Supplemental Online Content

Cunha AR, Compton K, Xu R, et al. The global, regional, and national burden of adult lip, oral, and pharyngeal cancer in 204 countries and territories: a systematic analysis for the Global Burden of Disease Study 2019. *JAMA Oncol*. Published online September 7, 2023. doi:10.1001/jamaoncol.2023.2960

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This supplemental material has been provided by the authors to give readers additional information about their work.

Supplement to: GBD 2019 Lip, Oral, and Pharyngeal Cancer Collaborators. The global, regional, and national burden of lip, oral, and pharyngeal cancer in 204 countries and territories: a systematic analysis for the Global Burden of Disease Study 2019.

This appendix provides further methodological detail for "The global, regional, and national burden of lip, oral, and pharyngeal cancer in 204 countries and territories: a systematic analysis for the Global Burden of Disease study 2019." This study complies with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) recommendations.¹ It includes detailed tables and information on data to maximize transparency in our estimation processes and provides a comprehensive description of analytical steps. A completed GATHER checklist can be found in the eMethods section.

Please note that portions of this supplement were copied from the supplementary content to the recent GBD publications:

Kocarnik J, Compton K, Dean FE, et al*.* Cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life years for 29 cancer groups from 2010 to 2019: a systematic analysis for the Global Burden of Disease Study 2019. *JAMA Oncol.* 2022; **8**(3): 420–444. doi:10.1001/jamaoncol.2021.6987.²;

Force LM, Abdollahpour I, Advani SM, et al. The global burden of childhood and adolescent cancer in 2017: an analysis of the Global Burden of Disease Study 2017. *Lancet Oncol.* 2019; **20**: 1211–25.3 ;

Vos T, Lim SS, Abbafati C, et al*.* Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; **396**: 1204–22. 4 ;

and

Murray CJL, Aravkin AY, Zheng P, et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; **396**: 1223–49.⁵

References are provided and renumbered for reproduced sections.

eMethods.

THE GLOBAL BURDEN OF DISEASE (GBD) STUDY

The Global Burden of Disease (GBD) study was created in an effort to establish comprehensive and comparable health metrics. A key principle in the GBD approach to estimation of disease burden is that an individual can have only one cause of death, while recognising that this may underestimate disease burden due to intermediate causes of death. In addition to reporting estimates of mortality and years of life lost (YLLs) for over 300 diseases and injuries, the GBD study also quantifies non-fatal components of disease including years lived with disability (YLDs) and disability-adjusted life-years (DALYs), a metric that represents a combination of both the fatal and non-fatal components of disease. The GBD approach uses all relevant data sources, rather than a single type of data. Finally, as there is continual methodological refinement with each GBD iteration, the results in each successive iteration [supersede the results of prior GBD studies for the entire newly estimated time series.](http://www.healthdata.org/sites/default/files/files/Projects/GBD/GBD_Protocol.pdf) A protocol for the GBD study can be found online at

http://www.healthdata.org/sites/default/files/files/Projects/GBD/GBD_Protocol.pdf.

GATHER¹ Guidelines Checklist

Part I – Burden of Diseases Analysis

1. Overview and definition of indicator

This article presents and details the estimates (incidence, mortality, and DALYs) produced by the GBD Study 2019 for two types of cancer: Lip and oral cavity cancer (LOC) and Other pharynx cancer (OPC). "Other pharynx cancer" is used throughout this appendix for consistency with the standard naming system of the GBD 2019 study, but the term is considered interchangeable with "other pharyngeal cancer" in the main text for the purpose of this analysis. Details on LOC and OPC coding by the International Classification of Diseases (ICD) ninth and tenth revisions^{6,7} can be found on pages 11 & 12 of this appendix. We present the estimates by sex, five-year GBD age group (20 to 24, 25 to 29, 30 to 34, etc. until 95+) and region, for the years 1990–2019. The report by region considered three geographic classifications: GBD super-regions (seven categories), GBD world regions (21 categories), and countries and territories ($n = 204$). The regions were also classified by Sociodemographic Index (SDI) quintiles, which is explained further in this appendix.

2. GBD causes of death database

For GBD 2019 Study, all available data on causes of death (CoD) are standardized and pooled into a single database used to generate cause-specific mortality estimates by age, sex, year, and region. Figures S1 and S2 (pages 1439 and 1440) of Appendix 1 of "Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019^{"4} present the high-level view of data inputs, analytical steps, and outputs of the CoD analysis frame. In this appendix, we will highlight the processes for cancer estimation in GBD, specifically for LOC and OPC.

3. Data sources

The GBD 2019 Study [synthesizes many data input sources, including surveys,](http://ghdx.healthdata.org/gbd-2019/data-input-sources) censuses, vital statistics, and other health-related data sources. The data from these sources are used to estimate morbidity, illness, and injury, and attributable risk for 204 countries and territories from 1990 to 2019, while mortality deaths are estimated from 1980 to 2019. The input sources are accessible through an interactive citation tool available in the GHDx: http://ghdx.healthdata.org/gbd-2019/data-input-sources.

3.1. Cancer registry (CR) data sources

Cancer incidence and mortality data were sought from individual population-based cancer registries, such as the Surveillance, Epidemiology, and End Results (SEER) Program⁸; provided by collaborators; or downloaded from aggregated databases of cancer registry data such as "Cancer Incidence in Five Continents" (CI5) $9-19$, NORDCAN²⁰, and EUREG²¹. Only population-based cancer registries were incl[uded, with inclusion criteria that th](http://ghdx.healthdata.org/gbd-2019)ey included all cancers (i.e., were not specialty registries), reported data for all age groups (except for pediatric cancer registries), and reported data for both sexes. Pathology-based cancer registries were included if they had a defined population. Hospital-based cancer registries were excluded. Redundant cancer registry data were excluded from either the final incidence data input or the MIR model input if a more detailed source (e.g., providing more detailed age or diagnostic groups) was available for the same population. Preference was given to registries with national coverage over those with only local coverage, except those from countries where the GBD study provides subnational estimates. Data were excluded if the coverage population was unknown, except for in high SDI quintile locations with full geographic coverage where the GBD population could be substituted. A list of the cancer registries included in our analysis and the years covered can be found in the online GBD citation tool http://ghdx.healthdata.org/gbd-2019.

3.2. Mortality-to-incidence ratio (MIR) data sources

Most cancer registries only report cancer incidence. However, if a cancer registry also reported cancer mortality, mortality data were also extracted. CR sources with matching incidence and mortality data were used in the mortality-to-incidence ratio estimation.²

3.3. Cancer mortality data in the cause of death (CoD) database other than cancer registry data

In addition to cancer registry data, the GBD cause of death (CoD) database also contains cancer mortality data originating from multiple sources, including vital registration (VR) and verbal autopsy (VA) data. Most of the cause of death data in GBD, including mortality from cancer, is vital registration data obtained from the World Health Organization (WHO) Mortality Database. VR is also obtained from country‐spe[cific mortality databases operated b](http://ghdx.healthdata.org/gbd-2019)y official offices. In countries without VR systems, VA studies are a viable data source to inform CoD. VA data are obtained by trained interviewers who use a standardized questionnaire to ask relatives about the signs, symptoms, and demographic characteristics of recently deceased family members. CoD is assigned based on the answers to the questionnaires. Each cause is coded directly to the most detailed CoD when possible, whereas cause codes in data tabulated by International Classification of Disease (ICD-) are coded to aggregated cause groups. A detailed description of the data sources and processing steps for the CoD database can be found in Section 2 (page 20), Appendix 1 of "Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019,"⁴ as well as in the online GBD citation tool http://ghdx.healthdata.org/gbd-2019.

3.4. Bias of categories of input cancer data

Potential biases of the input data included for the CoD database can also be found in the Supplementary Appendix 1 to the GBD 2019 paper "Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019."4 Cancer registry data can be biased in multiple ways. A high proportion of ill-defined cancer cases in the cancer registry data requires redistribution of these cases to other cancers, which introduces a potential for bias. Changes between coding systems can lead to artificial differences in disease estimates; however, we adjust for this bias by mapping the different coding systems to GBD cancer causes. Underreporting of cancers that require advanced diagnostic techniques can be an issue in cancer registries from low-income countries. On the other hand, misclassification of metastatic sites as primary cancer can lead to overestimation of cancer sites that are common sites for metastases. Since many cancer registries are located in urban areas, the representativeness of the registry for the general non-urban population can also be problematic. The accuracy of mortality data reported in cancer registries usually depends on the quality of the vital registration system. If the vital registration system is incomplete or of poor quality, the mortality-to-incidence ratio can be biased to lower ratios.

4. CoD cause-specific modeling descriptions – neoplasms

eFigure 1. Input data and methodological summary for mortality and Years of Life Lost (YLLs) for all cancers, including LOC and OPC Abbreviations: CoD, causes of death; CODEm, cause of death ensemble model; DB, database; DisMod-MR, disease model – Bayesian meta-regression; HAQ Index, Healthcare Access and Quality Index; ICD, International Classification of Diseases; ST-GPR, spaciotemporal Gaussian process regression; MIR, mortality-to-incidence ratio; NASH, nonalcoholic steatohepatitis; VR, vital registration; YLL, years of life lost

4.1 Cancer registry data processing

Cancer registry data went through multiple processing steps before entering the CoD database,

1. Formatting incidence and mortality data. First, the original data are transformed into standardized files, which included standardization of format, categorization, and registry names $(#1$ in eFigure 1).

2. Subtotal recalculation. Some cancer registries report individual codes as well as aggregated totals. An example of this would be where the registry data reports C18, C19, and C20 individually, and also the aggregated group of C18–C20 (colon and rectum cancer). The data processing step, "subtotal recalculation" (#2 in eFigure 1), verifies these totals and subtracts the values of any individual codes from the aggregates.

