

Global, regional, and national burden of colorectal cancer and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019



GBD 2019 Colorectal Cancer Collaborators*



Summary

Background Colorectal cancer is the third leading cause of cancer deaths worldwide. Given the recent increasing trends in colorectal cancer incidence globally, up-to-date information on the colorectal cancer burden could guide screening, early detection, and treatment strategies, and help effectively allocate resources. We examined the temporal patterns of the global, regional, and national burden of colorectal cancer and its risk factors in 204 countries and territories across the past three decades.

Methods Estimates of incidence, mortality, and disability-adjusted life years (DALYs) for colorectal cancer were generated as a part of the Global Burden of Diseases, Injuries and Risk Factors Study (GBD) 2019 by age, sex, and geographical location for the period 1990–2019. Mortality estimates were produced using the cause of death ensemble model. We also calculated DALYs attributable to risk factors that had evidence of causation with colorectal cancer.

Findings Globally, between 1990 and 2019, colorectal cancer incident cases more than doubled, from 842 098 (95% uncertainty interval [UI] 810 408–868 574) to 2.17 million (2.00–2.34), and deaths increased from 518 126 (493 682–537 877) to 1.09 million (1.02–1.15). The global age-standardised incidence rate increased from 22.2 (95% UI 21.3–23.0) per 100 000 to 26.7 (24.6–28.9) per 100 000, whereas the age-standardised mortality rate decreased from 14.3 (13.5–14.9) per 100 000 to 13.7 (12.6–14.5) per 100 000 and the age-standardised DALY rate decreased from 308.5 (294.7–320.7) per 100 000 to 295.5 (275.2–313.0) per 100 000 from 1990 through 2019. Taiwan (province of China; 62.0 [48.9–80.0] per 100 000), Monaco (60.7 [48.5–73.6] per 100 000), and Andorra (56.6 [42.8–71.9] per 100 000) had the highest age-standardised incidence rates, while Greenland (31.4 [26.0–37.1] per 100 000), Brunei (30.3 [26.6–34.1] per 100 000), and Hungary (28.6 [23.6–34.0] per 100 000) had the highest age-standardised mortality rates. From 1990 through 2019, a substantial rise in incidence rates was observed in younger adults (age <50 years), particularly in high Socio-demographic Index (SDI) countries. Globally, a diet low in milk (15.6%), smoking (13.3%), a diet low in calcium (12.9%), and alcohol use (9.9%) were the main contributors to colorectal cancer DALYs in 2019.

Interpretation The increase in incidence rates in people younger than 50 years requires vigilance from researchers, clinicians, and policy makers and a possible reconsideration of screening guidelines. The fast-rising burden in low SDI and middle SDI countries in Asia and Africa calls for colorectal cancer prevention approaches, greater awareness, and cost-effective screening and therapeutic options in these regions.

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Introduction

In 2019, colorectal cancer was the third leading cause of cancer deaths and the second leading cause of disability-adjusted life years (DALYs) for cancer worldwide.¹ Around 70–75% of colorectal cancer cases occur sporadically and are associated with modifiable risk factors, whereas 25–30% of cases are linked to non-modifiable risk factors such as genetic factors, a personal history of polyps or adenoma, or a family history of colorectal cancer or hereditary risk (eg, Lynch syndrome or familial adenomatous polyposis).^{2–5} Because of the increased prevalence of modifiable risk factors such as smoking, alcohol consumption, unhealthy diets, sedentary behaviour, physical inactivity, obesity, increasing life

expectancy, increasing awareness and affordability of colorectal cancer screening, and increasing screening capacity, incident cases of colorectal cancer are growing rapidly in low-income and middle-income countries (LMICs).^{6,7}

The UN Sustainable Development Goal (SDG) target 3.4 focuses on reduction of premature mortality from non-communicable diseases (including cancers) by a third by 2030.⁸ Colorectal cancer can be prevented by ameliorating modifiable risk factors, and deaths can be prevented through early detection of polyps with proven screening interventions;^{9–11} therefore, addressing the global colorectal cancer burden must serve as one of the considerations towards progress on SDG 3.4 relating to

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*Collaborators are listed at the end of the Article

Correspondence to:

Dr Rajesh Sharma, University

School of Management and

Entrepreneurship, Delhi

Technological University,

Delhi 110095, India

rajesh.sharma@dtu.ac.in

Research in context

Evidence before this study

Colorectal cancer is one of the leading causes of cancer deaths worldwide. Previously, the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017 provided estimates for colorectal cancer incidence, deaths, and disability-adjusted life years (DALYs) for the period 1990–2017. Apart from GBD 2017, the International Agency for Research on Cancer (IARC) provided estimates for colorectal cancer for 2020 under the GLOBOCAN project. The present study was done as a part of GBD 2019, which produced estimates for 302 causes of death, 369 diseases and injuries, and 87 risk factors for 204 countries and territories for 1990–2019.

Added value of this study

In this study, we provide age-sex-location-specific estimates of colorectal cancer incidence, deaths, and DALYs for 204 countries and territories between 1990 and 2019. GBD 2019 produced estimates with technical collaboration from WHO, which has led to the inclusion of nine more WHO member countries. 28 714 site-years of data were used to estimate colorectal cancer incidence, deaths, and DALYs in GBD 2019, 16% more than in GBD 2017. In comparison with GLOBOCAN 2020, which provided colorectal cancer estimates for 2020, we provide estimates for full time series through 1990 to 2019 for all 204 countries and territories included in GBD 2019. Apart from estimates of incident cases, deaths, and age-standardised rates, as was done in GLOBOCAN 2020, we also estimated the burden of deaths and disability quantified with DALYs. The colorectal cancer burden was also examined in the light of country-level socioeconomic

development measured by Socio-demographic Index (SDI). The contribution of the main risk factors to colorectal cancer DALYs was also examined by sex in 21 world regions.

Implications of all the available evidence

Incident cases of colorectal cancer doubled or more than doubled in 16 of 21 world regions, and the number of deaths doubled or more than doubled in 15 of 21 world regions in the past three decades. The age-standardised incidence and death rates (per 100 000 person-years) either remained the same or decreased in high SDI quintiles and increased in low SDI and middle SDI quintiles. Large increases in colorectal cancer incidence rates were observed in middle SDI countries, as well as in people aged 20–49 years in high SDI countries. Further research is required to understand the causes of the colorectal cancer burden in younger adults (aged <50 years) and the main risk factors, including obesity, physical inactivity, alcohol consumption, smoking, and an altered gut microbiome, that might have led to the rise in the colorectal cancer burden. The increasing incidence of colorectal cancer in people younger than 50 years in high SDI countries also necessitates reconsideration of screening recommendations to include younger age groups (ie, those aged 40–49 years). The public health interventions for colorectal cancer awareness, screening, and prevention through containment of modifiable risk factors such as alcohol, smoking, an unhealthy diet (high in processed meat and fat, and low in fruits and vegetables), and obesity are key to stemming the tide of colorectal cancer worldwide.

non-communicable diseases. In this endeavour, recent changes in the colorectal cancer burden should be tracked at the global, regional, and national levels to identify those countries making progress and those countries and regions where more work is needed.

This study aimed to investigate the global, regional, and national burden of colorectal cancer in 204 countries and territories from 1990 to 2019. We examined the age-sex-location-specific burden of colorectal cancer using estimates from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019.^{1,12–14} The colorectal cancer burden was examined in light of the development status of countries measured by the Socio-demographic Index (SDI). We also aimed to quantify health loss due to colorectal cancer using DALYs, which encompasses the burden of a disease due to both deaths and disabilities caused by it. Last, we also examined the risk-attributable burden of the main risk factors for colorectal cancer. Apart from GBD, the International Agency for Research on Cancer (IARC) produced cancer estimates for 2020; however, GBD estimates facilitate examination of temporal patterns at global, regional, and national levels. An assessment of recent trends at the global, regional, and national levels, and the associated risk factors for countries at different levels of

development, can help track progress, map resource requirements, and help in policy making and implementation towards prevention and tackling the growing burden of colorectal cancer.

This manuscript was produced as part of the GBD Collaborator Network and in accordance with the GBD Protocol.

Methods

Overview

The GBD 2019 estimates were generated for 286 causes of death, 369 causes of non-fatal burden, and 87 risk factors.^{1,12–14} In comparison with the 195 countries and territories included in GBD 2017, nine more countries (Cook Islands, Monaco, San Marino, Nauru, Niue, Palau, Saint Kitts and Nevis, Tokelau, and Tuvalu) were included in GBD 2019, providing full time-series estimates from 1990 to 2019 for 204 countries and territories, which were grouped under seven super-regions and 21 regions. The colorectal cancer estimates mapped to the International Classification of Diseases (ICD) codes are available in the appendix (p 14).¹⁵ The GBD estimation framework and calculation of all the metrics are detailed in GBD 2019 capstone publications and the supplementary appendices published with these reports.^{1,12–14}

See Online for appendix

Data sources

For GBD 2019, input data from various sources such as vital registration, verbal autopsy, and cancer registries were used to generate the colorectal cancer estimates. 28714 site-years of data (22849 site-years for vital registration, 516 site-years for verbal autopsy, and 5349 site-years for cancer registries) were used to estimate the colorectal cancer burden in GBD 2019, 3962 site-years (16%) more than GBD 2017. The vital registration system records data of vital events in a person's life (birth, death, and cause of death). Verbal autopsy is a data collection method generally used in populations without a complete vital registration system; in this method, a trained interviewer uses a questionnaire to collect information about signs, symptoms, and demographic characteristics of a recently deceased person from someone familiar with the deceased. Cancer registries are a data collection system that record and manage the data relating to a person with cancer. The information on various input sources of data used in GBD 2019 can be obtained from the GBD 2019 Data Input Sources Tool.

Mortality estimation

GBD estimation begins with mortality estimation in multiple steps. The mortality data from cancer registries might be sparse, although incidence data can be available; therefore, to maximise data availability, mortality-to-incidence ratios (MIRs) were generated from the cancer registries that contained both incidence and mortality data. In the first step, incidence and mortality data from cancer registries were processed before they were matched by cancer, age, sex, year, and location to generate crude MIRs. Final MIRs were estimated by use of spatio-temporal Gaussian Process Regression (ST-GPR) using the Healthcare Access and Quality (HAQ) index, age, and sex¹⁶ as covariates. The MIR estimates from the ST-GPR model were multiplied with incidence data to generate crude mortality estimates. The final mortality estimates were produced with the Cause of Death Ensemble Model (CODEm) using crude mortality estimates from the last step and those from vital registration and verbal autopsy as inputs along with other variables taken as covariates.¹⁵ Only those variables were chosen that have been found to have a plausible relation with death due to colorectal cancer. The list of covariates at different levels used in CODEm for colorectal cancer is presented in the appendix (pp 15–16).¹⁵ The final mortality estimates from CODEm were then divided by the MIRs from ST-GPR to generate age-sex-location-specific estimates for incident cases.

Non-fatal estimation

The mortality estimates generated from CODEm were combined with reference life tables to generate estimates for years of life lost (YLLs).¹² The 10-year prevalence was divided into four sequelae of a fixed

duration based on expected person-time spent in each of the sequelae: diagnosis and primary therapy (4·0 months), metastatic phase (9·7 months), and terminal phase (1·0 month), with the remaining duration assigned to the controlled phase.¹⁵ Sequela-specific years lived with disability (YLDs) were calculated by multiplying disability weights with sequelae-specific prevalence. Total YLDs were calculated by summing the sequela-specific YLDs. The sum of YLLs and YLDs produced the DALYs estimates, with one DALY being equivalent to 1 year of healthy life lost.¹⁷

The age-specific rates of incidence, mortality, and DALYs were expressed per 100 000 person-years and calculated with GBD population estimates,¹² and the age-standardised rates were calculated as weighted averages of age-specific rates per 100 000 people, in which weights are the proportion of people in corresponding age groups as per the GBD world population age standard.¹² All GBD estimates in this Article are provided with 95% uncertainty intervals (UIs). For each computational step, 1000 draws are generated; 95% UIs are calculated by taking values at the 2·5th and 97·5th percentile from the 1000 draws, and are provided alongside the mean estimates.¹²

Socio-demographic Index

The colorectal cancer burden was evaluated against country-level development measured with the SDI,^{12,15} which is a composite indicator of three indicators: lag-distributed income per capita, average educational attainment for people aged 15 years and older, and the total fertility rate (in people aged <25 years). Each of these indicators was first rescaled on a scale of 0 (lowest) to 1 (highest) based on country-specific values. The geometric mean of these three indices provided the final value of the country-level SDI. Based on SDI values, the 204 countries and territories were categorised into five groups: low SDI (<0·45), low-middle SDI ($\geq 0\cdot45$ and <0·61), middle SDI ($\geq 0\cdot61$ and <0·69), high-middle SDI ($\geq 0\cdot69$ and <0·80), and high SDI ($\geq 0\cdot80$).

Risk factors

Estimation of GBD risk factors is based on a comparative risk assessment framework and involves six steps. The first is identification of risk-outcome pairs: only those risk-outcomes that have convincing or plausible evidence, as per World Cancer Research Fund criteria,¹⁸ are included in GBD risk factor estimation. The second is estimation of relative risk (RR) as a function of exposure for each risk-outcome pair. The third is distribution of exposure for each risk factor by age, sex, location, and year. The fourth is determining the theoretical minimum risk exposure level (TMREL). The fifth is estimation of the population attributable fraction (PAF) and attributable burden. The RR for each risk-outcome pair, exposure levels, and TMREL are used to model the PAF.¹³ The PAF of a particular risk factor is multiplied by colorectal cancer

For the GBD 2019 Data Input Sources Tool see <http://ghdx.healthdata.org/gbd-2019/data-input-sources>

DALYs to generate the DALYs attributable to that risk factor. The sixth is estimating the PAF and attributable burden for the combination of risk factors.

The details of each of these steps and the underlying methodology are provided elsewhere.¹³ In this GBD iteration, 87 risk factors were included, of which ten (alcohol use, diet high in processed meat, diet high in red meat, diet low in calcium, diet low in fibre, diet low in milk, high body-mass index [BMI], high fasting plasma glucose, low physical activity, and smoking) have a non-zero contribution to colorectal cancer deaths and DALYs. We assessed the percentage contribution of these ten risk factors to colorectal cancer DALYs in 2019. The total number of input data sources used for the exposure of different risk factors in GBD 2019 are detailed elsewhere,¹³ of which we present the number of input data sources for the ten risk factors related to colorectal cancer (appendix p 17).

