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Supplementary appendix

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

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Contents

Supplemental methods

Study design

In this population-based study we calculated the impact of alcohol consumption on the incidence of cancer worldwide in 2020 using a Levin-based population attributable fraction (PAF) method¹ adapted from Shield et al. 2020², and based on a theoretical minimum-risk exposure of lifetime abstention from alcohol consumption. PAFs were estimated by combining data on alcohol consumption and the relative risk (RR) of developing cancer. Due to a delay between alcohol consumption and possible development of cancer, it is necessary to factor in a latency period between the year of alcohol exposure data and the year of cancer outcome. A 10-year latency period between exposure and cancer diagnosis was chosen based on an observed approximate latency period of 11 to 12 years for breast, colorectal, oral cavity, oesophageal (squamous cell carcinoma) and pharyngeal cancers and 8 to 9 years for laryngeal and liver cancers in a previous Canadian study, 3 and has been used in other PAF studies.^{2,4}

Selection of cancer sites and national incidence estimates

The selection of cancers included in this study was based on the most recent International Agency for Research on Cancer (IARC) monograph on personal habits for cancer types with sufficient evidence of a causal relationship with the consumption of alcoholic beverages (appendix p 6).⁵ The underlying cancer incidence estimates were taken from the GLOBOCAN 2020 database which models global burden of primary cancers based on data from several sources;⁶ highquality cancer registry data, new sources in sub-Saharan Africa retrieved through the African Cancer Registry Network, targeted searches for new registry data online, and the most recent mortality data from the WHO.⁷ For countries where high-quality population-based cancer registry data were lacking, complex methods incorporating other data sources such as national mortality records and averages from neighbouring countries were used.

Country-specific estimates of cancer cases for 2020 by sex and five-year age group (from 0–4 to 85 years of age and over) were obtained for: lip and oral cavity cancer (International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10] C00-06); pharyngeal cancer (C09-10, C12-C13); oesophageal cancer (C15); colon cancer (C18); rectal cancer (C19-20); liver cancer (C22); laryngeal cancer (C32); breast cancer (C50, only female); and all cancers combined excluding non-melanoma skin cancer (C00-C97 excl. C44). Due to the specific causality with hepatocellular carcinoma (HCC) and oesophageal squamous cell carcinoma (SCC), estimates of HCC (International Classification of Diseases for Oncology, 3rd edition [ICD-O-3] morphology codes 8170-8175) and oesophageal SCC (ICD-O-3 8050-8078, 8083-8084) were obtained from two studies that have estimated cases based on observed distributions of the histological subtypes of liver and oesophageal cancer using cancer registry data (liver cancer results: Rumgay H, unpublished).⁸ We included cancers of the stomach (C16) and pancreas (C25) in sensitivity analysis due to evidence suggesting a causal association with alcohol consumption in World Cancer Research Fund (WCRF) classifications but a lack of sufficient evidence in the IARC monograph classification (appendix $p \theta$).^{5,9} In our aim to quantify the burden of avoidable cancers we did not include the potential reduction in kidney cancer incidence despite probable evidence of a protective effect from alcohol intake of up to 30 $\frac{g}{day}$.⁹

Cancer risks related to alcohol consumption

For each cancer type included we took risk estimates for the association with alcohol consumption (measured per 10 grams increase in alcohol [as ethanol] consumed per day) from the systematic literature reviews conducted as part of the WCRF Continuous Update Project (appendix p 7).⁹ To obtain the HCC-specific risk estimate we conducted a randomeffects meta-analysis selecting the RRs from studies with HCC as the outcome which were presented in the liver cancer systematic literature review (appendix p 31).¹⁰ The variance of the linear RRs was calculated from their 95% confidence intervals. Due to the presence of a non-linear dose-response curve for oesophageal SCC, the RR function and variancecovariance matrix for oesophageal SCC risk were taken from Shield et al.,² originally obtained from Bagnardi et al. 2015.¹¹ The risks of colon and rectum cancers were modelled for alcohol consumption above 20 g per day based on the non-linear dose-response curve showing no significant increased risk of colorectal cancer at less than 20 g per day in the WCRF Continuous Update Project systematic review for colorectal cancer.¹² Similarly, the risks of pancreatic cancer and stomach cancer were modelled for alcohol consumption above 45 g per day only due to the decision made by WCRF that conclusions below this intake were not possible.⁹ Former drinking was included in sensitivity analysis using sex-specific RRs from the WCRF Continuous Update Project report¹⁰ for liver cancer, Schütze et al.¹³ for colon and rectal cancer, Marron et al.¹⁴ for upper aerodigestive cancers, and Corrao et al.¹⁵ for pancreas and stomach cancers, as previously described by Shield and colleagues.²