3. Mapping data to GBD causes. In the third step (#3 in eFigure 1), cancer registry incidence data and cancer registry mortality data are mapped to GBD causes. A different map is used for incidence and for mortality data because of the assumption that there are no deaths for certain cancers. One example is benign or in situ neoplasms. Because cancer registries do not collect nonmalignant neoplasms in a standardized way, any benign or in situ neoplasms reported in a cancer registry incidence dataset are dropped from that dataset. The same neoplasms reported in a cancer registry mortality dataset are instead mapped to the respective invasive cancer. Maps of ICDcodes to GBD LOC and OPC causes for incidence and mortality data can be found in eTable 1. A full list of ICD mapping to all cancers estimated in the GBD study can be found in eTables 1 & 2 in the Supplementary Appendix to "Cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life years for 29 cancer groups from 2010 to 2019: a systematic analysis for the Global Burden of Disease Study 2019."2

eTable 1. List of International Classification of Diseases (ICD) codes mapped to the Global Burden of Disease causes Lip and oral cavity cancer and Other pharynx cancer for cancer incidence data

Cause	ICCC3	ICD-10	$ICD-9$
Lip and oral cavity cancer	XIf1	C00, C00.0, C00.1, C00.2, C00.3, C00.4, C00.5, C00.6, C00.8, C00.9, C01, C01.9, C02, C02.0, C02.1, C02.2, C02.3, C02.4, C02.8, C02.9, C03, C03.0, C03.1, C03.9, C04, C04.0, C04.1, C04.8, C04.9, C05, C05.0, C05.1, C05.2, C05.8, C05.9, C06, C06.0, C06.1, C06.2, C06.8, C06.80, C06.89, C06.9, C07, C07.0, C07.9, C08, C08.0, C08.1, C _{08.8} , C _{08.9}	140, 140.0, 140.1, 140.2, 140.3, 140.4, 140.5, 140.6, 140.7, 140.8, 140.9, 141, 141.0, 141.1, 141.2, 141.3, 141.4, 141.5, 141.6, 141.8, 141.9, 142, 142.0, 142.1, 142.2, 142.3, 142.8, 142.9, 143, 143.0, 143.1, 143.8, 143.9, 144, 144.0, 144.1, 144.4, 144.8, 144.9, 145, 145.0, 145.1, 145.2, 145.3, 145.4, 145.5, 145.6, 145.8, 145.9
Other pharynx cancer	NA	C09, C09.0, C09.1, C09.8, C09.9, C1, C10, C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, C10.9, C12, C12.0, C12.9, C13, C13.0, C13.1, C13.2, C13.8, C _{13.9}	146, 146.0, 146.1, 146.2, 146.3, 146.4, 146.5, 146.6, 146.7, 146.8, 146.9, 148, 148.0, 148.1, 148.2, 148.3, 148.4, 148.5, 148.8, 148.9

4. Age/sex splitting. In the fourth data processing step (#4 in eFigure 1), cancer registry data are standardized to the GBD age groups. For each cancer, the minimum age group estimated was determined as the youngest age-group where SEER reported at least 50 cases over the period 1990 to 2015.⁸ The modeled starting and ending age groups for each cancer included in this analysis are reported in eTable 2. Reference global age-specific incidence rates are generated using hospital inpatient data as described in Section 4.3 of the appendix to the GBD 2019 paper "Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019."4 Reference age-specific mortality rates were generated using aggregated deaths from processed VR data, using the approach described in Section 2.5 of the appendix to the aforementioned GBD 2019 paper.

For incidence or mortality datasets that require age-splitting, age-specific proportions are then generated by applying the reference age-specific rates to the registry population to produce the expected number of cases (or deaths for a mortality dataset) for that registry by age. The expected number of cases (or deaths) for each sex, age, and cancer were normalized to 1, creating final, age-specific proportions. These proportions were then applied to the total number of cases (or deaths) by sex and cancer to get the GBD age group-specific number of cases (or deaths) related to that dataset.

In the rare case that the cancer registry only contains data for both sexes combined, the agespecific cases or deaths are split and reassigned to separate sexes using the same weights that are used for the age-splitting process. Starting from the expected number of deaths, global proportions are generated by sex for each age. For example, if for ages 15–19 years old there are 6 expected deaths for males from cause of death data and 4 expected deaths for females, then 60% of the combined-sex deaths for ages 15–19 years would be assigned to males and the remaining 40% would be assigned to females.

5. Cause disaggregation. In the fifth step (#5 in eFigure 1), data for cause entries that are aggregates of GBD causes were redistributed across those GBD causes. Examples of these aggregated causes include some cancer registries reporting ICD-10 codes C00-C14 together as "lip, oral cavity, and pharyngeal cancer." These groups are broken down into subcauses that can be individually mapped to single GBD causes. In this example, the more specific ICD-10 codes within C00–C14 are "lip and oral cavity cancer" (C00–C08), "nasopharynx cancer" (C11), "cancer of other parts of the pharynx" (C09–C10, C12–C13), and "Malignant neoplasm of other and ill-defined sites in the lip, oral cavity, and pharynx" (C14). To redistribute the data, weights were created using the same "rate-applied-to-population" method employed in age-sex splitting (see step four above). For the undefined code (C14 in the example) an "average all cancer" weight was used, calculated on the high-quality cancer registry data from $SEER^{8}/NORDCAN^{20}/CIS^{9-19}$ by dividing the sum of the cases across these registries by the combined population across these registries. Then, proportions were generated by subcause for each aggregate cause as in the sexsplitting example above (see step four). The total number of cases from the aggregated group (C00–C14) was recalculated for each subgroup and the undefined code (C14). C14 was then redistributed as a "garbage code" in step six.

*6. Redistribution***.** In the sixth step (#6 in eFigure 1), unspecified ICD codes ("garbage codes") such as "ill-defined cancer site" (for example, C76 or C80) are redistributed across relevant causes estimated within the GBD hierarchy. Redistribution of cancer registry incidence and mortality data mirrored the process of the redistribution used in the cause of death database and utilized the same redistribution maps as specified in Section 2.4 of the Supplementary Appendix 1 to the GBD 2019 Diseases and Injuries capstone, "Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019."4 Sources and targets of garbage codes can be found in eTable 6 of the Supplementary Appendix to "Cancer Incidence, Mortality, Years of Life Lost, Years Lived with Disability, and Disability-Adjusted Life Years for 29 Cancer Groups from 2010 to 2019: A Systematic Analysis of Cancer Burden Globally, Nationally, and by Socio-demographic Index for the Global Burden of Disease Study 2019."2

7. Removal of duplicates. In the seventh step (#7 in eFigure 1), duplicate or redundant data sources were removed from the processed cancer registry dataset. Duplicate sources were present if, for example, a cancer registry was part of the CI5 database but we also had data from that registry directly. Redundancies occurred and were removed as described in "Cancer Incidence Data Sources," where more detailed data were available, or when national registry data could replace regionally representative data. From here, two parallel selection processes were run; one to generate input data for the mortality-to-incidence ratio (MIR) models, and one to generate incidence for final mortality estimation. When creating the final incidence input, higher priority was given to registry data from the most standardized source; whereas for the MIR model input, only sources that reported both incidence and mortality were used.

8. Combine matching incidence and mortality data and model MIRs. In the eighth step (#8 in eFigure 1), the processed incidence and mortality data from cancer registries were matched by cancer cause, age, sex, year, and location to generate MIRs. The resulting MIRs were used as input for a three-step modeling approach using the general GBD spatiotemporal Gaussian process regression (ST-GPR⁵) approach, with the Healthcare Access and Quality (HAQ) Index as a covariate in the linear mixed effects model using logit transformed MIR as outcome.²²

$$
logit(MIR_{c,a,s,t}) = \alpha + \beta_1(HAQIndex_{c,t}) + \sum_{a}^{A} \beta_2 I_a + \beta_3 I_s + \epsilon_{c,a,s,t}
$$

MIR: mortality-to-incidence ratio

c: country (or subnational for subnationally modeled locations), a: age group, t: time (years); s: sex

HAQ Index: Healthcare Access and Quality Index I: indicator variable $\epsilon_{c,a,s,t}$: error term

Information on ST-GPR can be found in "Section 4.3.3: Spatiotemporal Gaussian process regression (ST-GPR) modeling" in Supplementary Appendix 1 to "Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019."4 Predictions were made without the random effects. The ST-GPR model has three main hyper-parameters that control for smoothing across time, age, and geography.4 These hyper-parameters were adjusted for GBD 2019 in order to improve model performance in locations with sparse data. The time adjustment parameter lambda (λ) aims to borrow strength from neighboring time points (i.e., the value in this year is highly correlated with the value in the previous year but less so further back in time). For GBD 2019, lambda was lowered from 2 to 0.05, increasing the weight of more distant years. The age adjustment parameter omega (ω) borrows strength from data in neighboring age groups and was lowered from 1.0 to

0.5, increasing the weight of more distant age groups. The space adjustment parameter zeta (ξ) aims to borrow strength across the hierarchy of geographical locations. Zeta was lowered from 0.95 to 0.01, reducing the weight of more distant geographical data at the region or super region level. For the remaining parameters in the Gaussian process regression, we lowered the amplitude from 2 to 1 (reducing fluctuation from the mean function) and reduced the scale value from 15 to 10 (reducing the time distance over which points are correlated).

Data-cleaning steps for MIR estimation were similar to those for GBD 2017. For each cancer, MIRs from locations in HAQ Index quintiles 1–4 were dropped if they were below the median of MIRs from locations in HAQ Index quintile 5. We also dropped MIRs from locations in HAQ Index quintiles 1–4 if the MIRs were above an outlier threshold calculated as the third quartile + 1.5 * IQR (inter-quartile range). We dropped all MIR data that were based on fewer than 15 incident cases to avoid excessive variation in the ratio due to small numbers (this threshold was 25 cases in GBD 2017, but was lowered in GBD 2019 in order to include additional data). For the lower end of the age spectrum where cancers are generally rarer, we also aggregated incidence and mortality to the youngest five-year age bin where $SEER⁸$ reported at least 50 cases from 1990 to 2015, to avoid unstable MIR predictions in young age groups because of too few data. The MIR estimates in this SEER-based minimum age-bin were then copied down to all younger GBD age groups estimated for that cancer.

Since MIRs can be above 1, especially in older age groups and cancers with low cure rates, we used the 95th percentile (by age group) of the cleaned dataset (detailed above) to cap the MIR input data. These "upper cap" values were used to allow MIRs over 1 in some age groups but to constrain the MIRs to a maximum level. Any MIR values over this cap were Winsorized to the cap value. To run the logit model, the input data were first divided by the upper caps to get proportional data ranging from 0 to 1. Model predictions from ST-GPR were then rescaled back by multiplying them by the upper caps. To constrain the MIRs at the lower end, we used the fifth percentile of the cancer and age-specific cleaned MIR input data to Winsorize all model predictions below this lower cap.

9. Generate mortality estimates from incidence and MIRs. Final estimated MIRs were matched with the cleaned cancer registry incidence dataset finalized in the ninth step (#9 in eFigure 1) to generate mortality estimates (#10 in eFigure 1):

$$
MIR_{estimates} * incidence_{registry} = mortality_{CR\ inputs}
$$

These mortality estimates were then smoothed by a Bayesian noise-reduction algorithm (to deal with zero counts; this is also applied to the VR and VA data), as specified in Section 2.14 of the Supplementary Appendix 1 to the GBD 2019 paper "Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019."⁴ These data were uploaded into the CoD database as CR data (#11 in eFigure 1). Cancer-specific mortality modeling then followed the general CODEm process²³ using the totality of VA, VR, and CR data.

4.2 Causes of death (CoD) data processing

Formatting of data sources for the cause of death (CoD) database, including VR and VA data, is similar to many of the steps outlined above for CR data (#11 in eFigure 1) and is described in Section 2 of the Supplementary Appendix 1 to the GBD 2019 paper "Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019."4

VA data may not capture cancer deaths as accurately or comprehensively as cancer registries or vital registration systems, but provides a useful contribution to cancer models in locations without VR or CR data. Additional processing and restrictions are performed on VA to ensure quality standards and feasible inputs. More details on VA data processing are provided in the appendix noted above, particularly Sections 2.2 (VA overview), 2.10 (VA cause restrictions), 2.14 (noise reduction), 2.15 (outlier identification), and 2.16 (data quality ratings).

