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The Global Burden of Adolescent and Young Adult Cancer in 2019: A Systematic Analysis for the Global Burden of Disease Study 2019

Elysia M. Alvarez

Lisa M. Force

Rixing Xu

Kelly Compton

Dan Lu

See next page for additional authors

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Author(s)

Elysia M. Alvarez, Lisa M. Force, Rixing Xu, Kelly Compton, Dan Lu, Ismaeel Yunusa Ph. D., and Et Al.

The global burden of cancer attributable to risk factors, 2010–19: a systematic analysis for the Global Burden of Disease Study 2019



GBD 2019 Cancer Risk Factors Collaborators*



Summary

Background Understanding the magnitude of cancer burden attributable to potentially modifiable risk factors is crucial for development of effective prevention and mitigation strategies. We analysed results from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019 to inform cancer control planning efforts globally.

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*Collaborators are listed at the end of the paper

†Co-first authors

‡Co-senior authors

Correspondence to:
Prof Christopher J L Murray,
Institute for Health
Metrics and Evaluation,
University of Washington,
Seattle, WA 98195, USA
cjlm@uw.edu

Methods The GBD 2019 comparative risk assessment framework was used to estimate cancer burden attributable to behavioural, environmental and occupational, and metabolic risk factors. A total of 82 risk–outcome pairs were included on the basis of the World Cancer Research Fund criteria. Estimated cancer deaths and disability-adjusted life-years (DALYs) in 2019 and change in these measures between 2010 and 2019 are presented.

Findings Globally, in 2019, the risk factors included in this analysis accounted for 4.45 million (95% uncertainty interval 4.01–4.94) deaths and 105 million (95.0–116) DALYs for both sexes combined, representing 44.4% (41.3–48.4) of all cancer deaths and 42.0% (39.1–45.6) of all DALYs. There were 2.88 million (2.60–3.18) risk-attributable cancer deaths in males (50.6% [47.8–54.1] of all male cancer deaths) and 1.58 million (1.36–1.84) risk-attributable cancer deaths in females (36.3% [32.5–41.3] of all female cancer deaths). The leading risk factors at the most detailed level globally for risk-attributable cancer deaths and DALYs in 2019 for both sexes combined were smoking, followed by alcohol use and high BMI. Risk-attributable cancer burden varied by world region and Socio-demographic Index (SDI), with smoking, unsafe sex, and alcohol use being the three leading risk factors for risk-attributable cancer DALYs in low SDI locations in 2019, whereas DALYs in high SDI locations mirrored the top three global risk factor rankings. From 2010 to 2019, global risk-attributable cancer deaths increased by 20.4% (12.6–28.4) and DALYs by 16.8% (8.8–25.0), with the greatest percentage increase in metabolic risks (34.7% [27.9–42.8] and 33.3% [25.8–42.0]).

Interpretation The leading risk factors contributing to global cancer burden in 2019 were behavioural, whereas metabolic risk factors saw the largest increases between 2010 and 2019. Reducing exposure to these modifiable risk factors would decrease cancer mortality and DALY rates worldwide, and policies should be tailored appropriately to local cancer risk factor burden.

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Introduction

Cancer is the second leading cause of death worldwide, and exposure to risk factors plays an important role in the biology and burden of many cancer types.^{1–4} Understanding the relative contribution of modifiable risk factors to cancer burden and their trends over time is crucial to informing cancer control efforts both locally and globally. In 2015, the UN released the Sustainable Development Goals (SDGs), with SDG target 3.4 focusing on reducing global premature mortality by a third for non-communicable diseases, including cancer, by 2030. Effectively addressing the growing burden of cancer globally will require comprehensive measures that incorporate both curative and preventive interventions, particularly in light of the anticipated challenges that the COVID-19 pandemic will bring in progress towards SDG target 3.4.^{5–7}

Although some cancer cases are not preventable, governments can work on a population level to support an environment that minimises exposure to known cancer risk factors. Primary prevention, or the prevention of a cancer developing, is a particularly cost-effective strategy,⁸ although it must be paired with more comprehensive efforts to address cancer burden, including secondary prevention initiatives, such as screening programmes, and ensuring effective capacity to diagnose and treat those with cancer. As part of cancer control strategies, prevention requires identification of causal risk factors, determination of contribution to local cancer burden, and development of effective strategies for their mitigation. Previous studies have quantified the burden of cancer attributable to individual risk factors globally or for several risk factors in select countries and regions,^{9–20} providing crucial location and

For more on SDG target 3.4 see
<https://unstats.un.org/sdgs/metadata/>

Research in context

Evidence before this study

We identified previous work that primarily estimated the attributable cancer burden for single risk factors globally or multiple risk factors for single countries. The Global Cancer Observatory also provides estimates of cancer-attributable burden for select risk factor categories separately. One previous comparative risk assessment project estimated risk-attributable cancer mortality for nine risk factors. We searched titles and abstracts in PubMed for English-language research papers that were published between Jan 1, 2010, and June 1, 2021, using the search terms “cancer or neoplasm or tumor or malignancy” and “risk factor or attributable risk or population attributable fraction” and “global or international or worldwide or world” and “burden or metrics or incidence or mortality”, but did not identify additional informative studies. There is a gap in the literature on global estimates of risk-attributable cancer burden for a comprehensive list of risk factors that incorporate both cancer-related mortality and disability.

Added value of this study

We report, for the first time, the global cancer burden attributable to a comprehensive list of behavioural, metabolic, and environmental and occupational risk factors using Global

Burden of Diseases, Injuries, and Risk Factors 2019 results. By estimating risk-attributable cancer burden nationally and globally using both mortality and disability-adjusted life-years (DALYs), this study provides a new perspective on attributable cancer burden. Globally, a large portion of cancer deaths and DALYs were attributable to the modifiable risk factors included, with behavioural risks representing the largest attributable burden. We identified substantial differences in attributable cancer death and DALY burden across Socio-demographic Index quintiles and between sexes. Risk-attributable cancer death and DALY burden increased globally from 2010 to 2019, with metabolic risk factors contributing to the largest percentage increases, most notably in low and low-middle Socio-demographic Index countries.

Implications of all the available evidence

The burden of cancer remains an important public health challenge that is growing in magnitude globally. Modifiable risk factors are important contributors to cancer mortality and DALYs globally, with contribution varying by setting. The results from this study highlight the need for context-specific policies aimed at reducing exposure to risk factors as part of comprehensive cancer control efforts.

risk-factor-specific information. However, comprehensive cancer risk factor estimates do not exist for many countries, leaving an important void as countries develop and update their cancer control plans. The Global Cancer Observatory from the International Agency for Research on Cancer provides estimates of global, regional, and national risk-attributable cancer burden for a subset of potentially modifiable risk factors (eg, obesity, alcohol consumption, infections, and ultraviolet radiation), but these estimates are not provided together in a comprehensive fashion across time, and some potentially modifiable risk factors are not estimated as part of this effort.^{21–24}

To our knowledge, the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) is the only study to date that quantifies cancer burden attributable to a broad set of modifiable risk factors for each GBD round, for all countries around the world, across age groups, for both sexes, and over time. GBD 2019, the most recent iteration of the GBD study, provides an opportunity to evaluate the global burden of cancer attributable to risk factors. A previous study used a similar comparative risk framework to estimate mortality from 12 cancer types and nine behavioural and environmental risk factors based on WHO cancer mortality data, but this analysis was limited to 2001 and has not been updated in a formal GBD analysis since.²⁵ Herein, we present estimates of 82 risk–outcome pairs, including cancer deaths and disability-adjusted life-years (DALYs) attributable to risk factors at global, regional, and national levels in 2019, and assess

the temporal trends from 2010 to 2019 of cancer burden attributable to environmental and occupational, behavioural, and metabolic risk factors to inform efforts to reduce exposure to cancer risk factors (appendix pp 157–60).²⁶ This manuscript was produced as part of the GBD Collaborator Network and in accordance with the GBD Protocol.

Methods

Overview of the GBD study

The GBD study was developed to provide global health estimates that are comprehensive and comparable for causes of death, disability, and their associated risk factors. GBD 2019 estimates mortality, incidence, prevalence, years of life lost (YLLs), years of life lived with disability (YLDs), and DALYs for 369 causes of death and disability and 87 risk factors, and groups of risk factors at the global level, regionally, and for 204 countries and territories. The 2019 iteration of the GBD is the most up to date and supersedes all previous iterations. This Article reports estimates from 2010 to 2019, but extended years of estimates (1990–2019) are available online via the GBD Compare Tool and GBD Results Tool. Rates are reported per 100 000 person-years, and age-standardised rates were calculated with the GBD world population standard.²⁷ Select results in this Article are presented by Socio-demographic Index (SDI) to describe differences in cancer burden attributable to risk factors across the spectrum of sociodemographic development.²⁸ SDI is a summary index calculated from the total fertility rate in

For the Global Cancer
Observatory see
<https://gco.iarc.fr/>

For the GBD Compare Tool see
<https://vizhub.healthdata.org/gbd-compare/>

For the GBD Results Tool see
<http://ghdx.healthdata.org/gbd-results-tool>

women younger than 25 years, lag-distributed income per capita, and mean education for individuals aged 15 years and older (appendix p 55). The index ranges from 0 (low SDI) to 100 (high SDI), with quintiles used to describe low, low-middle, middle, high-middle, and high SDI countries in 2019. Although both cancer deaths and DALYs attributable to risk factors are presented here, the majority of cancer DALYs globally are due to YLLs, reflective of cancer deaths with weighting for the age at death.¹ Thus, we do not present here estimates of risk-attributable YLLs and YLDs, but they are available in the online tools.

The GBD study is compliant with the Guidelines for Accurate and Transparent Health Estimates Reporting, and additional details from this Article and the appendix are available in the GBD 2019 summary papers.^{1,26–29}

Data sources for cancer burden estimates

Cancers included in the GBD study were those defined in chapter 2 (neoplasms) in the tenth revision of the International Classification of Diseases, with the exception of Kaposi sarcoma, for which most deaths are attributed to HIV/AIDS (appendix p 29).³⁰ Data sources used to inform the cancer estimates were obtained from vital registration systems, sample vital registration systems, verbal autopsy reports, and national and subnational population-based cancer registries. All data sources are provided with a unique identifier and compiled in the Global Health Data Exchange, which is publicly accessible.

Cancer burden estimation

Cancer registry, vital registration systems, and verbal autopsy data are used to inform cancer mortality modelling in the GBD study, as one of these data sources might exist in a location where others do not. In some locations, cancer mortality data are sparse, but cancer incidence is reported by national or subnational population-based cancer registries. To maximise data informing mortality models, cancer incidence data were transformed into cancer mortality estimates with modelled mortality-to-incidence ratios (MIRs). MIRs specific to cancer causes (cancer types) were modelled with a spatiotemporal Gaussian process regression (appendix pp 30–31).^{1,26} Mortality estimates from MIR-transformed incidence data were then pooled with mortality data from vital registration systems and verbal autopsies and used as inputs in cancer-specific Cause of Death Ensemble models.³¹ These models use all available data and location-level covariates to test individual and ensemble models, and produce estimates of death for every cause, sex, age group, location, and year estimated within GBD 2019, selecting models on the basis of out-of-sample predictive validity. Finally, the predicted mortality estimates were adjusted to align with independently modelled all-cause mortality estimates for each age, group, sex, location, and year.²⁸

Non-fatal cancer-specific computations began by generating incidence estimates from the modelled

cancer mortality estimates using the MIRs corresponding to each cancer cause, age group, sex, location, and year. Cancer 10-year prevalence was modelled with incidence, background mortality, and estimated relative survival curves and their correlation with modelled MIRs (appendix pp 49–53). Cancer-specific prevalence for each sequela, age, group, sex, location, and year combination is made up by four sequelae phases: (1) diagnosis and treatment, (2) remission, (3) metastatic and disseminated, and (4) terminal. To generate YLDs, each sequela prevalence was multiplied by its corresponding sequela-specific disability weight (appendix pp 53–54). Disability weights describe the severity of health loss associated with a sequela-specific condition and range from 0 (equivalent to full health) to 1 (equivalent to death).²⁸ YLLs were computed by multiplying the number of deaths in a specific age group for each cancer cause by the remaining standard life expectancy at the age of death.²⁷ Finally, DALYs were calculated as the sum of YLDs and YLLs.

Risk-factor-attributable cancer burden estimation

GBD 2019 includes risk factors that are broadly categorised into three groups: (1) environmental and occupational, (2) behavioural, and (3) metabolic. This study includes 82 cancer risk–outcome pairs (23 cancer types and 34 risk factors), with risk factors identified with the World Cancer Research Fund criteria³² (appendix pp 154–56). Risk–outcome pairs are organised into four mutually exclusive levels with increasing risk factor resolution (appendix pp 152–53). The general approach to risk factor estimation in the GBD study is described in this paper, and details on the modelling approach for each risk factor are available in the GBD 2019 risk factors summary paper²⁶ and the appendix (pp 72–145). For percentages of risk-attributable cancer deaths or DALYs reported, the total cancer burden (risk and non-risk cancer burden) included non-melanoma skin cancers.

The GBD comparative risk assessment framework was used to compute the fraction of cancer-specific burden attributable to each risk factor. The framework is divided into six main steps that are followed for each risk–outcome pair. First, the World Cancer Research Fund criteria were used to identify risk factors with convincing or probable evidence for a causal association.³² For GBD 2019, systematic reviews were updated to ensure appropriate inclusion of risk–outcome pairs.²⁶ Second, to estimate relative risks for each risk–outcome pair as a function of exposure, existing systematic reviews were updated and meta-analyses of relative risks were done. In GBD 2019, the meta-analytic approach was updated for a selected set of continuous risk factors with GBD's meta-regression-Bayesian, regularised, trimmed tool (appendix pp 58–59). Third, risk factor exposure levels and distributions were modelled for each age, sex, location, and year combination with data available from

See Online for appendix

For the Global Health Data Exchange see <http://ghdx.healthdata.org/gbd-2019>

published studies, household surveys, censuses, administrative data, ground monitor data, or remote sensing data. To model risk factor exposure level, the GBD uses either Bayesian meta-regression modelling (DisMod-MR 2.1), a flexible approach that can incorporate sex-specific and age-specific data, or spatiotemporal Gaussian process regression, the preferred approach when exposure is stable across age groups (appendix p 62). Fourth, for each risk factor, the theoretical minimum risk exposure level was identified, a counterfactual scenario in which a given population receives the optimal level of risk exposure (ie, no exposure for monotonically increasing risk functions such as smoking, the lowest point of the risk function of exposure for J-shaped or U-shaped risks such as high BMI, and the 85th percentile of exposure in cohorts and trials for protective risks such as fruit intake, weighted by the relative global magnitude of each outcome). Fifth, the population attributable fraction for each risk–outcome pair was calculated across age, sex, location, and year, taking into account the risk function (ie, relative risk), exposure level, and the theoretical minimum risk exposure level (appendix pp 62–64). Sixth, for some risk factors it was necessary to estimate the population attributable fraction in combination with other risk factors by considering mediation. For instance, calculating the population attributable fraction for fruit intake should account for the potential mediating effect of fibre intake. Thus, a mediation matrix was used to correct for population attributable fraction overestimation that would occur if independence of specific risk factors was assumed.²⁶ Last, to estimate the cancer burden attributable to each estimated risk factor, the YLLs, YLDs, and deaths for a given cancer type were multiplied by the corresponding risk factor population attributable fraction. The sum of YLLs and YLDs was used to estimate the cancer DALYs attributable to risk factors.

Estimating uncertainty

To account for uncertainty in the attributable burden estimates, a total of 1000 draws were estimated, from which the lower and upper bounds of the 95% uncertainty interval (UI) were obtained from the 25th and 975th ranked values. Error was propagated through each estimation step, including the estimation of cancer deaths and DALYs, exposure, relative risk functions, and for relevant risk factors the theoretical minimum risk exposure level.

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

In 2019, the total number of cancer deaths globally attributable to all estimated risk factors was 4.45 million

(95% UI 4.01–4.94) for both sexes combined, accounting for 44.4% (41.3–48.4) of all cancer deaths. There were 2.88 million (2.60–3.18) risk-attributable cancer deaths in males and 1.58 million (1.36–1.84) in females, representing 50.6% (47.8–54.1) of all cancer deaths in males and 36.3% (32.5–41.3) in females (appendix pp 191–99). The total number of cancer DALYs globally attributable to all estimated risk factors in 2019 was 105 million (95.0–116) for both sexes combined, which accounted for 42.0% (39.1–45.6) of all cancer DALYs. Males were estimated to have 67.5 million (60.8–75.1) cancer DALYs attributable to risk factors, or 48.0% (45.3–51.5) of all cancer DALYs in males, whereas females were estimated to have 37.6 million (32.8–43.1) cancer DALYs attributable to risk factors, or 34.3% (30.9–38.7) of all cancer DALYs in females.

The leading Level 2 risk factor (appendix pp 152–53) in males in terms of attributable cancer DALYs was tobacco (figure 1), which accounted for 33.9% (32.3–35.4) of all cancer DALYs in males in 2019 (appendix pp 191–93). Alcohol use, dietary risks, and air pollution were the next greatest risk factors, accounting for 7.4% (6.7–8.2), 5.9% (4.4–8.3), and 4.4% (3.4–5.5), respectively, of all male cancer DALYs in 2019. Tobacco was also the leading Level 2 risk factor for females globally in terms of attributable cancer DALYs (figure 1) and accounted for 10.7% (9.9–11.5) of all female cancer DALYs in 2019 (appendix pp 191–93). Unsafe sex was the second leading risk factor for females, accounting for 8.2% (7.0–8.8) of all female cancer DALYs in 2019, followed by dietary risks (5.1% [4.0–6.7]), high BMI (4.7% [2.8–7.0]), and high fasting plasma glucose (3.6% [1.0–7.5]). Ranking of Level 2 risk factors by attributable cancer deaths globally in 2019 showed similar ranking as by attributable cancer DALYs (appendix pp 181–87).