In terms of cancer risk by type of alcoholic beverage, there is little-to-no observed difference in the risk of cancer between consumption of beers, wines or spirits.⁹ With regards to differences by drinking patterns and the potential effect of heavy episodic drinking or binge drinking on cancer risk, it is believed that it is the total average intake of alcohol which is most at play with no difference whether this is spread over several occasions or consumed all at once.¹⁶ Further on drinking patterns, the risk of cancer may vary by changes in patterns of drinking over the life-course, or alcohol consumption trajectory, in individuals; a cohort study in Thailand with more than 30 years of follow-up observed double the cancer mortality in those who were consistent-regular drinkers throughout their life compared with consistentoccasional drinkers,¹⁷ but the risk of cancer among former heavy drinkers was not discussed. Cancer risk among former drinkers may vary by intensity and duration of past drinking. In our analysis we were not able to distinguish these discrepancies in the alcohol consumption data, although there is evidence that the elevated risk of head and neck cancer in former drinkers reduces back to that of lifetime abstainers after 20 years of quitting.¹⁴

Global prevalence of alcohol consumption

Alcohol consumption estimates for 2010 were obtained from the Global Information System on Alcohol and Health as adult per capita alcohol consumption in litres of alcohol per year by country disaggregated by age (15–19, 20–24, 25–34, 35–49, 50–64, and 65 years of age and older) and sex.¹⁸ The per capita alcohol consumption data, i.e. population level alcohol exposure data, were derived from three sources: recorded, unrecorded, and tourist per capita alcohol consumption. Recorded per capita data were based on production, sales, and taxation statistics;¹⁹ unrecorded per capita data were based on population surveys and expert opinion (measured through Delphi analysis).²⁰; and tourist per capita data were derived based on data from the World Tourism Organization. Per capita alcohol consumption estimates were corrected by a factor of 0·8 to take into account alcohol not consumed (wastage) and the under-reporting of alcohol consumption from population-based surveys being larger than that in risk relations studies;²¹ this correction factor of 0.8 was found to be appropriate by a recent systematic review of coverage of per capita alcohol consumption recorded in population surveys compared with that recorded in risk relations studies.²²

The distribution of daily adult alcohol consumption among past year drinkers was estimated using the methodology developed by Rehm and colleagues, 23 and Kehoe and colleagues, 24 whereby alcohol consumption distributions can be modelled using a Gamma distribution. This method assumes that there is a strong correlation between the mean and the standard deviation of the Gamma distribution where the standard deviation of the Gamma distribution for alcohol

consumption can be accurately estimated based on the mean of the Gamma distribution. We then estimated the scale and the shape parameter from the mean (μ) and the standard deviation (σ) of the Gamma distribution using Formula 1.

Formula 1

$$
\sigma = (1 \cdot 171 + 0 \cdot 087 \cdot \text{sex}) \cdot \mu
$$

In Formula 1, the coefficient of sex is 1 for women and 0 for men.

Estimation of population attributable fraction

PAFs were calculated for each age, sex, country, and cancer site by combining the age-, sex- and country-specific prevalence of current drinking (P_{CD}) with the cancer RRs (RR) . Amount of alcohol consumed for current drinking (x) was modelled with an upper integration limit of 150 g per day based on the observation that intakes greater than 150 g of alcohol per day are not sustained for a long period of time.²⁵ We modelled the contribution of different levels of alcohol consumption by splitting alcohol prevalence into three categories: moderate drinking (0·1 to 20 g per day, the equivalent of up to two alcoholic drinks per day), risky drinking (20 to 60 g per day, the equivalent of between two and six alcoholic drinks per day), and heavy drinking (>60 g per day, the equivalent more than six alcoholic drinks per day). We also split alcohol consumption by 10g per day increment from 0.1 to 10 g per day up to 140 to 150 g per day. Formula 2 was used to calculate PAFs for total current drinking and Formula 3 was used to estimate PAFs by the three categories of alcohol consumption and by 10 g increment by changing the lower and upper integration limits in the numerator appropriately, where *y* is the lower bound of the category and *z* is the upper bound.

