

Original Article

A cross-database global assessment of lip and oral cavity cancer: global burden, risk factors, and socioeconomic inequalities

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Abstract: Background: Lip and oral cavity cancer remains a substantial global health burden, yet most descriptive studies have drawn on a single data source and analysed temporal trends, attributable risk factors, socioeconomic inequalities, and future projections separately. We integrated multiple international data sources to identify epidemiologic patterns that are consistent across databases and to relate the disease burden to modifiable risk factors and to gaps in cancer care. Methods: We combined six data sources. These were the Global Cancer Observatory (GLOBOCAN) 2022, International Agency for Research on Cancer (IARC) Cancer Tomorrow, the Global Burden of Disease (GBD) 2021 study, the World Health Organization, the World Bank, and the United Nations Development Programme. From these we assessed GBD-GLOBOCAN concordance and trends from 2000 to 2021, summarized as the average annual percent change (AAPC). We also examined pandemic-period deviations, risk-factor profiles by Human Development Index (HDI), disability-adjusted life-year inequalities, and socioeconomic correlates of the mortality-to-incidence ratio (MIR). Projections to 2050 were modelled under tobacco-exposure scenarios. Results: GLOBOCAN 2022 reported 389,846 new cases and 188,438 deaths worldwide, with the heaviest burden in South Central Asia. The GBD 2021 global age-standardized incidence rate (ASIR) was 4.74 per 100,000. Across 159 countries, the two databases agreed moderately to strongly, yet they were not interchangeable at the national level. Between 2000 and 2021 the global ASIR rose only slightly (AAPC 0.36; 95% confidence interval [CI] 0.24-0.48), while mortality held steady. Smoking and smokeless tobacco use were positively associated with ASIR. The mortality-to-incidence ratio was highest in low-HDI countries, where it tracked with health-system capacity: lower health spending and physician supply, alongside heavier out-of-pocket payment. From demographic change alone, cases may reach 613,311 by 2050 (+57.3%). Conclusion: The burden of lip and oral cavity cancer is geographically concentrated and closely tied to development. Incidence is highest where tobacco and betel-quid use is common, whereas death relative to incidence is worst in the poorest countries. Reducing it depends less on any single measure than on repairing whichever part of the care pathway is weakest locally, from prevention through to affordable treatment.

Keywords: Lip and oral cavity cancer, global burden of disease, risk factor, socioeconomic inequality

Introduction

Lip and oral cavity cancer is one of the major head and neck malignancies, with nearly 390,000 new cases and 188,000 deaths worldwide in 2022 and a cross-cancer mortality-to-incidence ratio of 47.5% [1, 4]. Much of its damage comes from where it sits: the oral cavity does the everyday work of eating, speaking

and swallowing, and it is also a person's face to the world [1-3]. Advanced disease is rarely treated simply-surgery, radiotherapy, and systemic treatment are usually combined, and recovery is slow [2, 3]. The consequences seldom stop with the patient; lost work, the demands placed on carers, and the strain on already stretched services make this as much a social problem as a medical one [2-5].

Global control of lip and oral cavity cancer has proven hard. Prevention runs up against exposures that differ greatly from one region to the next [6-8]; early detection is undercut because the first lesions are so easily missed, and each delay-in coming forward, in getting a biopsy, in reaching surgery or radiotherapy-can turn a curable tumour into a fatal one [2, 5]. Poverty pulls in the same direction, raising risk and worsening outcomes: oral health tends to be poorer, problems are noticed later, and much of the cost of care is paid out of pocket [5, 9]. The central question is not so much the absolute number of cases, but the point at which the care pathway fails, whether at prevention, early detection, financial protection, or treatment capacity.

Earlier global analyses have provided only a partial account. Some have pooled lip, oral cavity, and pharyngeal cancers, tracked long-term trends, quantified selected attributable risk factors, or projected future case counts. Others have examined lifetime risk or socioeconomic gradients within a single data source or a comparatively narrow analytical framework [10-15]. Such studies establish the value of long-term monitoring but are less able to test whether major international databases agree at the country level or to integrate epidemiological burden, health-care inequality, and pandemic-related deviations within a single analysis. This leaves a gap between descriptive burden estimates and evidence capable of guiding clinical and policy decisions. Once high-burden settings are identified, the relevant questions are whether observed patterns are consistent across data sources, how closely they track risk-factor exposure, and whether poor outcomes reflect delayed diagnosis, limited treatment access, or inadequate financial protection. Addressing these together requires an integrated assessment linking epidemiology to prevention, screening, and resource allocation.

The present study was designed to address these gaps using Global Burden of Disease (GBD) 2021 and Global Cancer Observatory (GLOBOCAN) 2022 as complementary data sources, supplemented by International Agency for Research on Cancer (IARC) Cancer Tomorrow projections to characterise future demographic pressure [16-18]. We examined temporal trends from 2000 to 2021, assessed GBD-

GLOBOCAN concordance, compared observed incidence during 2020-2021 with a pre-pandemic counterfactual, described current incidence and mortality, and profiled smoking, smokeless tobacco use, and human papillomavirus (HPV) vaccination indicators. We further quantified inequalities in disability-adjusted life-years (DALYs) and modelled socioeconomic correlates of the mortality-to-incidence ratio (MIR) as a proxy for care inequality, and we summarised the projected burden to 2050. By linking disease burden to modifiable risk factors and to health-care inequality, we sought to inform targeted screening, prevention, resource allocation, and treatment-capacity planning, particularly for resource-limited settings.

Materials and methods

Data sources

Data regarding the burden of lip and oral cavity cancer (International Classification of Diseases, Tenth Revision [ICD-10] codes C00 for lip cancer and C02-C06 for intraoral subsites) were obtained from two complementary sources selected for their distinct strengths [1, 16, 17]. The GBD 2021 study, produced by the Institute for Health Metrics and Evaluation, provided age-standardized rates (per 100,000 population) for age-standardized incidence rate (ASIR), age-standardized mortality rate (ASMR), age-standardized prevalence rate (ASPR), DALYs, years of life lost, and years lived with disability from 2000 to 2021, stratified by sex and geographic region [16]. Country-level incidence and mortality estimates for 2022 were obtained from GLOBOCAN 2022 [1, 17]. GBD was used for temporal trend analyses because it provides internally consistent annual time-series data; GLOBOCAN 2022 was used for contemporary case counts, current cross-sectional maps, MIR calculations, and IARC Cancer Tomorrow projections. Accordingly, GBD 2021 rates and GLOBOCAN 2022 case counts were interpreted as complementary-rather than interchangeable-estimates. A matched-country comparison is presented in [Table S1](#), summary concordance metrics in [Table S2](#), concordance plots in [Figure S1](#), and Bland-Altman plots in [Figure S6](#) [19]. Countries were matched using International Organization for Standardization (ISO) 3 codes after harmonization of database-specific country names.

Relative level difference was defined as (GBD estimate - GLOBOCAN estimate)/GLOBOCAN estimate $\times 100$; positive values indicated higher GBD estimates.

Socioeconomic indicators

Country-level socioeconomic and health system indicators were compiled from the World Bank Open Data platform [20], the World Health Organization (WHO) Global Health Observatory [21], and the United Nations Development Programme (UNDP) [22]. Indicators included the Human Development Index (HDI), gross domestic product per capita (purchasing power parity), current health expenditure per capita and as a percentage of gross domestic product, out-of-pocket health expenditure as a proportion of current health expenditure, physician and nursing personnel density (per 10,000 population), the universal health coverage service coverage index, age-standardized tobacco smoking prevalence, adult smokeless tobacco use prevalence, HPV vaccination coverage among female individuals (last dose), alcohol consumption per capita, urban population proportion, adult literacy rate, and life expectancy at birth. Data were extracted for the most recent available year (2019-2024). In the merged analytic dataset, risk-factor indicators were available for 157 countries concerning smoking prevalence, 84 countries concerning smokeless tobacco prevalence, and 124 countries concerning HPV vaccination coverage. The number of countries with available data varied by indicator, ranging from 84 for smokeless tobacco prevalence to 173 for HDI and health expenditure measures, due to differences in reporting coverage across international databases. Indicators available for fewer than 30 countries in the merged analytic dataset, notably adult literacy rate and life expectancy at birth, were excluded from socioeconomic correlate analysis to ensure adequate statistical power. A complete-case approach was used. Potential effects of missing data on study conclusions are discussed in the Limitations section. Official data sources were the World Bank Open Data platform (<https://data.worldbank.org/>), WHO Global Health Observatory (<https://www.who.int/data/gho>), WHO Immunization Data Portal (<https://immunizationdata.who.int/>), and UNDP Human Development Reports Data Center (<https://hdr.undp.org/en/data>).

Statistical analysis

Temporal trends in ASIRs and ASMRs were quantified by average annual percent change (AAPC). AAPC was estimated by fitting a log-linear regression model of the form $\ln(\text{rate}) = \alpha + \beta \times \text{year}$ to the GBD time series (2000-2021), where $\text{AAPC} = (\exp(\beta) - 1) \times 100$ [23]. We used the full-period log-linear model, rather than Joinpoint regression, because the 22-year GBD time series provides limited power for stable changepoint selection across seven super-regions and sex strata. We sought to summarize the overall direction and magnitude of long-term trends, not to identify short-term local inflection points. Time-series fit plots and residual diagnostics for each super-region are provided in [Figure S2](#) to support the adequacy of this approach. As a method of sensitivity analysis, we fitted a Joinpoint-equivalent piecewise log-linear regression with up to two changepoints selected using the Akaike Information Criterion (AIC; parsimony margin $\Delta\text{AIC} \leq 4$) and a minimum segment length of 3 years, mirroring the NCI Joinpoint Regression Program default configuration [23]. Results are presented in [Table S8](#) and [Figure S7](#).

MIR for each country was calculated as the ratio of ASMR to ASIR from GLOBOCAN 2022 [24]. MIR was treated as an ecological proxy for outcome inequality and health system performance, rather than a direct estimate of individual-level survival. Given that lip cancer (ICD-10 C00) is aggregated with intraoral malignancies (ICD-10 C02-C06) in both GBD and GLOBOCAN reporting, countries with a larger proportion of lip cancer cases may exhibit lower MIR values partly because lip cancer has a more favorable prognosis. Associations between MIR and socioeconomic indicators were evaluated using Spearman rank correlation coefficients and ordinary least squares (OLS) regression models with heteroscedasticity-consistent (HC3) robust standard errors. Variance inflation factors for the primary multivariable model are reported in [Table S3](#). Sensitivity analyses for the bounded outcome are presented in [Table S4](#) [25].

Country-level risk-factor indicators were analyzed using established descriptive and ecological correlation methods. Smoking prevalence, adult smokeless tobacco prevalence,

and HPV vaccination coverage were summarized according to HDI group using medians and interquartile ranges. Associations between each risk-factor indicator and GLOBOCAN 2022 ASIR were assessed using Spearman rank correlation coefficients; available-country sample sizes are reported in [Table S7](#). These analyses examined correlations between risk-factor prevalence and ASIRs rather than crude incidence counts; they were intended as descriptive ecological analyses, not individual-level causal models. HDI-stratified risk-factor summaries are provided in [Table S6](#) and [Figure S5](#).

DALY inequality across HDI groups was quantified using two complementary indices. The Slope Index of Inequality (SII) was estimated by regressing age-standardized DALY rates on the midpoint of the cumulative population distribution ranked according to HDI. The SII represents the absolute difference in DALY burden between the theoretical lowest and highest HDI positions; negative values indicate a higher burden in less-developed countries [26, 27]. The Concentration Index, derived from the corresponding Lorenz-type concentration curve, quantifies relative inequality on a scale from -1 to +1; negative values indicate disproportionate burden among lower-HDI populations [27].

To assess the effect of the coronavirus disease 2019 (COVID-19) pandemic on lip and oral cavity cancer diagnosis, we compared observed ASIRs in 2020-2021 with counterfactual expected rates derived from log-linear extrapolation of pre-pandemic trends (2015-2019) for each GBD super-region. Percentage deviation was calculated as (observed - expected)/expected × 100. Global and regional deviations were reported separately to avoid implying a uniform pandemic effect across regions. Ninety-five percent prediction intervals for expected rates were computed from regression models ([Figure S3](#)); observed versus expected ASIR values are provided in [Table S5](#).