5. CODEm overview

Cause of death ensemble modeling (CODEm) is the framework used to model most cause-specific death rates in the GBD. It relies on four key components:

- 1. All available data are identified and gathered to be used in the modeling process. Although the data may vary in quality, they all contain some signal of the true epidemiological process.
- 2. A diverse set of plausible models are developed to capture well-documented associations in the estimates. Using a wide variety of individual models to create an ensemble predictive model has been shown to outperform techniques using only a single model both in CoD estimation and in more general prediction applications.
- 3. The out-of-sample predictive validity is assessed for all individual models, which are then ranked for use in the ensemble modeling stage.
- 4. Differently weighted combinations of individual models are evaluated to select the ensemble model with the highest out-of-sample predictive validity.

Separate models are run for different age ranges, when applicable. Restrictions were applied on age by each cancer type in GBD 2019 according to eTable 2.

Cause	Minimum Age	Maximum Age
Lip and oral cavity cancer		None
Other pharynx cancer	20	None

eTable 2. Age restrictions for LOC and OPC in GBD 2019 modeling

Additionally, separate models are developed for countries with extensive, complete, and representative VR for every cause to ensure that uncertainty can better reflect the more complete data in these locations.

To ensure the addition of subnational locations are not driving changes in estimates, in GBD 2019, we run a global model that excludes data from non-standard locations; the resulting covariate betas are then used as priors for the true global model.

5.1. Model pool development

Because many factors may co-vary with any given CoD, a range of plausible statistical models are developed for each cause. In the CODEm framework, four families of statistical models are used: linear mixed effects regression (LMER) models of the natural log of the cause-specific death rate, LMER models of the logit of the cause fraction, spatiotemporal Gaussian process regression (ST-GPR) models of the natural logarithm of the cause-specific death rate, and ST-GPR models of the logit of the cause fraction. For each family of models, all plausible relationships between covariates and the response variable are identified. Because all possible combinations of selected covariates are considered for each family of models, multi-collinearity between covariates may produce implausible signs on coefficients or unstable coefficients. Each combination is therefore tested for statistical significance (covariate coefficients must have a coefficient with p-value < 0.05) and plausibility (the coefficients must have the directions expected based on the literature). Only covariate combinations meeting these criteria are retained. This selection process is run for both cause fractions and death rates, then ST-GPR and LMER-only models are created for each set of covariates.

5.2. Data variance estimation

The families of models that go through ST-GPR incorporate information about data variance. The main inputs for a Gaussian process regression (GPR) are a mean function, a covariance function, and data variance for each data point. For GBD 2019, we have updated this calculation to incorporate garbage code redistribution uncertainty.

Three components of data variance are now used in CODEm: sampling variance, non-sampling variance, and garbage code redistribution variance. The computation of sampling variance and nonsampling variance has not changed since previous iterations of the GBD. Garbage code redistribution variance is computed in the CoD database process described in Section 2.7 (page 31) of the Appendix 1 of "Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019."4 Since variance is additive, we calculate total data variance as the sum of sampling variance, nonsampling variance, and redistribution variance. Increased data variance in GPR results in the GPR draws not following the data point as closely.

5.3. Testing model pool on 15% sample

The performance of all models (individual and ensemble) is evaluated by means of out-of-sample predictive validity tests. Thirty percent of the data are randomly excluded from the initial model fits. These individual model fits are evaluated and ranked by using half of the excluded data (15% of the total), then used to construct the ensembles on the basis of their performance. Data are held out from the analysis on the basis of the cause-specific missingness patterns for ages and years across locations. Out-of-sample predictive validity testing is repeated 20 times for each model, which has been shown to produce stable results. These performance tests include the root mean square error (RMSE) for the log of the cause-specific death rate, the direction of the predicted versus actual trend in the data, and the coverage of the predicted 95% UI.

5.4. Ensemble development and testing

The component models are weighted on the basis of their predictive validity rank to determine their contribution to the ensemble estimate. The relative weights are determined both by the model ranks and by a parameter ψ , whose value determines how quickly the weights taper off as rank decreases. The distribution of ψ is described in more detail in Foreman et al.²³ A set of ensemble models is then created by using the weights constructed from the combinations of ranks and ψ values. These ensembles are tested by using the predictive validity metrics described in Section "Testing model pool on 15% sample" on the remaining 15% of the data, and the ensemble with the best performance in out-of-sample trend and RMSE is chosen as the final model.

5.5. Final estimation

Once a weighting scheme has been chosen, 1000 draws are created for the final ensemble, and the number of draws contributed by each model is proportional to its weight. The mean of the draws is used as the final estimate for the CODEm process, and a 95% UI is created from the 0.025 and 0.975 quantiles of the draws. The validity of the UI can be checked via its coverage of the out-of-sample data; ideally, the 95% UI would capture 95% of these data. Higher coverage suggests that the UIs are too large, and lower coverage suggests overfitting.

5.6. Model-specific covariates

Modelers select covariates to be used in CODEm, but those covariates may not be significant or in the direction specified during the covariate selection step of CODEm and will therefore not be used in the model. Additionally, covariates may be selected by CODEm but only exist in submodels that perform poorly and may end up with zero draws included in the final ensemble. CODEm covariates used, level of covariate, and expected direction of covariate by cause, sex, and age for the cancers relevant to this analysis can be found in eTables $3 \& 4$ below; a comprehensive list for all causes of death modeled in the GBD 2019 study can be found in Table S16, page 1570, in Appendix 1 of "Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019."⁴

eTable 3. Covariates for lip and oral cavity cancer

Lag-distributed income per capita (I\$): gross domestic product per capita that has been smoothed over the preceding 10 years;

Summary exposure value (SEV): for definitions and calculations, please see Section 2.6: "Step 5. Estimate summary exposure values" in the Supplementary Appendix 1 to "Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019"⁵; covariates with "C" following a cancer site name refer to a cancer site (e.g., uterus $C =$ uterus cancer) and were shortened due to space limitations in covariate names.

Level	Covariate	Direction
1	Alcohol (liters consumed per capita)	
	Smoking prevalence	$^{+}$
	Log-transformed summary exposure value (SEV) scalar for other pharynx cancer	$+$
$\overline{2}$	Cumulative cigarettes (5 years)	$^{+}$
	Age- and sex-specific SEV for low fruits	$^{+}$
	Age- and sex-specific SEV for low vegetables	$^{+}$
	Population density (over 1000 ppl/sqkm, proportion)	$^{+}$
	Population density (under 150 ppl/sqkm, proportion)	$^{+}$
	Healthcare access and quality index	
3	Education (years per capita)	
	Lag-distributed income (I\$ per capita)	$^{+}$
	Socio-demographic Index	$^{+}$

eTable 4. Covariates for other pharynx cancer

Lag-distributed income per capita (I\$): gross domestic product per capita that has been smoothed over the preceding 10 years;

Summary exposure value (SEV): for definitions and calculations, please see Section 2.6: "Step 5. Estimate summary exposure values" in the Supplementary Appendix 1 to "Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019¹⁵; covariates with "C" following a cancer site name refer to a cancer site (e.g., uterus $C =$ uterus cancer) and were shortened due to space limitations in covariate names.

6. CoDCorrect

CODEm models estimate the individual cause-level mortality without taking into account the independently modeled all-cause mortality (#13 in eFigure 1). To ensure that all single causes add up to the all-cause mortality and that all child-causes add up to the parent cause, an algorithm called "CoDCorrect" is used (#14 and #15 in eFigure 1). Further details on the CoDCorrect algorithm can be found in Section 3.3.2 of the Supplementary Appendix 1 to the GBD 2019 paper "Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019.⁴⁴ Final mortality estimates at the 1000-draw level provide an estimated mean mortality with 95% uncertainty interval.

7. Years of life lost calculation

To calculate years of life lost (YLLs), final death estimates after CoDCorrect adjustment are multiplied by the standard GBD life expectancy given the age at death, sex, and location. Further details on GBD life expectancy values can be found in the GBD 2019 paper "Global age-sexspecific fertility, mortality, health life expectancy (HALE), and population estimates in 204 countries and territories, 1950–2019: a comprehensive demographic analysis for the Global Burden of Disease Study 2019."24 Uncertainty is propagated from the CoDCorrect mortality estimates, calculating YLLs for each of the 1000 CoDCorrect draws to provide estimated mean YLLs with corresponding 95% uncertainty intervals.

8. Non-fatal cause-specific modeling descriptions

eFigure 2. Flowchart of GBD cancer incidence and Years Lived with Disability (YLDs) estimation, including LOC and OPC.

Abbreviations: GBD, Global Burden of Disease Study; MIR, mortality-to-incidence ratio; SEER, Surveillance, Epidemiology and End Results Program; YLD, years lived with disability.

8.1 Incidence estimation

The final GBD cancer mortality estimates (after CoDCorrect adjustment) were transformed to incidence estimates by using the MIRs specific to that cancer cause (#1 in eFigure 2). Final mortality estimates at the 1000-draw level were divided by the modeled MIR estimates (also at the 1000-draw level) to generate 1000 draws of incidence estimates (which provides an estimated mean incidence with 95% uncertainty interval). It was assumed that uncertainty in the MIRs is independent of uncertainty in the estimated mortality.

8.2 Prevalence estimation

After transforming the final GBD cancer mortality estimates to incidence estimates (step 1 in eFigure 2), incidence was combined with annual relative survival estimates from 1 to 10 years after diagnosis (step 7 in eFigure 2). Previous reports suggest that the value of $(1 - MIR)$ may serve as a proxy for 5-year relative survival, with the exact correlation varying slightly by cancer type.²⁵ Because this correlation varies, we trained cancer-specific prediction models to estimate 5-year survival from MIRs, using data from SEER.⁸ We used SEER*Stat²⁶ to obtain mortality, incidence, and relative survival statistics from the nine SEER registries reporting from 1980–2014 (step 2), by cancer type, sex, 5-year blocks (i.e., 1980–84, 1985–1989, etc.), and 5-year age groups (except combining 80+). For each cancer, we modelled SEER 5-year relative survival using MIRs calculated from SEER mortality and incidence. For GBD 2019 we updated this model from the Poisson regression used in GBD 2017²⁷ to using a generalized linear model with a quasibinomial family and logit link, weighted by the number of index cases (step 3 in eFigure 2). To reduce variability due to small samples, we only included MIRs based on at least 25 incident cases (except for the cancers mesothelioma, nasopharynx cancer, and acute lymphoid leukemia, where MIRs based on at least 10 cases were included). These models were then applied to the GBD MIR estimates to predict an estimated 5-year survival for each age/sex/year/location (step 4). To prevent unrealistic values, predicted 5-year survival values were Winsorized to be between 0% and 100% survival.

To generate yearly survival estimates up to 10 years, we downloaded $SEER⁸$ sex- and age-specific annual 1- through 10-year relative survival data from persons diagnosed between 2001 and 2010 (2001 through 2010 so that all cases had at least 5 years of follow-up, with half having the full 10 years of follow-up). This is updated from GBD 2017, where we downloaded all-ages survival data from persons diagnosed in 2004 (2004 so that all cases had the full 10 years of follow-up²⁸). A proportional scalar was calculated as the predicted GBD 5-year survival estimate divided by the SEER 5-year survival statistic, and was then used to generate yearly survival estimates by scaling the 1–10 year SEER curve to the GBD survival predictions under the proportional hazard assumption (step 5).