Formula 2

$$
PAF = \frac{\int_{0.1}^{150} P_{CD}(x)(RR_{CD}(x) - 1)dx}{\int_{0.1}^{150} P_{CD}(x)(RR_{CD}(x) - 1)dx + 1}
$$

Formula 3

$$
PAF_{Category} = \frac{\int_{y}^{z} P_{CD}(x)(RR_{CD}(x) - 1)dx}{\int_{0.1}^{150} P_{CD}(x)(RR_{CD}(x) - 1)dx + 1}
$$

Former alcohol consumers have an elevated risk of cancer based on their lifetime alcohol consumption.⁹ However, the increase in cancer risk is thought to be heterogenous by country due to differences in alcohol consumption trajectories.²⁶ Accordingly, as country specific former drinker cancer risks are unknown, the elevated risk of cancer among former drinkers was not incorporated into the main analysis. As sensitivity analysis, the risk of cancer among former drinkers (P_{FD}) was calculated using Formula 4, and the PAF from current drinking and formerly drinking was subsequently recalculated using Formula 5.

Formula 4

$$
PAF_{FD} = \frac{P_{FD}(RR_{FD} - 1)}{P_{FD}(RR_{FD} - 1) + \int_{0.1}^{150} P_{CD}(x)(RR_{CD}(x) - 1)dx + 1}
$$

Formula 5

$$
PAF_{CD+FD} = \frac{P_{FD}(RR_{FD} - 1) + \int_{0.1}^{150} P_{CD}(x)(RR_{CD}(x) - 1)dx}{P_{FD}(RR_{FD} - 1) + \int_{0.1}^{150} P_{CD}(x)(RR_{CD}(x) - 1)dx + 1}
$$

To obtain estimates of alcohol-attributable cases the age-specific PAFs for each country, sex, and cancer site were applied to the cases of cancer in each five-year age group while factoring in the 10-year latency period; e.g. the PAF for laryngeal cancer in males for the 25–34 age group was applied to the number of cases of laryngeal cancer in males in the 35–39 and 40–44 age groups in each country. The PAFs for each cancer site and sex were calculated by summing the alcohol-attributable cases across all age groups then dividing by the total number of cases for all age groups combined. The total number of liver cancer cases was used as the denominator for the HCC calculations to obtain the PAF of total liver cancer, and the total number of oesophageal cancer cases was used as the denominator for the oesophageal SCC calculations.

Alcohol-attributable age-standardised incidence rates (ASIR) per 100 000 people were calculated using the age-, sex-, and country-specific number of alcohol-attributable cases in 2020, population estimates, and the Segi-Doll world standard.^{6,27} Countries were categorised into 17 world regions based on the United Nations definitions: Australia and New Zealand, Central and Eastern Europe, Eastern Africa, Eastern Asia, Latin America and the Caribbean, Melanesia, Micronesia and Polynesia, Middle Africa, North America, Northern Africa, Northern Europe, South-Central Asia, South-Eastern Asia, Southern Africa, Southern Europe, Western Africa, Western Asia, and Western Europe. Alcohol PAFs for 10 countries with missing alcohol prevalence data (French Guiana, French Polynesia, the State of Palestine, Guadeloupe, Guam, Martinique, New Caledonia, Puerto Rico, Reunion, and South Sudan) were imputed using the average age-, sexand cancer-specific PAFs from each pre-mentioned subregion they are located in. Subregion totals were subsequently recalculated including the imputed estimates of alcohol-attributable cases. We also grouped countries into the Human Development Index categories using the UN Development Programme human development data for 2019 (UNDP [http://www.hdr.undp.org/en/indicators/137506\)](http://www.hdr.undp.org/en/indicators/137506).

Estimates of uncertainty

Ninety five percent uncertainty intervals (95% UIs) were modelled using a Monte Carlo-like approach where 1 000 estimates of the drinking status, mean, and standard deviation of the alcohol consumption estimates and RRs were randomly simulated based on their respective uncertainty distributions. The methods explaining the creation of the variance and random samples of each parameter are further detailed by Gmel and colleagues.²⁸ These simulated estimates were used to create 1 000 PAF estimates using the formulae previously described. The 2·5th and 97·5th percentiles were taken from the 1 000 modelled PAF estimates to construct the 95% UIs.29

Appendix table 1. Summary of the classifications of evidence for a causal relationship between alcohol consumption and the risk of cancer by cancer site and organisation.