Future incidence and mortality counts for 2050 were derived from IARC Cancer Tomorrow projections [18], which apply GLOBOCAN 2022 age-specific rates to United Nations population projections under the medium-variant scenario [28]. This approach assumes constant age-specific incidence and mortality rates; projected changes reflect demographic shifts alone, including population growth and aging. The

model does not consider future changes in tobacco control, smokeless tobacco use, HPV vaccination, early detection, treatment capacity, or health care access. To contextualize this constant-rate baseline, we conducted a tobacco-exposure sensitivity analysis using the population attributable fraction (PAF) framework: $PAF = P(RR - 1) / [P(RR - 1) + 1]$, where relative risk (RR) concerning combustible tobacco use was 3.5 for oral cavity cancer (Hashibe et al., 2009, INHANCE pooled analysis [29]) and the RR for smokeless tobacco use was 2.7 (IARC Monograph 89, 2007). Three scenarios were evaluated: modest control (20% decrease), aggressive control (40% decrease), and continued increase (20% increase). These scenarios were applied to 2050 baseline case estimates for each continent. Results are presented in [Table S9](#) and [Figure S8](#). Percentage changes between the 2022 and 2050 estimates were calculated for each country and region.

Ethical considerations

All data came from publicly available, aggregated international databases and were used under their respective licenses. Because no individual-level data were accessed, ethical approval was not required.

Results

Global and regional burden

According to GLOBOCAN 2022, an estimated 389,846 new cases of lip and oral cavity cancer occurred worldwide (ASIR: 4.0 per 100,000 person-years). The estimated number of deaths was 188,438 (ASMR: 1.9 per 100,000). The global distributions of ASIR and ASMR are shown in [Figure 4](#). [Table 1](#) presents global and regional burden metrics from GBD 2021, including a global ASIR of 4.74 per 100,000. These GLOBOCAN 2022 counts and GBD 2021 rates are not expected to fully match because they arise from different databases, reference years, standard populations, and modeling frameworks. Concordance and systematic differences are examined in [Tables S1](#) and [S2](#) and [Figures S1](#) and [S6](#).

Cross-database concordance between GBD 2021 and GLOBOCAN 2022

Among 159 countries matched across databases, GBD 2021 and GLOBOCAN 2022 sh-

owed moderate-to-strong concordance for both incidence and mortality, with Pearson correlation coefficients of 0.7748 for ASIR and 0.7750 for ASMR (Figure S1; Tables S1 and S2). GBD estimates were systematically higher than GLOBOCAN estimates in 78.0% of ASIR comparisons and 88.1% of ASMR comparisons. Median country-level relative differences were 26.2% for ASIR and 56.8% for ASMR, with larger ASIR discrepancies observed in low-HDI settings (median relative difference, 66.8%) than in very-high-HDI settings (median relative difference, 18.7%). Absolute differences were largest in countries such as Pakistan, Bhutan, the Maldives, and Uganda, emphasizing that robust cross-database agreement does not produce interchangeable estimates at the country level. Bland-Altman plots are provided in Figure S6.

Sex-specific patterns

Sex differences in burden were large in every region. Worldwide, incidence in men was about twice that of women (GBD 2021: male ASIR, 6.32 vs female ASIR, 3.29 per 100,000), in line with men's higher use of tobacco and alcohol [29, 30]. The male-to-female ratio itself varied a great deal, from roughly 1.5:1 in parts of Southeast Asia to more than 3:1 in Eastern Europe. Mortality ratios diverged even more by sex, which points to higher incidence and, plausibly, more advanced disease at diagnosis in men. These sex and temporal patterns are shown in Figure 1.

Temporal trends, 2000-2021

Between 2000 and 2021 the global ASIR rose only modestly (AAPC 0.36; 95% confidence interval [CI] 0.24 to 0.48; $P < 0.0001$), while the ASMR stayed flat (AAPC 0.01; 95% CI -0.12 to 0.14; $P = 0.8657$). The picture differed across the seven GBD super-regions. ASIR fell significantly in the high-income super-region (AAPC -0.53%), and Latin America and the Caribbean saw a smaller decline (-0.21%). The opposite held elsewhere. The steepest rise was in North Africa and the Middle East (AAPC 1.07%), then South Asia (0.97%) and Sub-Saharan Africa (0.61%). Upward trends were also significant in Southeast Asia, East Asia, and Oceania (0.43%) and in Central Europe, Eastern Europe, and Central Asia (0.39%). AAPC estimates by super-region and sex appear in Table 2. Fit plots and residual diagnostics for the log-linear approxi-

mation are given in Figure S2. Figure 2 summarizes DALY inequality across HDI settings, where both the SII and the concentration curve showed burden concentrated in lower-HDI countries. Table 2 presents AAPC estimates stratified by super-region and sex. Time-series fit plots and residual diagnostics supporting the adequacy of the log-linear approximation are provided in Figure S2. DALY inequality across HDI settings is summarized in Figure 2. Both the SII and the concentration curve indicated a disproportionate concentration of disease burden in lower-HDI settings.

COVID-19-period deviations from pre-pandemic trends

Analysis of the COVID-19 period revealed heterogeneous-rather than uniformly negative-departures from pre-pandemic trajectories (Figures 3, S3). Globally, the observed average ASIR during 2020-2021 was 4.59 per 100,000, compared to an expected ASIR of 4.40 per 100,000, corresponding to a 4.3% excess. This global average should be interpreted in the context of substantial regional heterogeneity. The year 2021 contributed most of the global excess; South Asia showed the largest positive deviation; and Central Europe, Eastern Europe, and Central Asia remained below expected levels. Read together, these movements point to pandemic disruption of diagnosis and registry reporting that played out unevenly across regions, not to a genuine, across-the-board rise in how often the disease actually occurred.

Risk-factor profiles across HDI settings

Country-level risk-factor profiles based on official WHO data showed pronounced heterogeneity across HDI strata (Table S6; Figure S5). Median smoking prevalence increased from 11.0% in low-HDI countries to 21.2% in very-high-HDI countries; median smokeless tobacco prevalence was highest in medium-HDI settings (4.30%). Ecological analyses revealed that smoking prevalence was positively associated with GLOBOCAN 2022 ASIR (Spearman $\rho = 0.309$; $N = 157$; $P < 0.0001$), as was adult smokeless tobacco prevalence ($\rho = 0.233$; $N = 84$; $P = 0.0330$). HPV vaccination coverage showed no clear cross-country association with oral cavity cancer ASIR ($\rho = 0.094$; $N = 124$; $P = 0.2990$). These correlations are

Global burden and inequalities in lip and oral cavity cancer

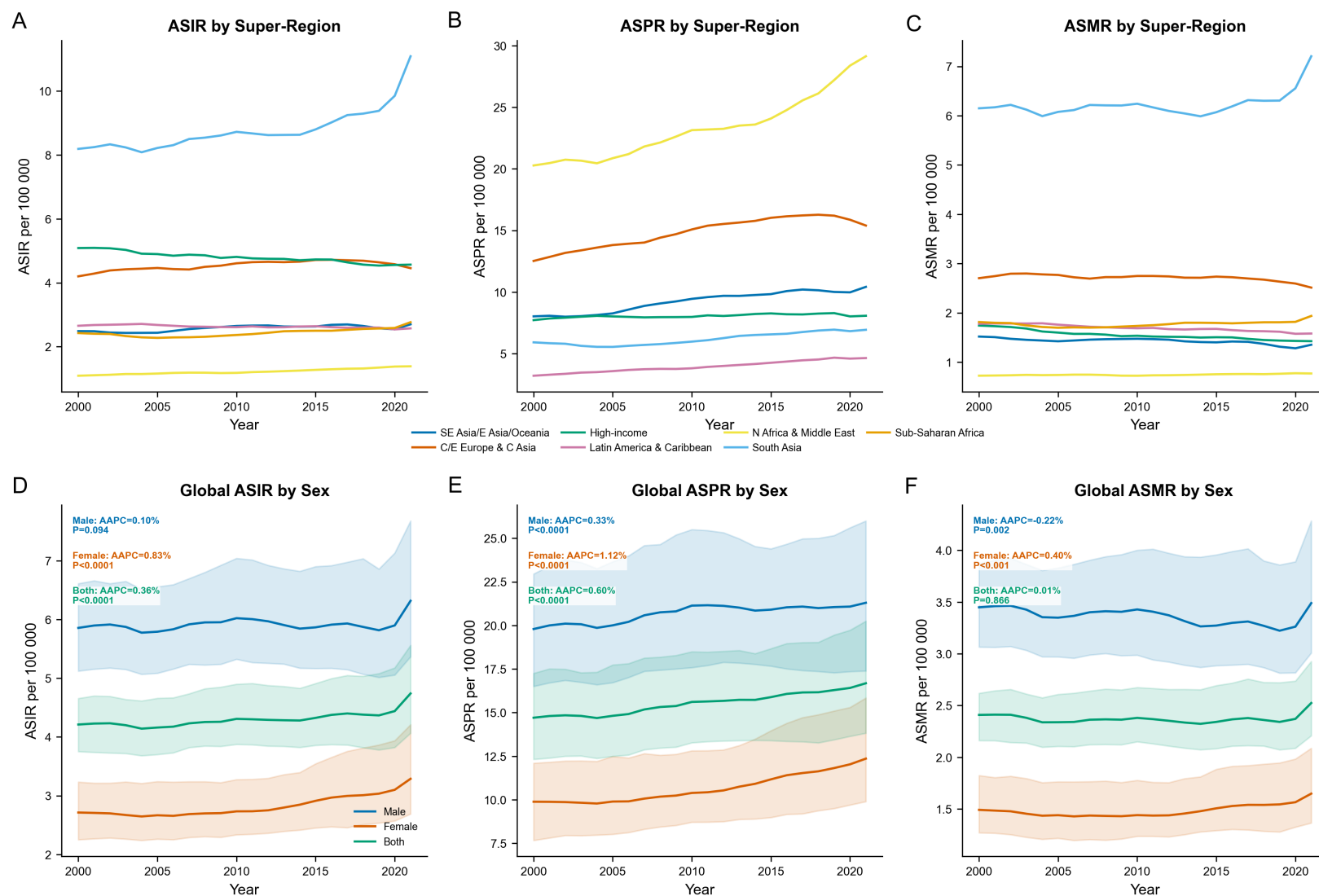


Figure 1. Temporal trends in age-standardized rates of lip and oral cavity cancer by GBD super-region and sex, 2000-2021. A-C. ASIR, ASPR, and ASMR by super-region, expressed per 100,000 population. D-F. Global sex-specific trends with 95% uncertainty intervals. AAPC values were estimated by full-period log-linear regression. Abbreviations: AAPC, average annual percent change; ASIR, age-standardized incidence rate; ASMR, age-standardized mortality rate; ASPR, age-standardized prevalence rate; GBD, Global Burden of Disease. Super-region location abbreviations: SE, Southeast; E, East; C/E, Central/Eastern; C, Central; N, North (SE Asia/E Asia/Oceania denotes Southeast Asia, East Asia, and Oceania; C/E Europe & C Asia denotes Central Europe, Eastern Europe, and Central Asia; N Africa & Middle East denotes North Africa and the Middle East).