The estimated relative survival is next transformed into absolute survival estimates (steps 6 and 7 in eFigure 2). To account for background mortality in the relative survival estimates, GBD 2019 lifetables were used to calculate lambda (λ) values²⁴:

$$
\lambda = \frac{\ln\left(\frac{nLx_n}{nLx_{n+1}}\right)}{5}
$$

 nLx = person-years lived between ages x and $x+n$ (from GBD lifetable).

Absolute survival was then calculated using an exponential survival function:

absolute survival = relative survival *
$$
e^{\lambda * t}
$$

 $t =$ time (in years)

Absolute survival is combined with incidence to estimate the prevalence at each year after diagnosis, which is then split into the four sequelae **(**step 8 in eFigure 2). For the purposes of calculating disability due to cancer, survivors beyond 10 years were considered cured.

For this group, the survivor population prevalence was divided into two sequelae (1. diagnosis and primary therapy; 2. controlled phase). For the population that did not survive beyond 10 years, the yearly prevalence was divided into the four sequelae by assigning the fixed durations for each of the diagnosis and primary therapy phase, metastatic phase, and terminal phase, and assigning the remaining prevalence to the controlled phase (step 8 in eFigure 2). eTable 5 lists the duration of each, along with the sources used to determine their length.

Phase	Lip and oral cavity cancer*	Other pharynx cancer*
(1) Diagnosis and primary treatment	5.3^{29}	5.329
(2) Controlled	Calculated based on the remainder of time after attributing other sequelae	Calculated based on the remainder of time after attributing other sequelae
(3) Metastatic	9.330	7.9^{30}
(4) Terminal		

eTable 5. Duration (months) of each sequalae for LOC and OPC

* Superscripts refer to references used to inform these values.

Lastly, the general sequelae prevalence were multiplied with their respective disability weights (eTable 6) to obtain the number of YLDs (steps 11 and 12 in eFigure 2). In brief, disability weights are created from survey data to represent the magnitude of health loss associated with an outcome. These disability weights range from 0, implying a state equivalent to full health, to 1, a state equivalent to death. The sum of these YLDs is the final YLD estimate associated with each cancer.

Health state	Lay description	Disability weight (95% uncertainty interval)	
Cancer, diagnosis and primary therapy All cancers	This person has pain, nausea, fatigue, weight loss and high anxiety.	0.288 $(0.193 \text{ to } 0.399)$	
Cancer, controlled phase All cancers	This person has a chronic disease that requires medication every day and causes some worry but minimal interference with daily activities.	0.049 $(0.031 \text{ to } 0.072)$	
Cancer, metastatic All cancers	This person has severe pain, extreme fatigue, weight loss and high anxiety.	0.451 $(0.307 \text{ to } 0.600)$	
Terminal phase, with medication All cancers	This person has lost a lot of weight and regularly uses strong medication to avoid constant pain. The person has no appetite, feels nauseous, and needs to spend most of the day in bed.	0.540 $(0.377 \text{ to } 0.687)$	

eTable 6. Lay description of cancer states and corresponding disability weights

9. Estimation process for DALYs

To estimate DALYs for GBD 2019, we started by estimating cause‐specific mortality and non‐fatal health loss. For each year for which YLDs have been estimated, we computed DALYs by adding YLLs and YLDs for each age-sex-location. Uncertainty in YLLs was assumed to be independent of uncertainty in YLDs. We calculated 1000 draws for DALYs by summing the first draw of the 1000 draws for YLLs and YLDs and then repeating for each subsequent draw. 95% UIs were computed by using the 25th and 975th ordered draw of the DALY uncertainty distribution. We calculated DALYs as the sum of YLLs and YLDs for each cause, location, age group, sex, and year.

10. Reporting Standards

The GBD world population age standard was used to calculate age-standardized rates presented throughout GBD. In GBD 2019, we used the non-weighted mean of the GBD year's age-specific proportional distributions for national locations with populations greater than 5 million in the GBD year to update the world population age standard.²⁴ The final values used for the age standard are specified in Appendix Table 13 of the GBD 2019 paper "Global age-sex-specific fertility, mortality, health life expectancy (HALE), and population estimates in 204 countries and territories, 1950–2019: a comprehensive demographic analysis for the Global Burden of Disease Study 2019."24

11. Socio-demographic Index (SDI) definition and calculation

Socio-demographic Index (SDI) is a summary indicator to represent background levels of social and economic conditions that can influence health outcomes in a given location. This summary indicator comprises three indices: lag-distributed income per capita, mean education for those aged 15 years or older, and total fertility rate for those younger than 25 years of age. Possible values for each of these three indices range from 0 to 1, representing the bounds with which lower or higher values of the level of development for that index would no longer worsen or improve health outcomes, respectively. The composite SDI is the geometric mean of these three indices for a given location-year. For reporting purposes, values were multiplied by 100 to obtain SDI on a scale of 0 to 100. The SDI cutoffs for determining SDI quintiles for analysis were computed by using the country-level estimates of SDI for the year 2019, excluding countries with populations less than 1 million. For GBD 2019 analyses, all locations are assigned to these quintiles according to their SDI value in the year 2019. See Section 6 in Supplementary Appendix 1 to the GBD 2019 Diseases & Injuries capstone⁴ for more details regarding SDI estimation, and page 54 of this Appendix for the SDI quintile estimate for each country or territory in the GBD 2019 study.

12. Uncertainty estimation

Uncertainty in cancer estimates begins with the availability of and variability in cancer cause-specific data by age, sex, location and year. The uncertainty in cancer mortality estimates arises from CODEm and CoDCorrect. For more information see the CODEm methodology paper by Foreman et al., and Supplementary Appendix 1 to "Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019."4,23 Uncertainty in cancer incidence estimates results from both the uncertainty in mortality estimates as well as the uncertainty in the

MIR estimates, which result from the ST-GPR models. Uncertainty from the mortality estimates and the MIRs were assumed to be independent. Cancer prevalence uncertainty results from both the incidence uncertainty as well as the uncertainty from survival estimates. These were assumed to be independent. Uncertainty in cancer YLD estimation results from the uncertainty in the prevalence of each cancer sequela and uncertainty in the disability weight and is propagated into the final comorbidity-corrected YLD result. The uncertainty in prevalence and the uncertainty in disability weights are assumed to have no correlation. Cancer YLL uncertainty results from uncertainty in mortality estimates as well as uncertainty in life expectancy estimates. Uncertainty in cancer DALY estimates results from the uncertainty in YLLs and the uncertainty in YLDs, which were assumed to be independent. The same technique for propagating uncertainty elsewhere in the GBD study is applied in the cancer estimation process. In brief, the distribution of each step in the computation process is stored in 1000 draws. The distributions are determined from the data input sampling error, the uncertainty of the model coefficients, and the uncertainty of severity distributions and disability weights. The 1000 draws are used for every step in the process, with final estimates computed using the mean estimate across 1000 draws. The 95% uncertainty intervals are determined by the 25th and 975th ranked values across all 1000 draws. ⁴ More specific information regarding uncertainty intervals can be found in the GBD 2019 capstone papers.^{4,5,24}

13. Limitations

There are certain limitations to consider when interpreting the GBD mortality cancer estimates. First, even though every effort is made to include the most recently available data for each country, data seeking resources are not limitless and new data cannot always be accessed as soon as they are made available. It is therefore possible that the GBD study does not include all available data sources for cancer incidence or cancer mortality. Second, different redistribution methods can potentially change the cancer estimates substantially if the data sources used for the estimated location contain a large number of undefined causes; however, neglecting to account for these undefined deaths would likely introduce an even greater bias in the disease estimates. Third, using mortality-to-incidence ratios to transform cancer registry incidence data to mortality estimates requires accurate MIRs. For GBD 2019 we have made further refinements to the estimation of MIRs, but the method remains sensitive to under-diagnosis of cancer cases or underascertainment of cancer deaths. However, given that the majority of data used for the cancer mortality estimation come from vital registration data and not cancer registry data, this is not a major limitation. Finally, no estimates are available for some locations, such as Western Sahara and French Guiana, as they were not modelled locations in the Global Burden of Diseases, Injuries, and Risk Factors Study 2019. These areas are shaded white in the global map figures included in this paper.

Part II – Risk Factors Analysis

1. Overview and definition of indicator

This study presents the proportion of mortality and DALYs from lip and oral cancer (LOC) attributed to three risk factors: smoking, chewing tobacco, and alcohol consumption; it also presented the proportion of mortality and DALYs from other pharynx cancer (OPC) attributed to two risk factors: smoking and alcohol consumption. These data were produced by the GBD 2019 study. Definitions related to risk factors are described in the sections dedicated to each risk factor, later in this appendix.

2. Data input sources overview

GBD 2019 incorporated a large number and wide variety of input sources to estimate mortality, causes of death and illness, and risk factors for 204 countries and territories from 1990–2019. These input sources are accessible through an interactive citation tool available in the GHDx: [http://ghdx.healthdata.org/gbd-](http://ghdx.healthdata.org/gbd-2019/data-inputsources)[2019/data-inputsources.](http://ghdx.healthdata.org/gbd-2019/data-inputsources)

3. Risk factor estimation

The comparative risk assessment (CRA) conceptual framework was developed by Murray and Lopez³¹, who established a causal web of hierarchically organized risks or causes that contribute to health outcomes, which allows for quantification of risks or causes at any level in the framework. In GBD 2019, as in previous iterations of the GBD study, we evaluated a set of behavioral, environmental and occupational, and metabolic risks, in which risk-outcome pairs were included based on evidence rules. These risks were organized in four hierarchical Levels, where:

- ⋅ **Level 1** represents the overarching categories (behavioral, environmental and occupational, and metabolic) nested within Level 1 risks;
- ⋅ **Level 2** contains both single risks and risk clusters
- ⋅ **Level 3** contains the disaggregated single risks from within Level 2 risk clusters
- ⋅ and **Level 4** details risks with the most granular disaggregation,

All risk factors analyzed in the GBD 2019 Study, and their respective hierarchy level, are listed in Table S2 (page 303) of Appendix 1 of "Global burden of 87 risk factors in 204 countries and territories, 1990– 2019: a systematic analysis for the Global Burden of Disease Study 2019."5 At each level of risk, we evaluated whether risk combinations were additive, multiplicative, or shared common pathways for intervention. This approach allows the quantification of the proportion of risk-attributable burden shared with another risk or combination of risks and the measurement of potential overlaps between behavioral, environmental and occupational, and metabolic risks. We do provide some insights into the potential magnitude of distal social, cultural, and economic factors through an analysis of the relationship between risk exposures and development measured by using the Socio-demographic Index (SDI).

Two types of risk assessments are possible within the CRA framework: attributable burden and avoidable burden. Attributable burden is the reduction in current disease burden that would have been possible if past population exposure had shifted to an alternative or counterfactual distribution of risk exposure. Avoidable burden is the potential reduction in future disease burden that could be achieved by changing the current distribution of exposure to a counterfactual distribution of exposure. Murray and Lopez identified four types of counterfactual exposure distributions: (1) theoretical minimum risk; (2) plausible minimum risk; (3) feasible minimum risk; and (4) cost-effective minimum risk.³² The TMREL is the level of risk exposure that minimizes risk at the population level or the level of risk that captures the maximum attributable burden. Other possible forms of risk quantification include plausible minimum risk – which reflects the distribution of risk that is conceivably possible and would minimize population-level risk if achieved – whereas feasible minimum risk describes the lowest risk distribution that has been attained within a population and costeffective minimum risk is the lowest risk distribution for a population that can be attained in a cost-effective manner. Because no robust set of forecasts for all components of GBD is available, in this study we focus on quantifying attributable burden by using the theoretical minimum risk counterfactual distribution.