The percentage changes between 1990 and 2019 were interpreted as statistically significant if the 95% UI did not include zero. All data analysis and data visualisation in this study were done with statistical software R (version 4.1.1), Stata (version 13.1), and Python (version 3.8.8).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Overview of the global burden

Globally, for both sexes combined, incident cases of colorectal cancer more than doubled, from 842 098 (95% UI 810 408–868 574) in 1990 to 2.17 million (2.00–2.34) in 2019 (figure 1A). Between 1990 and 2019, deaths due to colorectal cancer increased from 518 126 (493 682–537 877) to 1.09 million (1.02–1.15), and DALYs increased from 12.4 million (11.9–12.9) to 24.3 million (22.6–25.7). By 2019, 95.6% of colorectal cancer DALYs were due to YLLs and 4.4% were due to YLDs (appendix p 5). The global age-standardised incidence rate of colorectal cancer increased from an estimated 22.2 (21.3–23.0) per 100 000 to 26.7 (24.6–28.9) per 100 000 from 1990 through 2019 (figure 1B). By contrast, the global age-standardised mortality rate decreased from 14.3 (13.5–14.9) per 100 000 to 13.7 (12.6–14.5) per 100 000, and the age-standardised DALY rate decreased from 308.5 (294.7–320.7) per 100 000 to 295.5 (275.2–313.0) per 100 000 from 1990 through 2019.

Males experienced greater increases in colorectal cancer incidence, deaths, and DALYs, than females in terms of absolute counts, and the age-standardised rates increased in males and remained similar throughout or decreased in females (figure 1). In 2019, males accounted for 57.2% (1.2 million [95% UI 1.1–1.4]) of colorectal cancer incident cases, and 54.9% (594 176 [550 959–638 031]) of deaths due to colorectal cancer. In 2019, the age-standardised

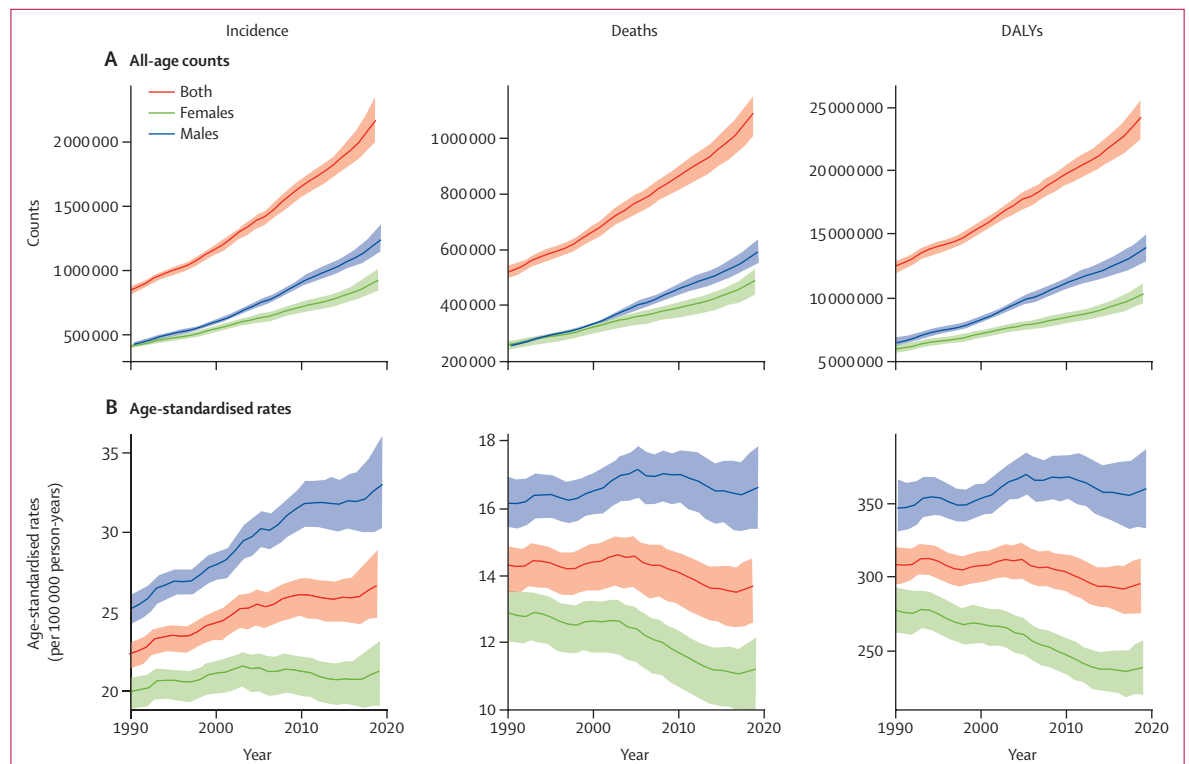


Figure 1: Global temporal patterns of colorectal cancer burden, 1990–2019

(A) All-age counts. (B) Age-standardised rates. Data source: Global Burden of Diseases, Injuries, and Risk Factors Study 2019. DALYs=disability-adjusted life-years.

incidence rate was 1.5-times higher in males than in females (33.1 [30.2–36.1] per 100 000 vs 21.2 [19.0–23.2] per 100 000), with a similar disparity between males and females in terms of the age-standardised mortality rate (16.6 [15.4–17.8] per 100 000 in males vs 11.2 [10.0–12.2] per 100 000 in females) and the age-standardised DALY rate (360.0 [333.1–387.8] per 100 000 in males vs 237.9 [218.7–257.1] per 100 000 in

females; figure 1). The number of incident cases increased in all SDI quintiles, whereas the age-standardised incidence rate decreased in the high SDI quintile only (appendix p 6). Similarly, deaths and DALYs increased in all SDI quintiles, but age-standardised mortality rates stagnated or decreased only in high-middle SDI and high SDI quintiles (appendix pp 7–8). Notably, the rise in all-age counts was steeper in all SDI quintiles than in the

	Incidence (95% UI)	Mortality (95% UI)	DALYs (95% UI)	Age-standardised incidence rate (95% UI)	Age-standardised mortality rate (95% UI)	Age-standardised DALY rate (95% UI)
Global	2166168 (1996298–2342842)	1085797 (1002795–1149679)	24284087 (22614920–25723221)	26.7 (24.6–28.9)	13.7 (12.6–14.5)	295.5 (275.2–313.0)
Andean Latin America	11094 (8935–13467)	5630 (4593–6791)	125578 (101753–151796)	20.0 (16.1–24.2)	10.3 (8.4–12.4)	220.8 (179.0–266.3)
Australasia	23671 (19439–28848)	8382 (7575–8978)	163248 (150872–173959)	48.3 (39.6–59.1)	16.2 (14.8–17.3)	348.6 (324.2–370.7)
Caribbean	13813 (11813–15959)	7995 (6935–9176)	172016 (147186–200175)	26.7 (22.9–30.9)	15.5 (13.4–17.7)	333.3 (285.2–387.9)
Central Asia	10949 (9999–12008)	7467 (6822–8166)	199841 (182012–219941)	15.2 (13.9–16.6)	11.2 (10.3–12.2)	256.8 (234.4–281.1)
Central Europe	84474 (74551–95453)	51567 (45636–57749)	1052146 (922923–1184246)	39.9 (35.2–45.1)	23.6 (20.8–26.4)	512.6 (448.7–577.9)
Central Latin America	37542 (32211–43870)	22470 (19542–25997)	539638 (465200–627069)	15.9 (13.7–18.6)	9.7 (8.4–11.2)	223.7 (193.1–259.5)
Central sub-Saharan Africa	3957 (3015–5113)	3544 (2705–4609)	100988 (75749–131447)	7.7 (5.9–10.1)	7.4 (5.7–9.9)	169.3 (129.2–220.2)
East Asia	637096 (548895–738549)	275604 (238238–317886)	6712862 (5774277–7735907)	30.9 (26.8–35.7)	14.1 (12.2–16.2)	325.2 (280.7–373.2)
Eastern Europe	106017 (96250–117074)	63476 (57180–70011)	1419105 (1287540–1571374)	31.1 (28.2–34.4)	18.3 (16.5–20.2)	423.7 (384.0–469.3)
Eastern sub-Saharan Africa	14227 (12130–16886)	12717 (10940–15001)	356433 (301931–425606)	8.8 (7.6–10.4)	8.5 (7.4–9.9)	193.9 (166.0–229.6)
High-income Asia Pacific	196371 (166417–225643)	76929 (64821–83603)	1327823 (1186117–1414814)	44.6 (38.4–51.1)	15.3 (13.4–16.4)	323.9 (298.6–342.1)
High-income North America	260911 (229909–295693)	95664 (88321–99688)	1987109 (1895869–2059774)	42.7 (37.6–48.6)	14.9 (13.9–15.5)	339.9 (325.9–351.9)
North Africa and Middle East	60010 (53354–67555)	39147 (34761–44107)	1013634 (896161–1146526)	13.9 (12.3–15.6)	9.8 (8.7–11)	218.7 (194.1–246.5)
Oceania	691 (555–855)	551 (443–682)	16315 (12915–20556)	10.0 (8.2–12.1)	8.8 (7.2–10.7)	203.6 (163.6–252.5)
South Asia	113711 (98190–129352)	94846 (81524–109075)	2419098 (2078019–2782570)	8.3 (7.2–9.4)	7.3 (6.2–8.3)	165.1 (141.7–189.9)
Southeast Asia	117010 (96631–136244)	82024 (67617–94606)	2142434 (1780490–2482287)	19.3 (16–22.4)	14.4 (11.9–16.6)	334.0 (276.6–386.4)
Southern Latin America	26866 (21480–33612)	17930 (16774–18975)	366436 (347729–385441)	32.2 (25.7–40.4)	21.2 (19.9–22.4)	447.6 (424.7–470.5)
Southern sub-Saharan Africa	7106 (6389–7882)	5922 (5329–6580)	147780 (132439–165539)	13.1 (11.8–14.5)	11.5 (10.4–12.7)	250.4 (225.1–279.3)
Tropical Latin America	42891 (40118–44928)	27704 (25668–29090)	660129 (625562–687740)	17.8 (16.6–18.6)	11.7 (10.8–12.3)	268.3 (253.7–279.8)
Western Europe	382442 (332800–432448)	172454 (155345–181815)	3008234 (2815060–3152895)	42.4 (37.1–48.3)	17.3 (15.8–18.1)	351.2 (332.0–366.8)
Western sub-Saharan Africa	15321 (12895–17824)	13773 (11698–16069)	353242 (295571–420704)	8.7 (7.4–10.0)	8.4 (7.3–9.7)	176.1 (149.0–206.2)

Numbers in parenthesis represent 95% uncertainty intervals (UIs). DALYs=disability-adjusted life years. The age-standardised incidence rate, age-standardised mortality rate, and age-standardised DALY rate are shown per 100 000 person-years. Source: Global Burden of Diseases, Injuries, and Risk Factors Study 2019.

Table: Region-wise colorectal cancer burden in 2019

high SDI quintile such that the share of low, low-middle, middle, and high-middle SDI quintiles in the total colorectal cancer burden increased from 47.3% to 62.1% in terms of incident cases, from 57.1% to 69.8% in terms of deaths, and from 62.4% to 74.6% in terms of DALYs between 1990 and 2019 (appendix pp 6–8).

Colorectal cancer burden by region

In 2019, east Asia was the worst-affected region, with 637 096 (95% UI 548 895–738 549) new cases, 275 604 (238 238–317 886) deaths, and 6.7 million (5.8–7.7) DALYs due to colorectal cancer (table). Australasia had the highest age-standardised incidence rate (48.3 [39.6–59.1] per 100 000) and central Europe had the highest age-standardised mortality rate (23.6 [20.8–26.4] per 100 000) across 21 regions in 2019. The age-standardised incidence rate was the lowest in central sub-Saharan Africa (7.7 [5.9–10.1] per 100 000) and south Asia (8.3 [7.2–9.4] per 100 000). South Asia also had the lowest

age-standardised mortality rate (7.3 [6.2–8.3] per 100 000). The age-standardised DALY rate was the highest in central Europe (512.6 [448.7–577.9] per 100 000) and lowest in south Asia (165.1 [141.7–189.9] per 100 000) in 2019 (table).

The preponderance of colorectal cancer in males in 2019, in terms of both age-standardised incidence rates and age-standardised mortality rates, was more apparent in developed regions (eg, Australasia, central Europe, and the high-income Asia Pacific) and differences between males and females were smaller in south Asia and regions of Africa (eg, eastern sub-Saharan Africa and western sub-Saharan Africa; figure 2).

Three patterns emerged from region-wise temporal trends of age-standardised rates in GBD regions (appendix p 9). First, in regions with already high incidence rates in 1990 (eg, Australasia and the high-income Asia Pacific), the age-standardised incidence rates either stagnated or decreased and age-standardised

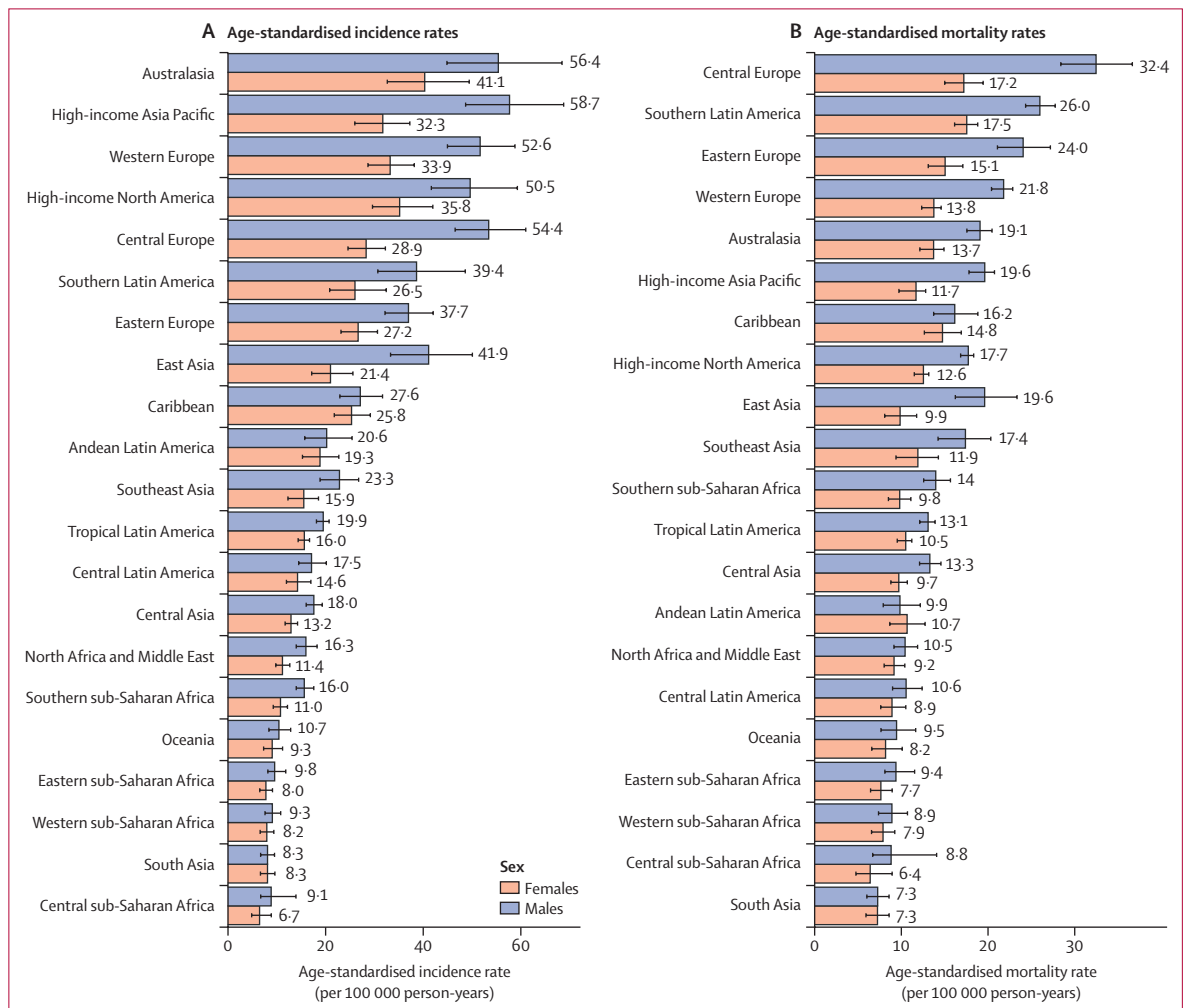


Figure 2: Age-standardised rates of colorectal cancer in 2019, by sex and region (A) Age-standardised incidence rate (per 100 000 person-years). (B) Age-standardised mortality rate (per 100 000 person-years). Error bars denote 95% uncertainty intervals. Data source: Global Burden of Diseases, Injuries, and Risk Factors Study 2019.

mortality rates decreased in the past three decades. Second, concomitant rises in age-standardised incidence and mortality rates were observed in a few regions of Asia, Africa (eg, western sub-Saharan Africa and south Asia), and Oceania. Third, large increases occurred in age-standardised incidence rates, whereas a smaller increase was observed in age-standardised mortality rates in a few regions (eg, east Asia and south east Asia).