Global burden and inequalities in lip and oral cavity cancer

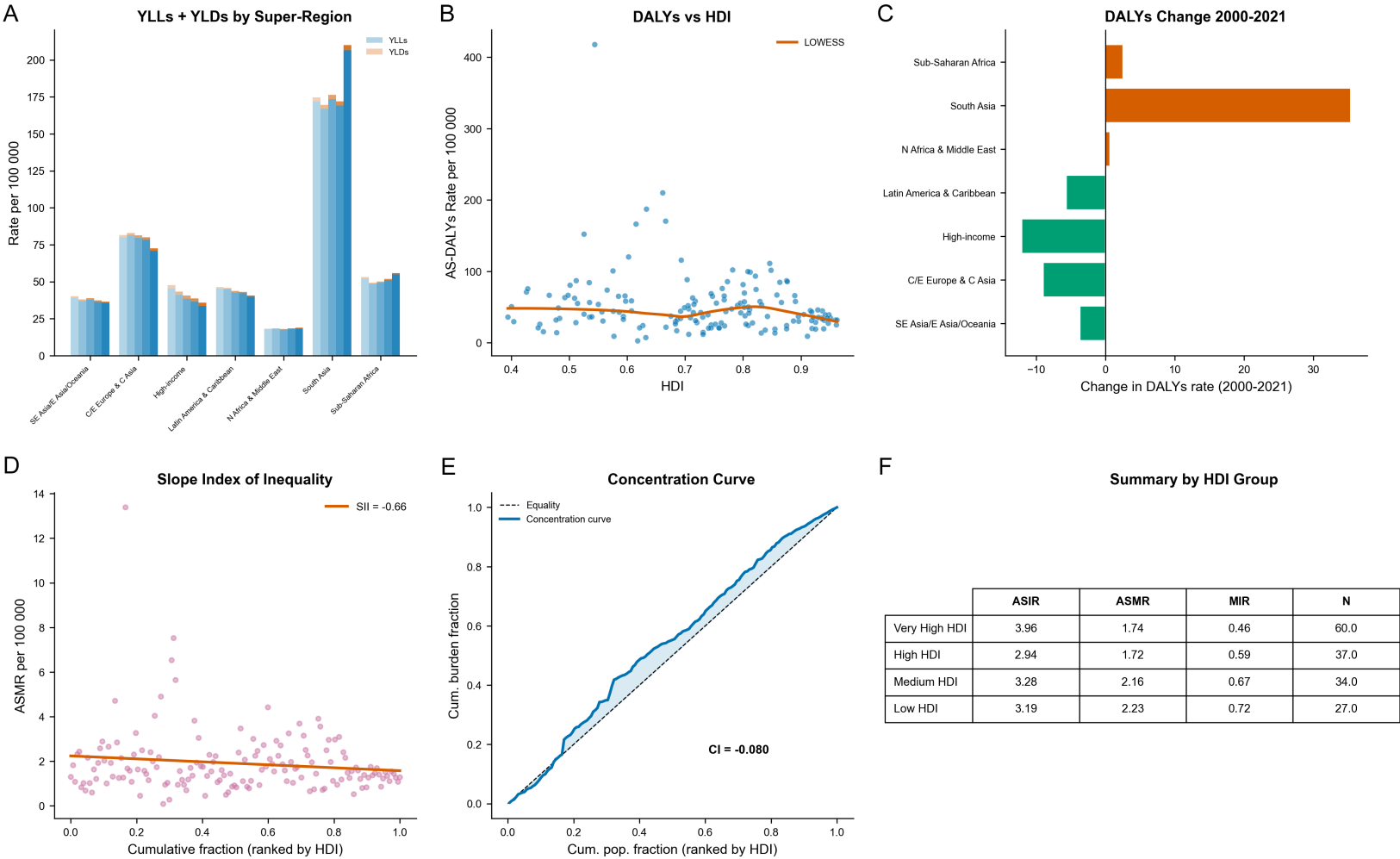


Figure 2. DALY inequality analysis for lip and oral cavity cancer. A. YLLs and YLDs by super-region. B. DALYs versus HDI with LOWESS smoothing. C. Change in DALYs from 2000 to 2021 versus HDI. D. Slope Index of Inequality. E. Concentration curve with Concentration Index. F. Summary by HDI group. Abbreviations: DALYs, disability-adjusted life-years; HDI, Human Development Index; LOWESS, locally weighted scatterplot smoothing; YLDs, years lived with disability; YLLs, years of life lost. Super-region location abbreviations: SE, Southeast; E, East; C/E, Central/Eastern; C, Central; N, North (SE Asia/E Asia/Oceania denotes Southeast Asia, East Asia, and Oceania; C/E Europe & C Asia denotes Central Europe, Eastern Europe, and Central Asia; N Africa & Middle East denotes North Africa and the Middle East).

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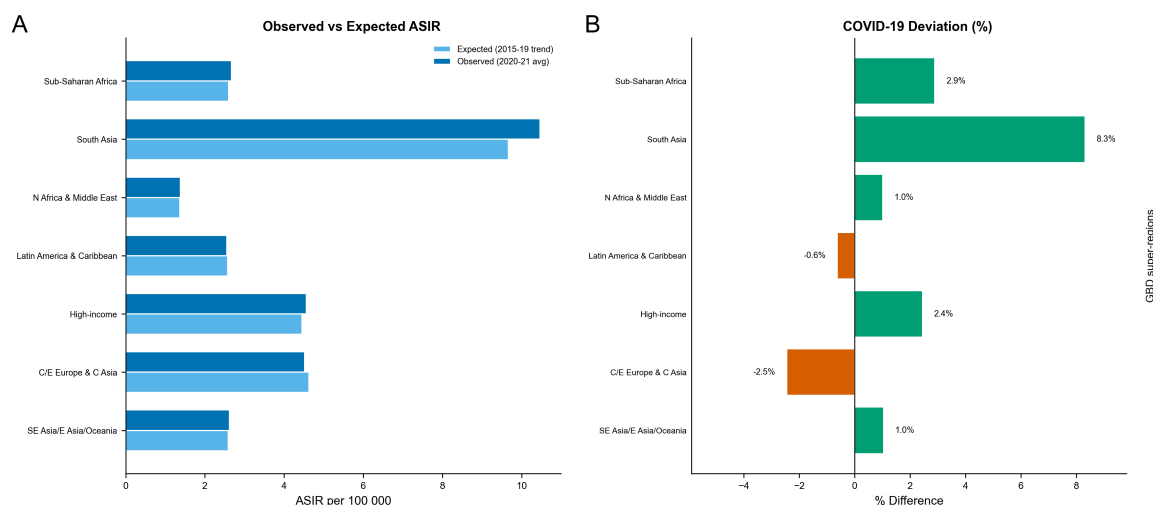


Figure 3. COVID-19-period deviations in lip and oral cavity cancer incidence, 2020-2021. A. Observed versus expected ASIR by GBD super-region based on log-linear extrapolation of 2015-2019 trends. B. Percentage deviation from pre-pandemic trends. Positive and negative departures are plotted apart because the regional picture was mixed; rather than a real short-term change in how common the disease is, they more plausibly reflect delayed diagnosis, disrupted referral, later catch-up, and uneven registry coverage. Abbreviations: ASIR, age-standardized incidence rate; GBD, Global Burden of Disease. Super-region location abbreviations: SE, Southeast; E, East; C/E, Central/Eastern; C, Central; N, North (SE Asia/E Asia/Oceania denotes Southeast Asia, East Asia, and Oceania; C/E Europe & C Asia denotes Central Europe, Eastern Europe, and Central Asia; N Africa & Middle East denotes North Africa and the Middle East).

summarized in [Table S7](#) and should be interpreted as ecological associations based on age-standardized rates.

Socioeconomic determinants of MIR

The country-level MIR greatly varied (median: 0.47, mean: 0.49). Countries with low HDI exhibited the highest MIR (0.70), followed by medium-HDI (0.58), high-HDI (0.45), and very-high-HDI countries (0.39). The Spearman correlation between HDI and MIR was -0.781 ($P < 0.0001$), indicating a strong inverse association. Country-level relationships of HDI with ASIR, ASMR, and MIR are shown in [Figure 5](#). Given that MIR is calculated from age-standardized rates and the disease definition combines lip cancer with intraoral cancers, lower MIR values in some high-income settings may reflect stronger health system performance and a larger proportion of favorable-prognosis lip cancer cases. In the prespecified high-completeness multivariable OLS model with HC3 robust standard errors ($N = 169$; [Table 3](#)), higher health expenditure per capita (multivariable beta = -0.0033, 95% CI -0.0044 to -0.0021; $P < 0.0001$) and greater physician density (multivariable beta = -0.0040, 95% CI -0.0054 to -0.0026; $P < 0.0001$) were independently asso-

ciated with lower MIR. In contrast, higher out-of-pocket expenditure was associated with higher MIR (multivariable beta = 0.0014, 95% CI 0.0001 to 0.0027; $P = 0.0383$). Univariate Spearman correlations and univariate OLS estimates showed directionally consistent associations across all 11 indicators ([Table 3](#)). Sensitivity analyses using logit-transformed OLS and boundary-adjusted beta regression yielded similar results ([Table S4](#)), supporting the robustness of primary OLS findings. Regression effect estimates are summarized in [Figure 6](#). Residual diagnostic plots for raw-MIR and logit-transformed MIR models are provided in [Figure S4](#).

Projections to 2050

Based on IARC Cancer Tomorrow demographic projections that assume constant age-specific rates [18], the global number of new lip and oral cavity cancer cases is projected to increase from 389,846 in 2022 to 613,311 in 2050, representing a 57.3% increase. Mortality is similarly projected to rise from 188,438 to 313,335 deaths, an increase of 66.3%. These projections reflect only the demographic component of future disease burden and exclude

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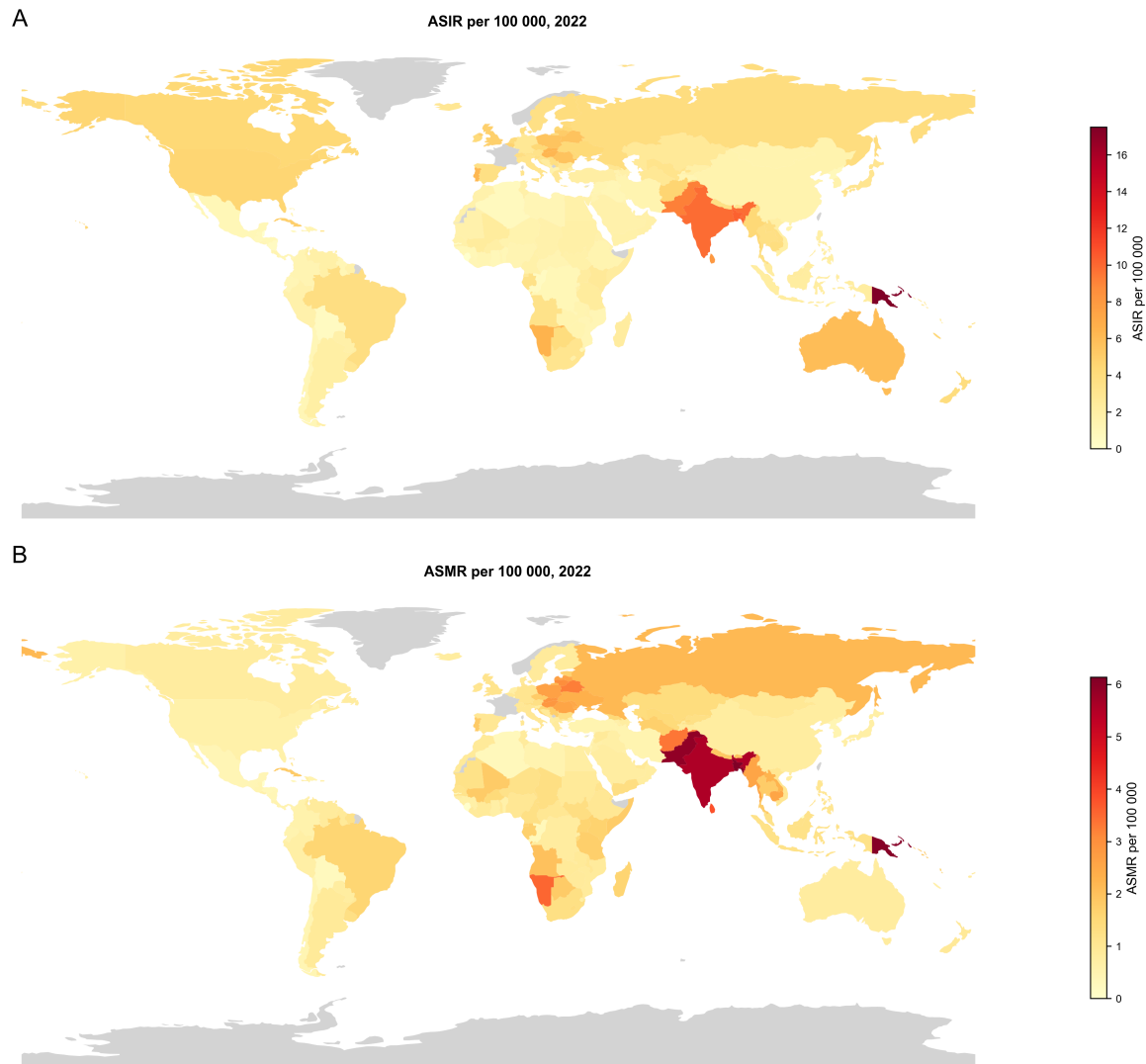


Figure 4. Contemporary global burden of lip and oral cavity cancer in 2022. A. World map of age-standardized incidence rate (ASIR) per 100,000 population. B. World map of age-standardized mortality rate (ASMR) per 100,000 population. Data source: GLOBOCAN 2022.

future changes in tobacco control, smokeless tobacco use, HPV vaccination, early detection, treatment access, or health care availability. In the PAF-based sensitivity analysis ([Table S9](#) and [Figure S8](#)), a modest 20% decrease in tobacco and smokeless tobacco exposure reduced the projected 2050 global incident case count to 577,480 (-5.8% versus baseline), whereas an aggressive 40% decrease lowered it to 534,972 (-12.8% versus baseline). Conversely, a continued-rise scenario with a 20% increase in exposure raised the projected case count to 643,859 (+5.0% versus baseline). The largest absolute reduction under the aggressive-control scenario was observed in

Asia (361,374 cases versus 419,244 under baseline scenario). A regional summary of the 2050 demographic baseline and the tobacco-exposure scenarios is presented in [Table 4](#). These projected trends and scenarios are illustrated in [Figures 7 and 8](#), and [S8](#).