A description with a high-level overview of the analytical logic and the sufficient detail on the methods and overall structure of the estimation process can be found on Section 2 (starting on page 16) of Appendix 1 of "Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019."5 Here we aim to provide a synthesis focused on smoking, chewing tobacco, and alcohol consumption risk factors.

4. GBD risk-specific methods summaries

The following section provides further methodological detail and GBD case or exposure definitions for risks where the estimation process differs from the general GBD risk factors modelling framework described above. These write-ups were copied from "Section 4: Risk-specific modelling descriptions" in the appendix to the GBD 2019 paper, "Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019".⁵

Modeling risk factors in GBD 2019 often requires disease context across many different communicable and non-communicable diseases; although cancers specifically are the focus of this analysis, the following risk factors methods section will often reference GBD causes (diseases and injuries) that are outside of the scope of this paper. This broader disease context is included for completeness and accuracy.

4.1. Smoking

Flowchart

IARC = International Agency for Research on Cancer; RR = relative risk; WHO = World Health Organization; ST-GPR = spaciotemporal Gaussian process regression; PAF = Population attributable fraction; TMREL = Theoretical minimum-risk exposure level.

Input data and methodological summary

Exposure

Case definition

We estimated the prevalence of current smoking and the prevalence of former smoking using data from cross-sectional nationally representative household surveys. We defined current smokers as individuals who currently use any smoked tobacco product on a daily or occasional basis. We defined former smokers as individuals who quit using all smoked tobacco products for at least six months, where possible, or according to the definition used by the survey.

Input data

We extracted primary data from individual level microdata and survey report tabulations. We extracted data on current, former, and/or ever smoked tobacco use reported as any combination of frequency of use (daily, occasional, and unspecified, which includes both daily and occasional smokers) and type of smoked tobacco used (all smoked tobacco, cigarettes, hookah, and other smoked tobacco products such as cigars or pipes), resulting in 36 possible combinations. Other variants of tobacco products, for example hand-rolled cigarettes, were grouped into the four type categories listed above based on product similarities.

For microdata, we extracted relevant demographic information, including age, sex, location, and year, as well as survey metadata, including survey weights, primary sampling units, and strata. This information allowed us to tabulate individual-level data in the standard GBD five-year age-sex groups and produce accurate estimates of uncertainty. For survey report tabulations, we extracted data at the most granular age-sex group provided.

Crosswalk

Our GBD smoking case definitions were current smoking of any tobacco product and former smoking of any tobacco product. All other data points were adjusted to be consistent with either of these definitions. Some sources contained information on more than one case definition and these sources were used to develop the adjustment coefficient to transform alternative case definitions to the GBD case definition. The adjustment coefficient was the beta value derived from a linear model with one predictor and no intercept. We used the same crosswalk adjustment coefficients as in GBD 2017, and thus we have not included a methods explanation in this appendix, as it has been detailed previously.

Age and sex splitting

As in GBD 2017, we split data reported in broader age groups than the GBD 5-year age groups or as both sexes combined by adapting the method reported in Ng et al. to split using a sex- geography- time specific reference age pattern.³³ We separated the data into two sets: a training dataset, with data already falling into GBD sex-specific 5-year age groups, and a split dataset, which reported data in aggregated age or sex groups. We then used spatiotemporal Gaussian process regression (ST-GPR) to estimate sex-geographytime-specific age patterns using data in the training dataset. The estimated age patterns were used to split each source in the split dataset.

The ST-GPR model used to estimate the age patterns for age-sex splitting used an age weight parameter value that minimizes the effect of any age smoothing. This parameter choice allowed the estimated age pattern to be driven by data, rather than being enforced by any smoothing parameters of the model. Because these age-sex split data points were to be incorporated in the final ST-GPR exposure model, we did not want to doubly enforce a modelled age pattern for a given sex-location-year on a given aggregate data point.

Modelling strategy

Smoking prevalence modelling

We used ST-GPR to model current and former smoking prevalence. The model is nearly identical to that in GBD 2017. Full details on the ST-GPR method can be found in "Section 4.3.3: Spatiotemporal Gaussian process regression (ST-GPR) modeling" in Supplementary Appendix 1 to "Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019."4 Briefly, the mean function input to GPR is a complete time series of estimates generated from a mixed effects hierarchical linear model plus weighted residuals smoothed across time, space, and age. The linear model formula for current smoking, fit separately by sex using restricted maximum likelihood in R, is:

$$
logit(p_{g,a,t}) = \beta_0 + \left|\beta_1 CPC_{g,t} + \sum_{k=2}^{19} \beta_k I_{A[a]} + \alpha_s + \alpha_r + \alpha_g + \epsilon_{g,a,t}\right|
$$

where CPC_{g,t} is the tobacco consumption covariate by geography g and time t , described above, $I_{A[a]}$ is a dummy variable indicating specific age group A that the prevalence point $p_{g,a,t}$ captures, and α_s , α_r , and α_g are super-region, region, and geography random intercepts, respectively. Random effects were used in model fitting but not in prediction.

The linear model formula for former smoking is:

$$
logit(p_{g,a,t}) = \beta_0 + \beta_1 PctChange_{A[a],g,t} + \beta_3 CSP_{A[a],g,t} + \sum_{k=3}^{20} \beta_k I_{A[a]} + \alpha_s + \alpha_r + \alpha_g + \epsilon_{g,a,t}
$$

where PctChange $A[a], g, t$ is the percentage change in current smoking prevalence from the previous year, and $CSP_{A[a],g,t}$ is the current smoking prevalence by specific age group A, geography g, and time t that point $p_{q, a, t}$ captures, both derived from the current smoking ST-GPR model defined above.

Supply-side estimation

The methods for modelling supply-side-level data were changed substantially from those used in GBD 2017. The raw data were domestic supply (USDA Global Surveillance Database and UN FAO) and retail supply (Euromonitor) of tobacco. Domestic supply was calculated as production + imports - exports. The data went through three rounds of outliering. First, they were age-sex split using daily smoking prevalence to generate number of cigarettes per smoker per day for a given location-age-sex-year. If more than 12

points for a particular source-location-year (equal to over 1/3 of the split points) were above the given thresholds, that source-location-year was outliered. A point would not be outliered if it was (in cigarettes per smoker): under five (10–14 year olds); under 20 (males, 15–19 year olds); under 18 (females, 15–19 year olds); under 38/35 and over three (males/females, 20+ year olds). These thresholds were chosen by visualising histograms of the data for each age-sex, as well as with expert knowledge about reasonable consumption levels. In the second round of outliering, the mean tobacco per capita value over a 10-year window was calculated. If a point was over 70% of that mean value away from the mean value, it was outliered. The 70% limit was chosen using histograms of these distances. Additionally, some manual outliering was performed to account for edge cases. Finally, data smoothing was performed by taking a three-year rolling mean over each location-year.

Next, a simple imputation to fill in missing years was performed for all series to remove compositional bias from our final estimates. Since the data from our main sources covered different time periods, by imputing a complete time series for each data series, we reduced the probability that compositional bias of the sources was leading to biased final estimates. To impute the missing years for each series, we modelled the log ratio of each pair of sources as a function of an intercept and nested random effects on super-region, region, and location. The appropriate predicted ratio was multiplied by each source that we did have, and then the predictions were averaged to get the final imputed value. For example, if source A was missing for a particular location-year, but sources B and C were present, then we predicted A twice: once from the modelled ratio of A to B, and again from the modelled ratio of A to C. These two predictions were then averaged. For some locations where there was limited overlap between series, the predicted ratio did not make sense, and a regional ratio was used.

Finally, variance was calculated both across series (within a location-year) as well as across years (within a location-source). Additionally, if a location-year had one imputed point was, the variance was multiplied by 2. If a location-year had two imputed points, the variance was multiplied by 4. The average estimates in each location-year were the input to an ST-GPR model. For this, we used a simple mixed effects model, which was modelled in log space with nested location random effects. Subnational estimates were then further modelled by splitting the country-level estimates using current smoking prevalence.

Theoretical minimum-risk exposure level

The theoretical minimum-risk exposure level is 0.

Exposure among current and former smokers

Identical to GBD 2017, we estimated exposure among current smokers for two continuous indicators: cigarettes per smoker per day and pack-years. Pack-years incorporates aspects of both duration and amount. One pack-year represents the equivalent of smoking one pack of cigarettes (assuming a 20- cigarette pack) per day for one year. Since the pack-years indicator collapses duration and intensity into a single dimension, one pack-year of exposure can reflect smoking 40 cigarettes per day for six months or smoking 10 cigarettes per day for two years.

To produce these indicators, we simulated individual smoking histories based on distributions of age of initiation and amount smoked. We informed the simulation with cross-sectional survey data capturing these indicators, modelled at the mean level for all locations, years, ages, and sexes using ST-GPR. We rescaled estimates of cigarettes per smoker per day to an envelope of cigarette consumption based on supply-side data. We estimated pack-years of exposure by summing samples from age- and time-specific distributions of cigarettes per smoker for a birth cohort in order to capture both age trends and time trends and avoid the common assumption that the amount someone currently smokes is the amount they have smoked since they began smoking. All distributions were age-, sex-, and region- specific ensemble distributions, which were found to outperform any single distribution.

We estimated exposure among former smokers using years since cessation. We utilized ST-GPR to model mean age of cessation using cross-sectional survey data capturing age of cessation. Using these estimates, we generated ensemble distributions of years since cessation for every location, year, age group, and sex.

Relative risk

The same risk-outcome pairs from GBD 2017 were used: tuberculosis; lower respiratory tract infections; esophageal cancer; stomach cancer; bladder cancer; liver cancer; larynx cancer; tracheal, bronchus, and lung cancer; breast cancer; cervical cancer; colon and rectum cancer; lip and oral cancer; nasopharynx cancer; other pharynx cancer; pancreatic cancer; kidney cancer; leukemia; ischemic heart disease; ischemic stroke; hemorrhagic stroke; subarachnoid hemorrhage; atrial fibrillation and flutter; aortic aneurysm; peripheral artery disease; chronic obstructive pulmonary disease; other chronic respiratory diseases; asthma; peptic ulcer disease; gallbladder and biliary tract diseases; Alzheimer's disease and other dementias; Parkinson disease (protective); multiple sclerosis; diabetes mellitus type 2; rheumatoid arthritis; low back pain; cataract; age-related macular degeneration; and fracture.

Dose-response risk curves

Input data for relative risks were nearly the same as in GBD 2017. The only addition was for chronic obstructive pulmonary disease, for which a few additional studies were included. We synthesized effect sizes by cigarettes per smoker per day, pack-years, and years since quitting from cohort and case-control studies to produce nonlinear dose-response curves using a Bayesian meta-regression model. For outcomes with significant differences in effect size by sex or age, we produced sex- or age-specific risk curves.