From 1990 to 2019, incident cases doubled or more than doubled in 16 of 21 regions, deaths doubled or more than doubled in 15 of 21 regions, and DALYs doubled or more than doubled in 13 of 21 regions, led by regions of Latin America and Asia (figure 3A). The changes in age-standardised rates were modest, with age-standardised incidence rates increasing by 50% or more in six GBD regions (east Asia, Andean Latin America, southeast Asia, central Latin America, North Africa and the Middle East, and south Asia; figure 3B). Age-standardised

incidence rates decreased, although these decreases were not statistically significant, in high-income North America (−10.0% [95% UI −21.1 to 2.5]) and Australasia (−6.2% [−22.7 to 14.7]) between 1990 and 2019. Age-standardised mortality rates increased the most in southeast Asia (46.7% [21.8 to 70.0]) followed by east Asia (37.1% [15.1 to 62.3]), and decreased in Australasia (−33.5% [−29.8 to −37.2]) and high-income North America (−25.3% [−23.5 to −27.3]) from 1990 through 2019, with a couple of other high-income regions experiencing a reduction (−22.1% [−25.0 to −19.6] in western Europe and −14.8% [−20.6 to −10.9] in the high-income Asia Pacific). Due to large increases in incidence and death rates, the age-standardised DALY rate increased the most in regions of Asia and Latin America, led by southeast Asia (41.6% [19.0 to 59.4]) and central Latin America (37.8% [19.0 to 59.4]) and decreased in high-income regions and regions of Europe (figure 3B).

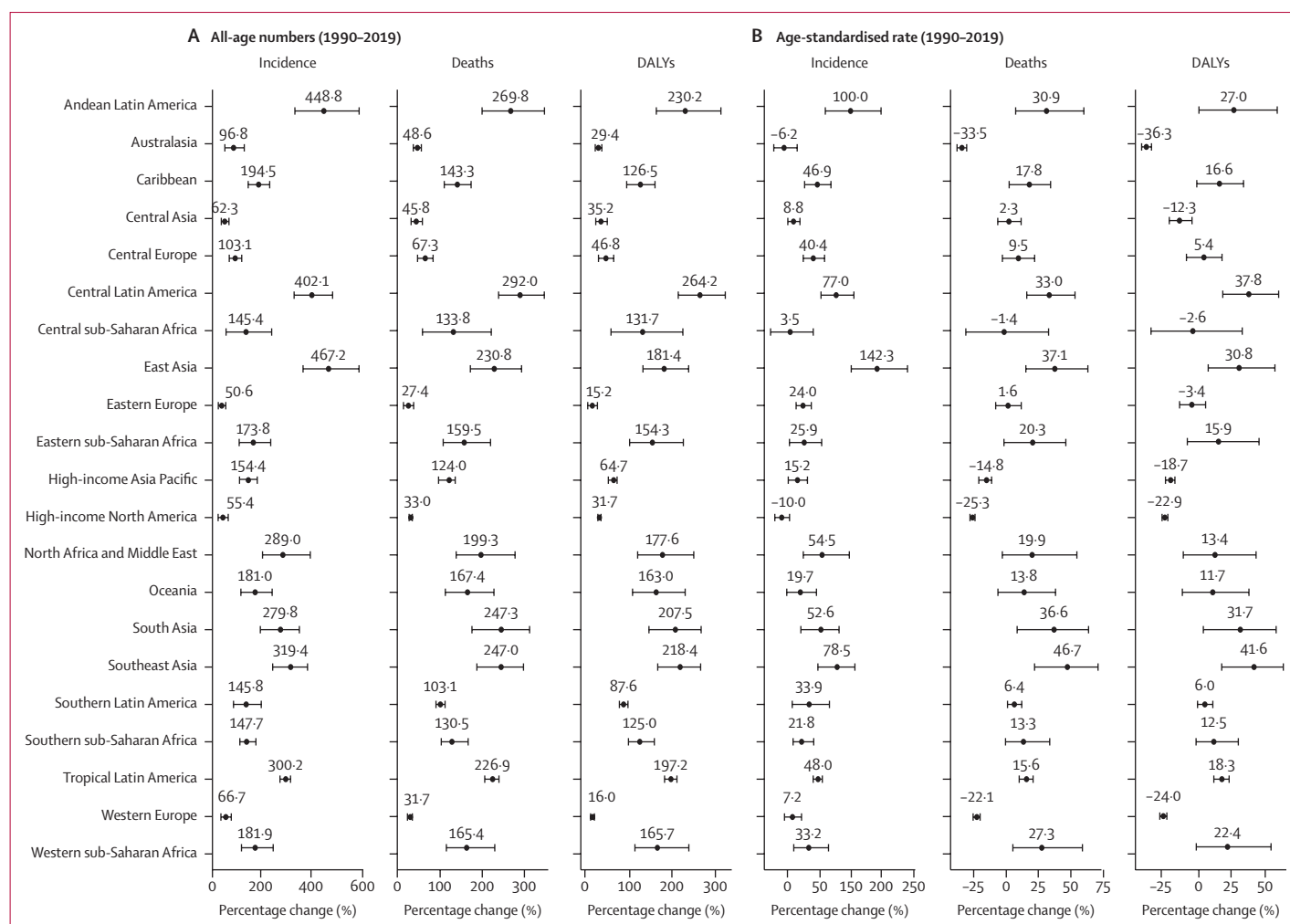


Figure 3: Region-wise percentage change in colorectal cancer burden, 1990–2019
 (A) All-age numbers. (B) Age-standardised rate (per 100 000). Data source: Global Burden of Diseases, Injuries, and Risk Factors Study 2019. Error bars denote 95% uncertainty intervals. DALYs=disability-adjusted life-years.

Colorectal cancer burden by country

China, the USA, and Japan had the highest all-age incident counts for both sexes combined, with 607 900 (95% UI 521 805–708 420) new cases in China, 227 242 (197 022–261 375) new cases in the USA, and 160 211 (130 730–186 831) new cases in Japan, in 2019 (appendix pp 18–43). China (261 777 [224 403–303 318]), India (79 098 [67 137–92 723]), and the USA (84 026 [77 987–87 516]) had the highest death counts. Somalia (5.0 [3.1–9.2] per 100 000), Niger (5.6 [4.2–7.6] per 100 000), and Bangladesh (5.6 [3.9–8.0] per 100 000) had the lowest age-standardised incidence rates, whereas Taiwan (province of China; 62.0 [48.9–80.0] per 100 000), Monaco (60.7 [48.5–73.6] per 100 000), and Andorra (56.6 [42.8–71.9] per 100 000) had the highest age-standardised incidence rates (figure 4A; appendix pp 18–43). Greenland (31.4 [26.0–37.1] per 100 000), Brunei (30.3 [26.6–34.1] per 100 000), and Hungary (28.6 [23.6–34.0] per 100 000) had the highest age-standardised mortality rates, whereas Bangladesh (4.9 [3.4–7.1] per 100 000), Somalia (5.0 [3.2–9.3]), and Nepal (5.4 [3.9–7.4] per 100 000) had the lowest age-standardised mortality rates among 204 countries and territories in 2019 (figure 4B; appendix pp 18–43). Age-standardised DALY rates varied from 107.4 (74.6–152.7) per 100 000 in Bangladesh to 680.3 (555.7–812.4) per 100 000 in Greenland in 2019 (figure 4C; appendix pp 18–43).

Between 1990 and 2019, for both sexes combined, incident cases doubled or more than doubled in 157 of 204 countries and territories and deaths doubled or more than doubled in 129 of 204 countries and territories (appendix pp 44–66). Austria was the only country that reported a significant reduction in the number of colorectal cancer deaths (–20.5% [–26.4 to –14.8]) and DALYs (–29.7% [–34.4 to –25.0]) between 1990 and 2019. The changes in age-standardised rates were modest across countries in comparison with changes in absolute counts. From 1990 through 2019, the largest increase in age-standardised rates occurred in Cape Verde (age-standardised incidence rate 180.6% [121.1 to 237.3], age-standardised mortality rate 152.9% [97.3 to 204.0], and age-standardised DALY rate 114.2% [71.8 to 159.4]) and the largest reduction occurred in Austria (age-standardised incidence rate –34.1% [–46.7 to –19.1], age-standardised mortality rate –50.2% [–53.3 to –46.8], and age-standardised DALY rate –53.2% [–56.2 to –50.0]; appendix pp 44–66).

The relationship between country-level age-standardised rates of colorectal cancer and SDI in 2019 is shown in the appendix (p 10). SDI seemed to exert a positive relationship with age-standardised rates, with the slope becoming steeper in the upper end of the development spectrum for age-standardised incidence rates, whereas a positive relationship between age-standardised DALY rates and SDI seemed to taper off slightly towards high SDI countries.

Colorectal cancer burden by age group

Figure 5 illustrates the colorectal cancer incidence count and age-specific rates (per 100 000 person-years) in 2019. The incidence count followed a bell-shaped distribution with a peak in individuals aged 60–74 years for both males and females. Incident cases were higher in males than in females in all age groups up to age 80–84 years, with a greater number of new cases in females aged 85 years and older (figure 5A). Unlike incident cases, incidence rates continued to increase with age, increasing much faster in those aged 50–54 years and older (figure 5B). Between 1990 and 2019, all age groups experienced a rise in incident cases, with the highest increases occurring in those aged 85 years and older (appendix p 11). Furthermore, incidence rates increased in younger age groups (20–49 years) and decreased in older age groups (50–80 years) only in the high SDI quintile (appendix p 12). Percentage changes in incidence rates were higher in females compared to males only in low SDI quintiles; in all other SDI quintiles, males had higher percentage changes in incidence rates. Moving up in the development spectrum, the contrast between increases (or decreases) in younger age groups (20–49 years) and older age groups (50–74 years) became more pertinent. For instance, in the high SDI quintile, the incidence rates either remained unchanged or decreased in older age groups (50–74 years), whereas large increases were observed in younger age groups (20–49 years; appendix p 12).

Risk factors

Figure 6 depicts the contribution of ten risk factors to all-age DALYs due to colorectal cancer, for both sexes combined, for 21 GBD regions in 2019. At the global level, a diet low in milk (15.6%), smoking (13.3%), a diet low in calcium (12.9%), and alcohol use (9.9%) were the main contributors to colorectal cancer DALYs, with the relative contribution of different risk factors varying as per the region's development status. In sub-Saharan Africa and Asia (barring the high-income Asia Pacific), a diet low in calcium and milk were the main risk factors, whereas smoking and alcohol use were the main risk factors in high-income regions (figure 6). At the global level, high BMI contributed only 8.3% of DALYs, with a higher contribution in comparatively high-income regions (eg, central Europe [14.0%] and high-income North America [13.8%]). The contribution of smoking to DALYs was greater than 15% in regions of Europe (eg, 18.2% in central Europe, 15.9% in western Europe, and 15.5% in eastern Europe) as well as in southern Latin America, east Asia, and high-income North America.

The severity of risk factors also varied by sex, with alcohol use contributing 13.9% of global DALYs and smoking contributing 18.9% of global DALYs in males, whereas alcohol use contributed only 4.5% of global DALYs and smoking contributed only 5.7% of global DALYs in females (appendix p 13). In females, a diet low in milk (15.5%), a diet low in calcium (12.0%), and high

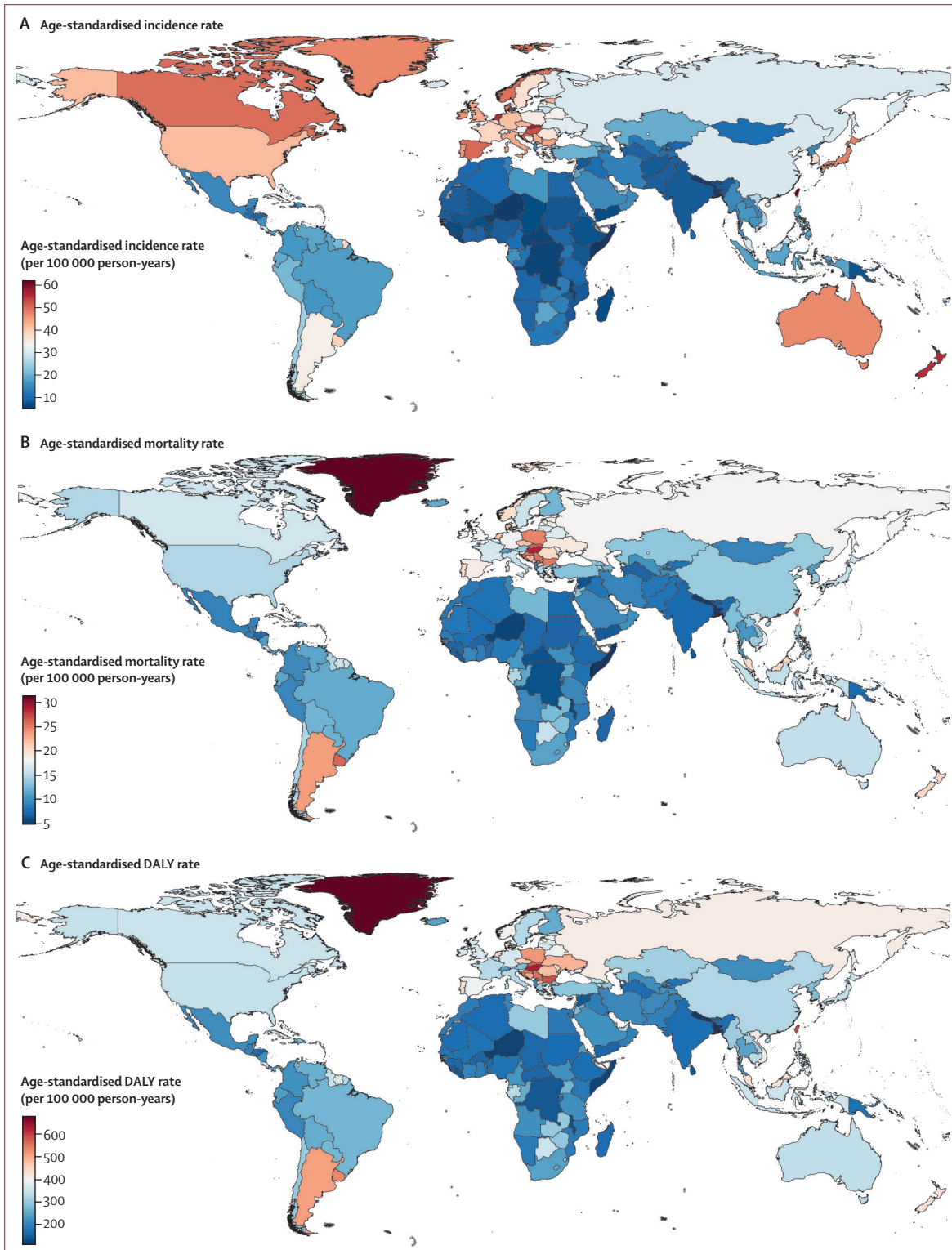


Figure 4: Geographical distribution of age-standardised rates of colorectal cancer in 2019

(A) Age-standardised incidence rate. (B) Age-standardised mortality rate. (C) Age-standardised DALY rate. Data source: Global Burden of Diseases, Injuries, and Risk Factors Study 2019. DALY=disability-adjusted life-year.