Countries with the highest burden

By raw counts, the most cases were in India, China, and the United States, a reflection of population size. Ranking by ASIR gave a different order. The five highest ASIRs per 100,000 were in Papua New Guinea (17.50), Bangladesh (10.31), India (9.91), Pakistan (9.17), and Sri Lanka (8.08). Papua New Guinea stands

Global burden and inequalities in lip and oral cavity cancer

Table 1. Global and regional burden of lip and oral cavity cancer in 2021

Location	Type	ASIR (95% UI)	ASMR (95% UI)	ASPR (95% UI)	DALYs Rate (95% UI)	MIR
Global	Global	4.74 (4.06-5.56)	2.52 (2.21-2.93)	16.68 (13.82-20.25)	73.00 (63.34-84.87)	0.53
Global - Male	Global	6.32 (5.37-7.68)	3.49 (3.01-4.28)	21.30 (17.39-25.99)	99.98 (85.13-124.12)	0.55
Global - Female	Global	3.29 (2.69-4.21)	1.65 (1.37-2.09)	12.36 (9.90-15.84)	47.52 (38.16-61.24)	0.5
Central Europe, Eastern Europe, and Central Asia	Super Region	4.46 (4.01-4.89)	2.51 (2.38-2.64)	15.40 (13.01-18.02)	72.48 (68.44-76.83)	0.56
High-income	Super Region	4.57 (3.98-5.23)	1.43 (1.31-1.54)	N/A	35.73 (33.08-38.86)	0.31
Latin America and Caribbean	Super Region	2.57 (2.34-2.81)	1.58 (1.51-1.64)	8.08 (6.86-9.47)	40.71 (38.85-42.13)	0.61
North Africa and Middle East	Super Region	1.39 (1.10-1.72)	0.77 (0.63-0.96)	4.64 (3.57-5.93)	18.84 (15.32-23.37)	0.56
South Asia	Super Region	11.09 (8.91-13.70)	7.21 (5.91-8.79)	29.14 (22.54-37.31)	209.95 (171.86-256.34)	0.65
Southeast Asia, East Asia, and Oceania	Super Region	2.70 (2.32-3.16)	1.35 (1.21-1.56)	10.42 (8.46-12.82)	36.59 (32.58-42.35)	0.5
Sub-Saharan Africa	Super Region	2.77 (2.15-3.47)	1.94 (1.53-2.50)	6.94 (5.30-8.88)	55.80 (43.71-71.28)	0.7
Andean Latin America	Region	1.86 (1.57-2.15)	1.14 (1.00-1.30)	5.35 (4.31-6.49)	28.61 (25.00-32.55)	0.61
Australasia	Region	4.80 (4.06-5.60)	1.44 (1.30-1.55)	25.67 (20.92-31.09)	34.78 (32.13-37.52)	0.3
Caribbean	Region	3.81 (3.40-4.30)	2.30 (2.09-2.51)	11.87 (9.96-14.25)	59.13 (53.36-64.53)	0.6
Central Asia	Region	2.30 (2.02-2.58)	1.46 (1.33-1.59)	6.93 (5.77-8.24)	38.90 (35.33-42.40)	0.64
Central Europe	Region	5.27 (4.80-5.77)	2.86 (2.73-3.01)	18.92 (15.90-22.28)	80.32 (76.37-84.59)	0.54
Central Latin America	Region	1.68 (1.52-1.87)	1.04 (0.97-1.13)	5.32 (4.51-6.30)	24.98 (23.32-27.16)	0.62
Central Sub-Saharan Africa	Region	2.24 (1.64-2.93)	1.66 (1.23-2.21)	5.32 (3.78-7.17)	45.19 (33.51-60.65)	0.74
East Asia	Region	2.15 (1.84-2.48)	1.04 (0.92-1.16)	8.71 (7.11-10.76)	27.10 (24.26-29.99)	0.48
Eastern Europe	Region	4.60 (4.07-5.13)	2.60 (2.38-2.82)	15.89 (13.17-18.84)	78.24 (71.64-84.71)	0.57
Eastern Sub-Saharan Africa	Region	3.69 (2.81-4.78)	2.60 (2.00-3.40)	9.05 (6.79-11.74)	76.01 (58.15-98.70)	0.7
High-income Asia Pacific	Region	2.01 (1.74-2.30)	1.18 (1.03-1.31)	N/A	26.26 (23.89-28.82)	0.58
High-income North America	Region	5.83 (4.91-6.80)	1.41 (1.28-1.54)	32.50 (26.66-39.18)	35.60 (32.64-39.13)	0.24
North Africa and Middle East	Region	1.39 (1.10-1.72)	0.77 (0.63-0.96)	4.64 (3.57-5.93)	18.84 (15.32-23.37)	0.56
Oceania	Region	2.90 (2.15-3.72)	1.73 (1.32-2.27)	9.49 (7.11-12.48)	49.79 (37.57-66.15)	0.6
South Asia	Region	11.09 (8.91-13.70)	7.21 (5.91-8.79)	29.14 (22.54-37.31)	209.95 (171.86-256.34)	0.65
Southeast Asia	Region	4.34 (3.51-5.39)	2.37 (1.95-2.87)	15.14 (11.80-19.22)	64.02 (52.21-78.27)	0.55
Southern Latin America	Region	2.35 (2.08-2.64)	1.29 (1.18-1.39)	8.47 (7.06-10.12)	32.53 (29.98-35.36)	0.55
Southern Sub-Saharan Africa	Region	3.27 (2.70-3.95)	2.25 (1.86-2.69)	7.99 (6.37-9.80)	63.27 (52.60-75.54)	0.69
Tropical Latin America	Region	3.37 (3.05-3.67)	2.08 (1.97-2.18)	10.71 (9.16-12.69)	55.61 (53.05-58.12)	0.62
Western Europe	Region	5.05 (4.42-5.78)	1.56 (1.43-1.67)	26.71 (22.75-31.41)	40.46 (37.38-43.59)	0.31
Western Sub-Saharan Africa	Region	1.92 (1.46-2.48)	1.31 (1.02-1.65)	5.17 (3.86-6.93)	38.22 (29.70-47.99)	0.69

Age-standardized incidence rate (ASIR), mortality rate (ASMR), prevalence rate (ASPR), and DALY rate with 95% uncertainty intervals, as well as mortality-to-incidence ratio (MIR). Data source: GBD 2021. Abbreviations: ASIR, age-standardized incidence rate; ASMR, age-standardized mortality rate; ASPR, age-standardized prevalence rate; DALYs, disability-adjusted life-years; GBD, Global Burden of Disease; MIR, mortality-to-incidence ratio; UI, uncertainty interval.

Table 2. Average annual percent change (AAPC) in age-standardized incidence and mortality rates of lip and oral cavity cancer by GBD super-region and sex, 2000-2021

Location	Sex	ASIR AAPC (95% CI)	ASIR <i>p</i> -value	ASMR AAPC (95% CI)	ASMR <i>p</i> -value
Global	Both	0.36 (0.24, 0.48)	<0.0001	0.01 (-0.12, 0.14)	0.8657
Global	Male	0.10 (-0.02, 0.22)	0.0942	-0.22 (-0.35, -0.09)	0.0023
Global	Female	0.83 (0.63, 1.03)	<0.0001	0.40 (0.20, 0.60)	0.0004
Central Europe, Eastern Europe, and Central Asia	Both	0.39 (0.24, 0.54)	<0.0001	-0.27 (-0.39, -0.15)	0.0002
Central Europe, Eastern Europe, and Central Asia	Male	-0.10 (-0.30, 0.09)	0.27	-0.67 (-0.83, -0.51)	<0.0001
Central Europe, Eastern Europe, and Central Asia	Female	1.75 (1.66, 1.84)	<0.0001	0.87 (0.78, 0.95)	<0.0001
High-income	Both	-0.53 (-0.59, -0.48)	<0.0001	-0.89 (-1.01, -0.78)	<0.0001
High-income	Male	-0.95 (-1.01, -0.89)	<0.0001	-1.32 (-1.43, -1.20)	<0.0001
High-income	Female	0.27 (0.19, 0.34)	<0.0001	-0.09 (-0.22, 0.04)	0.1649
Latin America and Caribbean	Both	-0.21 (-0.27, -0.15)	<0.0001	-0.59 (-0.65, -0.53)	<0.0001
Latin America and Caribbean	Male	-0.30 (-0.39, -0.22)	<0.0001	-0.61 (-0.70, -0.53)	<0.0001
Latin America and Caribbean	Female	0.08 (-0.01, 0.16)	0.0894	-0.45 (-0.53, -0.36)	<0.0001
North Africa and Middle East	Both	1.07 (1.00, 1.13)	<0.0001	0.24 (0.18, 0.30)	<0.0001
North Africa and Middle East	Male	0.62 (0.53, 0.70)	<0.0001	-0.06 (-0.13, 0.02)	0.1268
North Africa and Middle East	Female	1.67 (1.60, 1.74)	<0.0001	0.71 (0.63, 0.78)	<0.0001
South Asia	Both	0.97 (0.78, 1.15)	<0.0001	0.31 (0.15, 0.47)	0.0003
South Asia	Male	0.85 (0.64, 1.06)	<0.0001	0.27 (0.08, 0.46)	0.0055
South Asia	Female	1.21 (0.99, 1.43)	<0.0001	0.47 (0.29, 0.64)	<0.0001
Southeast Asia, East Asia, and Oceania	Both	0.43 (0.26, 0.60)	<0.0001	-0.52 (-0.69, -0.35)	<0.0001
Southeast Asia, East Asia, and Oceania	Male	0.84 (0.59, 1.10)	<0.0001	-0.11 (-0.35, 0.14)	0.3726
Southeast Asia, East Asia, and Oceania	Female	-0.43 (-0.61, -0.25)	<0.0001	-1.53 (-1.68, -1.37)	<0.0001
Sub-Saharan Africa	Both	0.61 (0.40, 0.83)	<0.0001	0.27 (0.08, 0.45)	0.0077
Sub-Saharan Africa	Male	0.26 (0.05, 0.48)	0.0188	0.03 (-0.17, 0.24)	0.7554
Sub-Saharan Africa	Female	1.16 (0.90, 1.42)	<0.0001	0.71 (0.48, 0.93)	<0.0001

AAPC values were estimated using log-linear regression; exact *P* values are provided in separate columns. Abbreviations: AAPC, average annual percent change; CI, confidence interval; GBD, Global Burden of Disease.

apart. Its high ASIR most likely reflects the widespread chewing of betel quid, tobacco, and slaked-lime mixtures across parts of Melanesia. Lip cancer (ICD-10 C00) is largely sun-driven and usually carries a better prognosis, yet both GBD and GLOBOCAN count it together with the intraoral sites (ICD-10 C02-C06), and the balance between the two shifts from country to country [31]. A nation with proportionally more lip cancer can therefore record a lower MIR through case mix rather than better care.

Discussion

We set out to describe the global burden of lip and oral cavity cancer by pairing GBD 2021 and GLOBOCAN 2022 against each other rather than leaning on either alone, working from a single set of countries and years. Within that frame, we tracked long-term trends and tested how closely the two databases agree, tied the burden to risk factors and to socioeconomic

inequality, asked what the pandemic years did to the numbers, and gauged the demographic pressure still to come. A few findings deserve emphasis.

The burden today is large—an estimated 389,846 new cases and 188,438 deaths in 2022—and it is far from evenly shared. South Central Asia carries a portion of both incidence and mortality well out of proportion to its population, in line with earlier work and with the heavy use of smokeless tobacco and betel quid across the Indian subcontinent [6, 32]. A pattern this skewed argues for prevention shaped to local exposures rather than a single global template [6, 8, 32, 33].