The leading cancer in terms of risk-attributable deaths globally in 2019 for both males and females was tracheal, bronchus, and lung cancer (36.9% [34.2–39.3] of all attributable cancer deaths), followed by colon and rectum cancer, oesophageal cancer, and stomach cancer in males, and cervical cancer, colon and rectum cancer, and breast cancer in females (figure 2, appendix p 210). Deaths caused by cancer and risk-attributable deaths caused by cancer tended to be greater in males than females for leading causes of cancer death globally, with the exception of cancer types that occur predominantly in women (eg, breast) or are exclusively estimated in women in the GBD study (eg, cervical, ovarian, and uterine cancers; figure 2; for male-to-female ratios for risk-attributable cancer deaths see appendix pp 206–07). When excluding the sex-specific cancers with risk-attributable burden (cervical, ovarian, uterine, and prostate cancers) the male-to-female ratios for risk-attributable cancer deaths tended to be smaller in high SDI countries than in non-high SDI countries (low, low-middle, middle, and high-middle SDI countries; appendix pp 213–14, 217–18). Cancer deaths and

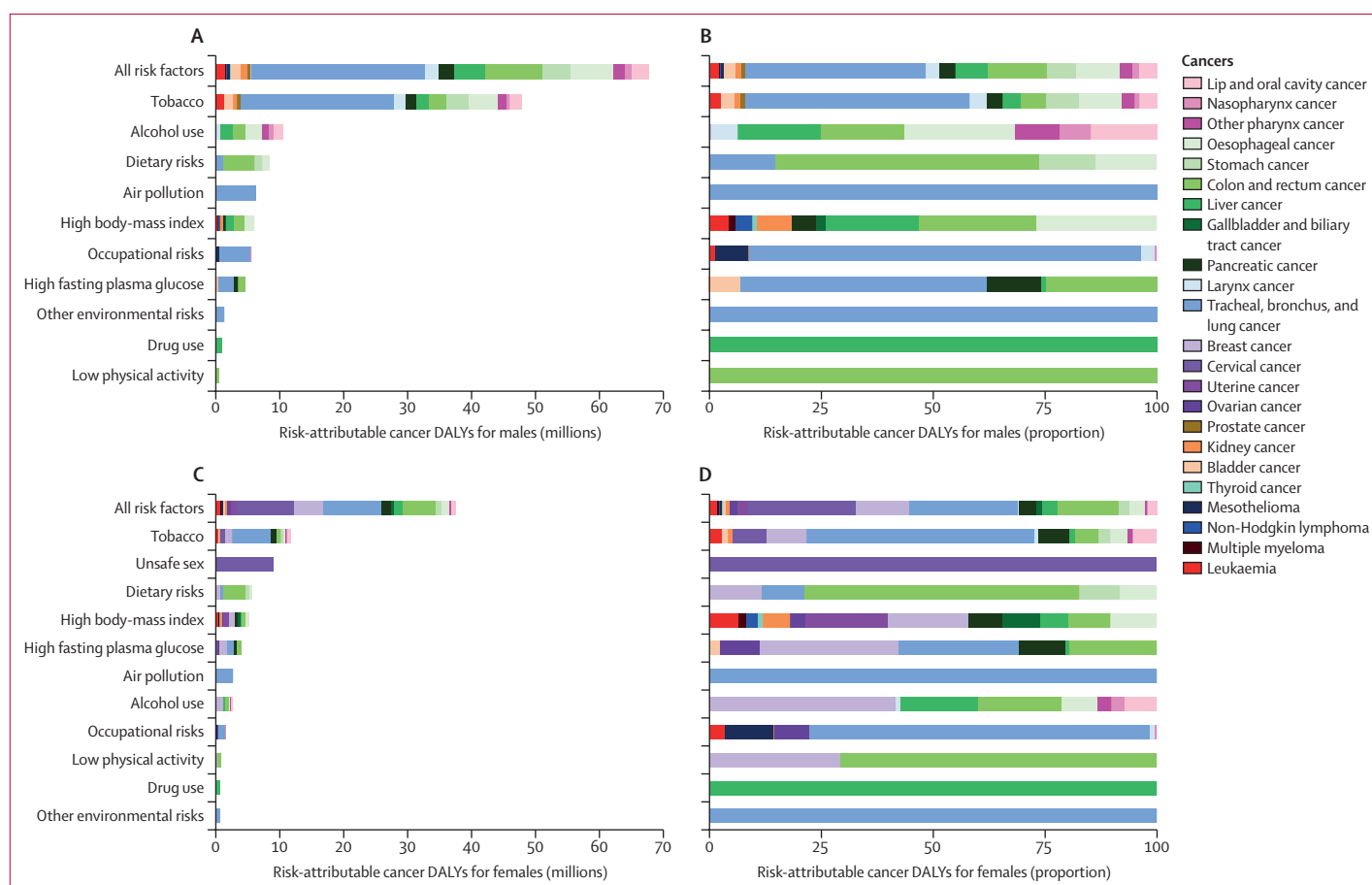


Figure 1: Cancer DALYs attributable to 11 Level 2 risk factors globally in 2019

(A) Absolute cancer DALYs for males. (B) Proportional cancer DALYs for males. (C) Absolute cancer DALYs for females. (D) Proportional cancer DALYs for females. Air pollution includes ambient particulate matter pollution and household air pollution from solid fuels. Other environmental risks include residential radon. Occupational risks include exposure to 13 specific carcinogens. Dietary risks include nine specific risk factors relevant to cancer. Tobacco includes smoking, chewing tobacco, and second-hand smoke. See appendix (pp 157–60) for details and definitions of each Level 2 risk factor on the y-axis. See appendix (p 161) for further details about global absolute and proportional cancer deaths attributable to Level 2 risk factors. DALYs=disability-adjusted life-years.

risk-attributable cancer deaths globally for both sexes combined in 2019 occurred over-proportionally frequently in high SDI countries, with 25·4% (24·0–26·7) of cancer deaths and 26·5% (24·9–28·1) of risk-attributable cancer deaths occurring in high SDI countries, even though these countries had only 13·1% (12·5–13·8) of the global population (appendix p 221). The leading cancers, sex analysis, and results by SDI remained largely the same when the cancers were ranked by risk-attributable DALYs instead of deaths (appendix p 162).

Geographical patterns for cancer age-standardised death and DALY rates attributable to environmental and occupational, behavioural, and metabolic risks in 2019 differed around the world (figure 3, appendix pp 165–66), with generally higher age-standardised DALY rates within these Level 1 risk factor categories (appendix pp 152–53) notable in high-income North America, and central, western, and eastern Europe, and variably elevated rates by risk category in east and southeast Asia, southern Latin America, and

southern Africa. Globally in 2019, the leading five regions in terms of risk-attributable cancer age-standardised death rates were central Europe (82·0 [71·0–94·9] per 100 000 person-years), east Asia (69·8 [58·0–83·0]), high-income North America (66·0 [60·5–72·1]), southern Latin America (64·2 [58·2–71·8]), and western Europe (63·8 [58·4–69·7]; appendix pp 174, 234–39). Details of risk-attributable cancer age-standardised death and DALY rates at the country level are available in the appendix (pp 234–239) and in the online GBD Compare and GBD Results Tools.

Figure 4 shows age-specific attributable cancer DALY rates in 2019 by SDI quintiles. For the same age group, cancer DALY rates attributable to behavioural risks were generally greater than those attributable to environmental and occupational risks and metabolic risks, and attributable cancer DALY rates were generally greater with increasing SDI quintile. Attributable cancer DALY rates increased with age for each Level 1 risk category, before peaking at ages 70–74 years or ages 75–79 years,

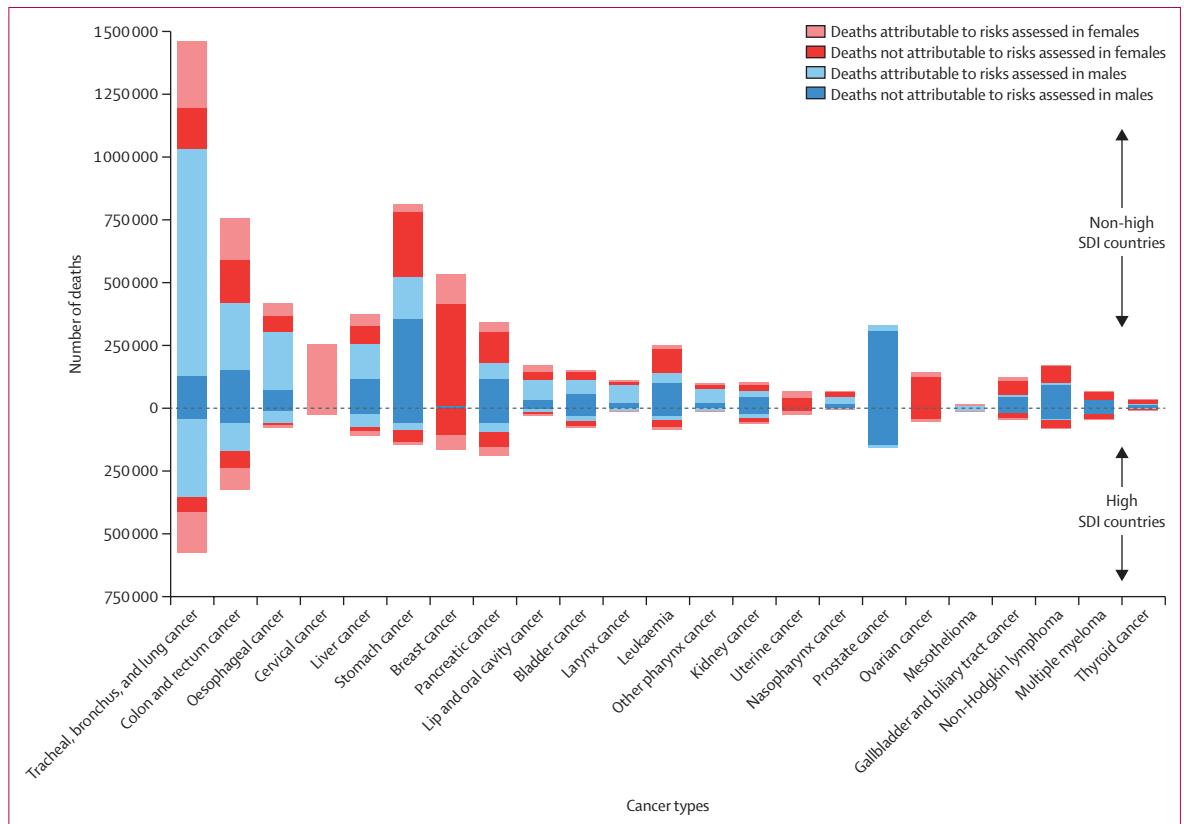


Figure 2: Global deaths from cancers attributable to risk factors in 2019 by sex and SDI
 Non-high SDI countries include low, low-middle, middle, and high-middle SDI countries. Cancer types are listed from left to right in order of greatest to least risk-attributable deaths. See appendix (pp 213–14, 217–18) for estimates for risk-attributable cancer deaths in high and non-high SDI locations by sex. See appendix (p 162) for further details about DALYs from cancers attributable to risk factors in 2019 by sex and SDI. For additional versions of this figure showing age-standardised mortality and DALY rates see appendix (pp 163–64). DALYs=disability-adjusted life-years. SDI=Socio-demographic Index.

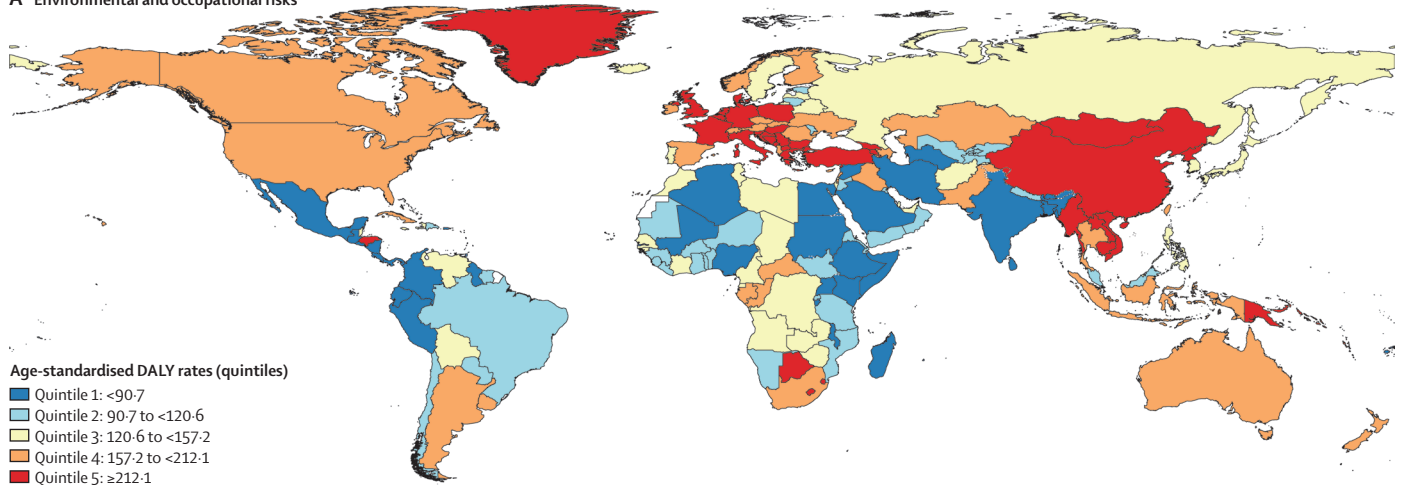
depending on the SDI quintile, with a later age peak generally on the higher end of the SDI spectrum.

For all risk factors estimated for both sexes combined between 2010 and 2019, global attributable cancer deaths increased by 20.4% (12.6–28.4) and DALYs by 16.8% (8.8–25.0), whereas the global age-standardised rates of attributable cancer deaths decreased by 6.9% (0.9–12.8) and cancer DALYs by 7.8% (1.4–14.0; appendix pp 240–42). The greatest percentage increase in attributable cancer deaths and DALYs among the Level 1 risk factor categories was in metabolic risks, which increased by 34.7% (27.9–42.8) and 33.3% (25.8–42.0), respectively, from 2010 to 2019, whereas behavioural risk-attributable cancer deaths and DALYs increased by 17.9% (10.4–26.0) and 14.4% (6.5–22.5), and environmental and occupational risk-attributable cancer deaths and DALYs increased by 16.7% (7.9–26.2) and 13.1% (3.9–23.1), respectively. Similarly, the greatest percentage increase in global risk-attributable cancer age-standardised death and DALY rates was in metabolic risk factors, which increased by 2.8% (–2.2 to 8.8) and 3.8% (–2.0 to 10.5), respectively, whereas behavioural risk factors decreased

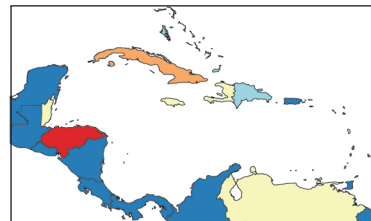
by 8.7% (2.7–14.5) and 9.6% (3.2–15.8), respectively, and environmental and occupational risk factors declined by 10.0% (2.8–16.7) and 11.4% (3.5–18.5), respectively.

Furthermore, the magnitude of change in risk-attributable cancer DALYs and deaths and age-standardised DALY and mortality rates varied greatly among super-regions and SDI quintiles (figure 5, appendix pp 148, 172, 223–25). The greatest increases in age-standardised DALY rates due to metabolic risks were seen in south Asia, north Africa and the Middle East, and sub-Saharan African super-regions, and in the low-middle and low SDI quintiles, whereas the greatest decreases in behavioural and environmental and occupational risks were seen in central Europe, eastern Europe, and central Asia; high-income; Latin American and the Caribbean super-regions; and in the high and high-middle SDI quintiles (appendix p 224). Generally, the super-regions and SDI quintiles with the greatest increase in age-standardised cancer DALY burden attributable to metabolic risks between 2010 and 2019 were those with the least improvement in cancer burden attributable to behavioural risks and environmental and