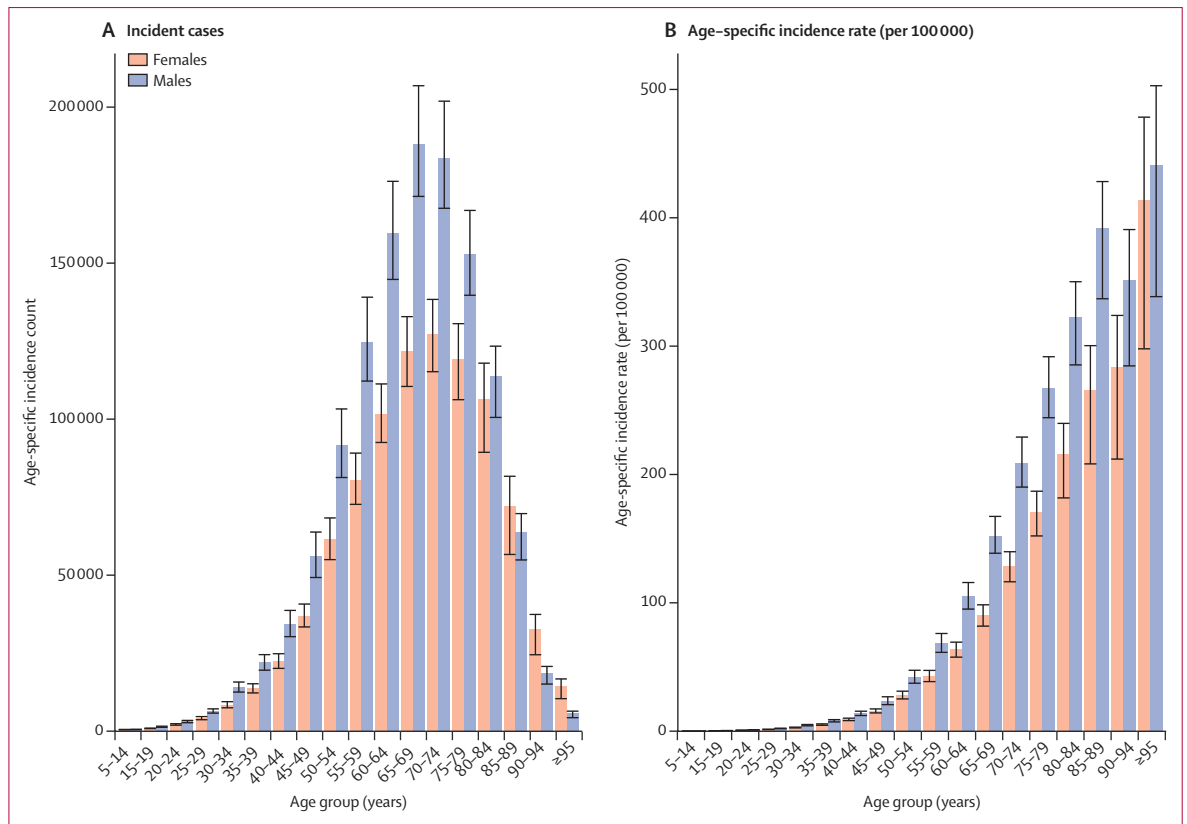


Figure 5: Age-specific burden of colorectal cancer in 2019

(A) Incident cases. (B) Age-specific incidence rate (per 100 000). Error bars denote 95% uncertainty intervals. Data source: Global Burden of Diseases, Injuries, and Risk Factors Study 2019.

fasting plasma glucose (7.5%) were the major contributors to colorectal cancer DALYs. Similar differences were observed between sexes with regard to the contribution of high BMI, which contributed 11.1% of DALYs in males and 4.6% in females. The differences between sexes in the contribution of risk factors to colorectal cancer DALYs were also apparent in all GBD regions. The distribution of inadequate dietary risk factors (eg, a diet low in milk and calcium) was similar across the two sexes across regions of sub-Saharan Africa and Asia (appendix p 13).

Discussion

Between 1990 and 2019, new cases of colorectal cancer doubled or more than doubled in 157 of 204 countries and territories, and deaths due to colorectal cancer doubled or more than doubled in 129 of 204 countries and territories, and large increases were experienced in low SDI and middle SDI countries. Incidence and mortality rates mostly decreased in high SDI countries, whereas several low SDI and middle SDI countries and regions saw increases in age-standardised rates. The incident cases shared by low SDI, low-middle SDI, middle SDI, and high-middle SDI countries increased from 47.3% to 62.1%, the share of death counts rose from

57.1% to 69.8%, and the share of DALYs increased from 62.4% to 74.6% from 1990 through 2019.

We found large increases in age-standardised incidence rates in Asia (eg, 142.3% in east Asia and 78.5% in southeast Asia) and Latin America (eg, 100.0% in Andean Latin America, and 77.0% in central Latin America) between 1990 and 2019. Due to fast economic growth and rapid industrialisation, the thriving middle class in developing countries is adopting a westernised lifestyle characterised by an unhealthy diet (low in fruits and vegetables and high in red meat and processed meat), sedentary behaviour (eg, spending a long time watching television), and less physical activity, along with substance abuse (alcohol and smoking).^{19,20} These behavioural changes have resulted in an increased incidence of lifestyle-related illnesses, including colorectal cancer.

The age-standardised mortality rate decreased in high-income regions (eg, -33.5% [95% UI -29.8 to -37.2] in Australasia and -25.3% [-23.5 to -27.3] in high-income North America) between 1990 and 2019. The reduction in incident cases and deaths, particularly among individuals older than 50 years, in high-SDI regions and countries suggests early detection of colorectal cancer due to screening, cancer registries, and technological improvements, as well as normalisation of early referral



Figure 6: Percentage contribution of risk factors to all-age DALYs of colorectal cancer in 2019, for both sexes, globally and by regions
 Data source: Global Burden of Diseases, Injuries, and Risk Factors Study 2019. DALYs=disability-adjusted life-years.

to physicians. In most high SDI countries, 50–75 years is also the age group in which colorectal cancer screening is generally recommended for early detection of adenomatous polyps and adenomas.²¹ In the USA, the impact of colorectal cancer screening in reduction of deaths due to colorectal cancer is notable given the considerable increases in colonoscopy screening in the 2000s.²²

We found more colorectal cancer cases and deaths among males than females, with male age-standardised rates being 1.5–2.0-times higher than females in different GBD regions and the difference between males and females growing over time. In the 1960s, when the first international reports were published on colorectal cancer, the age-standardised incidence rate used to be higher for females than males, but the incidence has since risen faster for males than for females.²³ The predominance of males in the global colorectal cancer burden has been attributed to the high prevalence of visceral fat,²⁴ higher smoking prevalence,¹⁹ and greater alcohol consumption among this demographic.²⁵ We also found a greater contribution of alcohol and smoking to colorectal cancer DALYs in males than in females. Some studies have also suggested protective effects of endogenous oestrogen against colorectal carcinogenesis in females.²⁶ Besides endogenous oestrogens, oral contraceptives might also contribute to the lowered colorectal cancer risk in females compared to males.²⁷ Besides the difference in incidence, there are also differences in mortality between males and females, with females tending to have better survival outcomes.^{28,29} Sex apparently modulates the circadian clocks of males and females differently, with respect to the effects of chemotherapy in colorectal cancer, which might also contribute to the sex-based differences in survival and mortality.³⁰ In terms of the age-specific burden of colorectal cancer in males versus females, the findings of GBD 2019 differ from a previous study in which colorectal cancer incidence and mortality were higher in females than in males in individuals aged 65 years and older, implying that colorectal cancer is a major health threat in older females;³¹ in the present study, however, such differences were mainly observed in individuals aged 80 years and older.

In line with previous studies,^{32–36} we observed large increases in new cases and age-specific rates in individuals aged 20–49 years between 1990 and 2019, especially in high SDI countries. In the USA, a previous study³⁷ also noted substantial increases in colorectal cancer incidence rates in individuals aged 20–49 years from 1975 to 2010 and the incidence rate of colon cancers is expected to increase by an estimated 90%, and the incidence rate of rectal cancers is expected to increase by 140%, by 2030.^{37,38} In most high-income countries, screening is recommended from the age of 50 years onwards; however, the recent trends in growing colorectal cancer incidence in younger adults (<50 years) have led to calls for a reconsideration of screening recommendations to

include individuals aged 40–49 years. In 2019, the American Cancer Society recommended colorectal cancer screening from the age of 45 years onwards,³⁶ which can be further modified to include younger people, especially targeting those with a high risk of colorectal cancer (eg, personal history of polyps or adenoma or family history of colorectal cancer or hereditary risk, males, smokers, and those with a high BMI).

The exact reasons for the increasing incidence of colorectal cancer in people younger than 50 years are less clear, but one possible reason could be due to the birth cohort effect, such that those born in the second half of the 20th century are increasingly exposed to potentially modifiable behavioural risk factors such as unhealthy diets, obesity, sedentary behaviour, low physical activity,¹⁸ and increased smoking prevalence in early adulthood.^{32,33,39,40} However, most of these risk factors have been implicated on the basis of evidence generated from patients with colorectal cancer aged 50 years or older, so the exact mechanisms or underlying risk factors remain less clear.^{40–42} A previous study has attributed prolonged sedentary television viewing time to early onset of colorectal cancer, particularly rectal cancer.⁴³ Early-onset colorectal cancer has also been attributed to the rising obesity prevalence in younger adults.^{44–46} A prospective cohort study of 94217 women showed that dietary and lifestyle factors leading to hyperinsulinaemia are associated with an increased risk of colorectal cancer in younger women in the USA.⁴⁷ Binge drinking (episodic heavy alcohol consumption) is also implicated as one of the risk factors, with binge drinking being higher among adults younger than 50 years than in adults aged 50 years and older (ie, those of screening age).⁴⁸

The GBD 2019 colorectal cancer estimates (2.17 million incident cases and 1.09 million deaths) are higher than GLOBOCAN estimates for 2020 (1.9 million incident cases and 935173 deaths).⁴⁹ The global age-standardised rates estimated by GBD are also higher (age-standardised incidence rate 26.7 per 100000; age-standardised mortality rate 13.7 per 100000) than those for GLOBOCAN (age-standardised incidence rate 19.5 per 100000 and age-standardised mortality rate 9.0 per 100000). Both GBD and GLOBOCAN report high incidence and mortality rates in high-income regions and countries in Europe, North America, and Asia, and low incidence and mortality rates in LMICs of sub-Saharan Africa and south Asia, yet there are a few differences in the estimates, which stem from the different methodologies and data sources used. One of the main differences is that GLOBOCAN mostly estimates cancer incidence and deaths from cancer registry data, whereas GBD also models estimates from data sources such as vital registration, cancer registries, verbal autopsy, and sample registration systems. Another key difference between GBD and GLOBOCAN estimates stems from the redistribution of deaths from unknown or non-specific cancers to other cancers in GBD estimates.¹⁵ The GBD estimation

framework has two key advantages over GLOBOCAN. In addition to producing incidence and mortality estimates, GBD produces estimates for YLLs, YLDs, and DALYs, which encompasses the disease burden due to both death and disability caused by the disease. Second, GLOBOCAN provides estimates for a single year (eg, 2002, 2008, 2012, 2018, and 2020) and there are some time series available for selected countries up to 2012 (the CI5Plus: Cancer Incidence in Five Continents Time Trends series); however, continuous time series of estimates of the colorectal cancer burden are not available from GLOBOCAN for sufficiently long time periods at the global and regional levels for all countries and territories. A track of temporal patterns can provide useful information; for instance, the rises in colorectal cancer incidence among younger adults (<50 years) in the past three decades, particularly in high-income regions, can allow researchers to examine the changing risk factors, set hypotheses, and help clinicians and policy makers to be more vigilant about the changing trends of colorectal cancer.

The major limitation of this study was the non-availability of data from cancer registries in many countries in Africa, the Caribbean, and Asia. Although GBD uses all available data from sources such as vital registration, verbal autopsy, and cancer registries, the accuracy of GBD estimates crucially depends upon cancer incidence and mortality data from cancer registries. Many LMICs in sub-Saharan Africa and Asia either do not have population-based cancer registries or the existing registries have insufficient coverage. Under-reporting also occurs because of poor documentation of cases, a shortage of medical facilities and adequately trained medical personnel, lack of a well established oncology centre, and as a result of misdiagnosis. Moreover, the 95% UIs reported in the study do not take into account several sources of bias, including measurement bias, selection bias due to missing data, and model specification bias. Second, the disease registration system was inadequate 30 years ago, especially in LMICs, and although it has improved in several LMICs in recent years, the estimates for the early years of the analysis (ie, the 1990s) are expected to be more biased, which is also reflected in the wider 95% UIs of the mean estimates and percentage changes. Third, there is a lag in the official reporting of cancer data for 2019 even in high SDI countries so the estimates for the most recent years are generated on the basis of recent trends and are provided with wider uncertainty intervals. GBD is an iterative estimation framework providing temporal estimates; the official data for 2019 will be updated as they become available and will be reflected in future GBD iterations.