We estimated risk curves of former smokers compared to never smokers taking into account the rate of risk reduction among former smokers seen in the cohort and case-control studies, and the cumulative exposure among former smokers within each age, sex, location, and year group.

Population attributable fraction

As in GBD 2017, we estimated PAFs based on the following equation:

$$
PAF = \frac{p(n) + p(f) \int \exp(x) * rr(x) + p(c) \int \exp(y) * rr(y) - 1}{p(n) + p(f) \int \exp(x) * rr(x) + p(c) \int \exp(y) * rr(y)}
$$

where $pp(nn)$ is the prevalence of never smokers, $pp(ff)$ is the prevalence of former smokers, $pp(cc)$ is the prevalence of current smokers, $exp(x x)$ is a distribution of years since quitting among former smokers, $rrrr(xx)$ is the relative risk for years since quitting, $exp(yy)$ is a distribution of cigarettes per smoker per day or pack-years, and $rrrr(\gamma \gamma)$ is the relative risk for cigarettes per smoker per day or pack-years.

We used pack-years as the exposure definition for cancers and chronic respiratory diseases, and cigarettes per smoker per day for cardiovascular diseases and all other health outcomes.
4.2. Chewing tobacco

Flowchart

TMREL = Theoretical minimum-risk exposure level; ST-GPR = spaciotemporal Gaussian process regression; PAF = Population attributable fraction; YLL = Years of life lost; YLD = Years lived with disability; DALYs = Disabilityadjusted life-years.

Input data and methodological summary

Exposure

Case definition

Current chewing tobacco use is defined as current use (use within the last 30 days where possible, or according to the closest definition available from the survey) of any frequency (any, daily, or less than daily). Chewing tobacco includes local products, such as betel quid with tobacco.

Input data

As in GBD 2017, we included sources that reported primary chewing tobacco, non-chew smokeless tobacco, and all smokeless tobacco use among respondents over age 10. To be eligible for inclusion, sources had to be representative for their level of estimation (i.e., national sources needed to be nationally representative, subnational sources subnationally representative). We included only self-reported use data and excluded data from questions asking about others' tobacco use behaviors.

We extracted primary data from individual-level microdata and survey report tabulations on chewing tobacco, non-chew smokeless tobacco, and all smokeless tobacco use. We extracted data on current, former, and/or ever use as well as frequency of use (daily, occasional, and unspecified, which includes both daily and occasional smokers). Products that do not include tobacco, such as betel quid without tobacco, were excluded or estimated separately as part of the drug use risk factor, if applicable.

For microdata, we extracted relevant demographic information, including age, sex, location, and year, as well as survey metadata, including survey weights, primary sampling units, and strata. This information allowed us to tabulate individual-level data in the standard GBD five-year age-sex groups and produce accurate estimates of uncertainty. For survey report tabulations, we extracted data at the most granular age-sex group provided.

Age and sex splitting

We split data reported in broader age groups than the GBD five-year age groups or as both sexes combined by adapting the method reported in Ng and colleagues to split using a sex-geography-timespecific reference age pattern.³³ We separated the data into two sets: a training dataset, with data already falling into GBD sex-specific five-year age groups, and a split dataset, which reported data in aggregated age or sex groups. We then used spatiotemporal Gaussian process regression (ST-GPR) to estimate sexgeography-time-specific age patterns using data in the training dataset. The estimated age patterns were then used to split each source in the split dataset.

The ST-GPR model used to estimate the age patterns for age-sex splitting used an age weight parameter value that minimizes the effect of any age smoothing. This parameter choice allows the estimated age pattern to be driven by data, rather than being enforced by any smoothing parameters of the model. Because these age-sex-split datapoints will be incorporated in the final ST-GPR exposure model, we do not want to doubly enforce a modelled age pattern for a given sex-location-year on a given aggregate datapoint. We run three separate ST-GPR models for age-sex splitting – one for each smokeless tobacco category (chew, non-chew, and all smokeless).

Modelling strategy

Prevalence modelling

We used a ST-GPR to model chewing tobacco prevalence. Full details on the ST-GPR method can be found in "Section 4.3.3: Spatiotemporal Gaussian process regression (ST-GPR) modeling" in Supplementary Appendix 1 to "Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019.^{*4} Briefly, the mean function input to GPR is a complete time series of estimates generated from a mixed effects hierarchical linear model plus

weighted residuals smoothed across time, space, and age. The linear model formula for chewing tobacco, fit separately by sex using restricted maximum likelihood in R, is:

$$
logit(p_{g,a,t}) = \beta_0 + \sum_{k=1}^{18} \beta_k I_{A[a]} + \alpha_s + \alpha_r + \alpha_g + \epsilon_{g,a,t}
$$

where

 $I_{A[a]}$ *is a dummy variable indicating specific age group A that the prevalence point* $p_{g,a,t}$ *captures, and αs, αr, and α^g are super-region, region, and geography random intercepts, respectively. The hyperparameters are the same as in GBD 2017.*

We run three ST-GPR models for each prevalence category – one for each smokeless tobacco category (chew, non-chew, and all smokeless).

All smokeless tobacco prevalence adjustment

Using the 1000 draws from each of the prevalence ST-GPR models, we calculated 1000 draws of chewing tobacco prevalence divided by the sum of chewing tobacco and non-chewing tobacco prevalence for each location, age group, sex, and year. The draws were unordered, as we did not want to enforce an assumption about the relationship between the levels of chewing tobacco and non-chewing tobacco prevalence.

The draws of the ratio of chewing to non-chewing tobacco were then multiplied by the draws from the all smokeless tobacco prevalence model to adjust the estimates to chewing tobacco prevalence. These were then averaged to get the mean estimate. The variance across the ratios was calculated for each location, year, age, and sex, and was added to the variance from the original all smokeless tobacco draws.

Final chewing tobacco prevalence model

To calculate the final chewing tobacco prevalence, we ran an additional ST-GPR model with both the original chewing tobacco data (post-age-sex splitting), as well as the adjusted data. These adjusted data add more information to the model – as surveys will often only ask about all smokeless tobacco consumption – while taking into consideration the uncertainty from the ratio calculation.

Theoretical minimum-risk exposure level

The theoretical minimum risk exposure level is that everyone in the population has been a lifelong nonuser of chewing tobacco.

Relative risk

As in GBD 2017, we included outcomes based on the strength of available evidence supporting a causal relationship. There was sufficient evidence to include Lip and oral cavity cancer and Esophageal cancer as health outcomes caused by chewing tobacco use.

Relative risk estimates were derived from prospective cohort studies and population-based case-control studies. We used the same underlying effect size estimates from prospective cohort studies and population-based case-control studies as in GBD 2017. Briefly, we did not include hospital-based case control studies due to concerns over representativeness. We only included sources that adequately adjusted for major confounders, especially smoking status. Summary effect size estimates were calculated in R, using the 'metafor' package. We performed a random effects meta-analysis using the DerSimonian and Laird method, which does not assume a true effect size but considers each input study as selected from a random sample of all possible sets of studies for the outcome of interest. The random-effects method allows for more variation between the studies, and incorporates this variance into the estimation process. We used an inverse-variance weighting method to determine component study weights. We found significantly different relative risks for oral cancer for males and females, and estimated relative risks separately by sex for Lip and oral cavity cancer alone.

4.3. Alcohol use

Flowchart

FAO = food and agriculture organization; WHO = World Health Organization; UWNTO = World Tourism Organization; MR BRT = a network meta-regression; DisMod ODE = the "engine" of DisMod-MR 2.1; TMREL = Theoretical minimum-risk exposure level; LPC = liters per capita; MVA = motor vehicle accidents; PAF = Population attributable fraction; FARS = Fatal Accident Reporting System; YLL = Years of life lost; YLD = Years lived with disability; DALYs = Disability-adjusted life-years.

Input data and methodological summary

Exposure

Case definition

We defined exposure as the grams per day of pure alcohol consumed among current drinkers. We constructed this exposure using the indicators outlined below:

- 1. Current drinkers, defined as the proportion of individuals who have consumed at least one alcoholic beverage (or some approximation) in a 12-month period.
- 2. Alcohol consumption (in grams per day), defined as grams of alcohol consumed by current drinkers, per day, over a 12-month period.
- 3. Alcohol liters per capita stock, defined in liters per capita of pure alcohol, over a 12-month period.

We also used three additional indicators to adjust alcohol exposure estimates to account for different types of bias:

1. Number of tourists within a location, defined as the total amount of visitors to a location within a 12-month period.

2. Tourists' duration of stay, defined as the number of days resided in a hosting country.

Unrecorded alcohol stock, defined as a percentage of the total alcohol stock produced outside established markets.

Input data

A systematic review of the literature was performed to extract data on our primary indicators. The Global Health Exchange (GHDx), IHME's online database of health-related data, was searched for population survey data containing participant-level information from which we could formulate the required alcohol use indicators on current drinkers and alcohol consumption. Data sources were included if they captured a sample representative of the geographical location under study. We documented relevant survey variables from each data source in a spreadsheet and extracted using STATA 13.1 and R 3.3. A total of 6172 potential data sources were available in the GHDx, of which 5091 have been screened and 1125 accepted.

Estimates of current drinking prevalence were split by age and sex where necessary. First, studies that reported prevalence for both sexes were split using a region-specific sex ratio estimated using MR-BRT. Second, where studies reported estimates across non-GBD age groups, these were split into standard fiveyear age groups using the global age pattern estimated by ST-GPR.

**Adjustment factor is the transformed beta coefficient in normal space and can be interpreted as the factor by which the alternative case definition is adjusted to reflect the ratio by which both-sex data points were split.*

To allow for the inclusion of data that did not meet our reference definition for current drinking, two crosswalks were performed using MR-BRT. The first crosswalk converted estimates of one-month drinking prevalence to what they would be if data represented estimates of 12-month drinking prevalence. This crosswalk incorporated two binary covariates: male and age \geq 50. The second crosswalk converted estimates of one-week drinking prevalence to 12-month drinking prevalence. This crosswalk incorporated age < 20 and male as covariates. The covariates utilized in both crosswalks were included as both x and z covariates. A uniform prior of 0 was set as the upper bound for the beta coefficients to enforce the logical constraint that one-month and one-week prevalence could not be greater than 12-month prevalence.

The methods for modelling supply-side-level data were changed substantially from those used in GBD 2017. The raw data are domestic supply $(FAO^{34}; WHO GISAH^{35})$ and retail supply (Euromonitor) of liters of pure ethanol consumed. Domestic supply is calculated as the sum of production and imports, subtracting exports. The WHO and FAO sources were combined, so that FAO data were only used if there were no data available for that location-year from WHO. This was done because the WHO source takes into consideration FAO values when available. Since the WHO data are given in more granular alcohol types, the following adjustments were made:

LPC Pure Ethanol =
$$
0.13 * \left(\frac{Wine}{0.973}\right)
$$

\nLPC Pure Ethanol = $0.05 * \left(\frac{Beer}{0.989}\right)$
\nLPC Pure Ethanol = $0.4 * \left(\frac{Spirtits}{0.91}\right)$

Three outliering strategies are used to omit implausible datapoints and data that created implausible model fluctuations. First, estimates from the current drinking model are used to calculate the grams of alcohol consumed per drinker per day. A point is outliered if the grams of pure ethanol per drinker per day for a given source-location-year is greater than 100 (approximately ten drinks). These thresholds were chosen by using expert knowledge about reasonable consumption levels. In the second round of outliering, the mean liters per capita value over a ten-year window is calculated. If a point is over 70% of that mean value away from the mean value, it is outliered. The 70% limit was chosen using histograms of these distances. Additionally, some manual outliering is performed to account for edge cases. Finally, data smoothing is performed by taking a three-year rolling mean over each location-year.