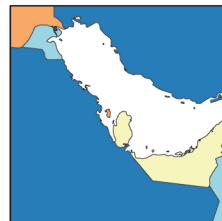
A Environmental and occupational risks



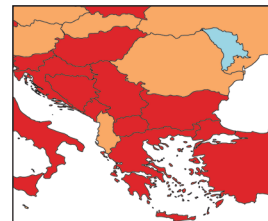
Caribbean and Central America



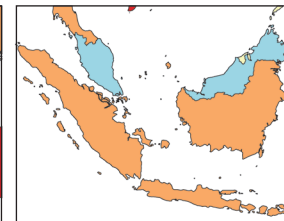
Persian Gulf



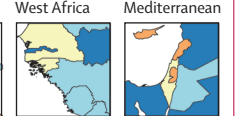
Balkan Peninsula



Southeast Asia



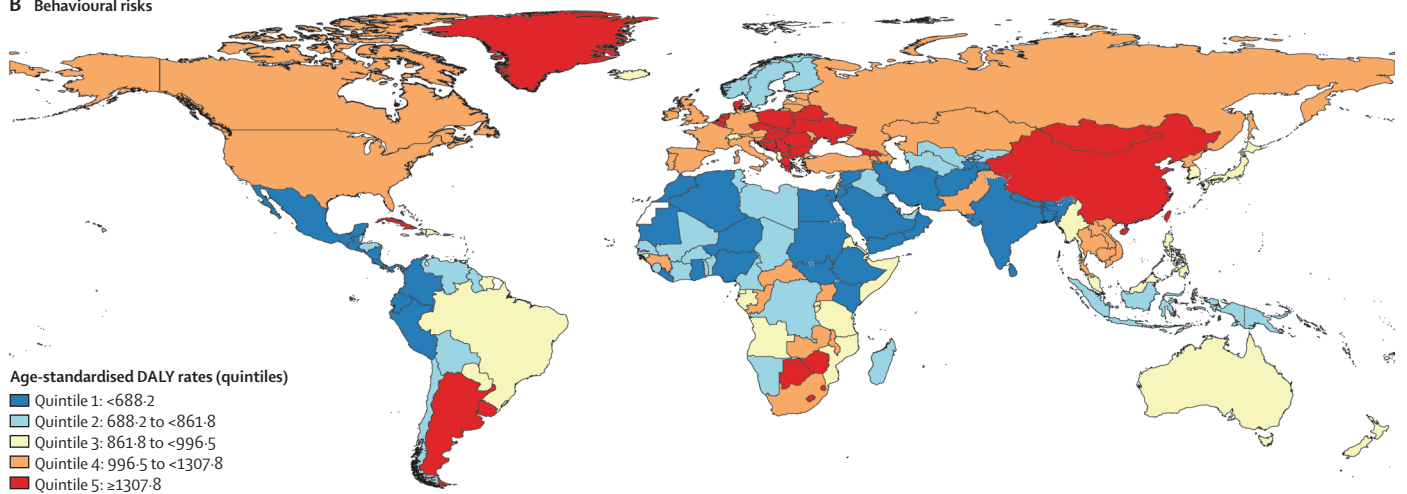
West Africa Eastern Mediterranean



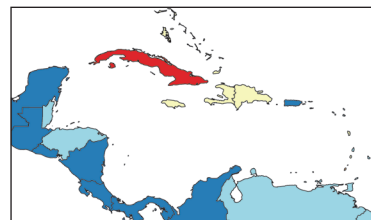
Northern Europe



B Behavioural risks



Caribbean and Central America



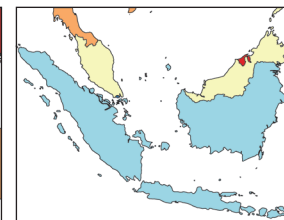
Persian Gulf



Balkan Peninsula



Southeast Asia



West Africa Eastern Mediterranean



Northern Europe



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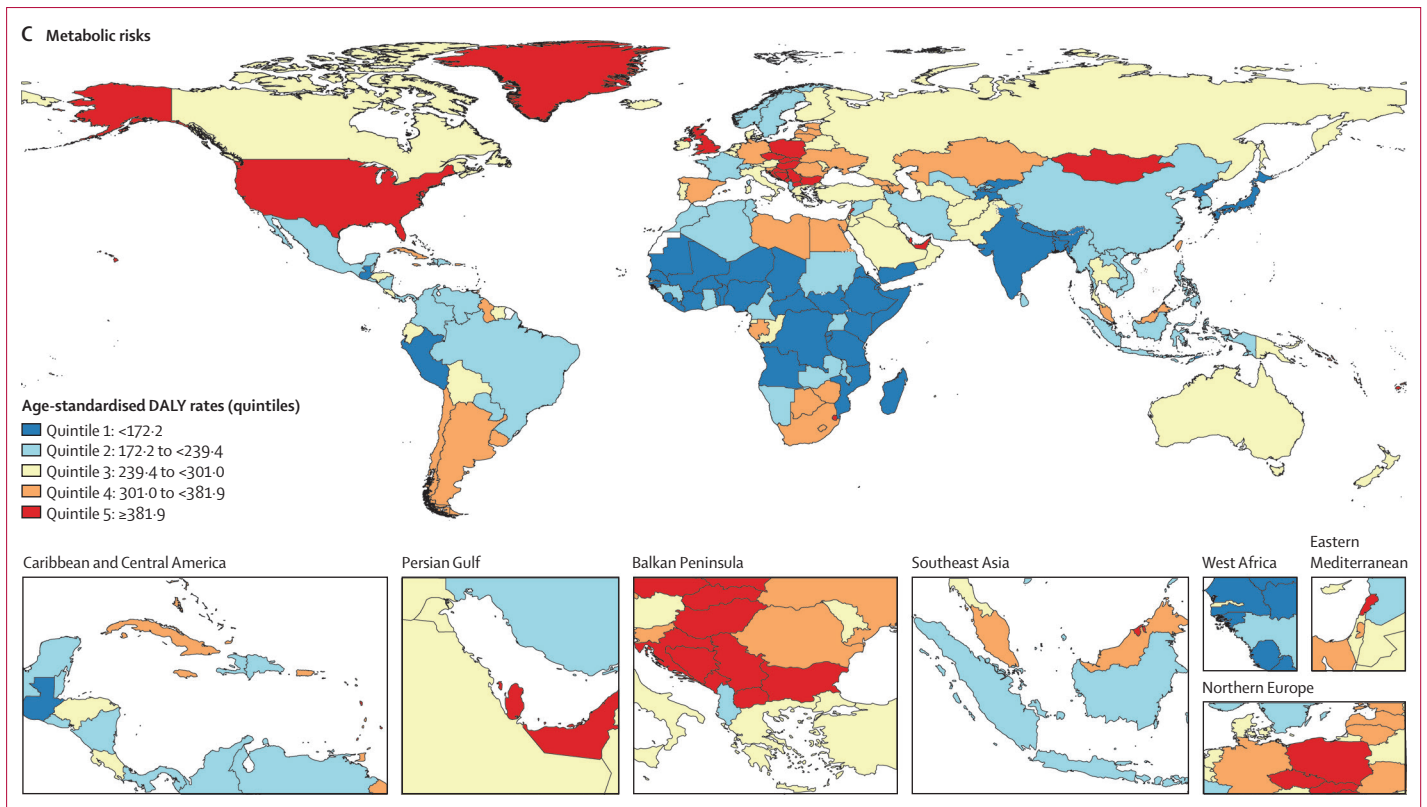


Figure 3: Global map of age-standardised DALY rate quintiles for risk-attributable cancer burden, both sexes combined, 2019

(A) Environmental and occupational risks. (B) Behavioural risks. (C) Metabolic risks. Each map represents estimates at the national level. Quintiles are based on age-standardised DALY rates per 100 000 person-years. See appendix (pp 165–68, 234–39) for further details of risk-attributable cancer deaths and DALYs for each country and territory. DALYs=disability-adjusted life-years.

occupational risks across the same time period (appendix p 224).

Finally, different patterns in the leading risk factors for attributable cancer age-standardised DALY rates were observed globally and across the SDI spectrum (figure 6, appendix pp 175–80). The leading nine risk factors at the most detailed level contributing to global cancer burden defined by age-standardised DALY rates did not change between 2010 and 2019, and the top three risk factors (smoking, alcohol use, and high BMI) were the same in the high SDI quintile as globally. Smoking and alcohol use remained the top two leading risk factors in the middle SDI quintile in 2010 and 2019, with unsafe sex decreasing from third to fifth position, high BMI rising from fourth to third position, and ambient particulate matter pollution rising from fifth to fourth position (appendix p 178). In the low SDI quintile, smoking remained the leading risk factor for risk-attributable cancer burden, with unsafe sex ranked second and alcohol use third in both 2010 and 2019. Within the top five leading risk factors in the low SDI quintile, high BMI and high fasting plasma glucose both increased (fifth to fourth, and sixth to fifth, respectively), and household air pollution from solid fuels decreased (fourth to sixth) between 2010 and 2019 (appendix pp 175–80).

Discussion

Our analysis found that 44.4% (95% UI 41.3–48.4) of global cancer deaths and 42.0% (39.1–45.6) of global cancer DALYs were attributable to estimated risk factors in 2019. These findings highlight that a substantial proportion of cancer burden globally has potential for prevention through interventions aimed at reducing exposure to known cancer risk factors but also that a large proportion of cancer burden might not be avoidable through control of the risk factors currently estimated. Thus, cancer risk reduction efforts must be coupled with comprehensive cancer control strategies that include efforts to support early diagnosis and effective treatment. Most attributable cancer DALYs were accounted for by behavioural risk factors, such as tobacco use, alcohol use, unsafe sex, and dietary risks, suggesting a need for concerted efforts to address behavioural risk factors to effectively reduce cancer burden globally. Attributable cancer DALYs from each Level 1 risk factor group generally increased with increasing SDI, and although there were similarities in the leading risk factors across the SDI spectrum for both sexes combined (ie, smoking and alcohol use), there were differences in risk factor patterns following these leading risks, highlighting the need for cancer risk reduction efforts to be context

specific. Between 2010 and 2019, age-standardised cancer DALYs attributable to all risk factors declined by 7·8% (1·4 to 14·0). Despite this decline, a global increase in age-standardised cancer DALYs (3·8% [−2·0 to 10·5]) attributable to metabolic risks was seen, largely driven by substantial increases in low and low-middle SDI countries. Furthermore, total risk-attributable cancer absolute DALY burden globally and in all SDI quintiles grew between 2010 and 2019, underscoring an expanding need for health systems around the world with capacity to comprehensively care for individuals with cancer, while developing and implementing cancer control efforts that consider risk reduction strategies. These estimates might help inform cancer control planning by identifying leading modifiable risk factors for cancer around the world, including for countries that might not have previous local research on cancer burden and cancer risk factor exposures.

To our knowledge, this study represents the largest effort to date to determine the global burden of cancer attributable to risk factors, and it contributes to a growing body of evidence aimed at estimating the risk-attributable burden for specific cancers nationally,^{9,13–20,33,34} internationally,³⁵ and globally.^{21–25} Our study builds on existing evidence by estimating both deaths and DALYs due to risk-attributable cancer burden, across a spectrum of cancer types and risk factors, for all countries, age groups, and sexes, over time. When comparing the results from this study with studies reporting national-level population attributable fraction estimates, GBD 2019 generally reported higher values for all risk factors combined. These comparisons are between cases and deaths for a subset of countries and differences might be due to a greater number of risk factors estimated and greater estimates for select risk factors, such as smoking, potentially due to differences in exposure definitions and risk–outcome pairs estimated.^{13–20} When compared with a previous effort to quantify the fatal burden of cancer attributable to risk factors globally, this study found a greater percentage of cancer deaths attributable to risk factors when estimating more risk factors (44·4% [95% UI 41·6–48·2] in 2001 in GBD 2019 compared with 35% in 2001 in the previous study), although both studies found leading contributions by smoking and alcohol use globally and unsafe sex in lower-income settings.²⁵ Comparisons to comprehensive global risk-attributable cancer burden in the Global Cancer Observatory are not possible, as incidence estimates are provided only for individual risk categories, but for alcohol consumption and elevated BMI, risk factors estimated by both studies, similar estimates of risk-attributable cancer burden were noted (4·1% of new cancer cases in 2020 attributable to alcohol consumption in the Global Cancer Observatory and 4·9% [4·4–5·5] of cancer deaths in 2019 attributable to alcohol use in the GBD study; 3·6% of new cancer cases in 2012 attributable to high BMI in the Global Cancer Observatory and 4·6% [2·7–7·1] of cancer deaths

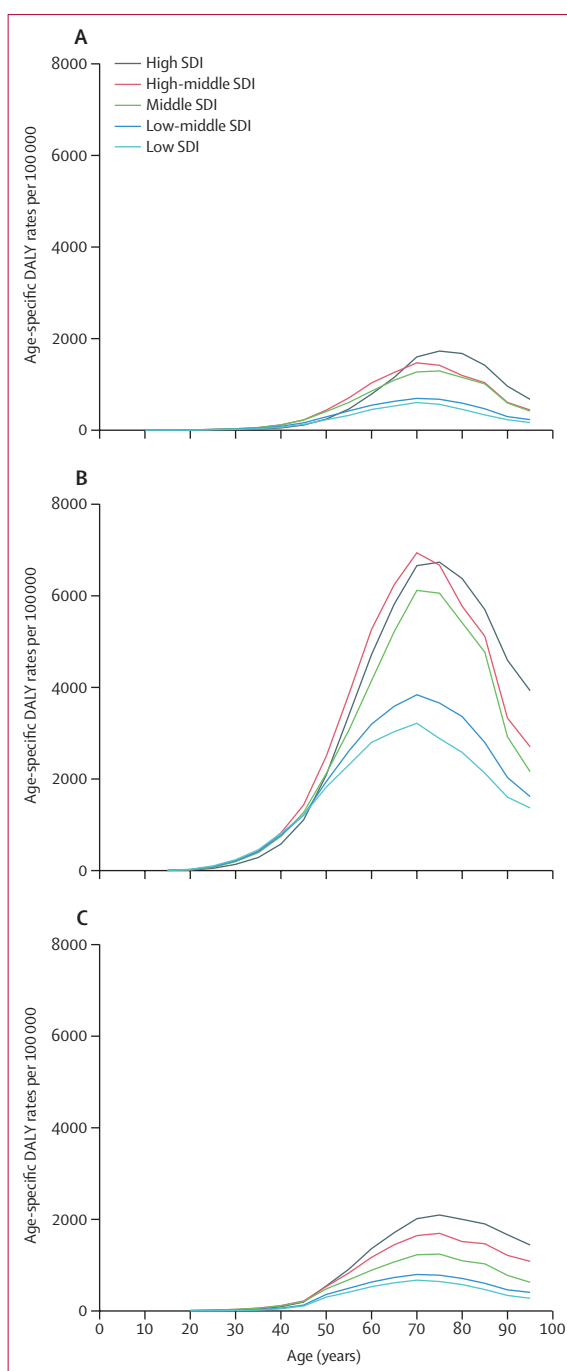


Figure 4: Estimates of age-specific rates of risk-attributable cancer DALYs, SDI quintiles, both sexes combined, 2019

(A) Environmental and occupational risks. (B) Behavioural risks. (C) Metabolic risks. Rates are expressed per 100 000 person-years. See appendix (pp 146–47) for details and definitions of the SDI regions. DALYs=disability-adjusted life-years. SDI=Socio-demographic Index.

in 2019 attributable to high BMI in the GBD study).^{21,22} For cancer risk factors not included in this study, estimates from the Global Cancer Observatory suggest that an additional approximately 8·9% of cancer cases would

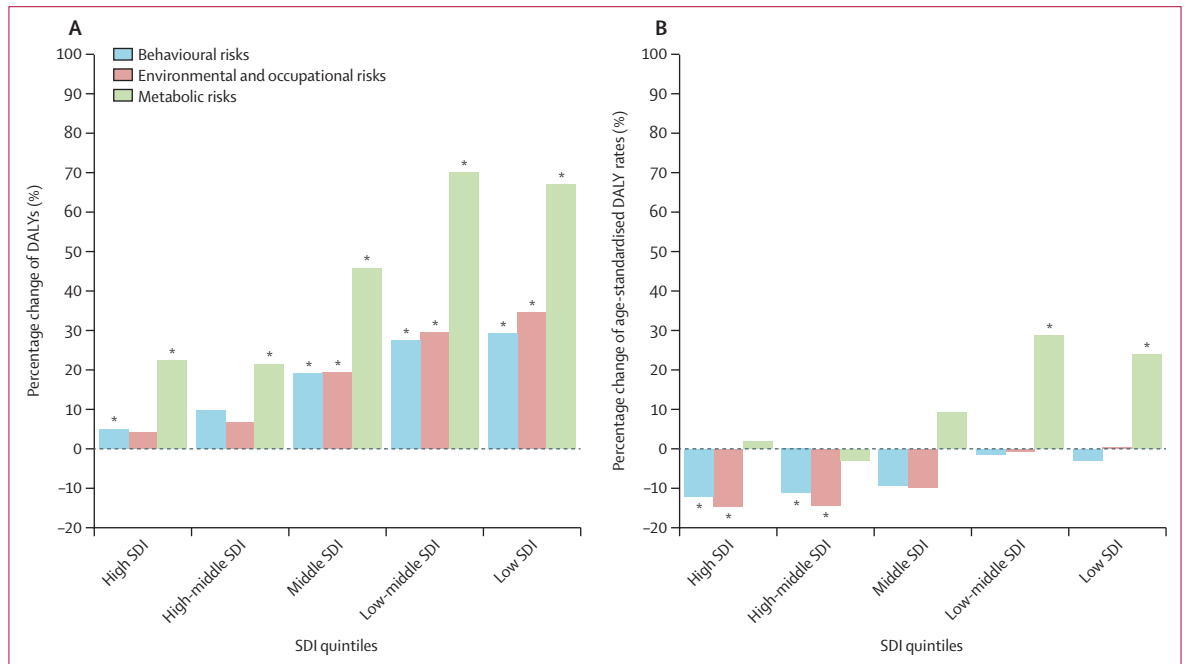


Figure 5: Percentage change of risk-attributable cancer DALY counts and age-standardised DALY rates for Level 1 risk factors by SDI quintile, both sexes combined, 2010–19

(A) Percentage change of risk-attributable cancer DALY counts by SDI quintile. (B) Percentage change of risk-attributable age-standardised cancer DALY rates by SDI quintile. See appendix (pp 146–47) for more information on SDI quintiles. See appendix (p172) for further information about the percentage change of risk-attributable cancer DALYs and age-standardised DALY rates for risk factors by GBD world super-region. See appendix (p 173) for percentage change of risk-attributable cancer deaths and age-standardised mortality rates by SDI quintile and GBD world super-region. DALYs=disability-adjusted life-years. GBD=Global Burden of Disease, Injuries, and Risk Factors Study. SDI=Socio-demographic Index. *95% uncertainty intervals that do not include zero.

be attributable to infections²³ (appendix p 67) and an additional 1.2% of cancer cases would be attributable to ultraviolet radiation.²⁴ These estimates should be interpreted with some caution given the different estimation approaches used, but might provide useful information for crucial remaining risk factors not yet included in the GBD study.

In GBD 2019, large all-age sex differences were seen in the global cancer burden attributable to all risk factors combined (48.0% [95% UI 45.3–51.5] of male cancer DALYs versus 34.3% [30.9–38.7] of female cancer DALYs). These sex differences are well documented, with several studies reporting higher attributable cancer burden in males compared with females.^{13,17–19} In this study, we identified sex differences across two primary risk factor groupings. For instance, there were disparities in cancer DALYs attributable to behavioural risk factors, such as smoking (33.2% [31.7–34.7] for males vs 8.9% [8.3–9.6] for females) and alcohol use (7.4% [6.7–8.2] for males vs 2.3% [2.0–2.6] for females), which might be driven by higher exposure to these behavioural risk factors among males than females. Similarly, for environmental and occupational risks, for example, the cancer DALYs attributable to occupational carcinogens were three times higher among males (3.9% [3.1–4.8]) than females (1.3% [1.0–1.6]), which might reflect that males are more likely than females to

be employed in workplaces with higher risk of exposure to carcinogens. Between 2010 and 2019, the change in global age-standardised risk-attributable cancer DALY rates decreased slightly among females (–4.6% [–11.0 to 2.2]), whereas there was a more notable decline among males (–9.6% [–17.6 to –1.3]). This result might suggest inequities in our approach to cancer prevention by sex and a need for future sex-specific assessments of effective cancer risk factor interventions.