In conclusion, colorectal cancer incident cases and deaths have more than doubled worldwide in the past three decades. Reducing the prevalence of modifiable risk factors and increasing screening uptake are key to reducing deaths from colorectal cancer, in line with achieving target 3.4 of the SDGs.⁸ Low SDI and middle

SDI (including low-middle, middle, and high-middle SDI) countries, which together comprise close to 75% of colorectal cancer DALYs, are expected to experience further increases in colorectal cancer incidence as a result of population ageing and increasing life expectancy, improved screening and detection, and changing lifestyles. Strategies such as dietary and lifestyle modifications, early screening among high-risk individuals, access to high-quality health care, and better treatment modalities (including improved personalised therapy and access to clinical trials) are imperative to face this global challenge. Population-based cancer registries are important for monitoring colorectal cancer incidence and survival. The increase in colorectal cancer incidence in people younger than 50 years should serve as an early warning signal, necessitating greater awareness of these trends among clinicians, researchers, and policy makers, as well as more research into the risk factors and mechanisms that underpin these trends.

The data generated through GBD are an important resource for people and health-care providers, as they provide information on the effect of current treatment strategies, the effects of previous interventions, and the need for preventive measures. The findings from GBD 2019 can be used by policy makers and provide new perspectives for scientists and physicians throughout the world. These results provide comprehensive and comparable estimates that can inform efforts for equitable colorectal cancer control worldwide, with the larger goal of reducing the global burden of cancer.

GBD 2019 Colorectal Cancer Collaborators

Rajesh Sharma, Mohsen Abbasi-Kangevari, Rami Abd-Rabu, Hassan Abidi, Eman Abu-Gharbieh, Juan Manuel Acuna, Sangeet Adhikari, Shailesh M Advani, Muhammad Sohail Afzal, Mohamad Aghaie Meybodi, Bright Opoku Ahinkorah, Sajjad Ahmad, Ali Ahmadi, Sepideh Ahmadi, Haroon Ahmed, Luai A Ahmed, Muktar Beshir Ahmed, Hanadi Al Hamad, Fares Alahdab, Fahad Mashhour Alanezi, Turki M Alanzi, Fadwa Alhalaqa Naji Alhalaqa, Yousef Alimohamadi, Vahid Alipour, Syed Mohamed Aljunid, Motasem Alkhayyat, Sami Almustanyir, Rajaa M Al-Raddadi, Saba Alvand, Nelson Alvis-Guzman, Saeed Amini, Robert Ancuceanu, Amir Anoushiravani, Ali Arash Anoushiravani, Alireza Ansari-Moghaddam, Jalal Arabloo, Armin Aryannejad, Mohammad Asghari Jafarabadi, Seyyed Shamsadin Athari, Floriane Ausloos, Marcel Ausloos, Atalel Fentahun Awedew, Mamaru Ayenew Awoke, Tegegn Mulatu Ayana, Sina Azadnajafabad, Hiva Azami, Mohammadreza Azangou-Khyavy, Amirhossein Azari Jafari, Ashish D Badiye, Sara Bagherieh, Saeed Bahadory, Atif Amin Baig, Jennifer L Baker, Maciej Banach, Amadou Barrow, Alemshet Yirga Berhie, Sima Besharat, Devidas S Bhagat, Akshaya Srikanth Bhagavathula, Neeraj Bhala, Kritika Bhattacharyya, Vijayalakshmi S Bhojaraja, Sadia Bibi, Ali Bijani, Antonio Biondi, Tone Bjørge, Belay Boda Abule Bodicha, Dejana Braithwaite, Hermann Brenner, Daniela Calina, Chao Cao, Yin Cao, Giulia Carreras, Felix Carvalho, Ester Cerin, Raja Chandra Chakinala, William C S Cho, Dinh-Toi Chu, Joao Conde, Vera Marisa Costa, Natália Cruz-Martins, Omid Dadras, Xiaochen Dai, Lalit Dandona, Rakhi Dandona, Anna Danielewicz, Feleke Mekonnen Demeke, Getu Deballie Demissie, Rupak Desai, Deepak Dhannetiya, Mostafa Dianatinasab, Daniel Diaz, Mojtaba Didehdar, Saeid Doaei, Linh Phuong Doan, Milad Dodangeh, Fatemeh Eghbalian, Debela Debela Ejeta, Michael Ekholuetale, Temitope Cyrus Ekundayo, Iman El Sayed, Muhammed Elhadi,

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Daniel Berhanie Enyew, Tahir Eyayu, Rana Ezzeddini, Ildar Ravisovich Fakhraiyev, Umar Farooque, Hossein Farrokhpour, Farshad Farzadfar, Ali Fatehizadeh, Hamed Fattahi, Nima Fattahi, Masood Fereidoonnehad, Eduarda Fernandes, Getahun Fetensa, Irina Filip, Florian Fischer, Masoud Foroutan, Peter Andras Gual, Mohamed M Gad, Silvano Gallus, Tushar Garg, Tamiru Getachew, Seyyed-Hadi Ghamari, Ahmad Ghashghae, Nermin Ghith, Maryam Gholamalizadeh, Jamshid Gholizadeh Navashenaq, Abraham Tamirat Gizaw, James C Glasbey, Mahaveer Golechha, Pouya Goleij, Kebebe Bekele Gonfa, Giuseppe Gorini, Avirup Guha, Sapna Gupta, Veer Bala Gupta, Vivek Kumar Gupta, Rasool Haddadi, Nima Hafezi-Nejad, Arvin Haj-Mirzaian, Rabih Halwani, Shafiu Haque, Sanam Hari, Ahmed I Hasaballah, Soheil Hassanipour, Simon I Hay, Claudiu Herteliu, Ramesh Holla, Mohammad-Salar Hosseini, Mehdi Hosseinzadeh, Mihaela Hostiu, Mowafa Househ, Junjie Huang, Ayesha Humayun, Ivo Iavicoli, Olayinka Stephen Ilesanmi, Irena M Ilic, Milena D Ilic, Farhad Islami, Masao Iwagami, Mohammad Ali Jahani, Mihajlo Jakovljevic, Tahereh Javaheri, Ranil Jayawardena, Rime Jebai, Ravi Prakash Jha, Tamas Joo, Nitin Joseph, Farahnaz Joukar, Jacek Jerzy Jozwiak, Ali Kabir, Rohollah Kalhor, Ashwin Kamath, Neeti Kapoor, Ibraheem M Karaye, Amirali Karimi, Joonas H Kauppila, Asma Kazemi, Mohammad Keykhaei, Yousef Saleh Khader, Himanshu Khajuria, Rovshan Khalilov, Javad Khanali, Maryam Khayamzadeh, Mahmoud Khodadost, Hanna Kim, Min Seo Kim, Adnan Kisa, Sezer Kisa, Ali-Asghar Kolahi, Hamid Reza Kohestani, Jacek A Kopec, Rajasekaran Koteeswaran, Ai Koyanagi, Yuvaraj Krishnamoorthy, G Anil Kumar, Manoj Kumar, Vivek Kumar, Carlo La Vecchia, Faris Hasan Lami, Iván Landires, Caterina Ledda, Sang-woong Lee, Wei-Chen Lee, Yeong Yeh Lee, Elvynna Leong, Bingyu Li, Stephen S Lim, Stany W Lobo, Joana A Loureiro, Raimundas Lunevicius, Farzan Madadizadeh, Ata Mahmoodpoor, Azeem Majeed, Mohammad-Reza Malekpoor, Reza Malekzadeh, Ahmad Azam Malik, Fariborz Mansour-Ghanaei, Lorenzo Giovanni Mantovani, Miquel Martorell, Sahar Masoudi, Prashant Mathur, Jitendra Kumar Meena, Entezar Mehrabi Nasab, Walter Mendoza, Alexios-Fotios A Mentis, Tomislav Mestrovic, Junmei Miao Jonasson, Bartosz Miazgowski, Tomasz Miazgowski, Gelana Fekadu Worku Mijena, Seyyedmohammadsadeq Mirmoeni, Mohammad Mirza-Aghazadeh-Attari, Hamed Mirzaei, Sanjeev Misra, Karzan Abdulmuhsin Mohammad, Esmail Mohammadi, Saeed Mohammadi, Seyyede Momeneh Mohammadi, Abdollah Mohammadian-Hafshejani, Shafiu Mohammed, Teroj Abdulrahman Mohammed, Nagabhishek Moka, Ali H Mokdad, Zeinab Mokhtari, Mariam Molokhia, Sara Momtazmanesh, Lorenzo Monasta, Ghabad Moradi, Rahmatollah Moradzadeh, Paula Moraga, Joana Morgado-da-Costa, Sumaira Mubarik, Francesk Multa, Mohsen Naghavi, Mukhammad David Naimzada, Hae Sung Nam, Zuhair S Natto, Biswa Prakash Nayak, Javad Nazari, Ehsan Nazemalhosseini-Mojarad, Ionut Negoii, Cuong Tat Nguyen, Son Hoang Nguyen, Nurulamin M Noor, Maryam Noori, Seyyed Mohammad Ali Noori, Virginia Nuñez-Samudio, Chimezie Igwegbe Nzoputam, Bogdan Oancea, Oluwakemi Ololade Odukoya, Ayodipupo Sikiru Oguntade, Hassan Okati-Aliabad, Andrew T Olagunju, Tinuke O Olagunju, Sokking Ong, Samuel M Ostroff, Alicia Padron-Monedero, Reza Pakzad, Adrian Pana, Anamika Pandey, Fatemeh Pashazadeh Kan, Urvish K Patel, Uttam Paudel, Renato B Pereira, Navaraj Perumalsamy, Richard G Pestell, Zahra Zahid Piracha, Richard Charles G Pollok, Akram Pourshams, Naeimeh Pourtaheri, Akila Prashant, Mohammad Rabiee, Navid Rabiee, Amir Radfar, Sima Rafiei, Mosiur Rahman, Amir Masoud Rahmani, Vahid Rahmanian, Nazanin Rajai, Aashish Rajesh, Vajihed Ramezani-Doroh, Kiana Ramezanzadeh, Kamal Ranabhat, Sina Rashedi, Amirfarzan Rashidi, Mahsa Rashidi, Mohammad-Mahdi Rashidi, Mandana Rastegar, David Laith Rawaf, Salman Rawaf, Reza Rawassizadeh, Mohammad Sadegh Razeghinia, Andre M N Renzaho, Negar Rezaei, Nima Rezaei, Saeid Rezaei, Mohsen Rezaei, Sahba Rezaezadeh-Khadem, Gholamreza Roshandel, Maha Mohamed Saber-Ayad, Bahar Saberzadeh-Ardestani, Basema Saddik, Hossein Sadeghi, Umar Saeed, Maryam Sahebazzamani, Amirhossein Sahebkar, Amir Salek Farrokhi,

Amir Salimi, Hamideh Salimzadeh, Pouria Samadi, Mehrnoosh Samaei, Abdallah M Samy, Juan Sanabria, Milena M Santric-Milicevic, Muhammad Arif Nadeem Saqib, Arash Sarveazad, Brijesh Sathian, Maheswar Satpathy, Ione Jayce Ceola Schneider, Mario Šekerija, Sadaf G Sepanlou, Allen Seylani, Feng Sha, Sayed Mohammad Shafiee, Zahra Shaghghi, Saeed Shahabi, Elaheh Shaker, Maede Sharifian, Javad Sharifi-Rad, Sara Sheikhbaehaei, Jeevan K Shetty, Reza Shirkoohi, Parnian Shobeiri, Sudeep K Siddappa Malleshappa, Diego Augusto Santos Silva, Guilherme Silva Julian, Achintya Dinesh Singh, Jasvinder A Singh, Md Shahjahan Siraj, Gholam Reza Sivandzadeh, Valentin Yurievich Skryabin, Anna Aleksandrovna Skryabina, Bogdan Socea, Marco Solmi, Mohammad Sadegh Soltani-Zangbar, Suhang Song, Viktória Szerencsés, Miklós Szócska, Rafael Tabarés-Seisdedos, Elnaz Tabibian, Majid Taheri, Yasaman Taheri Abkenar, Amir Taherkhani, Iman M Talaat, Ker-Kan Tan, Abdelghani Tbakhi, Bekele Tesfaye, Amir Tiyuri, Daniel Nigusse Tollosa, Mathilde Touvier, Bach Xuan Tran, Biruk Shalmeno Tusa, Irfan Ullah, Saif Ullah, Marco Vacante, Sahel Valadan Tahbaz, Massimiliano Veroux, Bay Vo, Theo Vos, Cong Wang, Ronny Westerman, Melat Woldemariam, Seyed Hossein Yahyazadeh Jabbari, Lin Yang, Fereshteh Yazdanpanah, Chuanhua Yu, Deniz Yuce, Ismaeel Yunusa, Vesna Zadnik, Mazyar Zahir, Iman Zare, Zhi-Jiang Zhang, and Mohammad Zoladl.