Next, an imputation to fill in missing years is performed for all series to remove compositional bias from our final estimates. Since the data from our main sources cover different time periods, by imputing a complete time series for each data series, we reduce the probability that compositional bias of the sources is leading to biased final estimates. To impute the missing years for each series, we model the log ratio of each pair of sources as a function of an intercept and nested random effects on superregion, region, and location. The appropriate predicted ratio is multiplied by the source that we do have, which generates an estimated value for the missing source. For some locations where there was limited overlap between series, the predicted ratio did not make sense, and a regional ratio was used.

Finally, variance was calculated both across series (within a location-year) as well as across years (within a location-source). Additionally, if a location-year had one imputed point, the variance was multiplied by 2. If a location-year had two imputed points, the variance was multiplied by 4. The average estimates in each location-year were the input to an ST-GPR model. This uses a mixed-effects model modelled in log space with nested location random effects.

We obtained data on the number of tourists and their duration of stay from the UNWTO.³⁶ We applied a crosswalk across different tourist categories, similar to the one used for the liters per capita data, to arrive at a consistent definition (i.e., visitors to a country).

We obtained estimates on unrecorded alcohol stock from data available in WHO GISAH database,³⁵ consisting of 189 locations. For locations with no data available, the national or regional average was used.

For relative risks, in GBD 2016 we performed a systematic literature review of all cohort and case-control studies reporting a relative risk, hazard ratio, or odds ratio for any risk-outcome pairs studied in GBD 2016. Studies were included if they reported a categorical or continuous dose for alcohol consumption, as well as uncertainty measures for their outcomes, and the population under study was representative.

Modelling strategy

While population-based surveys provide accurate estimates of the prevalence of current drinkers, they typically underestimate real alcohol consumption levels.^{37–39} As a result, we considered the liter per capita input to be a better estimate of overall volume of consumption. Per capita consumption, however, does not provide age- and sex-specific consumption estimates needed to compute alcohol attributable burden of disease. Therefore, we use the age-sex pattern of consumption among drinkers modelled from the population survey data and the overall volume of consumption from FAO, GISAH, and Euromonitor to determine the total amount of alcohol consumed within a location. In the paragraphs below, we outline how we estimated each primary input in the alcohol exposure model, as well as how we combined these inputs to arrive at our final estimate of grams per day of pure alcohol. We estimated all models below using 1000 draws.

For data obtained through surveys, we used spatiotemporal Gaussian process regression (ST-GPR) to construct estimates for each location/year/age/sex. We chose to use ST-GPR due to its ability to leverage information across the nearby locations or time periods. We also modelled the alcohol liters per capita (LPC) data, as well as the total number of tourists, using ST-GPR.

Given the heterogeneous nature of the estimates on unrecorded consumption, as well as the wide variation across countries and time periods, we took 1000 draws from the uniform distribution of the lowest and highest estimates available for a given country. We did this to incorporate the diffuse uncertainty within the unrecorded estimates reported. We used these 1000 draws in the equation below.

We adjusted the alcohol LPC for unrecorded consumption using the following equation:

$$
Alcohol \, \text{LPC} = \frac{Alcohol \, \text{LPC}}{(1 - \% \, \text{Unrecorded})}
$$

We then adjusted the estimates for alcohol LPC for tourist consumption by adding in the per capita rate of consumption abroad and subtracting the per capita rate of tourist consumption domestically.

> Alcohol LPC_d = Unadjusted Alcohol LPC_d + Alcohol LPC _{Domestic} consumption abroad $-$ Alcohol LPC $_{Tourist\ consumption\ domestically}$

Alcohol LPC $_i =$ Σ_l Tourist Population $_l$ * Proportion of tourists $_{i,l}$ * Unadjusted Alcohol LPC $_l$ * $\frac{Average length of stay_{i,l}}{365}$ * Population_d

where:

l is the set of all locations, i is either Domestic consumption abroad *or* Tourist consumption domestically*, and d is a domestic location.*

After adjusting alcohol LPC by tourist consumption and unrecorded consumption for all location/years reported, sex-specific and age-specific estimates were generated by incorporating estimates modelled in ST-GPR for percentage of current drinkers within a location/year/sex/age, as well as consumption trends modelled in the ST-GPR grams per day model. We do this by first calculating the proportion of total consumption for a given location/year by age and sex, using the estimates of alcohol consumed per day, the population size, and the percentage of current drinkers. We then multiply this proportion of total stock for a given location/year/sex/age by the total stock for a given location/year to calculate the consumption in terms of liters per capita for a given location/year/sex/age. We then convert these estimates to be in terms of grams/per day. The following equations describe these calculations:

> Proportion of total consumption $_{l,y,s,a}$ $= \frac{Alcohol \ g/day \ _{l,y,s,a} * Population \ _{l,y,s,a} * % Current \ drinkers \ _{l,y,s,a}}{\sum_{s,a} Alcohol \ g/day \ _{l,y,s,a} * Population \ _{l,y,s,a} * % Current \ drinkers \ _{l,y,s,a}}$

$$
Alcohol \, LPC_{l,y,s,a} = \frac{Alcohol \, LPC_{l,y} * Population_{l,y} * Proportion \, of \, total \, consumption_{l,y,s,a}}{\% \, Current \, drinks, a * Population_{l,y,s,a}}
$$
\n
$$
Alcohol \, g/day_{l,y,s,a} = Alcohol \, LPC_{l,y,s,a} * \frac{1000}{365}
$$

where:

l is a location, y is a year, s is a sex, and a is an age group.

We then used the gamma distribution to estimate individual-level variation within location, year, sex, age drinking populations, following the recommendations of other published alcohol studies. $40,41$ We chose parameters of the gamma distribution based on the mean and standard deviation of the 1,000 draws of alcohol g/day exposure for a given population. Standard deviation was calculated using the following formula.40 We tested several alternative models using our data and found this model performed best.

standard deviation = mean $*(0.087 * female + 1.171)$

Theoretical minimum-risk exposure level

We calculated TMREL by first calculating the overall risk attributable to alcohol. We did this by weighting each relative risk curve by the share of overall DALYs for a given cause. We then took the minimum of this overall-risk curve as the TMREL of alcohol use. More formally,

 $TMREL = argmin average overall risk_{\omega}(g/day)$

$$
Average\ overall\ risk_{\omega}(g/day) = \sum_{i}^{\omega} RR_i(g/day) * \frac{DALY_i}{\sum_{i}^{\omega} DALY_i}
$$

where:

ω is the set of causes associated with alcohol, i is a given cause from that set, DALY is the global DALY rate in 2010, and RR is the dose response curve for a given cause and exposure level in grams per day.

In other words, we chose TMREL as being the exposure that minimizes your risk of suffering burden from any given cause related to alcohol. We weight the risk for a particular cause in our aggregation by the proportion of DALYs due to that cause (e.g., since more observed people die from ischemic heart disease [IHD], we weight the risk for IHD more in the above calculation of average risk compared to, say, diabetes, even if both have the same relative risk for a given level of consumption).

Relative risks

We used the studies identified through the systematic review to calculate a dose-response, modelled using DisMod ODE. We chose DisMod ODE rather than a conventional mixed effects meta-regression because of its ability to estimate nonparametric splines over doses (i.e., for most alcohol causes, there is a nonlinear relationship with different doses) and incorporate heterogeneous doses through dose integration (i.e., most studies report doses categorically in wide ranges. DisMod ODE estimates specific doses when categories overlap across studies, through an integration step.). We used the results of the meta-regression to estimate a non-parametric curve for all doses between zero and 150 g/day and their corresponding relative risks. For all causes, we assumed the relative risk was the same for all ages and sexes, with the exception of ischemic heart disease, ischemic stroke, hemorrhagic stroke, and diabetes, which we estimated by sex.

For outcomes that are by definition caused by alcohol, such as liver cancer due to alcohol use or cirrhosis due to alcohol use, PAFs are set to 1. PAFs for cirrhosis due to all causes that are in excess of the proportion of all cirrhosis burden due to alcohol are proportionally redistributed over cirrhosis due to hepatitis B, cirrhosis due to hepatitis C, and cirrhosis due to other causes.

Regarding injuries outcomes, we constructed relative risks based on chronic exposure to alcohol rather than acute exposure immediately preceding injury, which has a weaker relationship to the outcome, though still significant.^{42–47} We decided to use chronic exposure given the lack of available data on acute exposure, as well as the lack of cohort studies using acute exposure as a metric. Further, using chronic exposure allowed us to construct relative risks curves for unintentional injuries, interpersonal violence, motor vehicle road injuries, and self-harm using the same method as reported above.

In the case of motor vehicle road injuries, we adjusted the PAF to account for victims of drunk drivers who are involved in accidents. Using data from the Fatality Analysis Reporting System (FARS) in the US,⁴⁸ we calculated the average number of fatalities in a car crash involving alcohol, as well as the percentage of those fatalities distributed by age and sex. We aggregated FARS data across the years 1985–2015, given there was little variation in the data temporally and the number of cases in old age groups had too much variance when constructing estimates by year. To adjust PAFs, we multiplied attributable deaths by the average number of fatalities from FARS and redistributed the PAF among each population, based on the probability of being a victim to a certain drunk driver by age and sex, based on the FARS data. The following equation describes this process:

$$
adjusted\ PAF_i = \frac{\sum_{d} PAF_d * DALY_d * Avg\ Fatalities_d * P(i \text{ is a victim})_d}{DALY_i}
$$

where:

i is a population by location, year, age, sex and d is the set of all age and sex exposed groups within that location and year.

Population attributable fraction

For all causes, we defined PAF as:

$$
PAF(x) = \frac{P_A + \int_0^{150} P(x) * RR_C(x) dx - 1}{P_A + \int_0^{150} P(x) * RR_C(x) dx} \qquad P(x) = P_C * \Gamma(\boldsymbol{p})
$$

where:

 P_c *is the prevalence of current drinkers,* P_a *is the prevalence of abstainers, RR_c(x) is the relative risk function for current drinkers and p are parameters determined by the mean and sd of exposure*

We performed the above equation for 1000 draws of the exposure and relative risk models. We then used the estimated PAF draws to calculate YLL, YLDs, and DALYs, as per the other risk factors.