Our results show a gradient across the socio-demographic spectrum in 2019, with the risk-attributable cancer age-standardised DALY rates generally increasing with higher SDI quintiles. However, from 2010 to 2019, age-standardised cancer DALY rates attributable to all risks combined declined in high, high-middle, and middle SDI countries, whereas these values increased in low-middle SDI countries or were approximately stable in low SDI countries. This increase was largely due to metabolic risks, which include risk factors such as high BMI. The growth in metabolic risk-attributable cancer burden might be the result of these countries experiencing an epidemiological transition in which improvements in country-level developmental status are related to increasing obesity levels.^{36,37}

Globally, there has been substantial progress in reducing exposure to tobacco that can be linked to coordinated international and national prevention

Leading risk 2010	Age-standardised rate of DALYs, 2010	Leading risk 2019	Age-standardised rate of DALYs, 2019	Percentage change in age-standardised rate of DALYs, 2010–19
1 Smoking	774.1 (729.9 to 818.1)	1 Smoking	677.3 (616.4 to 740.3)	-12.5 (-19.6 to -4.8)
2 Alcohol use	164.4 (148.3 to 182.3)	2 Alcohol use	155.2 (138.4 to 173.5)	-5.6 (-12.9 to 2.2)
3 High body-mass index	127.9 (71.4 to 200.3)	3 High body-mass index	133.9 (76.2 to 206.8)	4.8 (-1.8 to 12.9)
4 Unsafe sex	112.6 (99.2 to 125.4)	4 Unsafe sex	107.2 (90.5 to 119.4)	-4.8 (-12.7 to 3.7)
5 High fasting plasma glucose	101.3 (27.4 to 207.0)	5 High fasting plasma glucose	104.2 (28.7 to 212.9)	2.9 (-2.8 to 9.5)
6 Ambient particulate matter pollution	86.3 (63.0 to 109.0)	6 Ambient particulate matter pollution	84.2 (62.1 to 108.3)	-2.4 (-12.5 to 10.1)
7 Occupational exposure to asbestos	61.1 (45.0 to 77.6)	7 Occupational exposure to asbestos	50.9 (37.8 to 64.7)	-16.7 (-21.8 to -11.5)
8 Diet low in whole grains	48.1 (18.4 to 63.0)	8 Diet low in whole grains	46.3 (17.8 to 61.1)	-3.6 (-9.1 to 1.9)
9 Diet low in milk	45.3 (29.4 to 61.2)	9 Diet low in milk	46.1 (29.8 to 62.2)	1.7 (-4.8 to 8.9)
10 Diet low in fruits	43.6 (22.1 to 68.7)	10 Second-hand smoke	38.5 (24.8 to 55.5)	-5.2 (-13.7 to 4.0)
11 Second-hand smoke	40.7 (26.6 to 57.9)	12 Diet low in fruits	36.0 (18.5 to 56.2)	-17.5 (-26.5 to -8.1)

■ Behavioural risks
■ Environmental and occupational risks
■ Metabolic risks

Figure 6: Leading risk factors at the most detailed level for risk-attributable cancer age-standardised DALY rates globally, both sexes combined, 2010–19

Top ten risk factors for age-standardised rates of cancer DALYs and risk factors moving in or out of the top ten between 2010 and 2019 are displayed for the global level. Dashed lines indicate decrease in rank. Solid lines indicate increase or no change in rank. Data in parentheses are 95% uncertainty intervals. Risk factors at the most detailed level reflect the GBD hierarchy in which these categories of risks fall, ranging from Levels 2 to 4 (see appendix p 152 for more information on risk factor levels in the GBD hierarchy). See appendix (pp 175–80) for an expanded version of this figure, which contains the top ten risk factors for risk-attributable cancer age-standardised DALY rates in males, females, and both sexes combined globally and by SDI quintile. See appendix (pp 181–87) for further details about the top ten risk factors for risk-attributable cancer age-standardised death rates for males, females, and both sexes combined globally and by SDI quintile. DALYs=disability-adjusted life-years. GBD=Global Burden of Disease, Injuries, and Risk Factors Study. SDI=Socio-demographic Index.

efforts.^{38,39} Interventions through taxation and regulatory policies for tobacco smoking, including smoke-free policies, increased tobacco taxes, and advertisement bans guided by the WHO Framework Convention on Tobacco Control, have played a major role in these efforts.^{38,40} Similar efforts, including taxation and advertisement bans, have been recommended to help reduce the harmful use of alcohol.^{41–43} Behavioural risk factors are strongly influenced by the environment in which people live and individuals with cancer should not be blamed for their disease. Future research is needed to investigate the effect of population health approaches to cancer risk factor reduction that go beyond individual-oriented prevention and might be more effective long-term strategies than placing the onus on individuals to modify exposures to prevent cancer.⁴⁴ Many risk factors for cancer have been well established for decades, but greater political commitment to implementing policies addressing cancer prevention is needed. Improving social determinants of health, such as access to education and reduction of poverty, might be a feasible approach to reducing exposure to certain risks across populations.^{45,46} Population-based approaches aimed at improving social determinants of health might provide an equitable cancer control approach to overcome the systemic barriers promoting disproportionate risk-attributable cancer burden growth in some regions, countries, and subpopulations within countries. For these reasons, future research should not overlook the importance of context-specific interventions that are guided or led by those with an understanding of local cultural and behavioural patterns. Finally, cancers remain

fundamentally linked to genetics and ageing, and although addressing contributing risk factors is crucial for cancer prevention, this will never eliminate cancer burden. As a result, countries should continue to invest in comprehensive cancer control strategies beyond risk factor reduction, which include health-care systems capable of early diagnosis, detection through screening for select cancers, and effective treatment options for those diagnosed with cancer.

Although GBD 2019 is the largest effort to date to estimate the global burden of cancer attributable to risk factors, there remain opportunities for improvement. First, some limitations are inherent in the data sources available. For instance, some countries do not have population-based cancer registries, which are an important data source for estimating cancer burden. As is apparent in the relative uncertainty of risk-attributable cancer burden estimated by GBD 2019 (appendix p 171), there is greater uncertainty relative to point estimates in many lower SDI countries as compared with higher SDI countries. GBD study models rely on available data, and estimates should not supplant but rather complement the ongoing crucial work to expand and improve directly observed data around the world. Cancer registry development and support are integral in cancer control efforts and should be considered in broader cancer control planning initiatives. Delays are inherent with the release of cancer registry and vital statistics reports, which result in more recent cancer mortality estimates often relying on historical data. The data used to estimate risk factor exposure is at times sparse and many data sources do not provide sufficient information to assess for potential measurement error or

bias. Where there is information available, the GBD study aims to correct for systematic bias in risk exposure data by establishing a reference definition of each risk exposure and adjusting acceptable alternative exposure measurements on the basis of studies with observed data pairs of the two different definitions. However, after these adjustments, residual measurement bias is likely to persist and might vary around the world, over time, and by risk factor. Formal assessments of exposure model performance would be beneficial in future GBD iterations. Second, the risk factors included in this study are based on current knowledge of risk factors for cancer, but as knowledge expands there might be additional risk factors important to incorporate in future iterations of the GBD study. In addition, there are known risk factors for cancer, such as sunlight exposure (ie, ultraviolet radiation), and infectious agents, such as *Helicobacter pylori*, which are not included in the GBD study.^{47,48} Unsafe sex is estimated as a risk factor, but human papillomavirus, a known risk factor for several cancer types, is not explicitly estimated; and although liver cancer burden due to hepatitis B and C is estimated within the GBD cause hierarchy, these viral infections are not estimated as risk factors, making their inclusion in robust risk-attributable cancer burden estimation challenging. Infection-associated cancers are more notable in lower SDI settings, so addressing these will be important to producing comprehensive global assessments of cancer-attributable risk and disparities. Third, second-order measures of cancer-relevant risk factors, including aspects such as income inequality and racism, would be challenging to comprehensively account for, but could add important context for future health policy work. Finally, GBD 2019 results were estimated before the COVID-19 pandemic. Evaluating the effect of the COVID-19 pandemic on risk-attributable cancer burden is an important area for future research. However, several leading risk factors identified in this study are also linked to an increase in the severity of illness in individuals with COVID-19 and to burden of other non-communicable diseases besides cancer. Thus, reducing exposure to these harmful risk factors might not only have a positive effect on cancer burden reduction efforts, but synergistically improve population health more broadly.

Worldwide, a large percentage of cancer deaths and DALYs were attributable to risk factors in 2019, with most being attributable to behavioural risks. Smoking continues to be the leading cancer risk factor globally, with other substantial contributors to cancer burden varying around the world. Targeting leading location-specific cancer risk factors might help countries make progress towards reducing non-communicable disease premature mortality by a third by 2030, as highlighted in SDG target 3.4. Although progress has been seen in high and high-middle SDI countries for behavioural and environmental and occupational risk-attributable cancer age-standardised DALY rates between 2010 and 2019, in low and low-middle SDI countries, metabolic

risk-attributable cancer burden has grown considerably. Considerable cancer burden is not avoidable through the currently estimated risk factors, and, as such, countries should continue to simultaneously invest in risk reduction strategies while strengthening health systems to support early diagnosis and effective treatment of those with cancer. Given the increasing burden of cancer worldwide, this study can help policy makers and researchers identify important modifiable risk factors that could be targeted in efforts to reduce cancer burden globally, regionally, and nationally.

GBD 2019 Cancer Risk Factors Collaborators

Khanh Bao Tran†, Justin J Lang†, Kelly Compton, Rixing Xu, Alistair R Acheson, Hannah Jacqueline Henrikson, Jonathan M Kocarnik, Louise Penberthy, Amirali Aali, Qamar Abbas, Behzad Abbasi, Mohsen Abbasi-Kangevari, Zeinab Abbasi-Kangevari, Hedayat Abbastabar, Michael Abdelmasseh, Sherief Abd-Elsalam, Ahmed Abdelwahab Abdelwahab, Gholamreza Abdoli, Hanan Abdulkadir Abdulkadir, Aidin Abedi, Kedir Hussein Abegaz, Hassan Abidi, Richard Gyan Aboagye, Hassan Abolhassani, Abdorrahim Absalan, Yonas Derso Abtew, Hiwa Abubaker Ali, Eman Abu-Gharbieh, Basavaprabhu Achappa, Juan Manuel Acuna, Daniel Addison, Isaac Yeboah Addo, Oyelola A Adegboye, Miracle Ayomikun Adesina, Mohammad Adnan, Qorinah Estiningtyas Sakilah Adnani, Shailesh M Advani, Sumia Afrin, Muhammad Sohail Afzal, Manik Aggarwal, Bright Opoku Ahinkorah, Araz Ramadan Ahmad, Rizwan Ahmad, Sajjad Ahmad, Sohail Ahmad, Sepideh Ahmadi, Haroon Ahmed, Luai A Ahmed, Muktar Beshir Ahmed, Tarik Ahmed Rashid, Wajeeha Aiman, Marjan Ajami, Gizachew Taddesse Akalu, Mostafa Akbarzadeh-Khiavi, Addis Aklilu, Maxwell Akonde, Chisom Joyqueenet Akunna, Hanadi Al Hamad, Fares Alahdab, Fahad Mashhour Alanezi, Turki M Alanzi, Saleh Ali Alessy, Abdelazeem M Algammal, Mohammed Khaled Al-Hanawi, Robert Kaba Alhassan, Beriwan Abdulqadir Ali, Liaqat Ali, Syed Shujait Ali, Yousef Alimohamadi, Wahid Alipour, Syed Mohamed Aljunid, Motasem Alkhayyat, Sadeq Ali Ali Al-Maweri, Sami Almustanyir, Nivaldo Alonso, Shehabaldin Alqalyoobi, Rajaa M Al-Raddadi, Rami H Hani Al-Rifai, Salman Khalifah Al-Sabah, Ala'a B Al-Tammemi, Haya Altawalah, Nelson Alvis-Guzman, Firehiwot Amare, Edward Kwabena Ameyaw, Javad Javad Aminian Dehkordi, Mohammad Hosein Amirzade-Iranaq, Hubert Amu, Ganiyu Adeniyi Amusa, Robert Ancuceanu, Jason A Anderson, Yaregal Animum Animum, Amir Anoushiravani, Ali Arash Anoushiravani, Alireza Ansari-Moghaddam, Mustafa Geleto Ansha, Benny Antony, Maxwell Hubert Antwi, Sumadi Lukman Anwar, Raziq Anwer, Anayochukwu Edward Anyasodor, Jalal Arabloo, Morteza Arab-Zozani, Olatunde Aremu, Ayele Mamo Argaw, Hany Ariffin, Timur Aripov, Muhammad Arshad, Al Artaman, Judie Arulappan, Raphael Taiwo Aruleba, Armin Aryannejad, Malke Asaad, Mulusew A Asemahagn, Zatollah Asemi, Mohammad Asghari-Jafarabadi, Tahira Ashraf, Reza Assadi, Mohammad Athar, Seyyed Shamsadin Athari, Maha Moh'd Wahbi Atout, Sameh Attia, Avinash Aujayeb, Marcel Ausloos, Leticia Avila-Burgos, Atalel Fentahun Awedew, Mamaru Ayenew Awoke, Tewachew Awoke, Beatriz Paulina Ayala Quintanilla, Tegegn Mulatu Ayana, Solomon Shitu Ayen, Davood Azadi, Sina Azadnajafabad, Saber Azami-Aghdash, Melkalem Mamuye Azanaw, Mohammadreza Azangou-Khyavy, Amirhossein Azari Jafari, Hosein Azizi, Ahmed Y Y Azzam, Amirhesam Babajani, Muhammad Badar, Ashish D Badiye, Nayereh Baghcheghi, Nader Bagheri, Sara Bagherieh, Saeed Bahadory, Atif Amin Baig, Jennifer L Baker, Ahad Bakhtiari, Ravleen Kaur Bakshi, Maciej Banach, Indrajit Banerjee, Mainak Bardhan, Francesco Barone-Adesi, Fabio Barra, Amadou Barrow, Nasir Z Bashir, Azadeh Bashiri, Saurav Basu, Abdul-Monim Mohammad Batiha, Aeysha Begum, Alehegn Bekele Bekele, Alemayehu Sayih Belay, Melaku Ashagrie Belete, Uzma Iqbal Belgaumi, Arielle Wilder Bell, Luis Belo, Habib Benzian,