Affiliations

University School of Management and Entrepreneurship (R Sharma PhD), Delhi Technological University, New Delhi, India; Social Determinants of Health Research Center (M Abbasi-Kangevari MD, M Azangou-Khyavy MD, S Ghamari MD, J Khanali MD, A Kolahi MD, M Rashidi MD, A Salimi MD), Department of Epidemiology (A Ahmadi PhD), School of Advanced Technologies in Medicine (S Ahmadi PhD), Department of Community Nutrition (S Doaei PhD), Cancer Research Center (M Gholamalizadeh PhD), Department of Pharmacology (A Haj-Mirzaian MD, K Ramezanzadeh PharmD), Obesity Research Center (A Haj-Mirzaian MD), Department of Health & Community Medicine (A Kolahi MD), Gastroenterology and Liver Diseases Research Center (E Nazemalhosseini-Mojarad PhD), Medical Genetics Genomic Research Center (H Sadeghi PhD), Phytochemistry Research Center (J Sharifi-Rad PhD, Y Taheri Abkenar PharmD), Medical Ethics and Law Research Center (M Taheri PhD), Shahid Beheshti University of Medical Sciences, Tehran, Iran (M Khayamzadeh MD); Evidence-Based Practice Center (R Abd-Rabu MD), Mayo Clinic, Rochester, MN, USA; Laboratory Technology Sciences Department (H Abidi PhD), Department of Nursing (M Zoladi PhD), Yasuj University of Medical Sciences, Yasuj, Iran; Clinical Sciences Department (E Abu-Gharbieh PhD, Prof R Halwani PhD, M M Saber-Ayad MD, Prof I M Talaat PhD), College of Medicine (Prof R Halwani PhD), Sharjah Institute for Medical Research (B Saddik PhD), University of Sharjah, Sharjah, United Arab Emirates; Department of Epidemiology and Population Health (Prof J M Acuna MD), Khalifa University, Abu Dhabi, United Arab Emirates; FIU Robert Stempel College of Public Health & Social Work (Prof J M Acuna MD), Department of Epidemiology (R Jebai MPH), Florida International University, Miami, FL, USA; Biodesign Center for Environmental Health Engineering (S Adhikari MS), Arizona State University, Tempe, AZ, USA; Terasaki Institute for Biomedical Innovation, Los Angeles, CA, USA (S M Advani PhD); School of Medicine (S M Advani PhD), Georgetown University, Washington DC, USA; Department of Life Sciences (M S Afzal PhD), School of Sciences (M N Saqib PhD), University of Management and Technology, Lahore, Pakistan; Department of Medicine (M Aghaie Meybodi MD), Rutgers University, Newark, NJ, USA; The Australian Centre for Public and Population Health Research (ACPPHR) (B O Ahinkorah MPH), University of Technology Sydney, Sydney, NSW, Australia; Department of Health and Biological Sciences (S Ahmad PhD), Abasyn University, Peshawar, Pakistan; Department of Epidemiology and Biostatistics (A Ahmadi PhD, A Mohammadian-Hafshejani PhD), Shahrekord University of Medical Sciences, Shahrekord, Iran; Department of Biosciences (H Ahmed PhD), COMSATS Institute of Information Technology, Islamabad, Pakistan; Institute of Public Health (L A Ahmed PhD, A S Bhagavathula PharmD), United Arab Emirates University, Al Ain, United Arab Emirates;

Department of Epidemiology (M B Ahmed MPH), Department of Health, Behavior and Society (A T Gizaw MPH), Jimma University, Jimma, Ethiopia; Australian Center for Precision Health (M B Ahmed MPH), University of South Australia, Adelaide, SA, Australia; Geriatric and Long Term Care Department (H Al Hamad MD, B Sathian PhD), Rumailah Hospital (H Al Hamad MD), Hamad Medical Corporation, Doha, Qatar; Mayo Evidence-based Practice Center (F Alahdab MSc), Mayo Clinic Foundation for Medical Education and Research, Rochester, MN, USA; Health Information Management and Technology Department (T M Alanzhi PhD), Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia (F M Alanezi PhD); Faculty of Nursing (F A N Alhalaqi PhD), Philadelphia University, Amman, Jordan; Psychological Sciences Association, Amman, Jordan (F A N Alhalaqi PhD); Pars Hospital (Y Alimohamadi PhD), Health Management and Economics Research Center (V Alipour PhD, J Arabloo PhD), Department of Health Economics (V Alipour PhD), Department of Internal Medicine (A Anoushirvani MD), School of Medicine (M Dodangeh MD), Minimally Invasive Surgery Research Center (A Kabir MD), Student Research Committee (M Noori MD), The Five Senses Health Institute (S Rezaei MD), Colorectal Research Center (A Sarvezad PhD), Trauma and Injury Research Center (M Taheri PhD), Department of Epidemiology (A Tiyuri MSc), Iran University of Medical Sciences, Tehran, Iran (F Pashazadeh Kan BSN); Department of Epidemiology and Biostatistics (Y Alimohamadi PhD), Liver and Pancreatobiliary Diseases Research Center (S Alvand MD), Digestive Diseases Research Institute (A Anoushirvani MD, S Hariri MD, Prof R Malekzadeh MD, S Masoudi MSc, Prof A Pourshams MD, H Salimzadeh PhD, S G Sepanlou MD), Non-communicable Diseases Research Center (A Aryannejad MD, S Azadnajafabad MD, M Azangou-Khyavy MD, Prof F Farzadfar DSc, N Fattahi MD, S Ghamari MD, M Keykhaei MD, J Khanali MD, M Malekpour MD, S Momtazmanesh MD, M Rashidi MD, N Rezaei PhD, S Rezaezadeh-Khadem MD), Experimental Medicine Research Center (A Aryannejad MD), Iranian Research Center for HIV/AIDS (IRCHA) (O Dadras DrPH), School of Medicine (H Farrokhpour MD, N Hafezi-Nejad MD, A Karimi MD, S Momtazmanesh MD), Students Scientific Research Center (SSRC) (M Keykhaei MD), Tehran Heart Center (E Mehrabi Nasab MD), Faculty of Medicine (E Mohammadi MD), Department of Cardiology (S Rashedi MD), Endocrinology and Metabolism Research Center (N Rezaei PhD), Research Center for Immunodeficiencies (Prof N Rezaei PhD), Faculty of Medicine (E Shaker MD, P Shobeiri MD), Cancer Research Center (R Shirkoohi PhD), Cancer Biology Research Center (R Shirkoohi PhD), Radiology Department (E Tabibian MD), Pediatric Allergy, Immunology, and Immunodeficiency Department (F Yazdanpanah MD), Department of Pharmacology (M Zahir MD), Tehran University of Medical Sciences, Tehran, Iran; Department of Health Policy and Management (Prof S M Aljunied PhD), Kuwait University, Safat, Kuwait; International Centre for Casemix and Clinical Coding (Prof S M Aljunied PhD), National University of Malaysia, Bandar Tun Razak, Malaysia; Department of Internal Medicine (M Alkhatyat MD, A D Singh MD), Department of Cardiovascular Medicine (M M Gad MD), Cleveland Clinic, Cleveland, OH, USA; College of Medicine (S Almustanyir MD), Alfaisal University, Riyadh, Saudi Arabia; Ministry of Health, Riyadh, Saudi Arabia (S Almustanyir MD); Department of Community Medicine (R M Al-Raddadi PhD), Rabigh Faculty of Medicine (A A Malik PhD), Department of Dental Public Health (Z S Natto DrPH), King Abdulaziz University, Jeddah, Saudi Arabia; Research Group in Hospital Management and Health Policies (Prof N Alvis-Guzman PhD), Universidad de la Costa (University of the Coast), Barranquilla, Colombia; Research Group in Health Economics (Prof N Alvis-Guzman PhD), University of Cartagena, Cartagena, Colombia; Department of Health Services Management (S Amini PhD), Khomein University of Medical Sciences, Khomein, Iran; Pharmacy Department (Prof R Ancuceanu PhD), Internal Medicine Department (M Hostiu PhD), Department of General Surgery (I Negroi PhD, B Socea PhD), Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; Department of Epidemiology and Biostatistics (Prof A Ansari-Moghaddam PhD), Health Promotion Research Center (H Okati-Aliabad PhD), Zahedan University of Medical Sciences, Zahedan, Iran; Department of Biostatistics and Epidemiology (Prof M Asghari Jafarabadi PhD), Student Research Committee (M Hosseini MD), Anesthesiology and Critical Care Department (Prof A Mahmoodpoor MD), Department of Radiology (M Mirza-Aghazadeh-Attari MD), Department of Immunology (M Soltani-Zangbar MSc), Department of Pediatric Allergy and Immunology (F Yazdanpanah MD), Tabriz University of Medical Sciences, Tabriz, Iran; Department of Biostatistics and Epidemiology (Prof M Asghari Jafarabadi PhD), Department of Immunology (S Athari PhD), Department of Anatomical Sciences (S Mohammadi PhD), Zanjan University of Medical Sciences, Zanjan, Iran; Gastro-enterology Department (F Ausloos MD), University of Liège, Liège, Belgium; School of Business (Prof M Ausloos PhD), University of Leicester, Leicester, UK; Department of Statistics and Econometrics (Prof M Ausloos PhD, Prof C Herteliu PhD, A Pana MD), Bucharest University of Economic Studies, Bucharest, Romania; Department of Surgery (A F Awedew MD), Addis Ababa University, Addis Ababa, Ethiopia; Department of Epidemiology and Preventive Medicine (M A Awoke MPH), University of Melbourne, Melbourne, VIC, Australia; School of Nursing (T M Ayana MSc), Biomedical Sciences Department (B B A Bodicha MSc, T Getachew MSc), Department of Medical Laboratory Science (M Woldemariam MSc), Arba Minch University, Arba Minch, Ethiopia; Department of Medical-Surgical Nursing (H Azami MSc), Department of Medicine (Prof F Eghbalian MD), Department of Pharmacology and Toxicology (R Haddadi PhD), Health Management and Economics (V Ramezani-Doroh PhD), Research Center for Molecular Medicine (A Taherkhani PhD), Hamadan University of Medical Sciences, Hamadan, Iran; School of Medicine (A Azari Jafari MD, S Mirmoeeini MD), Shahrood University of Medical Sciences, Shahrood, Iran; Department of Forensic Science (A D Badiye MSc, N Kapoor MSc), Government Institute of Forensic Science, Nagpur, India; School of Medicine (S Bagherieh BSc), Department of Environmental Health Engineering (A Fatehizadeh PhD), Research Institute for Primordial Prevention of Non-Communicable Disease (S Hariri MD), Food Security Research Center (Z Mokhtari PhD), Isfahan University of Medical Sciences, Isfahan, Iran; Department of Parasitology (S Bahadory PhD), Department of Clinical Biochemistry (R Ezzeddini PhD), Tarbiat Modares University, Tehran, Iran; Department of Parasitology (S Bahadory PhD), Alborz University of Medical Sciences, Karaj, Iran; Unit of Biochemistry (A A Baig PhD), Universiti Sultan Zainal Abidin (Sultan Zainal Abidin University), Kuala Terengganu, Malaysia; Center for Clinical Research and Prevention (J L Baker PhD), Bispebjerg University Hospital, Frederiksberg, Denmark; Department of Hypertension (Prof M Banach PhD), Medical University of Lodz, Lodz, Poland; Polish Mothers' Memorial Hospital Research Institute, Lodz, Poland (Prof M Banach PhD); Department of Public & Environmental Health (A Barrow MPH), University of The Gambia, Brikama, The Gambia; Epidemiology and Disease Control Unit (A Barrow MPH), Ministry of Health, Kotu, The Gambia; School of Nursing (A Y Berhie MSc), University of Gondar, Bahir Dar, Ethiopia; Golestan Research Center of Gastroenterology and Hepatology (S Besharat PhD, G Roshandel PhD), Medical Genetics Department (H Sadeghi PhD), Golestan University of Medical Sciences, Gorgan, Iran; Department of Forensic Chemistry (D S Bhagat PhD), Government Institute of Forensic Science, Aurangabad, India; Department of Social and Clinical Pharmacy (A S Bhagavathula PharmD), Charles University, Hradec Kralova, Czech Republic; Institutes of Applied Health Research and Translational Medicine (N Bhala PhD), Queen Elizabeth Hospital Birmingham, Birmingham, UK; Institute of Applied Health Research (N Bhala PhD), NIHR Global Health Research Unit on Global Surgery (J C Glasbey MSc), University of Birmingham, Birmingham, UK; Department of Statistical and Computational Genomics (K Bhattacharyya MSc), National Institute of Biomedical Genomics, Kalyani, India; Department of Statistics (K Bhattacharyya MSc), University of Calcutta, Kolkata, India; Department of Anatomy (V S Bhojaraja MD), Department of Biochemistry (J K Shetty MD), Manipal University College Melaka, Melaka, Malaysia; Institute of Soil and Environmental Sciences (S Bibi PhD, S Ullah PhD), University of Agriculture, Faisalabad, Faisalabad, Pakistan; Social Determinants of Health Research Center (A Bijani PhD, M A Jahani PhD),