Temporal trends varied considerably across GBD super-regions. ASIR declined significantly in the high-income super-region (AAPC -0.53%), likely reflecting decades of tobacco-control policy, public-health campaigns, and improv-

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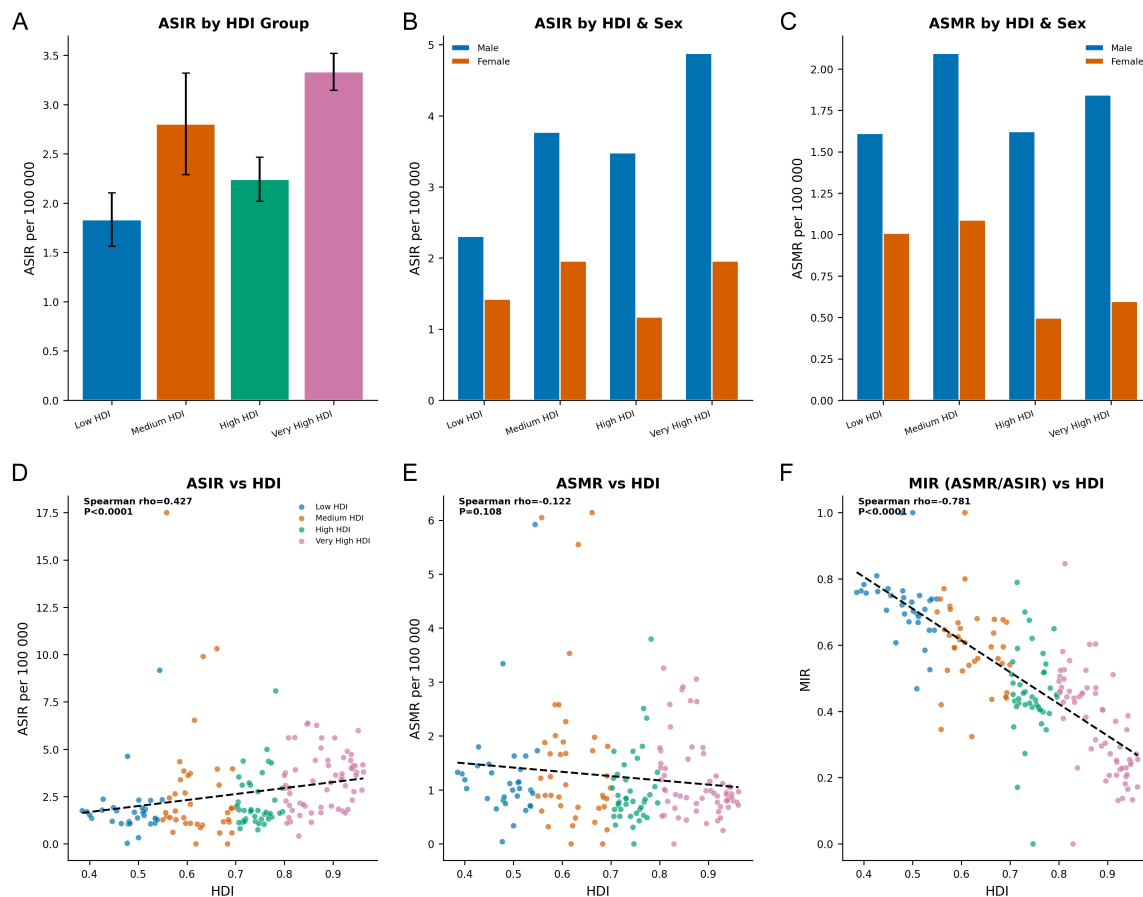


Figure 5. HDI analysis of lip and oral cavity cancer burden using country-level GLOBOCAN 2022 estimates. A. ASIR by HDI group. B, C. Sex-stratified ASIR and ASMR by HDI group. D-F. Country-level scatter plots of ASIR, ASMR, and MIR versus HDI. MIR was defined as ASMR/ASIR, and panel annotations represent Spearman rank correlations. Abbreviations: ASIR, age-standardized incidence rate; ASMR, age-standardized mortality rate; HDI, Human Development Index; MIR, mortality-to-incidence ratio.

ed dental care [8, 34, 35], and Latin America and the Caribbean showed a modest decline (-0.21%). The incidence increased in all other super-regions, most steeply in North Africa and the Middle East (AAPC 1.07%), followed by South Asia (0.97%) and Sub-Saharan Africa (0.61%), increases that may reflect rising tobacco and smokeless tobacco use, betel quid exposure, population aging, and improving cancer-registry completeness [32, 33, 36]. Country-level analyses were consistent with this interpretation: both smoking prevalence and smokeless tobacco use correlated positively with ASIR, with smokeless tobacco use concentrated in lower- and middle-development settings, whereas HPV vaccination coverage showed no clear etiologic association with oral cavity cancer ASIR, consistent with the predominant role of HPV in oropharyngeal can-

cers that lay outside the disease scope of this study (ICD-10 C00 and C02-C06) [7, 37].

The COVID-19-period analysis is more consistent with disrupted detection than with uniform suppression of cancer detection. Observed ASIRs during 2020-2021 exceeded pre-pandemic expectations globally and in South Asia, Sub-Saharan Africa, and the high-income super-region but remained below expectation in Central Europe, Eastern Europe, and Central Asia, a split largely attributable to timing: some regions experienced temporary reductions in diagnosis during 2020 followed by rebounds in 2021 as deferred cases were identified, whereas others had not yet restored referral pathways, pathology services, or registry reporting. Because treatment delays are associated with worse cancer outcomes [38], these short-term

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Table 3. Socioeconomic correlates of the mortality-to-incidence ratio (MIR) for lip and oral cavity cancer

Indicator	N	Spearman r (p-value)	Univariate Beta (95% CI, p)	Multivariate Beta (95% CI, p)
hdi_value	173	-0.781 (P<0.0001)	-0.9586 (-1.0613, -0.8559, P<0.0001)	Not in primary multivariable model
GDP per capita PPP (per 1000 USD)	168	-0.751 (P<0.0001)	-0.0042 (-0.0054, -0.0031, P<0.0001)	Not in primary multivariable model
Health expenditure per capita (per 100 USD)	173	-0.757 (P<0.0001)	-0.0055 (-0.0069, -0.0042, P<0.0001)	-0.0033 (-0.0044, -0.0021, P<0.0001)
Current health expenditure (% of GDP)	173	-0.389 (P<0.0001)	-0.0194 (-0.0354, -0.0035, P=0.0169)	Not in primary multivariable model
Out-of-pocket expenditure (% of CHE)	173	0.392 (P<0.0001)	0.0040 (0.0025, 0.0055, P<0.0001)	0.0014 (0.0001, 0.0027, P=0.0383)
Medical doctors (per 10,000 population)	169	-0.673 (P<0.0001)	-0.0067 (-0.0082, -0.0052, P<0.0001)	-0.0040 (-0.0054, -0.0026, P<0.0001)
Nursing and midwifery personnel (per 10,000 population)	171	-0.671 (P<0.0001)	-0.0033 (-0.0038, -0.0027, P<0.0001)	Not in primary multivariable model
Tobacco smoking prevalence (age-standardized %)	155	-0.244 (P=0.0023)	-0.0033 (-0.0058, -0.0008, P=0.0085)	Not in primary multivariable model
Alcohol per capita (15+) consumption (litres pure alcohol)	166	-0.128 (P=0.1015)	-0.0020 (-0.0069, 0.0029, P=0.4293)	Not in primary multivariable model
UHC service coverage index	173	-0.715 (P<0.0001)	-0.0082 (-0.0096, -0.0068, P<0.0001)	Not in primary multivariable model
Urban population (% of total)	173	-0.608 (P<0.0001)	-0.0049 (-0.0061, -0.0038, P<0.0001)	Not in primary multivariable model
GDP per capita (per 1000 USD)	28	-0.634 (P=0.0003)	-0.0065 (-0.0103, -0.0027, P=0.0008)	Not in primary multivariable model
Literacy rate adult total (%)	15	-0.711 (P=0.0030)	-0.0052 (-0.0072, -0.0032, P<0.0001)	Not in primary multivariable model
Life expectancy at birth (years)	28	-0.689 (P<0.0001)	-0.0195 (-0.0265, -0.0125, P<0.0001)	Not in primary multivariable model

Spearman correlations, univariate OLS regression with HC3 robust standard errors, and a prespecified high-completeness multivariable OLS model. Economic variables were rescaled for interpretability (GDP per 1,000 USD; health expenditure per 100 USD). Sample size varied according to indicator availability (see Methods). Abbreviations: CI, confidence interval; GDP, gross domestic product; HC3, heteroscedasticity-consistent (type 3); MIR, mortality-to-incidence ratio; OLS, ordinary least squares.

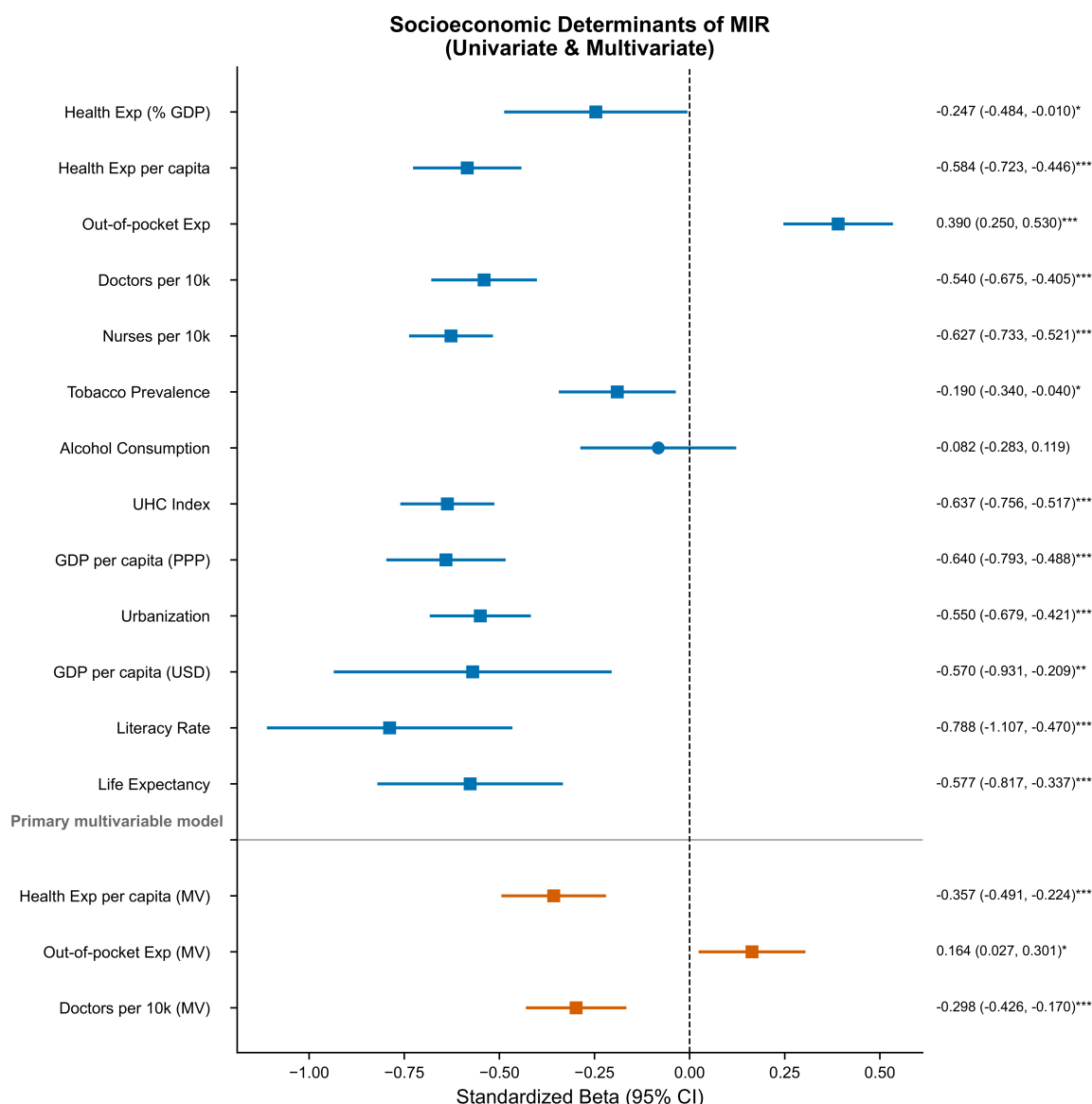


Figure 6. Forest plot of socioeconomic predictors of the mortality-to-incidence ratio. The upper section shows univariate standardized beta coefficients with 95% confidence intervals. The lower section shows the prespecified high-completeness multivariable model including health expenditure per capita, out-of-pocket expenditure, and physician density. Symbols denote statistical significance of the plotted coefficients (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$). Abbreviations: CI, confidence interval; MIR, mortality-to-incidence ratio.

disruptions carry clinical implications even where underlying incidence is unchanged; the present ecological analysis cannot separate delayed diagnosis, backlog clearance, and incomplete reporting, and the regional pattern appears to track health-system capacity and screening policy more than any single cause, with early declines predominating where screening was organised or registries were robust and apparent increases where reporting relies on later registry consolidation.