Alemshet Yirga Berhie, Amiel Nazer C Bermudez, Eduardo Bernabe, Akshaya Srikanth Bhagavathula, Neeraj Bhala, Bharti Bhandari Bhandari, Nikha Bhardwaj, Pankaj Bhardwaj, Krittika Bhattacharyya, Vijayalakshmi S Bhojaraja, Soumitra S Bhuyan, Sadia Bibi, Awraris Hailu Bilchut, Bagas Suryo Bintoro, Antonio Biondi, Mesfin Geremaw Birega Birega, Habitu Eshetu Birhan, Tone Bjørge, Oleg Blyuss, Belay Boda Abule Bodicha, Srinivasa Rao Bolla, Archith Boloor, Cristina Bosetti, Dejana Braithwaite, Michael Brauer, Hermann Brenner, Andrey Nikolaevich Briko, Nikolay Ivanovich Briko, Christina Maree Buchanan, Norma B Bulamu, Maria Teresa Bustamante-Teixeira, Muhammad Hammad Butt, Nadeem Shafique Butt, Zahid A Butt, Florentino Luciano Caetano dos Santos, Luis Alberto Cámera, Chao Cao, Yin Cao, Giulia Carreras, Márcia Carvalho, Francieli Cembranel, Ester Cerin, Promit Ananyo Chakraborty, Periklis Charalampous, Vijay Kumar Chattu, Odgerel Chimed-Ochir, Jesus Lorenzo Chirinos-Caceres, Daniel Youngwhan Cho, William C S Cho, Devasahayam J Christopher, Dinh-Toi Chu, Isaac Sunday Chukwu, Aaron J Cohen, Joao Conde, Sandra Cortés, Vera Marisa Costa, Natália Cruz-Martins, Garland T Culbreth, Omid Dadras, Fentaw Teshome Dagnaw, Saad M A Dahlawi, Xiaochen Dai, Lalit Dandona, Rakhi Dandona, Parnaz Daneshpajouhnejad, Anna Danielewicz, An Thi Minh Dao, Reza Darvishi Cheshmeh Soltani, Aso Mohammad Darwesh, Saswati Das, Dragos Virgil Davitoiu, Elham Davtalab Esmaeili, Fernando Pio De la Hoz, Sisay Abebe Debela, Azizallah Dehghan, Berniyam Demisse, Fitsum Wolde Demisse, Edgar Denova-Gutiérrez, Afshin Derakhshani, Meseret Derbew Molla, Diriba Dereje, Kalkidan Solomon Deribe, Rupak Desai, Markos Desalegn Desalegn, Fikadu Nugusu Dessalegn, Samuel Abebe A Dessalegn, Gashaw Dessie, Abebaw Alemayehu Desta, Syed Masudur Rahman Dewan, Samath Dhammintha Dharmaratne, Meghnath Dhimal, Mostafa Dianatinasab, Nancy Diao, Daniel Diaz, Lankamo Ena Digesa, Shilpi Gupta Dixit, Saeid Doaei, Linh Phuong Doan, Paul Narh Doku, Deepa Dongarwar, Wendel Mombaqué dos Santos, Tim Robert Driscoll, Haneil Larson Dsouza, Oyewole Christopher Durojaiye, Sareh Edalati, Fatemeh Eghbalian, Elham Ehsani-Chimeh, Ebrahim Eini, Michael Ekholuenetale, Temitope Cyrus Ekundayo, Donatus U Ekwueme, Maha El Tantawi, Mostafa Ahmed Elbahnasawy, Iffat Elbarazi, Hesham Elghazaly, Muhammed Elhadi, Waseem El-Huneidi, Mohammad Hassan Emamian, Luchuo Engelbert Bain, Daniel Berhanie Enyew, Rychindorj Erkhembayar, Tegegne Eshetu, Babak Eshtrati, Sharareh Eskandarieh, Juan Espinosa-Montero, Farshid Etaee, Azin Etemadimaneh, Tahir Eyayu, Ifeanyi Jude Ezeonwumelu, Sayeh Ezzikouri, Adeniyi Francis Fagbami, Saman Fahimi, Ildar Ravisovich Fakhriyev, Emerito Jose A Faraon, Jawad Fares, Abbas Farmany, Umar Farooque, Hossein Farrokhpour, Abidemi Omolara Fasanmi, Ali Fatehizadeh, Wafa Fatima, Hamed Fattahi, Ginenus Fekadu, Berhanu Eflu Feleke, Allegra Allegra Ferrari, Simone Ferrero, Lorenzo Ferro Desideri, Irina Filip, Florian Fischer, Roham Foroumadi, Masoud Foroutan, Takeshi Fukumoto, Peter Andras Gaal, Mohamed M Gad, Muktar A Gadanya, Abduzzhappar Gaipov, Nasrin Galehdar, Silvano Gallus, Tushar Garg, Mariana Gaspar Fonseca, Yosef Haile Gebremariam, Teferi Gebru Gebremeskel, Mathewos Alemu Gebremichael, Yohannes Fikadu Geda, Yibeltal Yismaw Gela, Belete Negesse Belete Gemed, Melaku Getachew, Motuma Erena Getachew, Kazem Ghaffari, Mansour Ghafourifard, Seyyed-Hadi Ghamari, Mohammad Ghasemi Nour, Fariba Ghassemi, Ajnish Ghimire, Nermin Ghith, Maryam Gholamalizadeh, Jamshid Gholizadeh Navashenaq, Sherief Ghozy, Syed Amir Gilani, Paramjit Singh Gill, Themba G Ginindza, Abraham Tamirat T Gizaw, James C Glasbey, Justyna Godos, Amit Goel, Mahaveer Golechha, Pouya Goleij, Davide Golinelli, Mohamad Golitaleb, Giuseppe Gorini, Bárbara Niegia García Goulart, Giuseppe Grosso, Habtamu Alganah Guadie, Mohammed Ibrahim Mohialdeen Gubari, Temesgen Worku Gudayu, Maximiliano Ribeiro Guerra, Damitha Asanga Gunawardane, Bhawna Gupta, Sapna Gupta, Veer Bala Gupta, Vivek Kumar Gupta, Mekdes Gondale Gurara, Alemu Guta, Parham Habibzadeh, Atlas Haddadi Avval, Nima Hafezi-Nejad, Adel Hajj Ali, Arvin Haj-Mirzaian, Esam S Halboub, Aram Halimi, Rabih Halwani, Randah R Hamadeh, Sajid Hameed, Samer Hamidi, Asif Hanif, Sanam Hariri, Netanja I Harlianto, Josep Maria Haro, Risky Kusuma Hartono, Ahmed I Hasaballah, S M Mahmudul Hasan, Hamidreza Hasani, Seyede Melika Hashemi, Abbas M Hassan, Soheil Hassanipour, Khezlar Hayat, Golnaz Heidari, Mohammad Heidari, Zahra Heidarymeybodi, Brenda Yuliana Herrera-Serna, Claudiu Herteliu, Kamal Hezam, Yuta Hiraike, Mbuzeleni Mbuzeleni Hlongwa, Ramesh Holla, Marianne Holm, Nobuyuki Horita, Mohammad Hoseini, Md Mahbub Hossain, Mohammad Bellal Hossain Hossain, Mohammad-Salar Hosseini, Ali Hosseinzadeh, Mehdi Hosseinzadeh, Mihaela Hostiu, Sorin Hostiu, Mowafa Househ, Junjie Huang, Fernando N Hugo, Ayesha Humayun, Salman Hussain, Nawfal R Hussein, Bing-Fang Hwang, Segun Emmanuel Ibitoye, Pulwasha Maria Iftikhar, Kevin S Ikuta, Olayinka Stephen Ilesanmi, Irena M Ilic, Milena D Ilic, Mustapha Immurana, Kaire Innos, Pooya Iranpour, Lalu Muhammad Irham, Md Shariful Islam, Rakibul M Islam, Farhad Islami, Nahlah Elkudssiah Ismail, Gaetano Isola, Masao Iwagami, Linda Merin J, Abhishek Jaiswal, Mihajlo Jakovljevic, Mahsa Jalili, Shahram Jalilian, Elham Jamshidi, Sung-In Jang, Chinmay T Jami, Tahereh Javaheri, Umesh Umesh Jayarajah, Shubha Jayaram, Seyed Behzad Jazayeri, Rime Jebai, Bedru Jemal, Wonjeong Jeong, Ravi Prakash Jha, Har Ashish Jindal, Yetunde O John-Akinola, Jost B Jonas, Tamas Joo, Nitin Joseph, Farahnaz Joukar, Jacek Jerzy Jozwiak, Mikko Jürisson, Ali Kabir, Salah Eddine Oussama Kacimi, Vidya Kadashetti, Farima Kahe, Pradnya Vishal Kakodkar, Laleh R Kalankesh, Leila R Kalankesh, Rohollah Kalhor, Vineet Kumar Kamal, Farin Kamangar, Ashwin Kamath, Tanuj Kanchan, Eswar Kandaswamy, Himal Kandel, Hyejung Kang, Girum Gebremeskel Kanno, Neeti Kapoor, Sitanshu Sekhar Kar, Shama D Karanth, Ibraheem M Karaye, André Karch, Amirali Karimi, Bekalu Getnet Kassa, Patrick DMC Katoto, Joonas H Kauppila, Harkiran Kaur, Abinet Gebremichael Kebede, Leila Keikavoosi-Arani, Gemechu Gemechu Kejela, Phillip M Kemp Bohan, Maryam Keramati, Mohammad Keykhaei, Himanshu Khajuria, Abbas Khan, Abdul Aziz Khan Khan, Ejaz Ahmad Khan, Gulfaraz Khan, Md Nuruzzaman Khan, Moien AB Khan, Javad Khanali, Khaled Khatab, Moawiah Mohammad Khatatbeh, Mahalaqua Nazli Khatib, Maryam Khayamzadeh, Hamid Reza Khayat Kashani, Mohammad Amin Khazeei Tabari, Mehdi Khezeli, Mahmoud Khodadost, Min Seo Kim, Yun Jin Kim, Adnan Kisa, Sezer Kisa, Miloslav Klugar, Jitka Klugarová, Ali-Asghar Kolahi, Pavel Kolkhir, Farzad Kompani, Parvaiz A Koul, Sindhura Lakshmi Koulmane Laxminarayana, Ai Koyanagi, Kewal Krishan, Yuvaraj Krishnamoorthy, Burcu Kucuk Bicer, Nurworza Kugbey, Mukhtar Kulimbet, Akshay Kumar, G Anil Kumar, Narinder Kumar, Om P Kurmi, Ambily Kuttikkattu, Carlo La Vecchia, Arista Lahiri, Dharmesh Kumar Lal, Judit Lám, Qing Lan, Iván Landires, Bagher Larijani, Savita Lasrado, Jerrald Lau, Paolo Lauriola, Caterina Ledda, Sang-woong Lee, Shaun Wen Huey Lee, Wei-Chen Lee, Yeong Yeh Lee, Yo Han Lee, Samson Mideksa Legesse, James Leigh, Elyvna Leong, Ming-Chieh Li, Stephen S Lim, Gang Liu, Jue Liu, Chun-Han Lo, Ayush Lohiya, Platon D Lopukhov, László Lorencz, Mojgan Lotfi, Joana A Loureiro, Raimundas Lunevicius, Farzan Madadizadeh, Ahmad R Mafi, Sameh Magdeldin, Soleiman Mahjoub, Ata Mahmoodpoor, Morteza Mahmoudi, Rashieh Mahmoudimanesh, Rashidul Alam Mahmud, Azeem Majeed, Jamal Majidpoor, Alaa Makki, Konstantinos Christos Makris, Elaheh Malakan Rad, Mohammad-Reza Malekpour, Reza Malekzadeh, Ahmad Azam Malik, Tauqeer Hussain Mallhi, Sneha Deepak Mallya, Mohammed A Mamun, Ana Laura Manda, Fariborz Mansour-Ghanaei, Borhan Mansouri, Mohammad Ali Mansournia, Lorenzo Giovanni Mantovani, Santi Martini, Miquel Martorell, Sahar Masoudi, Seyede Zahra Masoumi, Clara N Matei, Elezebeth Mathews, Manu Raj Mathur, Vasundhara Mathur, Martin McKee, Jitendra Kumar Meena, Khalid Mehmood, Entezar Mehrabi Nasab, Ravi Mehrotra, Addisu Melese, Walter Mendoza, Ritesh G Menezes, SIsay Derso Mengesha, Laverne G Mensah, Alexios-Fotios A Mentis, Andry Yasnid Mera Mera-Mamián,

- Tuomo J Meretoja, Mehari Woldemariam Merid, Amanual Getnet Mersha, Belsity Temesgen Meselu, Mahboobeh Meshkat, Tomislav Mestrovic, Junmei Miao Jonasson, Tomasz Miazgowski, Irmima Maria Michalek, Gelana Fekadu Worku Mijena, Ted R Miller, Shabir Ahmad Mir, Seyed Kazem Mirinezhad, Seyyedmohammadsadeq Mirmoeeni, Mohammad Mirza-Aghazadeh-Attari, Hamed Mirzaei, Hamid Reza Mirzaei, Abay Sisay Misganaw, Sanjeev Misra, Karzan Abdulmuhsin Mohammad, Esmaeil Mohammadi, Mokhtar Mohammadi, Abdollah Mohammadian-Hafshejani, Reza Mohammadpourhodki, Arif Mohammed, Shafiu Mohammed, Syam Mohan, Mohammad Mohseni, Nagabhishek Moka, Ali H Mokdad, Alex Molassiotis, Mariam Molokhia, Kaveh Momenzadeh, Sara Momtazmanesh, Lorenzo Monasta, Ute Mons, Ahmed Al Montasir, Fateme Montazeri, Arnulfo Montero, Mohammad Amin Moosavi, Abdolvahab Moradi, Yousef Moradi, Mostafa Moradi Sarabi, Paula Moraga, Lidia Morawska, Shane Douglas Morrison, Jakub Morze, Abbas Mosapour, Ebrahim Mostafavi, Seyyed Meysam Mousavi, Haleh Mousavi Isfahani, Amin Mousavi Khaneghah, Christine Mpundu-Kaambwa, Sumaira Mubarak, Francesc Mulita, Daniel Munblit, Sandra B Munro, Efrén Murillo-Zamora, Jonah Musa, Ashraf F Nabhan, Ahamarshan Jayaraman Nagarajan, Shankar Prasad Nagaraju, Gabriele Nagel, Mohammadreza Naghipour, Mukhammad David Naimzada, Tapas Sadasivan Nair, Atta Abbas Naqvi, Sreenivas Narasimha Swamy, Aparna Ichalagond Narayana, Hasan Nassereldine, Zuhair S Natto, Biswa Prakash Nayak, Rawlance Ndejo, Sabina Onyinye Nduaguba, Wogene Wogene Negash, Seyed Aria Nejadghaderi, Kazem Nejati, Sandhya Neupane Kandel, Huy Van Nguyen Nguyen, Robina Khan Niazi, Nurulamin M Noor, Maryam Noori, Nafise Noroozi, Hasti Nouraei, Ali Nowroozi, Virginia Nuñez-Samudio, Chimezie Igwegbe Nzopotam, Ogochukwu Janet Nzopotam, Bogdan Oancea, Oluwakemi Olofade Odukoya, Onome Bright Oghenetega, Ropo Ebenezer Ogunsakin, Ayodipupo Sikiru Oguntade, In-Hwan Oh, Hassan Okati-Aliabad, Akinkunmi Paul Okekunle, Andrew T Olagunju, Tinuke O Olagunju, Babayemi Oluwaseun Olakunde, Isaac Iyinoluwa Olufadewa, Emad Omer, Abidemi E Emmanuel Omonisi, Sokking Ong, Obinna E Onwujekwe, Hans Orru, Stanislav S Otstavnov, Abderahim Oulhaj, Bilcha Oumer, Oluwatomi Funbi Owopetu, Babatunji Emmanuel Oyinloye, Mahesh P A, Alicia Padron-Monedero, Jagadish Rao Padubidri, Babak Pakbin, Keyvan Pakshir, Reza Pakzad, Tamás Palicz, Adrian Pana, Anamika Pandey, Ashok Pandey, Suman Pant, Shahina Pardhan, Eun-Cheol Park, Eun-Keel Park, Seoyeon Park, Jay Patel, Siddhartha Pati, Rajan Paudel, Uttam Paudel, Mihaela Paun, Hamidreza Pazoki Toroudi, Minjin Peng, Jeevan Pereira, Renato B Pereira, Simone Perna, Navaraj Perumalsamy, Richard G Pestell, Raffaele Pezzani, Cristiano Piccinelli, Julian David Pillay, Zahra Zahid Piracha, Tobias Pischon, Maarten J Postma, Ashkan Pourabhari Langroudi, Akram Pourshams, Naeimeh Pourtaheri, Akila Prashant, Mirza Muhammad Fahd Qadir, Zahiruddin Quazi Syed, Mohammad Rabiee, Navid Rabiee, Amir Radfar, Raghu Anekal Radhakrishnan, Venkatraman Radhakrishnan, Mojtaba Raeesi, Ata Rafiee, Alireza Rafiee, Nasiru Raheem, Fakhre Rahim, Md Obaidur Rahman, Mosiur Rahman, Muhammad Aziz Rahman, Amir Masoud Rahmani, Shayan Rahmani, Vahid Rahmanian, Nazamin Rajai, Aashish Rajesh, Pradhun Ram, Kiana Ramezanzadeh, Jewel Rana, Kamal Ranabhat, Priyanga Ranasinghe, Chythra R Rao, Sowmya J Rao, Sina Rashedi, Amirfarzan Rashidi, Mahsa Rashidi, Mohammad-Mahdi Rashidi, Zubair Ahmed Ratan, David Laith Rawaf, Salman Rawaf, Lal Rawal, Reza Rawassizadeh, Mohammad Sadeqh Razeghinia, Ashfaq Ur Rehman, Inayat ur Rehman, Marissa B Reitsma, Andre M N Renzaho, Maryam Rezaei, Nazila Rezaei, Negar Rezaei, Nima Rezaei, Saeid Rezaei, Mohsen Rezaeian, Aziz Rezapour, Abanoub Riad, Reza Rikhtegar, Maria Rios-Blancas, Thomas J Roberts, Peter Rohloff, Esperanza Romero-Rodríguez, Gholamreza Roshandel, Godfrey M Rweggera, Manjula S, Maha Mohamed Saber-Ayad, Bahar Saberezhadeh-Ardestani, Siamak Sabour, Basema Saddik, Erfan Sadeghi, Mohammad Reza Saeb, Umar Saeed, Mohsen Safaei, Azam Safary, Maryam Sahebazzamani, Amirhossein Sahebkar, Harihar Sahoo, Mirza Rizwan Sajid, Hedayat Salari, Sana Salehi, Marwa Rashad Salem, Hamideh Salimzadeh, Yoseph Leonardo Samodra, Abdallah M Samy, Juan Sanabria, Senthilkumar Sankararaman, Francesco Sanmarchi, Milena M Santric-Milicevic, Muhammad Arif Nadeem Saqib, Arash Sarveezad, Fatemeh Sarvi, Brijesh Sathian, Maheswar Satpathy, Nicolas Sayegh, Ione Jayce Ceola Schneider, Michaël Schwarzinger, Mario Šekerija, Subramanian Senthilkumar, Sadaf G Sepanlou, Allen Seylani, Kenbon Seyoum, Feng Sha, Omid Shafaat, Pritik A Shah, Saeed Shahabi, Izza Shahid, Mohammad Amin Shahrba, Hamid R Shahsavari, Masood Ali Shaikh, Mohammed Feyisso Shaka, Elaheh Shaker, Mohammed Shannawaz, Mequannent Melaku Sharew Sharew, Azam Sharifi, Javad Sharifi-Rad, Purva Sharma, Bereket Beyene Shashamo, Aziz Sheikh, Mahdi Sheikh, Sara Sheikhabaei, Rahim Ali Sheikh, Ali Sheikhy, Peter Robin Shepherd, Adithi Shetty, Jeevan K Shetty, Ranjitha S Shetty, Kenji Shibuya, Reza Shirkoobi, Hesamaddin Shirzad-Aski, K M Shivakumar, Siddharudha Shivali, Velizar Shivarov, Parnian Shobeiri, Zahra Shokri Varniab, Seyed Afshin Shorofi, Sunil Shrestha, Migbar Mekonnen Sibhat, Sudeep K Siddappa Malleshappa, Negussie Boti Sidemo, Diego Augusto Santos Silva, Luís Manuel Lopes Rodrigues Silva, Guilherme Silva Julian, Nicola Silvestris, Wudneh Simegn, Achintya Dinesh Singh, Ambrish Singh, Garima Singh, Harpreet Singh, Jasvinder A Singh, Jitendra Kumar Singh, Paramdeep Singh, Surjit Singh, Dharendra Narain Sinha, Abiy H Sinke, Md Shahjahan Siraj, Freddy Sitas, Samarjeet Singh Siwal, Valentin Yurievich Skryabin, Anna Aleksandrova Skryabina, Bogdan Socea, Matthew J Soeberg, Ahmad Sofi-Mahmudi, Yonatan Solomon, Mohammad Sadeqh Soltani-Zangbar, Suhang Song, Yimeng Song, Reed J D Sorensen, Sergey Soshnikov, Houman Sotoudeh, Aliou Sowe, Mu'awiyah Babale Sufiyan, Ryan Suk, Muhammad Suleman, Rizwan Suliankatchi Abdulkader, Saima Sultana, Daniel Sur, Miklós Szócska, Seidamir Pasha Tabaieian, Rafael Tabarés-Seisdedos, Seyyed Mohammad Tabatabaei, Takahiro Tabuchi, Hooman Tadbiri, Ensiyeh Taheri, Majid Taheri, Moslem Taheri Soodejani, Ken Takahashi, Iman M Talaat, Mircea Tampa, Ker-Kan Tan, Nathan Y Tat, Vivian Y Tat, Ahmad Tavakoli, Arash Tavakoli, Arash Tehrani-Banihashemi, Yohannes Tekalegn, FisaHa Haile Tesfay, Rekha Thapar, Aravind Thavamani, Viveksandeep Theogulova Chandrasekar, Nihal Thomas, Nikhil Kenny Thomas, Jansje Henny Vera Ticoalu, Amir Tiyuri, Daniel Niguse Tolloza, Roman Topor-Madry, Mathilde Touvier, Marcos Roberto Tovani-Palome, Eugenio Traini, Mai Thi Ngoc Tran, Jaya Prasad Tripathy, Gebresilasea Gendisha Ukke, Irfan Ullah, Saif Ullah, Sana Ullah, Bhaskaran Unnikrishnan, Marco Vacante, Maryam Vaezi, Sahel Valadan Tahbaz, Pascual R Valdez, Constantine Vardavas, Shoban Babu Vartha, Siavash Vaziri, Diana Zuleika Velazquez, Massimiliano Veroux, Paul J Villeneuve, Francesco S Violante, Sergey Konstantinovich Vladimirov, Vasily Vlassov, Bay Vo, Linh Gia Vu, Abdul Wadood Wadood, Yasir Waheed, Mandaras Tariku Walde, Richard G Wamai, Cong Wang, Fang Wang, Ning Wang, Yu Wang, Paul Ward, Abdul Waris, Ronny Westerman, Nuwan Darshana Wickramasinghe, Melat Woldemariam, Berhanu Woldu, Hong Xiao, Suowen Xu, Xiaoyue Xu, Lalit Yadav, Seyed Hossein Yahyazadeh Jabbari, Lin Yang, Fereshth Yazdanpanah, Yigizie Yeshaw, Yazachew Yismaw, Naohiro Yonemoto, Mustafa Z Younis, Zabihollah Yousefi, Fatemeh Yousefian, Chuanhua Yu, Yong Yu, Ismaeel Yunusa, Mazyar Zahir, Nazar Zaki, Burhan Abdullah Zaman, Moein Zangiabadian, Fariba Zare, Iman Zare, Zahra Zarehsharabadi, Armin Zarrintan, Mikhail Sergeevich Zastrozhin, Mohammad A Zeineddine, Dongyu Zhang, Jianrong Zhang, Yunquan Zhang, Zhi-jiang Zhang, Linghui Zhou, Sanjay Zodepy, Mohammad Zoladl, Theo Vos, Simon I Hay, Lisa M Force, Christopher J L Murray†
- Affiliations**
Department of Molecular Medicine and Pathology (K B Tran MD, C M Buchanan PhD, Prof P R Shepherd PhD), University of Auckland,