Appendix table 2. Relative risks and variance used for the alcohol-attributable fraction calculations

Appendix table 3. Global number of alcohol-attributable cancer cases, population attributable fraction, and agestandardised incidence rate of alcohol-attributable cases in 2020, by world region, Human Development Index, and sex

Appendix table 4. Number of alcohol-attributable cancer cases, population attributable fraction, and age-standardised incidence rate of alcohol-attributable cases in 2020, by country and sex. Number of cases suppressed if less than five.

Appendix table 5. Global number of alcohol-attributable cancer cases in 2020, by alcohol consumption category, world region, Human Development Index, and sex. Number of cases suppressed if less than five.

Numbers in parentheses are 95% Uncertainty Intervals. Cases and percentages may not sum due to rounding. HDI, Human Development Index Missing HDI assigned to the following countries: French Guiana, French Polynesia, Guadeloupe, Guam, Korea (the Democratic People's Republic of), Martinique, New Caledonia, Puerto Rico, Reunion, and Somalia.

Appendix table 6. Global number of alcohol-attributable cancer cases, by 10 g per day increase in alcohol consumption and sex.

Appendix figure 1. Dose-response meta-analysis per 10 g per day of alcohol intake and liver cancer stratified by hepatocellular carcinoma (HCC) or total liver cancer.

Appendix figure 2. Cancers attributable to alcohol consumption according to cancer site in males, females, and both sexes combined, in 2020.

Appendix figure 3. Population attributable fraction and age-standardised incidence rate of alcohol-attributable cancer cases in both sexes combined in 2020, by country.

Appendix figure 4. Age-standardised incidence rate (ASIR) of alcohol-attributable cancer cases by alcohol consumption category, sex, and world region.

Appendix figure 5. Cancers attributable to alcohol consumption according to cancer site and region, both sexes combined, in 2020.

References

1. Levin ML. The occurrence of lung cancer in man. *Acta-Unio Internationalis Contra Cancrum* 1953; **9**(3): 531- 41. 2. Shield K, Manthey J, Rylett M, et al. National, regional, and global burdens of disease from 2000 to 2016 attributable to alcohol use: a comparative risk assessment study. *The Lancet Public Health* 2020; **5**(1): e51-e61. 3. Grundy A, Poirier AE, Khandwala F, McFadden A, Friedenreich CM, Brenner DR. Cancer incidence attributable to alcohol consumption in Alberta in 2012. *CMAJ Open* 2016; **4**(3): E507-E14. 4. Praud D, Rota M, Rehm J, et al. Cancer incidence and mortality attributable to alcohol consumption. *International journal of cancer* 2016; **138**(6): 1380-7. 5. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 2012.

6. Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. 2020.<https://gco.iarc.fr/today> (accessed 15/12 2020).

7. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer statistics for the year 2020: an overview. *International journal of cancer* 2021; 1– 12. https://doi.org/10.1002/ijc.33588

8. Arnold M, Ferlay J, van Berge Henegouwen MI, Soerjomataram I. Global burden of oesophageal and gastric cancer by histology and subsite in 2018. *Gut* 2020; **69**(9): 1564-71.

9. World Cancer Research Fund/American Institute for Cancer Research. Diet, Nutrition, Physical Activity and Cancer: a Global Perspective. Continuous Update Project Expert Report, 2018.

10. World Cancer Research Fund International. Systematic Literature Review. The Associations between Food, Nutrition and Physical Activity and the Risk of Liver Cancer, 2015.

11. Bagnardi V, Rota M, Botteri E, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose– response meta-analysis. *British Journal Of Cancer* 2014; **112**: 580.

12. World Cancer Research Fund International. Systematic Literature Review. The Associations between Food, Nutrition and Physical Activity and the Risk of Colorectal Cancer, 2017.

13. Schütze M, Boeing H, Pischon T, et al. Alcohol attributable burden of incidence of cancer in eight European countries based on results from prospective cohort study. *BMJ* 2011; **342**: d1584.