MIR declined steeply as development increased (Spearman $\rho = -0.781$). In the high-completeness multivariable model, lower health expenditure per capita, higher out-of-pocket spending, and lower physician density were each independently associated with a higher MIR. The gradient was pronounced, with MIR of 0.70 in low-HDI countries versus 0.39 in very-high-HDI countries, consistent with reports for other cancers [16, 17], suggesting that outcome inequality in lip and oral cavity cancer

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Table 4. Projected 2050 incident cases of lip and oral cavity cancer by region under the demographic baseline (constant age-specific rates) and tobacco-exposure sensitivity scenarios

Region	2050 baseline cases	Modest control (-20% exposure)	Aggressive control (-40% exposure)	Continued rise (+20% exposure)
Africa	36,112	34,561 (-4.3%)	32,860 (-9.0%)	37,531 (+3.9%)
Latin America and the Caribbean	35,856	34,272 (-4.4%)	32,502 (-9.4%)	37,282 (+4.0%)
Northern America	42,514	40,500 (-4.7%)	38,243 (-10.0%)	44,320 (+4.2%)
Europe	72,441	68,424 (-5.5%)	63,646 (-12.1%)	75,864 (+4.7%)
Oceania	7,144	6,769 (-5.2%)	6,347 (-11.2%)	7,478 (+4.7%)
Asia	419,244	392,954 (-6.3%)	361,374 (-13.8%)	441,384 (+5.3%)
Global	613,311	577,480 (-5.8%)	534,972 (-12.8%)	643,859 (+5.0%)

Figures are projected incident case counts, with percentages showing the change against each region's 2050 baseline. Scenarios: -20% and -40% represent modest and aggressive cuts in combustible and smokeless tobacco exposure, and +20% a continued rise. Source: IARC Cancer Tomorrow projections together with a population-attributable-fraction analysis (full detail in Table S9).

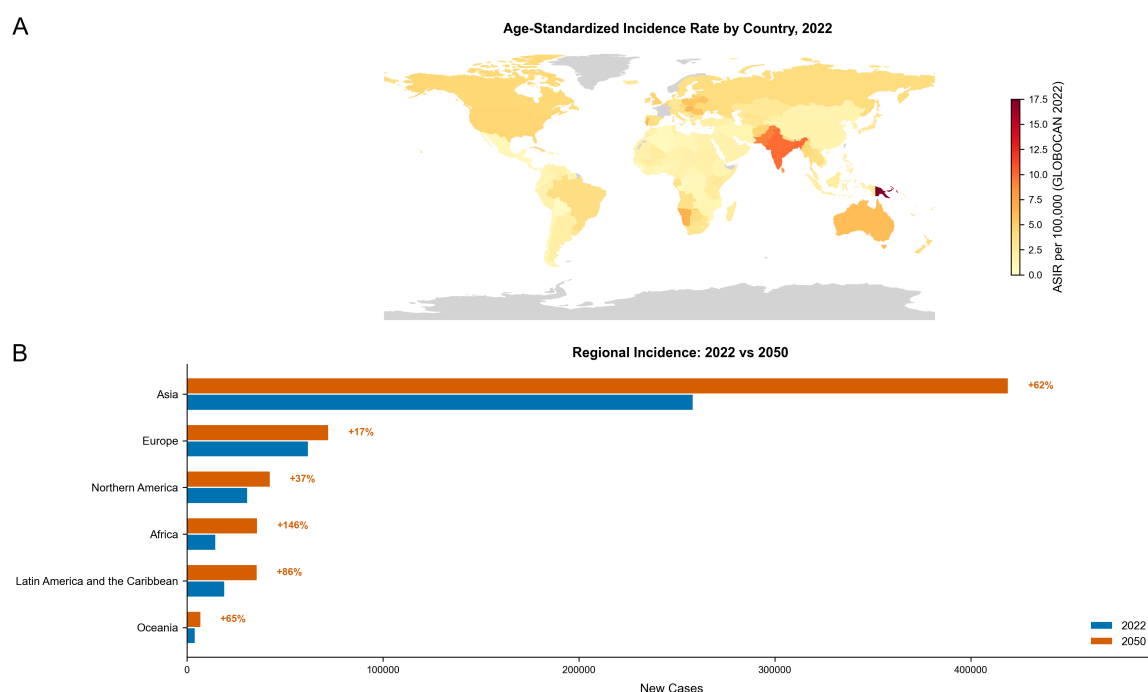


Figure 7. Global lip and oral cavity cancer incidence: current burden and 2050 demographic projections. A. Age-standardized incidence rate (ASIR) by country, GLOBOCAN 2022. B. Projected new cases compared between 2022 and 2050, holding age-specific rates constant as in IARC Cancer Tomorrow.

may be influenced by treatment capacity and financial protection. Plausible contributors include delayed presentation, limited access to surgery and radiotherapy, and inadequate pathology services in resource-limited settings [2, 5, 10].

Our analysis is ecological and describes associations at the population level rather than biological mechanism; those mechanisms are, however, well established. Tobacco smoke and

smokeless tobacco deliver carcinogens, including tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons, that form DNA adducts and drive field cancerization in the oral mucosa, with alcohol acting as a co-carcinogen, consistent with the dose-related risks reported in pooled analyses [29]. Socioeconomic position operates differently, acting upstream of tumourigenesis by shaping exposure, oral-health behaviour, health literacy, time to diagnosis, and cost, and thereby influencing

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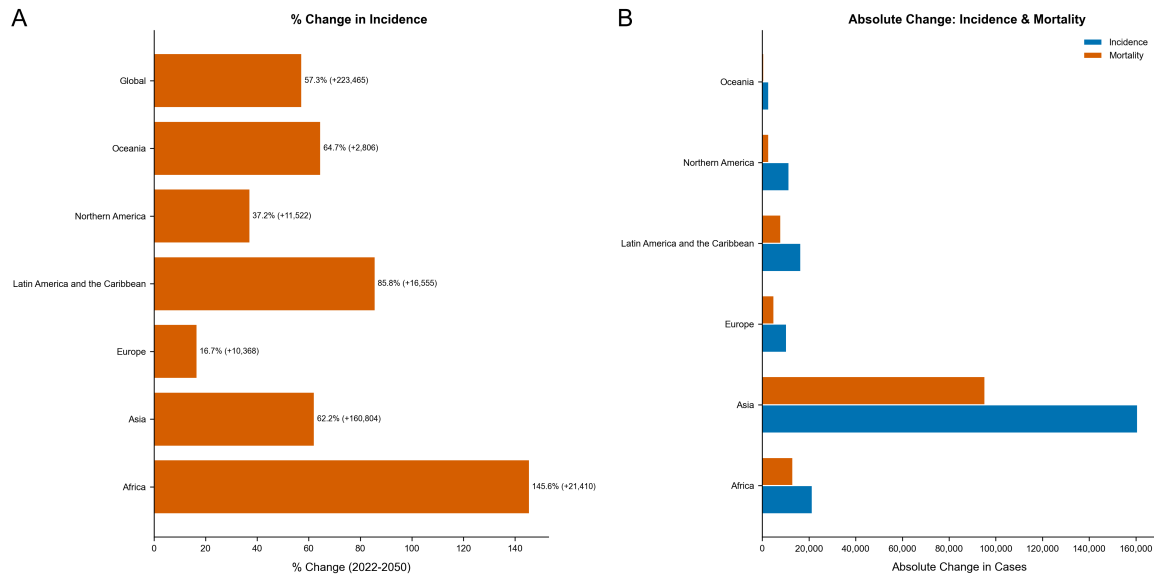


Figure 8. Projected changes in lip and oral cavity cancer burden, 2022-2050. A. Percentage change in incidence by region. B. Absolute changes in incident cases and deaths. The projections isolate demographic change and leave out any future shift in risk factors or health-system capacity.

both risk and outcome [5, 9]. We collected nothing molecular, cellular or animal, so none of these pathways can be tested with our data; we raise them only as established background, outside the scope of the present study.

By 2050 the case count looks set to climb steeply, and the arithmetic behind it is largely demographic—more people, living longer—with the sharpest rises falling where the burden is already heavy. Because IARC Cancer Tomorrow assumes constant age-specific rates, it isolates demographic effects while excluding epidemiologic transition; actual future trends will depend on risk-factor exposure, early detection, treatment access, and registry completeness, and the 2050 estimates should therefore be interpreted as a demographic baseline rather than a comprehensive forecast.

Whereas several earlier studies estimated burden from GBD or GLOBOCAN alone [10-12], we compared GBD 2021 and GLOBOCAN 2022 directly. The two databases agree on the broad picture but differ systematically at the country level, with discrepancies clustering in lower-HDI settings, differences traceable to data construction: GBD uses statistical modelling that borrows strength across locations and years, whereas GLOBOCAN relies on registry data whose coverage is sparser in many low-HDI

countries [16, 17]. The shared ICD grouping of lip (C00) and intraoral (C02-C06) cancers introduces further between-country differences in subsite mix. We therefore treated the databases as complementary rather than interchangeable and did not pool or rescale them into a single corrected value; the Bland-Altman analysis quantifies their disagreement without removing it [19], and where estimates diverged we interpreted the registry-based GLOBOCAN and modelled GBD figures side by side [14]. The analytical framework rests on standard inequality measures, namely the SII, the Concentration Index, MIR modelling, and Bland-Altman agreement, together with official WHO risk-factor indicators and IARC Cancer Tomorrow projections.

Alves-Costa et al. [13] recently undertook a broader GBD-based analysis of lip and oral cavity cancer together with dental caries and other oral conditions across 204 countries, projecting a larger increase in incidence by 2050. Although the overall projected trend is consistent with ours, their mixed-effects Socio-demographic Index model differs from our IARC Cancer Tomorrow analysis, which isolated the demographic component of future burden under constant age-specific rates; the two studies are therefore complementary rather than overlapping, with their analysis emphasising macro-level disease growth and

ours providing greater detail on cross-database concordance, health-care inequality, and pandemic-related deviations relevant to cancer-control planning.

These findings have direct implications for global cancer control. In lower-HDI settings with high MIRs, priorities are to expand post-diagnosis treatment and to strengthen the entire care pathway, from prevention and early recognition through referral, pathology, surgery, radiotherapy, and financial protection; primary care-based visual inspection, reliable referral, access to pathology, and affordable treatment are most effective as an integrated package rather than as isolated interventions [2, 39]. Because cancer care also imposes substantial macroeconomic costs, investment in earlier diagnosis and expanded treatment capacity is likely to yield both economic and survival benefits [40].

In South and Southeast Asia, prevention should remain focused on smokeless tobacco use, betel quid chewing, and combined tobacco-lime exposure, risk factors that help explain the coexistence of high absolute burden and elevated ASIRs in the region. Although HPV-related oropharyngeal cancer is a related entity, it lies beyond the disease definition used here, and the present findings should not be extrapolated to HPV-driven oropharyngeal cancers.

The collective evidence supports several concrete actions for cancer control. Primary prevention should continue to emphasise tobacco and smokeless tobacco control, given the positive associations with ASIR across HDI strata and the concentration of burden in South Asia and Sub-Saharan Africa, while early detection through primary care-based visual inspection is supported by the pronounced MIR gradient (0.70 in low-HDI versus 0.39 in very-high-HDI settings) and by improved survival among screened high-risk populations [39]. Financial protection should be strengthened where out-of-pocket expenditure independently predicts higher MIR (multivariable $\beta = 0.0014$, $P = 0.038$), particularly in lower- and middle-HDI countries, and treatment capacity expanded where physician density independently predicts lower MIR (multivariable $\beta = -0.0040$, $P < 0.0001$), reducing delays between diagnosis and treatment [38]. Finally, region-specific planning should integrate demographic projections with the tobacco-control scenarios in [Table S9](#), under which a 40% reduction in to-

bacco-related exposure could prevent approximately 78,000 cases worldwide by 2050 relative to the constant-rate baseline. Together, these measures translate the epidemiological, inequality, and projection findings into a practical framework for national cancer-control planning.

These priorities can be organised by development setting, translating broad recommendations into concrete, setting-specific action. In low-HDI countries, which carry the highest MIR, the most immediate gains lie in curbing smokeless tobacco and betel quid use, introducing low-cost visual inspection of the oral cavity in primary care, and ensuring dependable referral, pathology, and treatment supported by financial protection [5, 39]. Medium-HDI countries can additionally pursue opportunistic screening of high-risk adults, principally heavy tobacco or areca users, most effectively when treatment capacity grows in parallel [38, 39]. In high- and very-high-HDI countries, where incidence is comparatively low and often declining, the more appropriate target is the residual high-risk group, addressed through risk-based surveillance and prompt specialist referral rather than population-wide screening [9]; the care pathway is common to all settings, and only the point of entry shifts with available resources.