Babol University of Medical Sciences, Babol, Iran; Department of General Surgery and Medical-Surgical Specialties (Prof A Biondi PhD, M Vacante PhD), Clinical and Experimental Medicine (C Ledda PhD), Department of Medical and Surgical Sciences and Advanced Technologies (Prof M Veroux PhD), University of Catania, Catania, Italy; Department of Global Public Health and Primary Care (Prof T Bjørge PhD), University of Bergen, Bergen, Norway; Cancer Registry of Norway, Oslo, Norway (Prof T Bjørge PhD); Department of Epidemiology (D Braithwaite PhD), University of Florida, Gainesville, FL, USA; Cancer Population Sciences Program (D Braithwaite PhD), University of Florida Health Cancer Center, Gainesville, FL, USA; Division of Clinical Epidemiology and Aging Research (Prof H Brenner MD), German Cancer Research Center, Heidelberg, Germany; Clinical Pharmacy Department (Prof D Calina PhD), University of Medicine and Pharmacy of Craiova, Craiova, Romania; Program in Physical Therapy (C Cao MPH), Department of Surgery (Y Cao DSc), Washington University in St. Louis, St. Louis, MO, USA; Oncological Network, Prevention and Research Institute (G Gorini MD), Institute for Cancer Research, Prevention and Clinical Network, Florence, Italy (G Carreras PhD); Research Unit on Applied Molecular Biosciences (UCIBIO) (Prof F Carvalho PhD, V M Costa PhD), Department of Medicine (Prof N Cruz-Martins PhD), Associated Laboratory for Green Chemistry (LAQV) (Prof E Fernandes PhD), Laboratory for Process Engineering, Environment, Biotechnology and Energy (LEPABE) (J Loureiro PhD), University Hospital Center of Porto (J Morgado-da-Costa MSc), Department of Chemistry (R B Pereira PhD), University of Porto, Porto, Portugal; Mary MacKillop Institute for Health Research (Prof E Cerin PhD), Australian Catholic University, Melbourne, VIC, Australia; School of Public Health (Prof E Cerin PhD), University of Hong Kong, Hong Kong, China; Hospitalist Department (R Chakinala MD), Geisinger Health System, Danville, PA, USA; Department of Clinical Oncology (W C S Cho PhD), Queen Elizabeth Hospital, Hong Kong, China; Center for Biomedicine and Community Health (D Chu PhD), VNU-International School, Hanoi, Vietnam; Nova Medical School (J Conde PhD), Nova University of Lisbon, Lisbon, Portugal; Department of Health Sciences (Prof N Cruz-Martins PhD), Institute of Research and Advanced Training in Health Sciences and Technologies (CESPU), Famalicão, Portugal; School of Public Health (O Dadras DrPH), Walailak University, Nakhon Si Thammarat, Thailand; Institute for Health Metrics and Evaluation (X Dai PhD), Prof L Dandona MD, Prof R Dandona PhD, Prof S I Hay DSc, Prof S S Lim PhD, A H Mokdad PhD, Prof M Naghavi PhD, S M Ostroff PhD, Prof T Vos PhD), Department of Health Metrics Sciences, School of Medicine (X Dai PhD, Prof R Dandona PhD, Prof S I Hay DSc, Prof S S Lim PhD, A H Mokdad PhD, Prof M Naghavi PhD, Prof T Vos PhD), Henry M Jackson School of International Studies (S M Ostroff PhD), University of Washington, Seattle, WA, USA; Department of Research (A Pandey PhD), Public Health Foundation of India, Gurugram, India (Prof L Dandona MD, Prof R Dandona PhD, G Kumar PhD); Indian Council of Medical Research, New Delhi, India (Prof L Dandona MD); Department of Human Nutrition (A Danielewicz PhD), Uniwersytet Warmińsko-Mazurski w Olsztynie (University of Warmia and Mazury in Olsztyn), Olsztyn, Poland; Department of Medical Laboratory Sciences (F M Demeke MSc), Bahir Dar University, Bahir Dar, Ethiopia; Institute of Public Health (G D Demissie MPH), University of Gondar, Gondar, Ethiopia; Division of Cardiology (R Desai MBBS), Atlanta Veterans Affairs Medical Center, Decatur, GA, USA; Department of Community Medicine (D Dhannetiya MD, R P Jha MSc), Dr. Baba Saheb Ambedkar Medical College & Hospital, Delhi, India; Department of Epidemiology (M Dianatinasab MSc), Maastricht University, Maastricht, Netherlands; Department of Epidemiology (M Dianatinasab MSc), Nutrition Research Center (A Kazemi PhD), Non-communicable Disease Research Center (Prof R Malekzadeh MD, S G Sepanlou MD), Department of Clinical Biochemistry and Autophagy Research Center (S Shafiee PhD), Health Policy Research Center (S Shahabi PhD), Department of Internal Medicine (G R Sivandzadeh MD), Gastroenterohepatology Research Center (G R Sivandzadeh MD), Shiraz University of Medical Sciences, Shiraz, Iran; Center of Complexity Sciences (Prof D Diaz PhD), National Autonomous University of Mexico, Mexico City, Mexico; Faculty of Veterinary Medicine and Zootechnics (Prof D Diaz PhD), Autonomous University of Sinaloa, Culiacán Rosales, Mexico; Department of Parasitology and Mycology (M Didehdar PhD), Department of Epidemiology (R Moradzadeh PhD), Department of Pediatrics (J Nazari MD), Arak University of Medical Sciences, Arak, Iran; School of Health (S Doaei PhD), Gastrointestinal and Liver Diseases Research Center (S Hassanipour PhD, F Joukar PhD), Prof F Mansour-Ghanaei MD), Caspian Digestive Disease Research Center (S Hassanipour PhD, F Joukar PhD), Prof F Mansour-Ghanaei MD), Guilan University of Medical Sciences, Rasht, Iran; Institute for Global Health Innovations (L P Doan MSc), Faculty of Medicine (L P Doan MSc), Duy Tan University, Da Nang, Vietnam; Department of Medicine (D D Ejeta MD), Ambo University, Ambo, Ethiopia; Department of Epidemiology and Medical Statistics (M Ekholuonetale MSc), Faculty of Public Health (M Ekholuonetale MSc), Department of Community Medicine (O S Ilesanmi PhD), University of Ibadan, Ibadan, Nigeria; Department of Biological Sciences (T C Ekundayo PhD), University of Medical Sciences, Ondo, Ondo, Nigeria; Biomedical Informatics and Medical Statistics Department (I El Sayed PhD), Pathology Department (Prof I M Talaat PhD), Alexandria University, Alexandria, Egypt; Faculty of Medicine (M Elhadi MD), University of Tripoli, Tripoli, Libya; Department of Health Informatics (D B Enyew MSc), Department of Nursing (G F W Mijena MSc), Haramaya University, Harar, Ethiopia; Medical Laboratory Sciences (T Eyayu MSc), Debre Tabor University, Debre Tabor, Ethiopia; Head of the Laboratory of Experimental Medicine (I R Fakhradiyev PhD), Kazakh National Medical University, Almaty, Kazakhstan; Department of Internal Medicine (U Farooque MD), Dow University of Health Sciences, Karachi, Pakistan; Endocrinology and Metabolism Research Institute (H Farrokhpour MD), Department of Epidemiology (S Rashedi MD, E Shaker MD), Department of Medicine (A Salimi MD), Department of International Studies (P Shobeiri MD), Non-Communicable Diseases Research Center (NCDRC), Tehran, Iran (E Mohammadi MD); Centre for Primary Health Care Network Management (H Fattahi PhD), Ministry of Health and Medical Education, Tehran, Iran; Student Research Committee (N Fattahi MD), Social Determinants of Health Research Center (G Moradi PhD), Department of Epidemiology and Biostatistics (G Moradi PhD), Kurdistan University of Medical Sciences, Sanandaj, Iran; Department of Medicinal Chemistry (M Fereidoonzehad PhD), Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; Department of Nursing (G Fetensa MSc), Wollega University, Nekemte, Ethiopia; Psychiatry Department (I Filip MD), Kaiser Permanente, Fontana, CA, USA; School of Health Sciences (I Filip MD), AT Still University, Mesa, AZ, USA; Institute of Gerontological Health Services and Nursing Research (F Fischer PhD), Ravensburg-Weingarten University of Applied Sciences, Weingarten, Germany; Department of Medical Parasitology (M Foroutan PhD), Faculty of Medicine (M Foroutan PhD), Abadan University of Medical Sciences, Abadan, Iran; Health Services Management Training Centre (P A Gaal PhD, T Joo MSc, V Szerencsés MA), Faculty of Health and Public Administration (M Szócska PhD), Semmelweis University, Budapest, Hungary; Department of Applied Social Sciences (P A Gaal PhD), Sapientia Hungarian University of Transylvania, Târgu-Mureş, Romania; Gillings School of Global Public Health (M M Gad MD), University of North Carolina Chapel Hill, Chapel Hill, NC, USA; Department of Environmental Health Sciences (S Gallus DSc), Mario Negri Institute for Pharmacological Research, Milan, Italy; Department of Radiology (T Garg MBBS), King Edward Memorial Hospital, Mumbai, India; School of Public Health (A Ghashghaee BSc), Institute for Prevention of Non-communicable Diseases (R Kalhor PhD), Health Services Management Department (R Kalhor PhD), Social Determinants of Health Research Center (S Rafiei PhD), Qazvin University of Medical Sciences, Qazvin, Iran; Research Group for Genomic Epidemiology (N Ghith PhD), Technical University of Denmark, Copenhagen, Denmark; Non-communicable Diseases Research Center (J Gholizadeh Navashenaq PhD, N Pourtaheri PhD), Bam University of Medical Sciences, Bam, Iran; Health Systems and Policy Research (M Golechha PhD), Indian Institute of Public Health, Gandhinagar, India; Department of Genetics (P Goleij MSc), Sana Institute of Higher Education, Sari, Iran; Department of Surgery (K B Gonfa MD), Madda Walabu University,

Bale Robe, Ethiopia; Harrington Heart and Vascular Institute (A Guha MD), Department of Nutrition and Preventive Medicine (Prof J Sanabria MD), Case Western Reserve University, Cleveland, OH, USA; Division of Cardiovascular Medicine (A Guha MD), Ohio State University, Columbus, OH, USA; Toxicology Department (S Gupta MSc), Shriram Institute for Industrial Research, Delhi, Delhi, India; School of Medicine (V Gupta PhD), Deakin University, Geelong, VIC, Australia; Department of Clinical Medicine (Prof V K Gupta PhD), Macquarie University, Sydney, NSW, Australia; Department of Radiology and Radiological Science (N Hafezi-Nejad MD, S Sheikhbahaei MD), Johns Hopkins University, Baltimore, MD, USA; Research & Scientific Studies Unit (S Haque PhD), Jazan University, Jazan, Saudi Arabia; Department of Zoology and Entomology (A I Hasaballah PhD), Al Azhar University, Cairo, Egypt; School of Business (Prof C Herteliu PhD), London South Bank University, London, UK; Kasturba Medical College, Mangalore (R Holla MD, A Kamath MD), Manipal Academy of Higher Education, Manipal, India (A Kamath MD); Pattern Recognition and Machine Learning Lab (M Hosseinzadeh PhD), Gachon University, Seongnam, South Korea; College of Science and Engineering (Prof M Househ PhD), Hamad Bin Khalifa University, Doha, Qatar; Jockey Club School of Public Health and Primary Care (J Huang MD), The Chinese University of Hong Kong, Hong Kong, China; Department of Public Health and Community Medicine (Prof A Humayun PhD), Shaikh Khalifa Bin Zayed Al-Nahyan Medical College, Lahore, Pakistan; Department of Public Health (Prof I Iavicoli PhD), University of Naples Federico II, Naples, Italy; Department of Community Medicine (O S Ilesanmi PhD), Department of Medicine (A S Oguntade MSc), University College Hospital, Ibadan, Ibadan, Nigeria; Faculty of Medicine (I M Ilic PhD), Prof M M Santric-Milicevic PhD), School of Public Health and Health Management (Prof M M Santric-Milicevic PhD), University of Belgrade, Belgrade, Serbia; Department of Epidemiology (Prof M D Ilic PhD), Institute of Advanced Manufacturing Technologies (Prof M Jakovljevic PhD), Peter the Great St Petersburg Polytechnic University, St Petersburg, Russia; Surveillance and Health Services Research (F Islami PhD), American Cancer Society, Atlanta, GA, USA; Department of Health Services Research (M Iwagami PhD), University of Tsukuba, Tsukuba, Japan; Department of Non-Communicable Disease Epidemiology (M Iwagami PhD), London School of Hygiene & Tropical Medicine, London, UK; Institute of Comparative Economic Studies (Prof M Jakovljevic PhD), Hosei University, Tokyo, Japan; Health Informatic Lab (T Javaheri PhD), Department of Computer Science (R Rawassizadeh PhD), Boston University, Boston, MA, USA; Department of Physiology (R Jayawardena PhD), University of Colombo, Colombo, Sri Lanka; School of Exercise and Nutrition Sciences (R Jayawardena PhD), Queensland University of Technology, Brisbane, QLD, Australia; Department of Community Medicine (R P Jha MSc), Banaras Hindu University, Varanasi, India; Department of Community Medicine (N Joseph MD), Manipal Academy of Higher Education, Mangalore, India; Department of Family Medicine and Public Health (J J Jozwiak PhD), University of Opole, Opole, Poland; School of Health Professions and Human Services (I M Karaye MD), Hofstra University, Hempstead, NY, USA; Surgery Research Unit (J H Kauppila MD), University of Oulu, Oulu, Finland; Department of Molecular Medicine and Surgery (J H Kauppila MD), Karolinska Institute, Stockholm, Sweden; Department of Public Health (Prof Y S Khader PhD), Jordan University of Science and Technology, Irbid, Jordan; Amity Institute of Forensic Sciences (H Khajuria PhD, B P Nayak PhD), Amity University, Noida, India; Department of Biophysics and Biochemistry (Prof R Khalilov PhD), Baku State University, Baku, Azerbaijan; Russian Institute for Advanced Study (Prof R Khalilov PhD), Moscow State Pedagogical University, Moscow, Russia; The Iranian Academy of Medical Sciences, Tehran, Iran (M Khayamzadeh MD); Department of Epidemiology (M Khodadost PhD), School of Public Health (M Khodadost PhD), Larestan University of Medical Sciences, Larestan, Iran; College of Medicine (H Kim BN), Ewha Womans University, Seoul, South Korea; Department of Genomics and Digital Health (M Kim MD), Samsung Advanced Institute for Health Sciences & Technology (SAIHST), Seoul, South Korea; Public Health Center (M Kim MD), Ministry of Health and Welfare, Wando, South Korea; School of Health Sciences (Prof A Kisa PhD), Kristiania University College, Oslo, Norway; Department of Global Community Health and Behavioral Sciences (Prof A Kisa PhD), Tulane University, New Orleans, LA, USA; Department of Nursing and Health Promotion (S Kisa PhD), Oslo Metropolitan University, Oslo, Norway; Social Determinants of Health Research Center (H Koohestani PhD), Saveh University of Medical Sciences, Saveh, Iran; School of Population and Public Health (J A Kopec PhD), University of British Columbia, Vancouver, BC, Canada; Arthritis Research Canada, Richmond, BC, Canada (J A Kopec PhD); Microbiology & Molecular Cell Biology Department (R Koteeswaran MD), Eastern Virginia Medical School, Norfolk, VA, USA; Biomedical Research Networking Center for Mental Health Network (CIBERSAM) (A Koyanagi MD), San Juan de Dios Sanitary Park, Sant Boi de Llobregat, Spain; Catalan Institution for Research and Advanced Studies (ICREA), Barcelona, Spain (A Koyanagi MD); Department of Community Medicine (Y Krishnamoorthy MD), Employees' State Insurance Model Hospital, Chennai, India; Chemical and Biochemical Processing Division (M Kumar PhD), Central Institute for Research on Cotton Technology, Mumbai, India; Brigham and Women's Hospital (V Kumar MD), Oral Health Policy and Epidemiology Department (Z S Natto DrPH), Department of Internal Medicine (N Rajai MD), Harvard University, Boston, MA, USA; Department of Clinical Sciences and Community Health (Prof C La Vecchia MD), University of Milan, Milan, Italy; Department of Community and Family Medicine (F H Lami PhD), University of Baghdad, Baghdad, Iraq; Unit of Genetics and Public Health (Prof I Landires MD), Unit of Microbiology and Public Health (V Nuñez-Samudio PhD), Institute of Medical Sciences, Las Tablas, Panama; Department of Public Health (V Nuñez-Samudio PhD), Ministry of Health, Herrera, Panama (Prof I Landires MD); Pattern Recognition and Machine Learning Lab (Prof S Lee PhD), Gachon University, Seongnam, South Korea; The Office of Health Policy & Legislative Affairs (W Lee PhD), University of Texas, Galveston, TX, USA; Department of Medicine (Prof Y Lee PhD), School of Medical Sciences (Prof Y Lee PhD), University of Science Malaysia, Kota Bharu, Malaysia; Faculty of Science (E Leong PhD), Universiti Brunei Darussalam (University of Brunei Darussalam), Bandar Seri Begawan, Brunei; Department of Sociology (B Li PhD), Shenzhen University, Shenzhen, China; Department of Professional and Medical Education (S W Lobo PhD), Meharry Medical College, Nashville, TN, USA; Department of Biomedical Sciences (S W Lobo PhD), Mercer University, Macon, GA, USA; School of Health (J Loureiro PhD), Polytechnic Institute of Porto, Portugal; Department of General Surgery (Prof R Lunevicius DSc), Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK; Department of Surgery (Prof R Lunevicius DSc), University of Liverpool, Liverpool, UK; Department of Biostatistics and Epidemiology, School of Public Health (F Madadzadeh PhD), Yazd University of Medical Sciences, Yazd, Iran; Department of Primary Care and Public Health (Prof A Majeed MD), Prof S Rawaf MD), WHO Collaborating Centre for Public Health Education and Training (D L Rawaf MD), Imperial College London, London, UK; University Institute of Public Health (A A Malik PhD), The University of Lahore, Lahore, Pakistan; School of Medicine and Surgery (Prof L G Mantovani DSc), University of Milan Bicocca, Monza, Italy; Value-Based Healthcare Unit (Prof L G Mantovani DSc), IRCCS MultiMedica, Sesto San Giovanni, Italy; Department of Nutrition and Dietetics (M Martorell PhD), Centre for Healthy Living (M Martorell PhD) University of Concepcion, Concepción, Chile; National Centre for Disease Informatics and Research (P Mathur PhD), Indian Council of Medical Research, Bengaluru, India; Department of Preventive Oncology (J K Meena MD), All India Institute of Medical Sciences, New Delhi, India; Peru Country Office (W Mendoza MD), United Nations Population Fund (UNFPA), Lima, Peru; University Research Institute (A A Mentis MD), National and Kapodistrian University of Athens, Athens, Greece; Clinical Microbiology and Parasitology Unit (T Mestrovic PhD), Dr. Zora Profocic Polyclinic, Zagreb, Croatia; University Centre Varazdin (T Mestrovic PhD), University North, Varazdin, Croatia; School of Public Health and Community Medicine (J Miao Jonasson PhD), University of Gothenburg, Gothenburg, Sweden; Center for Innovation in Medical Education (M Miazgowski MD), Department of Propedeutics of Internal Diseases & Arterial Hypertension (Prof T Miazgowski MD), Pomeranian Medical