14. Marron M, Boffetta P, Zhang Z-F, et al. Cessation of alcohol drinking, tobacco smoking and the reversal of head and neck cancer risk. *International journal of epidemiology* 2010; **39**(1): 182-96.

15. Corrao G, Bagnardi V, Zambon A, La Vecchia C. A meta-analysis of alcohol consumption and the risk of 15 diseases. *Preventive Medicine* 2004; **38**(5): 613-9.

16. Sarich P, Canfell K, Egger S, et al. Alcohol consumption, drinking patterns and cancer incidence in an Australian cohort of 226,162 participants aged 45 years and over. *British Journal of Cancer* 2021; **124**(2): 513-23.

17. Jankhotkaew J, Bundhamcharoen K, Suphanchaimat R, et al. Associations between alcohol consumption trajectory and deaths due to cancer, cardiovascular diseases and all-cause mortality: a 30-year follow-up cohort study in Thailand. *BMJ Open* 2020; **10**(12): e038198.

18. World Health Organization. Global Information System on Alcohol and Health. Geneva, Switzerland, 2019. 19. Poznyak V, Fleischmann A, Rekve D, Rylett M, Rehm J, Gmel G. The world health organization's global monitoring system on alcohol and health. *Alcohol Res* 2013; **35**(2): 244-9.

20. Probst C, Fleischmann A, Gmel G, et al. The global proportion and volume of unrecorded alcohol in 2015. *J Glob Health* 2019; **9**(1): 010421-.

21. Gmel G, Rehm J. Measuring Alcohol Consumption. *Contemporary Drug Problems* 2004; **31**(3): 467-540. 22. Stockwell T, Zhao J, Sherk A, Rehm J, Shield K, Naimi T. Underestimation of alcohol consumption in cohort studies and implications for alcohol's contribution to the global burden of disease. *Addiction* 2018; **113**(12): 2245-9.

23. Rehm J, Kehoe T, Gmel G, Stinson F, Grant B, Gmel G. Statistical modeling of volume of alcohol exposure for epidemiological studies of population health: the US example. *Population Health Metrics* 2010; **8**(1): 3.

24. Kehoe T, Gmel G, Shield KD, Gmel G, Rehm J. Determining the best population-level alcohol consumption model and its impact on estimates of alcohol-attributable harms. *Population Health Metrics* 2012; **10**(1): 6.

25. Gmel G, Shield KD, Kehoe-Chan TAK, Rehm J. The effects of capping the alcohol consumption distribution and relative risk functions on the estimated number of deaths attributable to alcohol consumption in the European Union in 2004. *BMC Medical Research Methodology* 2013; **13**(1): 24.

26. Bloomfield K, Stockwell T, Gmel G, Rehn N. International comparisons of alcohol consumption. *Alcohol Res Health* 2003; **27**(1): 95-109.

27. Doll R, Payne P, Waterhouse J. Cancer Incidence in Five Continents: A Technical Report. Berlin: Union for International Cancer Control, 1966.

28. Gmel G, Shield KD, Frick H, Kehoe T, Gmel G, Rehm J. Estimating uncertainty of alcohol-attributable fractions for infectious and chronic diseases. *BMC Medical Research Methodology* 2011; **11**(1): 48.

29. Koehler E, Brown E, Haneuse SJPA. On the Assessment of Monte Carlo Error in Simulation-Based Statistical Analyses. *Am Stat* 2009; **63**(2): 155-62.

30. World Cancer Research Fund International. Systematic Literature Review. The Associations between Food, Nutrition and Physical. Activity and the Risk of Mouth, Pharynx and Larynx cancer, 2016.

31. World Cancer Research Fund International. Systematic Literature Review. The Associations between Food, Nutrition and Physical Activity and the Risk of Breast Cancer, 2017.

32. World Cancer Research Fund International. Systematic Literature Review. The Associations between Food, Nutrition and Physical Activity and the Risk of Pancreatic Cancer, 2012.

33. World Cancer Research Fund International. Systematic Literature Review. The Associations between Food, Nutrition and Physical Activity and the Risk of Stomach Cancer, 2015.

34. Shield KD, Marant Micallef C, Hill C, et al. New cancer cases in France in 2015 attributable to different levels of alcohol consumption. *Addiction* 2018; **113**(2): 247-56.