Auckland, New Zealand; Department of Clinical Hematology and Toxicology (K B Tran MD), Maurice Wilkins Centre, Auckland, New Zealand; Centre for Surveillance and Applied Research (J J Lang PhD), Public Health Agency of Canada, Ottawa, ON, Canada; Institute for Health Metrics and Evaluation (K Compton BS, R Xu BS, A R Acheson BA, J M Kocarnik PhD, L Penberthy MS, J A Anderson BS, Prof M Brauer DSc, A J Cohen DSc, G T Culbreth PhD, X Dai PhD, Prof L Dandona MD, Prof R Dandona PhD, Prof S D Dharmaratne MD, H J Henrikson BA, K S Ikuta MD, Prof S S Lim PhD, T Mestrovic PhD, A H Mokdad PhD, H Nassereldine MD, M B Reitsma BS, R J D Sorensen PhD, Prof T Vos PhD, Prof S I Hay FMedSci, L M Force MD, Prof C J L Murray DPhil), Department of Health Metrics Sciences, School of Medicine (X Dai PhD, Prof R Dandona PhD, Prof S D Dharmaratne MD, Prof S S Lim PhD, A H Mokdad PhD, Prof T Vos PhD, Prof S I Hay FMedSci, L M Force MD, Prof C J L Murray DPhil), Division of Allergy and Infectious Diseases (K S Ikuta MD), Division of Plastic and Reconstructive Surgery (S D Morrison MD), Department of Global Health (R J D Sorensen PhD), Division of Pediatric Hematology-Oncology (L M Force MD), University of Washington, Seattle, WA, USA; Health Informatic Lab (T Javaheri PhD), Department of Computer Science (R Rawassizadeh PhD), Boston University, Boston, MA, USA; Department of Medicine (H J Henrikson BA), Brigham and Women's Hospital, Boston, MA, USA; Faculty of Medicine (A Aali MD), Education Development Center (R Assadi PhD), E-Learning Center (M Ghasemi Nour MD), School of Medicine (A Haddadi Avval), Department of Nursing (R Mohammadpourhodki PhD), Applied Biomedical Research Center (A Sahebkar PhD), Biotechnology Research Center (A Sahebkar PhD), Department of Medical Informatics (S Tabatabaei PhD), Clinical Research Development Unit (S Tabatabaei PhD), Mashhad University of Medical Sciences, Mashhad, Iran (M Keramati MD); Health Policy Research Center (A Aali MD, S Shahabi PhD), Health Information Management (A Bashiri PhD), Department of Epidemiology (M Dianatinasab MSc), Research Center for Health Sciences (P Habibzadeh MD, M Hoseini PhD), Department of Environmental Health (M Hoseini PhD), Department of Radiology (P Iranpour MD), Non-communicable Disease Research Center (Prof R Malekzadeh MD, S G Sepanlou MD), Department of Medical Mycology and Parasitology (H Nouraei MSc, Prof K Pakshir PhD, Z Zareshahrabadi PhD), Shiraz University of Medical Sciences, Shiraz, Iran; Department of Biology (Q Abbas PhD), University of Bahrain, Manama, Bahrain; Uro-oncology Research Center (B Abbasi MD), Non-communicable Diseases Research Center (Z Abbasi-Kangevari BSc, A Aryannejad MD, S Azadnajafabad MD, M Azangou-Khyavy MD, S Ghamari MD, J Khanali MD, M Keykhaei MD, M Malekpour MD, S Momtazmanesh MD, F Montazeri MD, A Pourabbari Langroudi MD, S Rahmani MD, M Rashidi MD, N Rezaei MD, N Rezaei PhD, Z Shokri Varniab MD), Advanced Diagnostic and Interventional Radiology Research Center (H Abbastabar PhD), Research Center for Immunodeficiencies (H Abolhassani PhD, Prof N Rezaei PhD), Department of Epidemiology and Biostatistics (Y Alimohamadi PhD, H Azizi PhD, M Mansournia PhD), Universal Scientific Education and Research Network (USERN) (M Amirzadeh-Iranaq DDS), Digestive Diseases Research Institute (A Anoushiravani MD, S Fahimi MD, xiri MD, Prof R Malekzadeh MD, S Masoudi MSc, Prof A Pourshams MD, H Salimzadeh PhD, S G Sepanlou MD, M Sheikh PhD), Experimental Medicine Research Center (A Aryannejad MD), Department of Health Policy, Management, and Economics (A Bakhtiari PhD), National Institute for Health Research (E Ehsani-Chimeh PhD), Multiple Sclerosis Research Center (S Eskandari PhD), Department of Pathology (A Etemadimanesh MD), School of Medicine (H Farrokhpour MD, N Hafezi-Nejad MD, S Hashemi MD, A Karimi MD, S Momtazmanesh MD, A Nowroozi BMedSc), Endocrinology and Metabolism Research Institute (R Foroumadi MD, Prof B Larjani FACE, N Rezaei PhD), Department of Surgery (R Foroumadi MD), Ophthalmology Department (Prof F Ghassem MD), Digestive Oncology Research Center (Prof F Kamangar MD), Students' Scientific Research Center (SSRC) (M Keykhaei MD), Children's Medical Center (F Kompani MD), Department of Pediatrics and Pediatric Cardiology (Prof E Malakan Rad MD), Tehran Heart Center (E Mehrabi Nasab MD),

Department of Medical Immunology (H Mirzaei PhD), Faculty of Medicine (E Mohammadi MD, E Shaker MD, P Shobeiri MD), Department of Pharmacology (N Noroozi DVM, M Zahir MD), Metabolomics and Genomics Research Center (F Rahim PhD), Department of Cardiology (S Rashedi MD), Department of Gastroenterology (B Saberzadeh-Ardestani MD), Cancer Research Center (R Shirkoobi PhD), Cancer Biology Research Center (R Shirkoobi PhD), Department of Pediatric Allergy and Immunology (F Yazdanpanah MD), Department of Environmental Health (F Yousefian PhD), Tehran University of Medical Sciences, Tehran, Iran; Reproductive Biomedicine Research Center (B Abbasi MD), Royan Institution, Isfahan, Iran; Social Determinants of Health Research Center (M Abbasi-Kangevari MD, Z Abbasi-Kangevari BSc, M Azangou-Khyavy MD, S Ghamari MD, J Khanali MD, A Kolahi MD, M Rashidi MD), School of Advanced Technologies in Medicine (S Ahmadi PhD), Department of Pharmacology (A Babajani MD, A Haj-Mirzaian MD, K Ramezanzadeh PharmD), Department of Community Nutrition (S Doaei PhD, S Edalati PhD), Cancer Research Center (M Gholamalizadeh PhD), Obesity Research Center (A Haj-Mirzaian MD), Research Institute for Endocrine Sciences (A Halimi BSc), Functional Neurosurgery Research Center (E Jamshidi PharmD), Department of Neurosurgery (H Khayat Kashani MD), Department of Health & Community Medicine (A Kolahi MD), Department of Clinical Oncology (A R Mafi MD), School of Medicine (F Montazeri MD, S Nejadghaderi MD, M Zangiabadian MD), Student Research Committee (S Rahmani MD), Department of Epidemiology (S Sabour PhD), Faculty of Medicine (M Shahrabaf MD), Medical Ethics and Law Research Center (M Taheri PhD), Shahid Beheshti University of Medical Sciences, Tehran, Iran (M Khayamzadeh MD); Department of Surgery (M Abdelmasseh MD, Prof J Sanabria MD), Marshall University, Huntington, WV, USA; Tropical Medicine Department (S Abd-Elsalam PhD), Tanta University, Tanta, Egypt; Department of Internal Medicine (A A Abdelwahab MD), Baylor College of Medicine, Houston, TX, USA; Department of Epidemiology (G Abdoli PhD), Social Development and Health Promotion Research Center (M Khezeli PhD), Substance Abuse Prevention Research Center (B Mansouri PhD), Advanced Dental Sciences Research Center (M Safaei PhD), Department of Infectious Disease (Prof S Vaziri MD), Kermanshah University of Medical Sciences, Kermanshah, Iran; Department of Public Health (H A Abdulkadir MPH, Y H Gebremariam MPH), Department of Biomedical Science (Y D Abtey MSc, B B A Bodicha MSc), Department of Medical Laboratory Sciences (A Aklilu MSc), School of Nursing (T M Ayana MSc), Department of Medical Anatomy (A B Bekele MSc), Department of Nursing (B Demisse MSc, B B Shashamo MSc), Department of Midwifery (F W Demisse MSc, S A A Dessalegn MSc, B Oumer MPH, G G Ukke MSc), Department of Comprehensive Nursing (L E Digesa MSc), Department of Epidemiology and Biostatistics (M A Gebremichael MPH), School of Public Health (M K Gurara MPH, N B Sidemo MPH), Department of Anatomy (A G Kebede MA), Department of Medical Laboratory Science (M Woldemariam MSc), Arba Minch University, Arba Minch, Ethiopia; Department of Neurosurgery (A Abedi MD), Keck School of Medicine (A Abedi MD), Mark and Mary Stevens Neuroimaging and Informatics Institute (S Salehi MD), University of Southern California, Los Angeles, CA, USA; Department of Biostatistics (K H Abegaz MSc), Near East University, Nicosia, Cyprus; Department of Biostatistics and Health Informatics (K H Abegaz MSc), Department of Public Health (Y Tekalegn MPH), Mada Walabu University, Bale Robe, Ethiopia; Laboratory Technology Sciences Department (H Abidi PhD), Department of Nursing (M Zoladl PhD), Yasuj University of Medical Sciences, Yasuj, Iran; Department of Family and Community Health (R G Aboagye MPH), Institute of Health Research (R K Alhassan PhD, M Immurana PhD), Department of Population and Behavioural Sciences (H Amu PhD), University of Health and Allied Sciences, Ho, Ghana; Department of Biosciences and Nutrition (H Abolhassani PhD), Karolinska University Hospital, Huddinge, Sweden; Medical Laboratory Sciences (A Absalan PhD), Department of Laboratory Sciences (K Ghaffari MSc), Khomein University of Medical Sciences, Khomein, Iran; Research and Development (A Absalan PhD), Satras Biotechnology Company, Tehran, Iran; University of Human Development

(Prof H Abubaker Ali PhD), Department of Information Technology (A M Darwesh PhD), Department of Computer Science (M Hosseinzadeh PhD), University of Human Development, Sulaymaniyah, Iraq; Clinical Sciences Department (E Abu-Gharbieh PhD, Prof R Halwani PhD, Prof I M Talaat PhD), Department of Basic Medical Sciences (W El-Huneidi PhD), College of Medicine (Prof R Halwani PhD), Mass Communication Department (A Makki PhD), Department of Clinical Sciences (M M Saber-Ayad MD), Sharjah Institute for Medical Research (B Saddik PhD), University of Sharjah, Sharjah, United Arab Emirates; Department of Internal Medicine (B Achappa MD, A Bolor MD), Department of Forensic Medicine and Toxicology (H L Dsouza MD), Department of Community Medicine (N Joseph MD, R Thapar MD), Department of Obstetrics and Gynaecology (A Shetty MS), Kasturba Medical College (Prof B Unnikrishnan MD), Manipal Academy of Higher Education, Mangalore, India; Department of Epidemiology and Population Health (Prof J M Acuna MD, A Oulhaj PhD), Khalifa University, Abu Dhabi, United Arab Emirates; 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; Department of Internal Medicine (D Addison MD), Ohio State University, Columbus, OH, USA; Centre for Social Research in Health (I Y Addo PhD), Centre for Primary Health Care and Equity (CPHCE) (F Sitas PhD), School of Population Health (X Xu PhD), University of New South Wales, Sydney, NSW, Australia; Quality and Systems Performance Unit (I Y Addo PhD), Cancer Institute NSW, Sydney, NSW, Australia; Public Health and Tropical Medicine (O A Adegbeye PhD), James Cook University, Townsville, QLD, Australia; Slum and Rural Health Initiative Research Academy (M A Adesina BS, I I Olufadewa MHS), Slum and Rural Health Initiative, Ibadan, Nigeria; Department of Physiotherapy (M A Adesina BS), Department of Epidemiology and Medical Statistics (M Ekholuenetale MSc, A F Fagbamigbe PhD), Faculty of Public Health (M Ekholuenetale MSc, I I Olufadewa MHS), Department of Health Promotion and Education (S E Ibitoye MPH, Y O John-Akinola PhD), Department of Community Medicine (O S Ilesanmi PhD), Department of Obstetrics and Gynecology (O B Oghenetega MSc), College of Medicine (A P Okekunle PhD), University of Ibadan, Ibadan, Nigeria; Department of Neonatology (M Adnan MD), Indiana University Health Ball Memorial Hospital, Muncie, IN, USA; Faculty of Medicine (Q E S Adnani PhD), Universitas Padjadjaran (Padjadjaran University), Bandung, Indonesia; Terasaki Institute for Biomedical Innovation, Los Angeles, CA, USA (S M Advani PhD); School of Medicine (S M Advani PhD), Department of Oncology (D Zhang PhD), Georgetown University, Washington, DC, USA; Department of Conservative Dentistry (S Afrin DDS), Department of Population Sciences (Prof M B H Hossain PhD), University of Dhaka, Dhaka, Bangladesh; Department of Life Sciences (M S Afzal PhD, I Ullah PhD), School of Sciences (M N Saqib PhD), University of Management and Technology, Lahore, Pakistan; Department of Internal Medicine (M Aggarwal MD, M Alkhayyat MD, A D Singh MD), Department of Cardiovascular Medicine (M M Gad MD), Heart, Vascular, Thoracic Institute (A Hajj Ali MD), Cleveland Clinic, Cleveland, OH, USA; The Australian Centre for Public and Population Health Research (ACPPHR) (B O Ahinkorah MPH, E K Ameyaw MPhil), University of Technology Sydney, Sydney, NSW, Australia; College of Nursing (A R Ahmad PhD), International Relations & Diplomacy, Ranya, Iraq; International Relations & Diplomacy (A R Ahmad PhD), School of Pharmacy (B A Ali PhD), Tishk International University, Erbil, Iraq; Department of Natural Products and Alternative Medicine (R Ahmad PhD), Health Information Management and Technology Department (T M Alanzi PhD), Environmental Health Department (S M A Dahlawi PhD), Forensic Medicine Division (Prof R G Menezes MD), Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia (F M Alanezi PhD); Department of Health and Biological Sciences (S Ahmad PhD), Abasyn University, Peshawar, Pakistan; Faculty of Pharmacy (S Ahmad MSc), MAHSA University, Kuala Langat, Malaysia; 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, I Elbarazi DrPH), Department of Medical Microbiology & Immunology (Prof G Khan PhD), Family Medicine Department (M A Khan MSc), Computer Science and Software Engineering Big Data Analytics Center (Prof N Zaki PhD), United Arab Emirates University, Al Ain, United Arab Emirates; Department of Epidemiology (M B Ahmed MPH), Department of Biomedical Sciences (D Dereje MSc), Department of Public Health (M E Getachew MPH), Department of Health, Behavior and Society (A T T Gizaw MPH), Jimma University, Jimma, Ethiopia; Australian Center for Precision Health (M B Ahmed MPH), University of South Australia, Adelaide, SA, Australia; Department of Computer Science and Engineering (T Ahmed Rashid PhD), University of Kurdistan Hewler, Erbil, Iraq; Department of Neurology (W Aiman MD), Nishtar Medical University, Multan, Pakistan; Department of Food and Nutrition Policy and Planning Research (M Ajami PhD), National Institute of Nutrition, Tehran, Iran; National Nutrition and Food Technology Research Institute (M Ajami PhD), Shahid Beheshti University of Medical Sciences, Iran; Department of Microbiology, Immunology and Parasitology (G T Akalu MSc), St Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia; Microbial, Cellular and Molecular Biology Department (G T Akalu MSc), Department of Surgery (A F Awedew MD), Immunology Research Center (A Derakhshani MSc), Department of Preventive Medicine (K S Deribe MPH), Department of Anatomy (A G Kebede MA), Medical Laboratory Sciences (A S Misganaw MSc), Microbial cellular and molecular biology (A S Misganaw MSc), Addis Ababa University, Addis Ababa, Ethiopia; Liver and Gastrointestinal Diseases Research Center (M Akbarzadeh-Khiavi PhD), Road Traffic Injury Research Center (Prof M Asghari-Jafarabadi PhD, E Davtalab Esmaeili PhD), Department of Health Policy & Management (S Azami-Aghdash PhD), Research Center of Psychiatry and Behavioral Sciences (H Azizi PhD), Department of Medical Surgical Nursing (M Ghafourifard PhD, M Lotfi PhD), Student Research Committee (M Hosseini MD), School of Management and Medical Informatics (L R Kalankesh PhD), Medical Education Research Center (M Lotfi PhD), Anesthesiology and Critical Care (Prof A Mahmoodpoor MD), Liver and Gastrointestinal Disease Research Center (S Mirinezhad PhD), Department of Radiology (M Mirza-Aghazadeh-Attari MD, A Zarrintan MD), Connective Tissue Diseases Research Center (A Safary PhD), Department of Immunology (M Soltani-Zangbar MSc), Alzahra Teaching Hospital (M Vaezi MD), Women's Reproductive Health Research Center (M Vaezi MD), Department of Pediatric Allergy and Immunology (F Yazdanpanah MD), Tabriz University of Medical Sciences, Tabriz, Iran; Department of Epidemiology and Biostatistics (M Akonde MSc), Department of Clinical Pharmacy and Outcomes Sciences (I Yunusa PhD), University of South Carolina, Columbia, SC, USA; Department of Public Health (C J Akunna DMD), The Intercountry Centre for Oral Health (ICOH) for Africa, Jos, Nigeria; Department of Public Health (C J Akunna DMD), Federal Ministry of Health, Garki, Nigeria; 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; Department of Public Health (S A Alessy PhD), Saudi Electronic University, Riyadh, Saudi Arabia; Centre for Cancer, Society & Public Health (S A Alessy PhD), Faculty of Dentistry, Oral & Craniofacial Sciences (E Bernabe PhD), Faculty of Life Sciences and Medicine (M Molokhia PhD), King's College London, London, UK; Department of Bacteriology, Immunology, and Mycology (Prof A M Algamal PhD), Department of Physiology (Prof S Magdeldin PhD), Suez Canal University, Ismailia, Egypt; Department of Health Services and Hospital Administration (M K Al-Hanawi PhD), Health Economics Research Group (M K Al-Hanawi PhD), Department of Community Medicine (R M Al-Raddadi PhD), Department of Family and Community Medicine (N S Butt PhD), Rabigh Faculty of Medicine (A A Malik PhD), Department of Dental Public Health (Z S Natto DrPH), King Abdulaziz University, Jeddah, Saudi Arabia; Erbil Technical Health College (B A Ali PhD), Erbil Polytechnic University, Erbil, Iraq; Department of Biological Sciences (L Ali PhD), National University of Medical Sciences (NUMS), Rawalpindi, Pakistan; Centre for Biotechnology and Microbiology (S S Ali PhD), University of Swat, Swat, Pakistan; Pars Advanced and Minimally Invasive Medical Manners Research Center (Y Alimohamadi PhD), Health Management and Economics Research Center (V Alipour PhD, J Arabloo PhD, A Rezapour PhD), Department