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Additional Methodology Tables and Figures

eFigure 3. Socio-demographic Index quintiles for the Global Burden of Disease Study 2019 SDI = Socio-demographic Index.

eTable 7. Socio-demographic Index (SDI) quintiles for countries and territories estimated in GBD 2019

SDI Quintile	Locations included based on SDI values in 2019 from GBD 2019 results
High SDI	Andorra, Australia, Austria, Belgium, Bermuda, Brunei Darussalam, Canada, Cyprus,
	Czechia, Denmark, Estonia, Finland, France, Germany, Guam, Iceland, Ireland, Japan,
	Kuwait, Latvia, Lithuania, Luxembourg, Monaco, Netherlands, New Zealand, Norway,
	Puerto Rico, Qatar, San Marino, Saudi Arabia, Singapore, Slovakia, Slovenia, Republic
	of Korea, Sweden, Switzerland, Taiwan (Province of China), United Arab Emirates,
	United Kingdom, United States of America
High-middle SDI	American Samoa, Antigua and Barbuda, Argentina, Bahamas, Bahrain, Barbados,
	Belarus, Bosnia and Herzegovina, Bulgaria, Chile, Cook Islands, Croatia, Dominica,
	Georgia, Greece, Greenland, Hungary, Israel, Italy, Jordan, Kazakhstan, Lebanon, Libya,
	Malaysia, Malta, Mauritius, Republic of Moldova, Montenegro, Niue, North Macedonia,
	Northern Mariana Islands, Oman, Palau, Poland, Portugal, Romania, Russian Federation,
	Saint Kitts and Nevis, Serbia, Seychelles, Spain, Sri Lanka, Trinidad and Tobago, Turkey,
	Ukraine, United States Virgin Islands, Uruguay
Middle SDI	Albania, Algeria, Armenia, Azerbaijan, Botswana, Brazil, China, Colombia, Costa Rica,
	Cuba, Ecuador, Egypt, Equatorial Guinea, Fiji, Gabon, Grenada, Guyana, Indonesia, Iran
	(Islamic Republic of), Iraq, Jamaica, Mexico, Namibia, Nauru, Panama, Paraguay, Peru,
	Philippines, Saint Lucia, Saint Vincent and the Grenadines, Samoa, South Africa,
	Suriname, Syrian Arab Republic, Thailand, Tokelau, Tonga, Tunisia, Turkmenistan,
	Uzbekistan, Viet Nam
Low-middle SDI	Angola, Bangladesh, Belize, Bhutan, Bolivia (Plurinational State of), Cambodia,
	Cameroon, Cabo Verde, Congo, Djibouti, Dominican Republic, El Salvador, Eswatini,
	Ghana, Guatemala, Honduras, India, Kenya, Kiribati, Kyrgyzstan, Lao People's
	Democratic Republic, Lesotho, Maldives, Marshall Islands, Mauritania, Micronesia
	(Federated States of), Mongolia, Morocco, Myanmar, Nicaragua, Nigeria, Democratic
	People's Republic of Korea, Palestine, São Tomé and Príncipe, Sudan, Tajikistan, Timor-
	Leste, Tuvalu, Vanuatu, Venezuela (Bolivarian Republic of), Zambia, Zimbabwe

eFigure 4. Map of GBD world super-regions, 2019

There are several geographic locations where estimates are not available (e.g., Western Sahara, French Guiana) as they were not modelled locations in the Global Burden of Diseases, Injuries, and Risk Factors 2019 study; these locations are white in this map. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

eFigure 5. Map of GBD world regions, 2019

There are several geographic locations where estimates are not available (e.g., Western Sahara, French Guiana) as they were not modelled locations in the Global Burden of Diseases, Injuries, and Risk Factors 2019 study; these locations are white in this map. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

Additional Results in eTables and eFigures

eTable 8. Global and regional deaths, incidence, and DALYs counts and age-standardized rates (per 100 000) for Lip and oral cavity, both sexes combined, in 2019, and change in age-standardized rates from 1990 to 2019

SDI=Socio-demographic Index; DALYs=disability-adjusted life years; UI=uncertainty interval. See eFigure 3 (p53) and eTable 7 (p54) for details and definitions of the SDI regions.

eTable 9. Global and regional deaths, incidence, and DALYs counts and age-standardized rates (per 100 000) for Other pharynx cancer, both sexes combined, in 2019, and change in age-standardized rates from 1990 to 2019

SDI=Socio-demographic Index; DALYs=disability-adjusted life years; UI=uncertainty interval. See eFigure 3 (p53) and eTable 7 (p54) for details and definitions of the SDI regions.

eTable 10. Deaths, incidence, and DALYs counts and age-standardized rates (per 100 000) for Lip and oral cavity cancer (LOC), both sexes combined, by country or territory, in 2019, and change in age-standardized rates from 1990 to 2019

SDI=Socio-demographic Index; DALYs=disability-adjusted life-years; UI=uncertainty interval. See eFigure 3 (p53) and eTable 7 (p54) for details and definitions of the SDI regions.

eTable 11. Deaths, incidence, and DALYs counts and age-standardized rates (per 100 000) for Other pharynx cancer (OPC), both sexes combined, by country or territory, in 2019, and change in age-standardized rates from 1990 to 2019

SDI=Socio-demographic Index; DALYs=disability-adjusted life-years; UI=uncertainty interval. See eFigure 3 (p53) and eTable 7 (p54) for details and definitions of the SDI regions.

eFigure 6. Global map of age-standardized incidence rate quintiles for A) lip and oral cavity cancer, and B) other pharynx cancer, both sexes combined, 2019

Each map represents estimates at the national level and for the age range 20 to 95+ years. Quintiles are based on age-standardized incidence rates per 100,000 person-years. There are several geographic locations where estimates are not available (e.g., Western Sahara, French Guiana) as they were not modelled locations in the Global Burden of Diseases, Injuries, and Risk Factors 2019 study; these locations are white in this map.

eFigure 7. Global map of A) age-standardized mortality rate quintiles, and B) age-standardized incidence rate quintiles for lip and oral cavity cancer, males, 2019

Each map represents estimates at the national level and for the age range 20 to 95+ years. Quintiles are based on age-standardized mortality and incidence rates per 100,000 person-years. There are several geographic locations where estimates are not available (e.g., Western Sahara, French Guiana) as they were not modelled locations in the Global Burden of Diseases, Injuries, and Risk Factors 2019 study; these locations are white in this map.

eFigure 8. Global map of A) age-standardized mortality rate quintiles, and B) age-standardized incidence rate quintiles for other pharynx cancer, males, 2019

Each map represents estimates at the national level and for the age range 20 to 95+ years. Quintiles are based on age-standardized mortality and incidence rates per 100,000 person-years. There are several geographic locations where estimates are not available (e.g., Western Sahara, French Guiana) as they were not modelled locations in the Global Burden of Diseases, Injuries, and Risk Factors 2019 study; these locations are white in this map.

B

eFigure 9. Global map of A) age-standardized mortality rate quintiles, and B) age-standardized incidence rate quintiles for lip and oral cavity cancer, females, 2019

Each map represents estimates at the national level and for the age range 20 to 95+ years. Quintiles are based on age-standardized mortality and incidence rates per 100,000 person-years. There are several geographic locations where estimates are not available (e.g., Western Sahara, French Guiana) as they were not modelled locations in the Global Burden of Diseases, Injuries, and Risk Factors 2019 study; these locations are white in this map.

B

eFigure 10. Global map of A) age-standardized mortality rate quintiles, and B) age-standardized incidence rate quintiles for other pharynx cancer, females, 2019

Each map represents estimates at the national level and for the age range 20 to 95+ years. Quintiles are based on age-standardized mortality and incidence rates per 100,000 person-years. There are several geographic locations where estimates are not available (e.g., Western Sahara, French Guiana) as they were not modelled locations in the Global Burden of Diseases, Injuries, and Risk Factors 2019 study; these locations are white in this map.

Lip and oral cavity cancer

Other pharynx cancer

eFigure 11. Global absolute DALYs and age-specific DALY rates (per 100,000) for Lip and oral cavity cancer, and Other pharynx cancer by 5-year age group and sex in 2019 DALYs=disability-adjusted life years; bars indicate absolute numbers, and lines indicate rates,

with shaded areas representing respective 95% uncertainty intervals (UIs).

Lip and oral cavity cancer

eFigure 12. Time trends of age-standardized DALY rates for Lip and oral cavity cancer and Other pharynx cancer from 1990 to 2019, by SDI quintile

Results in this figure represent both sexes combined. Rates are expressed per 100,000 person-years. See eFigure 3 (p53) and eTable 7 (p54) for details and definitions of the SDI quintiles. SDI=Socio-demographic Index; DALYs=disability-adjusted life years.

eFigure 13. Time trends of age-standardized deaths, incidence, and DALY rates for Lip and oral cavity cancer and Other pharynx cancer from 1990 to 2019, by sex

Rates are expressed per 100,000 person-years. DALYs=disability-adjusted life-years.

eFigure 14. Time trends of age-specific deaths, incidence, and DALY rates for Lip and oral cavity cancer and Other pharynx cancer from 1990 to 2019, by ten-year age group globally

Results in this figure represent both sexes combined. Rates are expressed per 100,000 person-years. See eFigure 3 (p53) and eTable 7 (p54) for details and definitions of the SDI regions. SDI=Socio-demographic Index; DALYs=disability-adjusted life-years.

eFigure 15. Time trends of age-standardized deaths, incidence, and DALY rates for Lip and oral cavity cancer and Other pharynx cancer from 1990 to 2019, by GBD super-region

Rates are expressed per 100,000 person-years. SDI=Socio-demographic Index; DALYs=disability-adjusted life-years.

Lip and oral cavity cancer

eFigure 16. Proportion of deaths attributable to risk factors for Lip and oral cavity cancer and Other pharynx cancer for males and females in 2019 by GBD world region

GBD= Global Burden of Diseases, Injuries, and Risk Factors 2019 study.

A Lip and oral cavity cancer

Other pharynx cancer

B Lip and oral cavity cancer

Themale Male

DALYs (Disability-Adjusted Life Years) attributable to risk factors (%)

eFigure 17. Proportion of DALYs attributable to risk factors for Lip and oral cavity cancer and Other pharynx cancer A) by five-year age group globally, and B) by GBD world region, for males and females in 2019

The chewing tobacco and smoking risk factors were modeled with lower age restrictions of 30 years in the GBD 2019 study; thus, estimates were not produced for these risk factors in the age groups of 20 to 24 years and 25 to 29 years. GBD = Global Burden of Disease Study; DALYs = disabilityadjusted life-years.

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eTable 12. **Proportion of Lip and oral cavity cancer (LOC) deaths and DALYs attributable to risk factors, in 2019, by country or territory, both sexes combined**

DALYs=disability-adjusted life-years; UI=uncertainty interval.

eTable 13. **Proportion of Other pharynx cancer (OPC) deaths and DALYs attributable to risk factors, in 2019, by country or territory, both sexes combined**

DALYs=disability-adjusted life-years; UI=uncertainty interval.

A Lip and oral cavity cancer

B Other pharynx cancer

eFigure 18. Proportion of deaths attributable to risk factors for A) Lip and oral cavity cancer and B) Other pharynx cancer for males and females in 2019

The chewing tobacco and smoking risk factors were modeled with lower age restrictions of 30 years in the GBD 2019 study; thus, estimates were not produced for these risk factors in the age groups of 20 to 24 years and 25 to 29 years.