University, Szczecin, Poland (B Miazgowski MD); Social Determinants of Health Center (M Mirza-Aghazadeh-Attari MD), Urmia University of Medical Science, Urmia, Iran; Research Center for Biochemistry and Nutrition in Metabolic Diseases (H Mirzaei PhD), Kashan University of Medical Sciences, Kashan, Iran; Department of Surgical Oncology (Prof S Misra MCh), All India Institute of Medical Sciences, Jodhpur, India; Department of Biology (K A Mohammad PhD), Salahaddin University-Erbil, Erbil, Iraq; Infectious Diseases Research Center (S Mohammadi PhD), Golestan University of Medical Sciences, Gorgan, Iran; Health Systems and Policy Research Unit (S Mohammed PhD), Ahmadu Bello University, Zaria, Nigeria; Department of Health Care Management (S Mohammed PhD), Technical University of Berlin, Berlin, Germany; Dental Basic Sciences Department (T A Mohammed MSc), University of Duhok, Duhok, Iraq; Oncology Department (N Moka MD), Appalachian Regional Healthcare, Hazard, KY, USA; Department of Internal Medicine (N Moka MD), University of Kentucky, Lexington, KY, USA; Faculty of Life Sciences and Medicine (M Molokhia PhD), King's College London, London, UK; Clinical Epidemiology and Public Health Research Unit (L Monasta DSc), Burlo Garofolo Institute for Maternal and Child Health, Trieste, Italy; Computer, Electrical, and Mathematical Sciences and Engineering Division (P Moraga PhD), King Abdullah University of Science and Technology, Thuwal, Saudi Arabia; Department of Epidemiology and Biostatistics (S Mubarik MS, Prof C Yu PhD), School of Medicine (Z Zhang PhD), Wuhan University, Wuhan, China; Department of Surgery (F Mulita MD), General University Hospital of Patras, Patras, Greece; Medical School (F Mulita MD), University of Thessaly, Larissa, Greece; Laboratory of Public Health Indicators Analysis and Health Digitalization (M Naimzada MD), Moscow Institute of Physics and Technology, Dolgoprudny, Russia; Experimental Surgery and Oncology Laboratory (M Naimzada MD), Kursk State Medical University, Kursk, Russia; Department of Preventive Medicine and Public Health (Prof H Nam PhD), Chungnam National University School of Medicine, Daejeon, South Korea; Daejeon Regional Cancer Center (Prof H Nam PhD), Chungnam National University Hospital, Daejeon, South Korea; Department of General Surgery (I Negoi PhD), Emergency Hospital of Bucharest, Bucharest, Romania; Institute for Global Health Innovations (C T Nguyen MPH), Duy Tan University, Hanoi, Vietnam; Center of Excellence in Behavioral Medicine (S H Nguyen BS), Nguyen Tat Thanh University, Ho Chi Minh City, Vietnam; Medical Research Council Clinical Trials Unit (N M Noor MRCP), Institute of Cardiovascular Science (A S Oguntade MSc), University College London, London, UK; Department of Gastroenterology (N M Noor MRCP), Cambridge University Hospitals, Cambridge, UK; Department of Nutrition (S Noori PhD), Jundishapur University of Medical Sciences, Ahvaz, Iran; Center of Excellence in Reproductive Health Innovation (CERHI) (C I Nzopotam MPH), University of Benin, Benin City, Nigeria; Administrative and Economic Sciences Department (Prof B Oancea PhD), University of Bucharest, Bucharest, Romania; Department of Community Health and Primary Care (O O Odukoya MSc), University of Lagos, Idi Araba, Nigeria; Department of Family and Preventive Medicine (O O Odukoya MSc), University of Utah, Salt Lake City, UT, USA; Department of Psychiatry and Behavioural Neurosciences (A T Olagunju MD), Department of Pathology and Molecular Medicine (T O Olagunju MD), McMaster University, Hamilton, ON, Canada; Department of Psychiatry (A T Olagunju MD), University of Lagos, Lagos, Nigeria; Non-communicable Disease Prevention Unit (S Ong FAMS), Ministry of Health, Bandar Seri Begawan, Brunei; Early Detection & Cancer Prevention Services (S Ong FAMS), Pantai Jerudong Specialist Centre, Bandar Seri Begawan, Brunei; National School of Public Health (A Padron-Monedero PhD), Institute of Health Carlos III, Madrid, Spain; Department of Epidemiology (R Pakzad PhD), Ilam University of Medical Sciences, Ilam, Iran; Department of Health Metrics (A Pana MD), Center for Health Outcomes & Evaluation, Bucharest, Romania; Department of Neurology and Public Health (U K Patel MD), Icahn School of Medicine at Mount Sinai, New York, NY, USA; Research Section (U Paudel PhD), Nepal Health Research Council, Kathmandu, Nepal; Faculty of Humanities and Social Sciences (U Paudel PhD), Tribhuvan University, Kathmandu, Nepal; Department of Zoology (Prof N Perumalsamy PhD), Yadava College, Madurai, India; Zoology (Prof N Perumalsamy PhD), Annai Fathima College, Madurai, Madurai District, India; Pennsylvania Cancer and Regenerative Medicine Center (R G Pestell MD), Baruch S Blumberg Institute, Doylestown, PA, USA; Department of Medicine (R G Pestell MD), Xavier University School of Medicine, Woodbury, NY, USA; Department of Public Health (Z Z Piracha PhD), Health Services Academy, Islamabad, Pakistan; Institute of Infection and Immunity (R C G Pollok FRCP), St George's University of London, London, UK; Department of Biochemistry (Prof A Prashant PhD), Jagadguru Sri Shivarathreeswara University, Mysuru, India; Biomedical Engineering Department (Prof M Rabiee PhD), Amirkabir University of Technology, Tehran, Iran; Department of Physics (N Rabiee PhD), Sharif University of Technology, Tehran, Iran; College of Medicine (A Radfar MD), University of Central Florida, Orlando, FL, USA; Department of Population Science and Human Resource Development (M Rahman DrPH), University of Rajshahi, Rajshahi, Bangladesh; Future Technology Research Center (A Rahmani PhD), National Yunlin University of Science and Technology, Yunlin, Taiwan (province of China); Department of Epidemiology (V Rahmanian PhD), Jahrom University of Medical Sciences, Jahrom, Iran; Department of Surgery (A Rajesh MD), University of Texas Health Science Center at San Antonio, San Antonio, TX, USA; Health Emergency Operation Center (K Ranabhat MPH), Ministry of Health & Population, Kathmandu, Nepal; Central Department of Public Health (K Ranabhat MPH), Institute of Medicine, Kathmandu, Nepal; Epidemiology and Biostatistics (Prof M Rezaeian PhD), Department of Medical Biochemistry (M Sahebazzamani MSc), Rafsanjan University of Medical Sciences, Rafsanjan, Iran (A Rashidi MD); Department of Clinical Science (M Rashidi DVM), Islamic Azad University, Garmsar, Iran; Cellular and Molecular Research Center (M Rastegar PhD), Department of Epidemiology (A Tiyuri MSc), Birjand University of Medical Sciences, Birjand, Iran; University College London Hospitals, London, UK (D L Rawaf MD); Academic Public Health England (Prof S Rawaf MD), Public Health England, London, UK; Department of Immunology and Laboratory Sciences (M Razeghinia MSc), Medical Laboratory Sciences (M Sahebazzamani MSc), Sirjan School of Medical Sciences, Sirjan, Iran; Department of Immunology (M Razeghinia MSc), Kerman University of Medical Sciences, Kerman, Iran; School of Medicine (Prof A M N Renzaho PhD), Translational Health Research Institute (Prof A M N Renzaho PhD), Western Sydney University, Campbelltown, NSW, Australia; Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA) (Prof N Rezaei PhD), Universal Scientific Education and Research Network (USERN), Tehran, Iran; Eye and Skull Base Research Centers (S Rezaei MD), Rassoul Akram Hospital, Tehran, Iran; Department of Medical Pharmacology (M M Saber-Ayad MD), Cairo University, Giza, Egypt; Department of Gastroenterology (B Saberzadeh-Ardestani MD), Tehran University of Medical Sciences, Tehran, Iran; Research and Development (Prof U Saeed PhD), Islamabad Diagnostic Center Pakistan, Islamabad, Pakistan; Biological Production Division (Prof U Saeed PhD), National Institute of Health, Islamabad, Pakistan; Applied Biomedical Research Center (A Sahebkar PhD), Biotechnology Research Center (A Sahebkar PhD), Mashhad University of Medical Sciences, Mashhad, Iran; Department of Immunology (A Salek Farrokhi PhD), Semnan University of Medical Sciences and Health Services, Semnan, Iran; Research Center for Molecular Medicine (P Samadi PhD), Hamadan University of Medical Sciences, Hamadan, Iran; Emergency Department (M Samaei MD), Brown University, Providence, RI, USA; Department of Entomology (A M Sany PhD), Ain Shams University, Cairo, Egypt; Department of Surgery (Prof J Sanabria MD), Marshall University, Huntington, WV, USA; Research Development Coordination Section (M N S Saqib PhD), Pakistan Health Research Council, Islamabad, Pakistan; Faculty of Health & Social Sciences (B Sathian PhD), Bournemouth University, Bournemouth, UK; UGC Centre of Advanced Study in Psychology (M Satpathy PhD), Utkal University, Bhubaneswar, India; Udyam-Global Association for Sustainable Development, Bhubaneswar, India (M Satpathy PhD); Department of Health Sciences (I J C Schneider PhD), Federal University of Santa Catarina, Araranguá, Brazil; Department of Medical Statistics (M Šekerija PhD), University of Zagreb, Zagreb, Croatia; Department of Epidemiology and Prevention of Chronic

Non-communicable Diseases (M Šekerija PhD), Croatian Institute of Public Health, Zagreb, Croatia; National Heart, Lung, and Blood Institute (A Seylani BS), National Institute of Health, Rockville, MD, USA; Center for Biomedical Information Technology (F Sha PhD), Shenzhen Institutes of Advanced Technology, Shenzhen, China; Clinical Research Development Unit of Farshchian Heart Center (Z Shaghghi PhD), Hamedan University of Medical Sciences, Hamadan, Iran; Rajaei Cardiovascular Medical and Research Center (M Sharifian MD), Zabol University of Medical Sciences, Tehran, Iran; Department of Hematology-Oncology (S K Siddappa Malleshappa MD), Baystate Medical Center, Springfield, MA, USA; Department of Physical Education (Prof D A S Silva PhD), Federal University of Santa Catarina, Florianópolis, Brazil; Real World Insights (G Silva Julian MSc), IQVIA, São Paulo, Brazil; School of Medicine (Prof J A Singh MD), University of Alabama at Birmingham, Birmingham, AL, USA; Medicine Service (Prof J A Singh MD), US Department of Veterans Affairs (VA), Birmingham, AL, USA; Maternal and Child Health Division (M Siraj MSc), International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh; Department No.16 (V Y Skryabin MD), Moscow Research and Practical Centre on Addictions, Moscow, Russia; Therapeutic Department (A A Skryabina MD), Balashikha Central Hospital, Balashikha, Russia; Surgery (B Socea PhD), “Sf. Pantelimon” Emergency Clinical Hospital Bucharest, Bucharest, Romania; Department of Neurosciences (M Solmi MD), University of Ottawa, Ottawa, ON, Canada; Taub Institute for Research on Alzheimer’s Disease and the Aging Brain (S Song PhD), Columbia University Medical Center, New York, NY, USA; Department of Medicine (Prof R Tabarés-Seisdedos PhD), University of Valencia, Valencia, Spain; Carlos III Health Institute (Prof R Tabarés-Seisdedos PhD), Biomedical Research Networking Center for Mental Health Network (CiberSAM), Madrid, Spain; Department of Surgery (K Tan PhD), National University of Singapore, Singapore, Singapore; Department of Cell Therapy and Applied Genomics (A Tbakhi MD), King Hussein Cancer Center, Amman, Jordan; Department of Nursing (B Tesfaye MSc), Debre Markos University, Debre Markos, Ethiopia; Department of Public Health and Medicine (D N Tollosa PhD), University of Newcastle, Newcastle, NSW, Australia; Nutritional Epidemiology Research Team (EREN) (M Touvier PhD), National Institute for Health and Medical Research (INSERM), Paris, France; Health, Medicine and Human Biology (M Touvier PhD), Sorbonne Paris Nord University, Bobigny, France; Department of Health Economics (B X Tran PhD), Hanoi Medical University, Hanoi, Vietnam; Department of Epidemiology and Biostatistics (B S Tusa MPH), Haramaya University, Haramaya, Ethiopia; Department of Allied Health Sciences (I Ullah PhD), Iqra National University, Peshawar, Pakistan; Pakistan Council for Science and Technology (I Ullah PhD), Ministry of Science and Technology, Islamabad, Pakistan; Clinical Cancer Research Center (S Valadan Tahbaz PhD, S Yahyazadeh Jabbari MD), Milad General Hospital, Tehran, Iran; Department of Microbiology (S Valadan Tahbaz PhD), Faculty of Medicine (M Zahir MD), Islamic Azad University, Tehran, Iran; Faculty of Information Technology (B Vo PhD), HUTECH University, Ho Chi Minh City, Vietnam; Department of Medicine (C Wang MPH), Vanderbilt University, Nashville, TN, USA; Competence Center of Mortality-Follow-Up of the German National Cohort (R Westerman DSc), Federal Institute for Population Research, Wiesbaden, Germany; Cancer Epidemiology and Prevention Research (L Yang PhD), Alberta Health Services, Calgary, BC, Canada; Department of Oncology (L Yang PhD), University of Calgary, Calgary, AB, Canada; Cancer Institute (D Yuze MD), Hacettepe University, Ankara, Turkey; Department of Clinical Pharmacy and Outcomes Sciences (I Yunusa PhD), University of South Carolina, Columbia, SC, USA; Epidemiology and Cancer Registry Sector (Prof V Zadnik PhD), Institute of Oncology Ljubljana, Ljubljana, Slovenia; Independent Consultant, Tehran, Iran (I Zare BSc).

Contributors

The estimates of colorectal cancer were produced as part of GBD 2019. All the estimates are available in the public domain. Members of the core Institute for Health Metrics and Evaluation (IHME) had full access to the underlying data used to generate estimates presented in this Article. All other authors had access to and reviewed estimates as part of

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Data sharing

To download the data used in these analyses, please visit the Global Health Data Exchange GBD 2019 results website.

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