That projected growth makes these steps more pressing in South and Southeast Asia and in Sub-Saharan Africa, the regions whose health systems can least afford the extra case-load [2, 5, 40]. Looking ahead means reading the demographic projections together with what could change in risk: a constant-rate forecast captures population growth and aging, but it cannot show what tighter smokeless-tobacco control or wider early detection would actually achieve.

A few limitations follow from the design. Because it is ecological, every association is a statement about countries, not individuals, and reading it as individual-level cause and effect would be a mistake; with only aggregated data and no molecular, cellular or patient-level samples, the biological mechanisms we discuss come from earlier work rather than from anything we measured here. The pandemic-era figures are departures from extrapolated trends, and on their own they cannot separate delayed diagnosis from backlog clearance from plain

under-reporting, while country-to-country differences in how care is resourced and screening is organised cloud the picture further. GBD and GLOBOCAN cannot be used interchangeably, and because lip (C00) and the intraoral sites (C02-C06) sit in one shared ICD grouping, the data say little about individual subsites. Finally, the 2050 projections deliberately hold age-specific rates fixed to isolate demographic change, so they are not forecasts and reveal nothing about future shifts in risk factors, screening or treatment.

Conclusion

Lip and oral cavity cancer is a large and growing burden: some 389,846 new cases in 2022, and demographic change alone is on track to add 57.3% more by 2050. Placed side by side, GBD 2021 and GLOBOCAN 2022 tell broadly the same story at the global scale but cannot stand in for one another country by country, least of all in the poorest settings-where our inequality measures, the SII, the Concentration Index and the MIR, exposed the widest gaps in both who develops the disease and who survives it. Real progress will turn on sustained work against tobacco and smokeless tobacco, on catching disease earlier, and on making treatment both reachable and affordable, with the poorest health systems needing it most.

Disclosure of conflict of interest

None.

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Global burden and inequalities in lip and oral cavity cancer

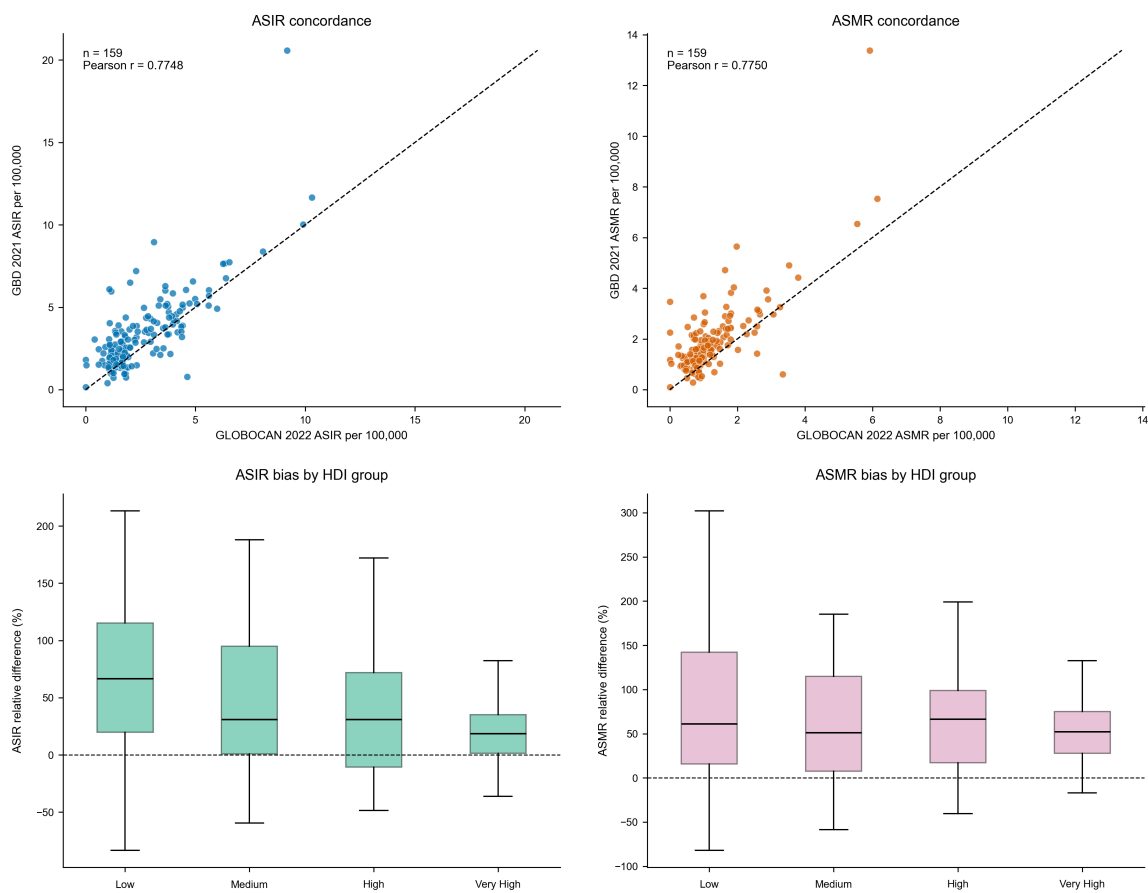


Figure S1. Concordance between GBD 2021 and GLOBOCAN 2022.

Global burden and inequalities in lip and oral cavity cancer

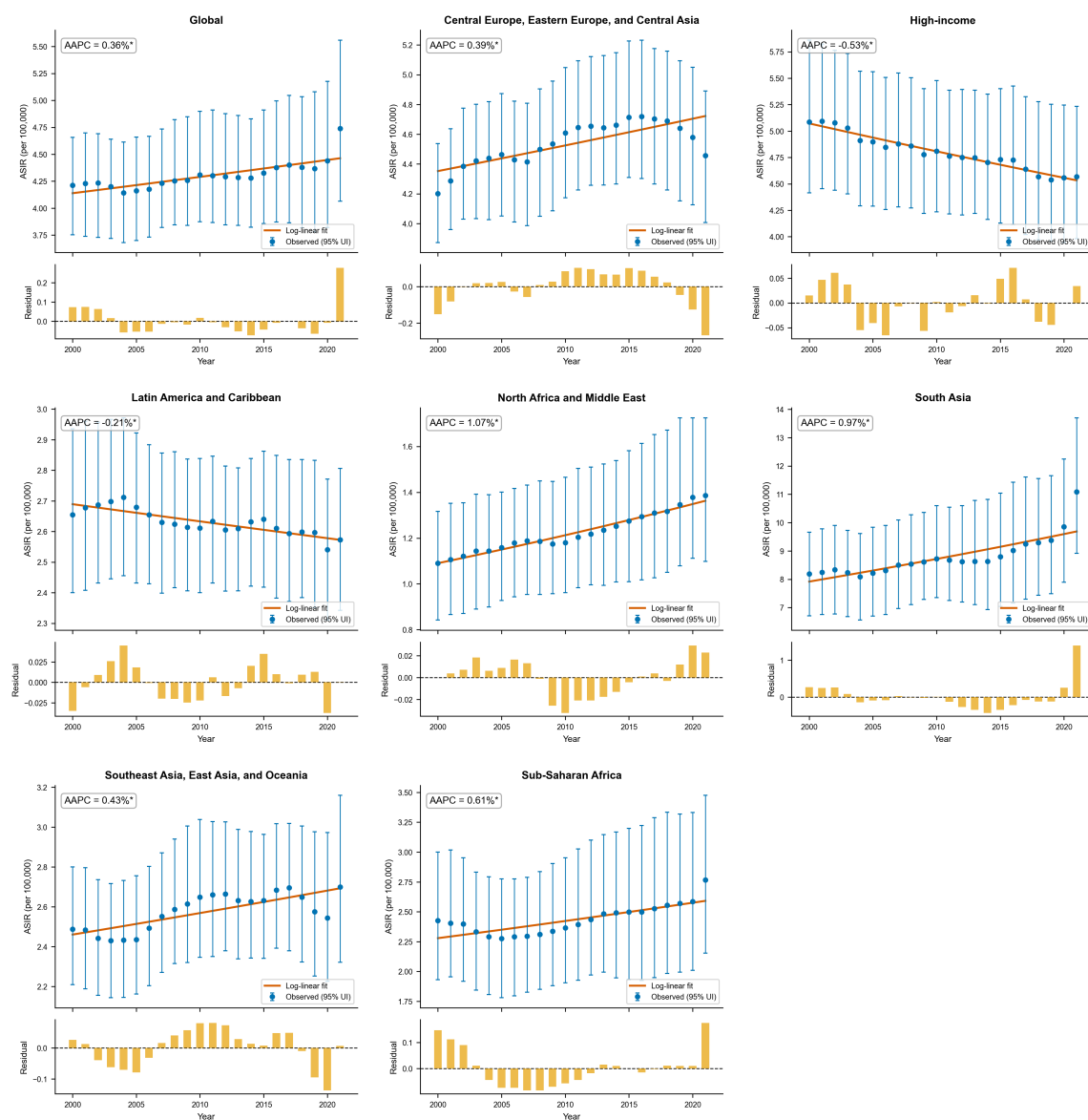


Figure S2. Age-standardized incidence rate time-series fits with residuals (2000-2021).

Global burden and inequalities in lip and oral cavity cancer

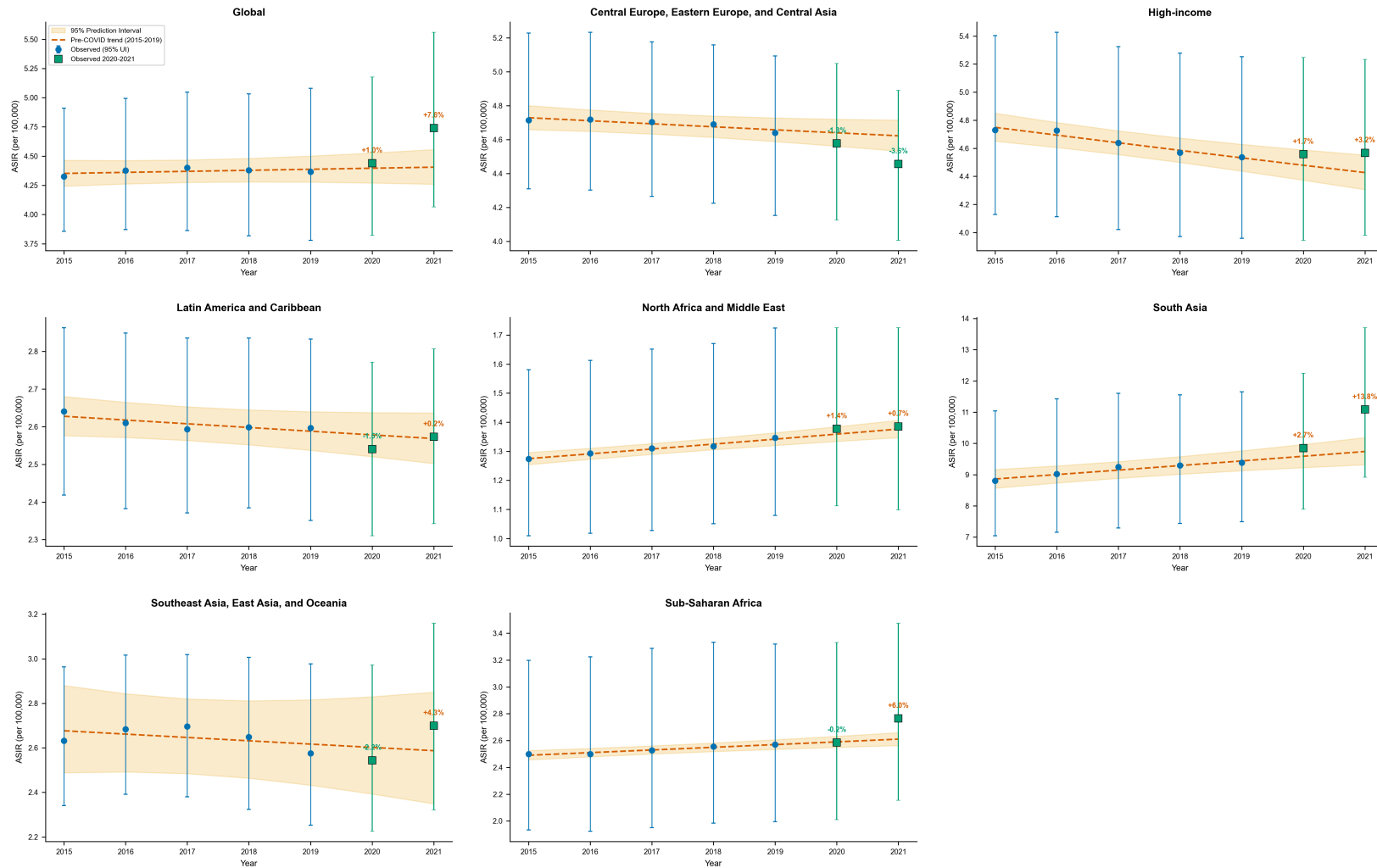


Figure S3. COVID-19 impact on ASIR with 95% prediction intervals.