of Health Economics (V Alipour PhD), Department of Internal Medicine (A Anoushirvani MD, S Tabaiean MD), Preventive Medicine and Public Health Research Center (B Eshtrati PhD, A Tehrani-Banihashemi PhD), Minimally Invasive Surgery Research Center (A Kabir MD), Department of Health Services Management (H Mousavi Isfahani PhD), Student Research Committee (M Noori MD), Department of Physiology (H Pazoki Toroudi PhD), Physiology Research Center (H Pazoki Toroudi PhD), The Five Senses Health Institute (S Rezaei MD), Colorectal Research Center (A Sarveazad PhD), Trauma and Injury Research Center (M Taheri PhD), Research Center of Pediatric Infectious Diseases (A Tavakoli PhD), Department of Medical Virology (A Tavakoli PhD), Department of Community and Family Medicine (A Tehrani-Banihashemi PhD), Department of Epidemiology and Biostatistics (A Tiyuri MSc), Iran University of Medical Sciences, Tehran, Iran; Department of Health Policy and Management (Prof S M Aljunid PhD), Department of Surgery (S K Al-Sabah MD), Department of Microbiology (H Altawalah FRCPath), Kuwait University, Kuwait, Kuwait; International Centre for Casemix and Clinical Coding (Prof S M Aljunid PhD), National University of Malaysia, Bandar Tun Razak, Malaysia; College of Dental Medicine (S A A Al-Maweri PhD), Qatar University, Doha, Qatar; Faculty of Dentistry (S A A Al-Maweri PhD), Sana'a University, Sanaa, Yemen; College of Medicine (S Almustanyir MD), Alfaisal University, Riyadh, Saudi Arabia; Ministry of Health, Riyadh, Saudi Arabia (S Almustanyir MD); Department of Surgery (N Alonso MD), University of Sao Paulo, São Paulo, Brazil; Department of Internal Medicine (S Alqalyoobi MD), East Carolina University, Greenville, NC, USA; Independent Consultant, Greenville, NC, USA (S Alqalyoobi MD); Institute of Public Health (R H Al-Rifai PhD), United Arab Emirates University, Abu Dhabi, United Arab Emirates; Jaber Al Ahmad Al Sabah Hospital (S K Al-Sabah MD), Clinical Virology Unit (H Altawalah FRCPath), Ministry of Health of Kuwait, Kuwait, Kuwait; Department of Family and Occupational Medicine (A Al-Tammemi MPH), University of Debrecen, Debrecen, Hungary; 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; School of Pharmacy (F Amare MSc), Department of Health Informatics (D B Enyew MSc), Department of Emergency and Critical Care Medicine (M Getachew MD), Department of Mental Health and Psychiatry (M T Walde MSc), Haramaya University, Harar, Ethiopia; Applied Science and Technology (J J Aminian Dehkordi PhD), University of California Berkeley, Berkeley, CA, USA; Chemical Engineering Department (J J Aminian Dehkordi PhD), Department of Parasitology (S Bahadory PhD), Department of Clinical Biochemistry (A Mosapour PhD), Tarbiat Modares University, Tehran, Iran; Department of Medicine (G A Amusa MD), Department of Obstetrics and Gynecology (J Musa MD), University of Jos, Jos, Nigeria; Department of Internal Medicine (G A Amusa MD), Jos University Teaching Hospital, Jos, Nigeria; Pharmacy Department (Prof R Ancuceanu PhD), Department of General Surgery (D V Davitoui PhD, A Manda MD, B Socea PhD), Internal Medicine Department (M Hostiu PhD), Department of Legal Medicine and Bioethics (S Hostiu PhD), Department of Dermatology (C N Matei PhD, M Tampa PhD), Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; Department of Epidemiology and Biostatistics (Y A Animut MPH, Y Yeshaw MPH), Department of Health Education and Behavioral Sciences (H E Birhan MPH), Department of Biochemistry (M Derbew Molla MSc), Biochemistry Department (G Dessie MSc), Department of Surgical Nursing (A A Desta MSc), Department of Medical Parasitology (T Eshetu MSc), Department of Human Physiology (Y Gela MSc), Department of Clinical Midwifery (T W Gudayy MPH), School of Medicine (A G Mersha MD), Institute of Public Health (M M S Sharew MPH), Social and Administrative Pharmacy (W Simegn MSc), Department of Hematology and Immunohematology (B Woldu MSc), University of Gondar, Gondar, Ethiopia; 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 Public Health (M G Ansha MPH, A H Bilchut PhD), Debre Berhan University, Debre Berhan, Ethiopia; Menzies Institute for Medical Research (B Antony PhD, A Singh M Tech), University of Tasmania, Hobart, TAS, Australia; Department of Medical Laboratory Science (M Antwi MPhil), Koforidua Technical University, Koforidua, Ghana; Department of Surgery (S Anwar PhD), Gadjah Mada University, Yogyakarta, Indonesia; Department of Pathology (R Anwer PhD), Imam Mohammad Ibn Saud Islamic University, Riyadh, Saudi Arabia; School of Community Health (A E Anyasodor PhD), Charles Sturt University, Orange, NSW, Australia; Social Determinants of Health Research Center (M Arab-Zozani PhD), Medical Toxicology & Drug Abuse Research Center (M Rezaei MD), Department of Epidemiology and Biostatistics (A Tiyuri MSc), Birjand University of Medical Sciences, Birjand, Iran; Department of Public Health (O Aremu PhD), Birmingham City University, Birmingham, UK; Clinical Pharmacy (A M Argaw MSc), Department of Nursing (W W Negash MSc), Mada Walabu University, Goba, Ethiopia; Department of Paediatrics (Prof H Ariffin MD), University of Malaya Medical Centre (Prof H Ariffin MD), University of Malaya, Kuala Lumpur, Malaysia; Department of Public Health and Healthcare Management (T Aripov PhD), Tashkent Institute of Postgraduate Medical Education, Tashkent, Uzbekistan; Boston Children's Hospital, Boston, MA, USA (T Aripov PhD); Center of Biotechnology and Microbiology (M Arshad PhD), University of Peshawar, Peshawar, Pakistan; Department of Health Sciences (A Artaman PhD), Zayed University, Dubai, United Arab Emirates; Department of Maternal and Child Health (J Arulappan DSc), Sultan Qaboos University, Muscat, Oman; Molecular and Cell Biology (R T Aruleba MSc), University of Cape Town, Cape Town, South Africa; Department of Plastic Surgery (M Asaad MD, A M Hassan MD), Health Science Center (D Dongarwar MS), Department of GI Medical Oncology (M A Zineddine MD), University of Texas, Houston, TX, USA; School of Public Health (M A Asemahagn PhD), Department of Medical Laboratory Sciences (T Awoke MSc, A Melese MSc), School of Health Sciences (A Y Berhie MSc), Department of Epidemiology and Biostatistics (B E Feleke MPH), Department of Health Informatics (H A Guadie MPH), Department of Pharmacology (Y Yismaw MSc), Bahir Dar University, Bahir Dar, Ethiopia; Research Center for Biochemistry and Nutrition in Metabolic Diseases (Z Asemi PhD, H Mirzaei PhD), Department of Environmental Health (F Yousefian PhD), Kashan University of Medical Sciences, Kashan, Iran; Cabrini Research (Prof M Asghari-Jafarabadi PhD), Cabrini Institute, Melbourne, VIC, Australia; University Institute of Radiological Sciences and Medical Imaging Technology (T Ashraf MS), Department of Public Health (W Fatima PhD), Faculty of Allied Health Sciences (Prof S Gilani PhD), University Institute of Public Health (S Hameed MPH, A Hanif PhD, A A Malik PhD), The University of Lahore, Lahore, Pakistan; Department of Medical Genetics (M Athar PhD), Science and Technology Unit (M Athar PhD), Umm Al-Qura University, Makkah, Saudi Arabia; Department of Immunology (S Athari PhD), Zanjan University of Medical Sciences, Zanjan, Iran; Faculty of Nursing (M M W Atout PhD, Prof A M Batiha PhD), Philadelphia University, Amman, Jordan; Department of Oral and Maxillofacial Surgery (S Attia MSc), Justus Liebig University of Giessen, Giessen, Germany; Northumbria HealthCare NHS Foundation Trust (A Aujayeb MBBS), National Health Service (NHS) Scotland, Newcastle upon Tyne, UK; 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; Center for Health Systems Research (L Avila-Burgos ScD), Center for Nutrition and Health Research (E Denova-Gutiérrez DSc), Center for Health System Research (M Rios-Blancas MPH), National Institute of Public Health, Cuernavaca, Mexico; Department of Epidemiology and Preventive Medicine (M A Awoke MPH), Department of General Practice (J Zhang MD), University of Melbourne, Melbourne, VIC, Australia; The Judith Lumley Centre (B Ayala Quintanilla PhD), School of Nursing and Midwifery (M Rahman PhD), La Trobe University, Melbourne, VIC, Australia; San Martin de Porres University, Lima, Peru (B Ayala Quintanilla PhD); Department of Midwifery (S S Ayen MSc, Y F Geda MSc), Wolkite University, Wolkite, Ethiopia; Department of Laboratory Sciences (D Azadi PhD), Arak University of Medical Sciences, Khomein, Iran; Department of Public Health (M M Azanaw MPH, F T Dagnaw MPH),

Medical Laboratory Sciences (T Eyayu MSc), Department of Midwifery (B G Kassa MSc), Debre Tabor University, Debre Tabor, Ethiopia; School of Medicine (A Azari Jafari MD, S Mirmoenei MD), Ophthalmic Epidemiology Research Center (M Emamian PhD), Department of Epidemiology (A Hosseinzadeh DrPH), Shahroud University of Medical Sciences, Shahroud, Iran (F Zare MSc); Department of Neurovascular Research (A Y Azzam MD), Nested Knowledge, Saint Paul, MN, USA; Faculty of Medicine (A Y Azzam MD), October 6 University, 6th of October City, Egypt; Gomal Center of Biochemistry and Biotechnology (M Badar PhD), Gomal University, Dera Ismail Khan, Pakistan; Department of Forensic Science (A D Badiye MSc, N Kapoor MSc), Government Institute of Forensic Science, Nagpur, India; Department of Nursing (N Baghcheghi PhD), Saveh University of Medical Sciences, Saveh, Iran; Basic Health Sciences Institute (N Bagheri PhD), Community-Oriented Nursing Midwifery Research Center (M Heidari PhD), Department of Epidemiology and Biostatistics (A Mohammadian-Hafshejani PhD), Shahrekord University of Medical Sciences, Shahrekord, Iran; School of Medicine (S Bagherieh BSc), Department of Pathology (P Daneshpajouhnejad MD), Department of Environmental Health Engineering (A Fatehizadeh PhD, E Taheri PhD), Research Institute for Primordial Prevention of Non-Communicable Disease (S Hariri MD), Department of Biology (M Meshkat MSc), Health Services Management (M Mohseni PhD), Biostatistics and Epidemiology (E Sadeghi PhD), Department of Radiology and Interventional Neuroradiology (O Shafaat MD), Isfahan University of Medical Sciences, Isfahan, Iran; Department of Parasitology (S Bahadory PhD), Department of Healthcare Services Management (L Keikavoosi-Arani 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; Division of RBMCH&N (R K Bakshi MD), Molecular Microbiology (M Bardhan MD), Biostatistics Department of (V K Kamal PhD), India Cancer Research Consortium (Prof R Mehrotra DPhil), Indian Council of Medical Research, New Delhi, India (Prof L Dandona MD); 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 Pharmacology (I Banerjee MD), Sir Seewoosagar Ramgoolam Medical College, Belle Rive, Mauritius; Molecular Microbiology and Bacteriology (M Bardhan MD), National Institute of Cholera and Enteric Diseases, Kolkata, India; Department of Translational Medicine (F Barone-Adesi PhD), University of Eastern Piedmont, Novara, Italy; Academic Unit of Obstetrics and Gynecology (F Barra MD), Department of Health Sciences (DISSAL) (A A Ferrari MD), Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOEMI) (Prof S Ferrero PhD), University Eye Clinic (L Ferro Desideri MD), University of Genoa, Genoa, Italy; Department of Public & Environmental Health (A Barrow MPH), University of The Gambia, Brikama, The Gambia; Epidemiology and Disease Control Unit (A Barrow MPH), Expanded Program on Immunization (A Sowe MSc), Ministry of Health, Kotu, The Gambia; School of Oral and Dental Sciences (N Z Bashir BDS), University of Bristol, Bristol, UK; Academics Department (S Basu MD), Indian Institute of Public Health, Gurgaon, India; Independent Consultant, Bogura, Bangladesh (A Begum MD); Nursing Department (A S Belay MSc), Department of Public Health (M G B Birega MPH), Mizan-Tepi University, Mizan Teferi, Ethiopia; Medical Laboratory Science (M A Belete MSc), Wollo University, Dessie, Ethiopia; Department of Oral Pathology and Microbiology (U I Belgaumi MD), Karad, India; Department of Global Health and Social Medicine (A W Bell MSW), Department of Environmental Health (N Diao DSc), Cardiovascular Department (F Kahe MD), Department of Orthopedic Surgery (K Momenzadeh MD), Department of Health Policy and Oral Epidemiology (Z S Natto DrPH), Department of Internal Medicine (N Rajai MD), Department of Global Health and Population (P Rohloff MD), Division of General Internal Medicine (Prof A Sheikh MD), Harvard University, Boston, MA, USA; Department of Social Services (A W Bell MSW), Tufts Medical Center, Boston, MA, USA; Biological Sciences Department (L Belo PhD), Research Unit on Applied Molecular Biosciences (UCIBIO) (L Belo PhD, M Carvalho PhD, V M Costa PhD), Department of Medicine (Prof N Cruz-Martins PhD), Laboratory for Process Engineering, Environment, Biotechnology and Energy (LEPABE) (J Loureiro PhD), Department of Chemistry (R B Pereira PhD), University of Porto, Porto, Portugal; Department of Epidemiology and Health Promotion (Prof H Benzi PhD), New York University, New York, NY, USA; Department of Epidemiology and Biostatistics (A C Bermudez MD), Department of Health Policy and Administration (E A Faraon MD), University of the Philippines Manila, Manila, Philippines; Department of Epidemiology (A C Bermudez MD), Brown University, Providence, RI, USA; 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; Physiology Department (B B Bhandari MD), Government Institute of Medical Sciences, Greater Noida, India; Department of Anatomy (Prof N Bhardwaj MD, Prof S G Dixit MD), Department of Community Medicine and Family Medicine (P Bhardwaj MD), School of Public Health (P Bhardwaj MD), Department of Forensic Medicine and Toxicology (T Kanchan MD), Department of Surgical Oncology (Prof S Misra MCh), Department of Community Medicine (G Singh MD), Department of Pharmacology (S Singh DM, S B Varthya MD), All India Institute of Medical Sciences, Jodhpur, India; 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), Royal College of Surgeons in Ireland Medical University of Bahrain, Busaiteen, Bahrain; Health Administration (S S Bhuyan PhD), Rutgers University, New Brunswick, NJ, USA; Institute of Soil and Environmental Sciences (S Bibi PhD, S Ullah PhD), University of Agriculture, Faisalabad, Faisalabad, Pakistan; Department of Health Behaviour, Environment and Social Medicine (B Bintoro MD), Center of Health and Behavior and Promotion (B Bintoro MD), Universitas Gadjah Mada (Gadjah Mada University), Sleman, Indonesia; Department of General Surgery and Medical-Surgical Specialties (Prof A Biondi PhD, M Vacante PhD), Department of Biomedical and Biotechnological Sciences (G Grosso PhD), Department of General Surgery and Surgical-Medical Specialties (Prof G Isola 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, O Dadras DrPH), University of Bergen, Bergen, Norway; Cancer Registry of Norway, Oslo, Norway (Prof T Bjørge PhD); Wolfson Institute of Population Health (O Blyuss PhD), Queen Mary University of London, London, UK; Department of Biomedical Sciences (S Bolla PhD), Nazarbayev University, Nur-Sultan City, Kazakhstan; Department of Oncology (C Bosetti PhD), Department of Environmental Health Sciences (S Gallus DSc), Mario Negri Institute for Pharmacological Research, Milan, Italy; Department of Epidemiology (D Braithwaite PhD), UF Health Cancer Center (S D Karanth PhD), University of Florida, Gainesville, FL, USA; Cancer Population Sciences Program (D Braithwaite PhD), University of Florida Health Cancer Center, Gainesville, FL, USA; School of Population and Public Health (Prof M Brauer DSc, P A Chakraborty MPH), University of British Columbia, Vancouver, BC, Canada; Division of Clinical Epidemiology and Aging Research (Prof H Brenner MD), German Cancer Research Center, Heidelberg, Germany; Department of Biomedical Technologies (A N Briko MSc), Bauman Moscow State Technical University, Moscow, Russia; Department of Epidemiology and Evidence-Based Medicine (Prof N I Briko DSc, P D Lopukhov PhD), Department of Paediatrics and Paediatric Infectious Diseases (Prof D Munblit PhD), Digital Biodesign and Personalized Healthcare Research Center (S K Vladimirov PhD), IM Sechenov First Moscow State Medical University, Moscow, Russia; Neurogenetics Research Clinic (C M Buchanan PhD), Auckland City Hospital, Auckland, New Zealand; Flinders Health and Medical Research Institute (N B Bulamu PhD), Health and Social Care Economics Group (C Mpundu-Kaambwa PhD), Nursing and Health Sciences

