable mortality indicator in Spain to help monitor the issue, starting with an analysis of the limitations of existing general health information systems. In this regard, statistics on alcohol consumption in population health surveys, as well as alcoholic beverage sales, need to be made more consistent and maintained over time. Frequent changes in the questionnaires of the National Health Survey during the period 2001-2017 in terms of the content and format of the questions on alcohol use, or the uncertainty associated with the data on sales of alcoholic beverages not subject to special tax (wine and cider) published by the TA or international institutions, made it extremely difficult to estimate the population's exposure to alcohol during this period. Adopting international instruments has not necessarily improved the situation because they are often not well adapted to the consumption patterns and types of beverages prevalent in Spain. Likewise, it would be helpful to determine the changes in the practices of certification and codification of causes of death in Spain, especially as regards circulatory diseases, in order to better interpret the findings on the changes in mortality attributable to alcohol by cause.

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## Conflict of interests

The authors declare no conflict of interest related to aspects discussed in this article.

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