Global burden and inequalities in lip and oral cavity cancer

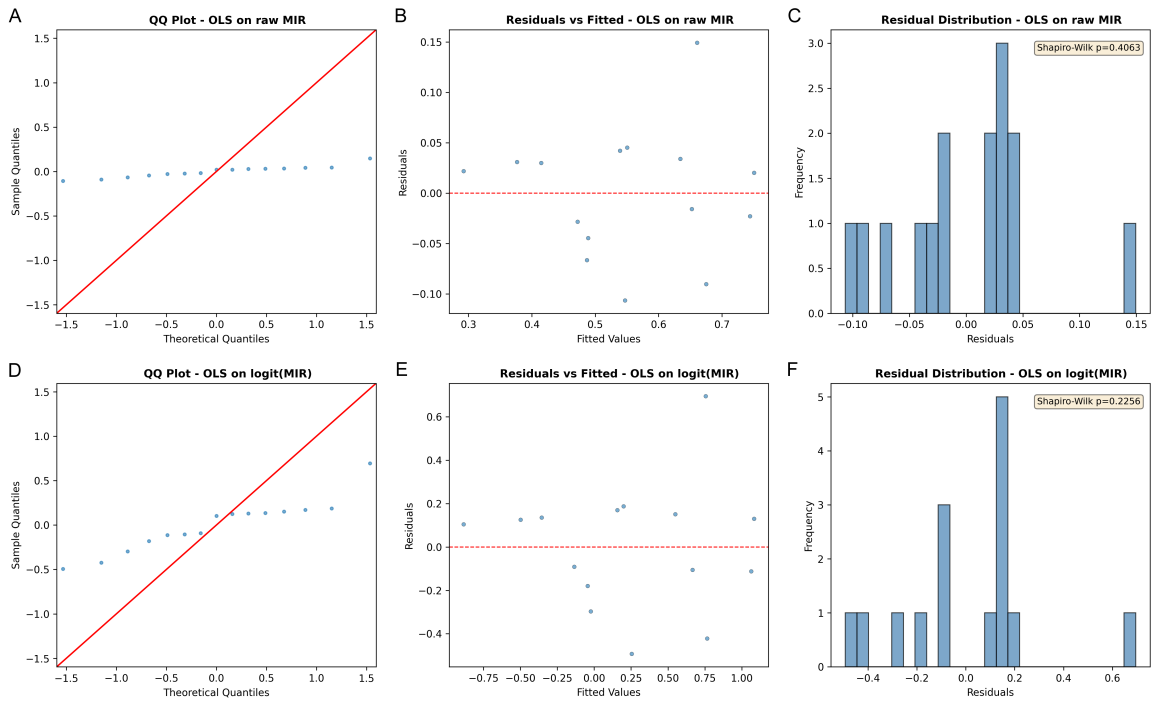


Figure S4. Residual diagnostics for MIR regression models.

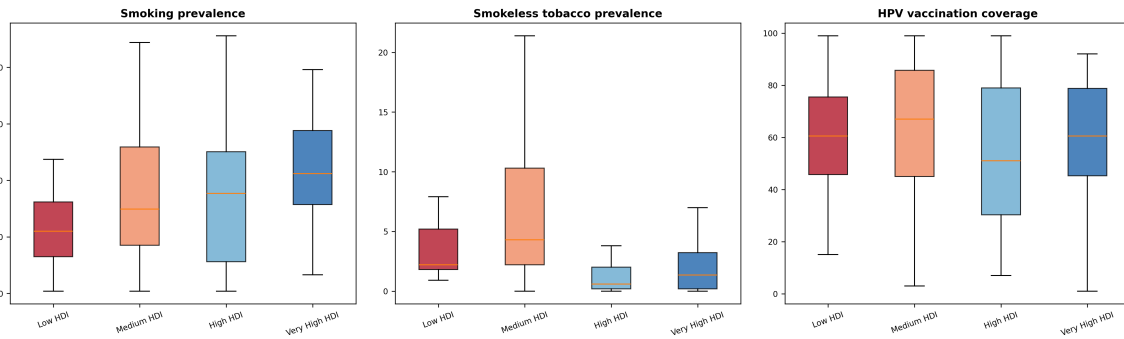


Figure S5. Country-level oral cancer risk-factor profiles by HDI group.

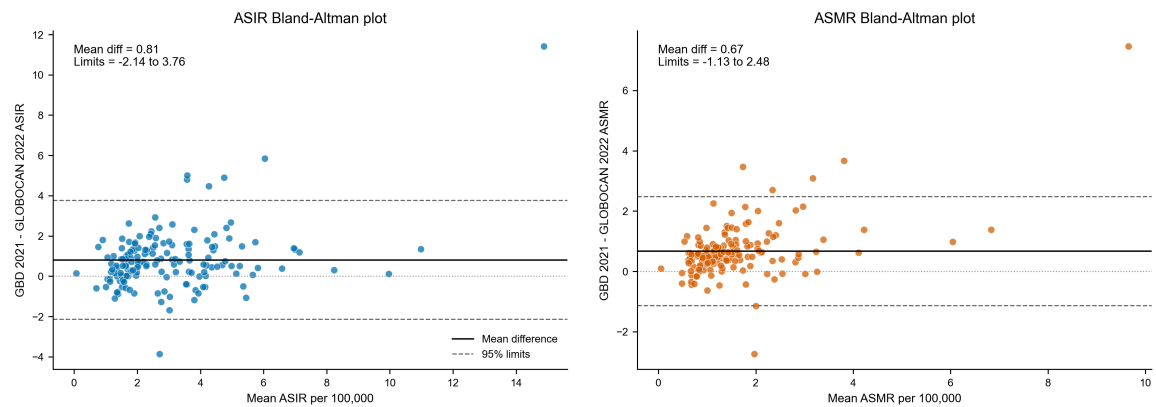
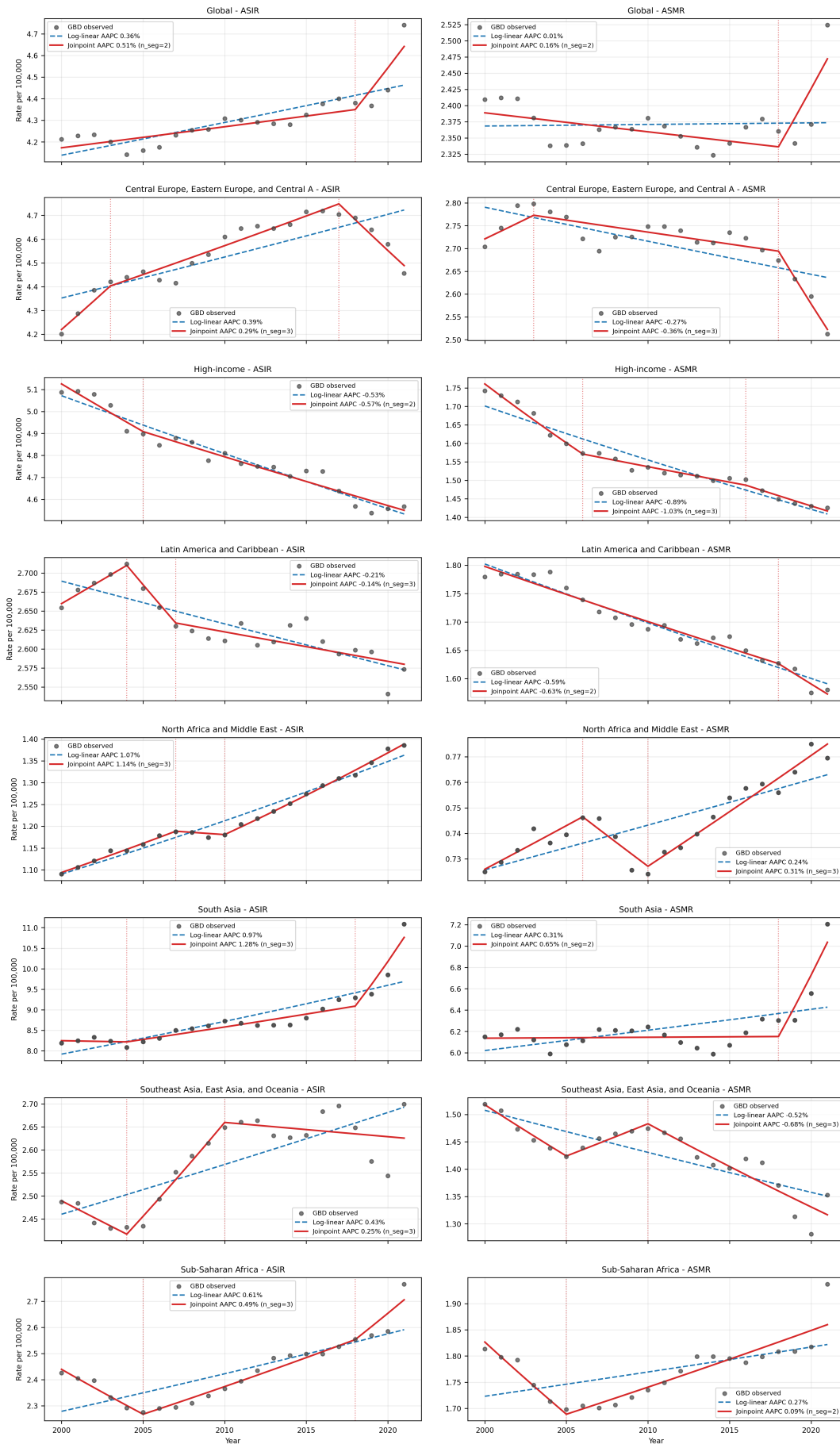


Figure S6. Bland-Altman comparison of GBD 2021 and GLOBOCAN 2022.

Global burden and inequalities in lip and oral cavity cancer



Global burden and inequalities in lip and oral cavity cancer

Figure S7. Joinpoint sensitivity analysis vs full-period log-linear regression (GBD 2021, both sexes, age-standardized rates, 2000-2021; min segment length = 3 years).

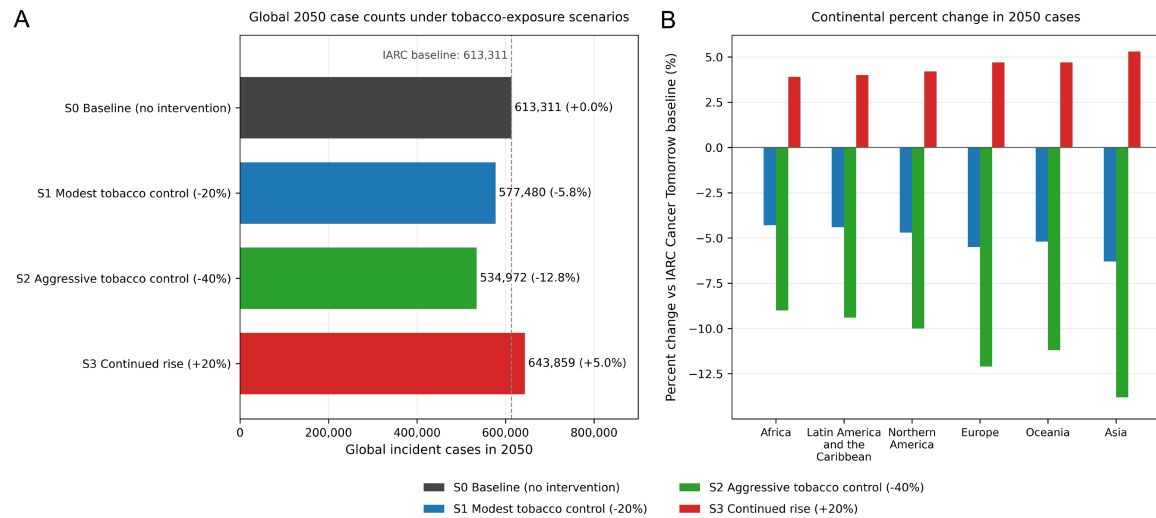


Figure S8. Risk-factor sensitivity analysis of 2050 lip and oral cavity cancer projections (PAF-based, using IARC Cancer Tomorrow as baseline).