(S Shorofi PhD), Southgate Institute for Health and Society (F H Tesfay PhD), Flinders University, Adelaide, SA, Australia; Department of Public Health (Prof M T Bustamante-Teixeira PhD, Prof M R Guerra PhD), Federal University of Juiz de Fora, Juiz de Fora, Brazil; Faculty of Pharmacy (M Butt MS), University of Central Punjab, Lahore, Pakistan; School of Public Health and Health Systems (Z A Butt PhD), University of Waterloo, Waterloo, ON, Canada; Al Shifa School of Public Health (Z A Butt PhD), Al Shifa Trust Eye Hospital, Rawalpindi, Pakistan; Institute of Microengineering (F Caetano dos Santos PhD), Federal Polytechnic School of Lausanne, Lausanne, Switzerland; Internal Medicine Department (Prof L A Cámara MD), Hospital Italiano de Buenos Aires (Italian Hospital of Buenos Aires), Buenos Aires, Argentina; Board of Directors (Prof L A Cámara MD), Argentine Society of Medicine, Buenos Aires, Argentina (Prof P R Valdez MEd); Program in Physical Therapy (C Cao MPH), Washington University in St Louis, St Louis, MO, USA; 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Department of Public Health and Health Policy (O Chimed-Ochir PhD), Hiroshima University, Hiroshima, Japan; Department of Public Health, Administration, and Social Sciences (J L Chirinos-Caceres DrPH), Cayetano Heredia University, Lima, Peru; Division of Plastic Surgery (D Y Cho MD), Children's Hospital of Philadelphia, Philadelphia, PA, USA; Department of Clinical Oncology (W C S Cho PhD), Queen Elizabeth Hospital, Hong Kong, China; Department of Pulmonary Medicine (Prof D J Christopher MD), Department of Endocrinology, Diabetes and Metabolism (Prof N Thomas PhD), Christian Medical College and Hospital (CMC), Vellore, India; Center for Biomedicine and Community Health (D Chu PhD), VNU-International School, Hanoi, Vietnam; Department of Surgery (I S Chukwu BMedSc), Federal Medical Centre, Umuahia, Nigeria; Health Effects Institute, Boston, MA, USA (A J Cohen DSc); Nova Medical School (J Conde PhD), Nova University of Lisbon, Lisbon, Portugal; Department of Public Health (S Cortés DrPH), Pontifical Catholic University of Chile, Santiago, Chile; Research Line in Environmental Exposures and Health Effects at Population Level (S Cortés DrPH), Centro de Desarrollo Urbano Sustentable (CEDEUS) (Advanced Center for Chronic Diseases [ACCDIS]), Santiago, Chile; 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 Dadrás DrPH), Walailak University, Thai Buri, Thailand; Research Department (H Kaur MPH), Health Policy Research (M R Mathur PhD), Department of Research (A Pandey PhD), Indian Institute of Public Health (Prof S Zodpey PhD), Public Health Foundation of India, Gurugram, India (Prof L Dandona MD, Prof R Dandona PhD, G Kumar PhD, D K Lal MD); Department of Pathology (P Daneshpajouhnejad MD), Department of Radiology and Radiological Science (N Hafezi-Nejad MD, O Shafaat MD, S Sheikhabaehi MD), Johns Hopkins University, Baltimore, MD, USA (H Tadbiri MD); Department of Human Nutrition (A Danielewicz PhD), Uniwersytet Warmińsko-Mazurski w Olsztynie (University of Warmia and Mazury in Olsztyn), Olsztyn, Poland; School of Public Health (A T Dao PhD), The University of Queensland, Brisbane, QLD, Australia; Epidemiology Department (A T Dao PhD), Hanoi Medical University, Hanoi, Vietnam; Department Environmental Health (R Darvishi Cheshmeh Soltani PhD), Department of Nursing (M Golitaleh PhD), Arak University of Medical Sciences, Arak, Iran; Department of Biochemistry (S Das MD), Ministry of Health and Welfare, New Delhi, India; Department of Surgery (D V Davitoui PhD), Clinical Emergency Hospital Sf Pantelimon, Bucharest, Romania; Department of Public Health (Prof F P De la Hoz PhD), National University of Colombia, Bogota, Colombia; School of Public Health (S Debelá MPH), Salale University, Fiche, Ethiopia; Department of Epidemiology and Community Medicine (A Dehghan PhD), Non-Communicable Diseases Research Center (NCDRC), Fasa, Iran; Division of Cardiology (R Desai MBBS), Atlanta Veterans Affairs Medical Center, Decatur, GA, USA; Department of Public Health (M D Desalegn MPH), Department of Pharmacy (G Fekadu MSc), Department of Public Health (M E Getachew MPH), Public Health Department (G G Kejela MPH), Wollega University, Nekemte, Ethiopia; Department of Public Health (F N Dessalegn MPH), Madda Walabu University, Bale Goba, Ethiopia; Department of Pharmacology (S Dewan PhD), Center for Life Sciences Research, Bangladesh, Dhaka, Bangladesh; Department of Life Sciences and Bioethics (S Dewan PhD), Tokyo Medical and Dental University, Tokyo, Japan; Department of Community Medicine (Prof S D Dharmaratne MD), University of Peradeniya, Peradeniya, Sri Lanka; Health Research Section (M Dhimal PhD), Research Section (A Ghimire BSc, U Paudel PhD), Research Department (A Pandey MPH), Clinical Research (S Pant MPH), Nepal Health Research Council, Kathmandu, Nepal; Department of Epidemiology (M Dianatinasab MSc), Maastricht University, Maastricht, Netherlands; 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, D Z Velazquez MSc), Autonomous University of Sinaloa, Culiacán Rosales, Mexico; School of Health (S Doaei PhD), Gastrointestinal and Liver Diseases Research Center (S Hassanipour PhD, F Joukar PhD, Prof F Mansour-Ghanaei MD, M Naghipour PhD), Caspian Digestive Disease Research Center (S Hassanipour PhD, F Joukar PhD, Prof F Mansour-Ghanaei MD), Caspian Digestive Diseases Research Center (M Naghipour PhD), Guilan University of Medical Sciences, Rasht, Iran; Institute for Global Health Innovations (L P Doan MSc, L G Vu MSc), Faculty of Medicine (L P Doan MSc, L G Vu MSc), Institute of Research and Development (M Hosseinzadeh PhD), Duy Tan University, Da Nang, Vietnam; School of Nursing and Midwifery (P N Doku PhD), University of Cape Coast, Cape Coast, Ghana; Responsabilidade Social (W M dos Santos PhD), Oswaldo Cruz German Hospital, São Paulo, Brazil; Brazilian Centre for Evidence-based Healthcare (W M dos Santos PhD), Joanna Briggs Institute, São Paulo, Brazil; Sydney School of Public Health (Prof T R Driscoll PhD), Save Sight Institute (H Kandel PhD), Asbestos Diseases Research Institute (J Leigh MD), NHMRC Clinical Trials Centre (R A Mahumud PhD), Menzies Centre for Health Policy (F Sitas PhD), University of Sydney, Sydney, NSW, Australia; Department of Forensic Medicine and Toxicology (H L Dsouza MD), Kasturba Medical College Mangalore, Mangalore, India; Infection and Tropical Medicine (O C Durojaiye MPH), University of Sheffield, Sheffield, UK; Department of Medicine (Prof F Eghbalian MD), Department of Health Sciences (A Farmany PhD), Department of Microbiology (M Jalili MSc), Department of Midwifery (S Masoumi PhD), Hamadan University of Medical Sciences, Hamadan, Iran; Department of Orthodontics (E Eini DDS), Department of Medical Virology (S Jalilian PhD, S Jalilian PhD), Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; Department of Biological Sciences (T C Ekundayo PhD), University of Medical Sciences, Ondo, Nigeria; Division of Cancer Prevention and Control (D U Ekwueme PhD), Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA; Pediatric Dentistry and Dental Public Health Department (Prof M El Tantawi PhD), Pathology Department (Prof I M Talaat PhD), Alexandria University, Alexandria, Egypt; Microbiology Department (M A Elbahnasawy PhD), Department of Zoology and Entomology (A I Hasaballah PhD), Al Azhar University, Cairo, Egypt; Department of Oncology (Prof H Elghazaly MD), Department of Obstetrics and Gynecology (Prof A F Nabhan PhD), Department of Entomology (A M Samy PhD), Ain Shams University, Cairo, Egypt; Department of Clinical Research (Prof H Elghazaly MD), Ain Shams Research Institute (MASRI), Cairo, Egypt; Faculty of Medicine (M Elhadi MD), University of Tripoli, Tripoli, Libya; Lincoln International Institute for Rural Health (L Engelbert Bain PhD), University of Lincoln, Lincoln, UK; Department of International Cyber Education (R Erkhembayar MD), Mongolian

National University of Medical Sciences, Ulaanbaatar, Mongolia; Department of Obesity, Diabetes and Cardiovascular risk (Prof J Espinosa-Montero PhD), National Institute of Public Health Mexico, Cuernavaca, Mexico; Department of Internal Medicine (F Etae MD), Yale University, New Haven, CT, USA; Institute for Health Science Research Germans Trias i Pujol (I J Ezeonwumelu MSc), Autonomous University of Barcelona, Badalona, Spain; IrsiCaixa AIDS Research Institute, Badalona, Spain (I J Ezeonwumelu MSc); Department of Virology (S Ezzikouri PhD), Pasteur Institute of Morocco, Casablanca, Morocco; Population and Behavioural Sciences Division (A F Fagbamigbe PhD), University of St Andrews, St Andrews, UK; Laboratory of Experimental Medicine (I R Fakhradiyev PhD), Atchabarov Scientific Research Institute of Fundamental Medicine (M Kulimbet MSc), Kazakh National Medical University, Almaty, Kazakhstan; Department of Neurological Surgery (J Fares MD), Center for Global Health (J Musa MD), Northwestern University, Chicago, IL, USA; 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 Nejadghaderi MD, S Rashedi MD, E Shaker MD), Research Department (A Sheikhy MD), Endocrinology and Metabolism Population Sciences Institute (A Sheikhy MD), Department of International Studies (P Shobeiri MD), Department of Oral Health (A Sofi-Mahmudi DDS), Non-communicable Diseases Research Center (NCDRC), Tehran, Iran (S Hashemi MD, E Mohammadi MD); Satcher Health Leadership Institute (A O Fasanmi PhD), Morehouse School of Medicine, Atlanta, GA, USA; School of Medicine (A O Fasanmi PhD), Department of Cardiology (P Ram MD), Emory University, Atlanta, GA, USA; Department of Public Health (W Fatima PhD), Afro-Asian Institute, Lahore, Pakistan (Prof S Gilani PhD); Centre for Primary Health Care Network Management (H Fattahi PhD), Ministry of Health and Medical Education, Tehran, Iran; School of Pharmacy (G Fekadu MSc), Jockey Club School of Public Health and Primary Care (J Huang MD), The Chinese University of Hong Kong, Hong Kong, China; 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 Public Health (F Fischer PhD), Charité Universitätsmedizin Berlin (Charité Medical University Berlin), Berlin, Germany; Department of Medical Parasitology (M Foroutan PhD), Faculty of Medicine (M Foroutan PhD), Abadan University of Medical Sciences, Abadan, Iran; Department of Dermatology (T Fukumoto PhD), Kobe University, Kobe, Japan; Health Services Management Training Centre (P A Gaal PhD, T Joo MSc), Faculty of Health and Public Administration (J Lám PhD, T Palicz MD, 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; Community Medicine Department (M A Gadanya FMCPH), Bayero University, Kano, Nigeria; Department of Community Medicine (M A Gadanya FMCPH), Aminu Kano Teaching Hospital, Kano, Nigeria; Department of Medicine (A Gaipov PhD), Nazarbayev University School of Medicine, Nur-Sultan, Kazakhstan; Surgical Technology (N Galehdar PhD), Department of Clinical Biochemistry and Department of Allied Medical Sciences (M Moradi Sarabi PhD), Lorestan University of Medical Sciences, Khorramabad, Iran; Department of Radiology (T Garg MBBS), King Edward Memorial Hospital, Mumbai, India; National Health Service, London, UK (M Gaspar Fonseca PhD); Reproductive and Family Health (T G Gebremeskel MPH), Aksum University, Axum, Ethiopia; Department of Nursing (B N B Gemeda MSc), Debre Berhan University, Debre Birhan, Ethiopia; Research Group for Genomic Epidemiology (N Ghith PhD), Technical University of Denmark, Copenhagen, Denmark; Non-communicable Diseases Research Center (J Gholizadeh Navashenaq PhD), Non-communicable Diseases Research Center (N Pourtaheri PhD), Bam University of Medical Sciences, Bam, Iran; Department of Radiology (S Ghozy MD), Mayo Clinic, Rochester, MN, USA; Warwick Medical School (Prof P S Gill DM), University of Warwick, Coventry, UK; Discipline of Public Health Medicine (T G Ginindza PhD, R E Ogunsakin PhD), School of Nursing and Public Health Medicine (M M Hlongwa PhD), University of KwaZulu-Natal, Durban, South Africa; Department of Laboratories (J Godos PhD), Oasi Research Institute, Troina, Italy; Department of Gastroenterology (Prof A Goel DM), Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India; 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 Biomedical and Neuromotor Sciences (D Golinelli MD, F Sanmarchi MD), Department of Medical and Surgical Sciences (Prof F S Violante MD), University of Bologna, Bologna, Italy; Postgraduate Program in Epidemiology (Prof B N G Goulart DSc), Department of Preventive and Social Dentistry (F N Hugo PhD), Federal University of Rio Grande do Sul, Porto Alegre, Brazil; Department of Family and Community Medicine (M I M Gubari PhD), University Of Sulaimani, Sulaimani, Iraq; Department of Community Medicine (D A Gunawardane MD), University of Peradeniya, Kandy, Sri Lanka; Department of Public Health (B Gupta PhD), Torrens University Australia, Melbourne, VIC, Australia; Toxicology Department (S Gupta MSc), Shriram Institute for Industrial Research, Delhi, India; School of Medicine (V Gupta PhD), Deakin University, Geelong, VIC, Australia; Department of Clinical Medicine (Prof V K Gupta PhD), School of Engineering (N Rabiee PhD), Macquarie University, Sydney, NSW, Australia; Faculty of Social Sciences (M K Gurara MPH), Katholieke Universiteit Leuven, Leuven, Belgium; Department of Midwifery (A Guta MSc), Department of Nursing (Y Solomon MSc), Dire Dawa University, Dire Dawa, Ethiopia; College of Dentistry (E S Halboub PhD), Substance Abuse and Toxicology Research Center (S Mohan PhD), Jazan University, Jazan, Saudi Arabia; School of Dentistry (E S Halboub PhD), Sana'a University, Sana'a, Yemen; Department of Family and Community Medicine (Prof R R Hamadeh PhD), Arabian Gulf University, Manama, Bahrain; School of Health and Environmental Studies (Prof S Hamidi DrPH), Hamdan Bin Mohammed Smart University, Dubai, United Arab Emirates; Faculty of Medicine (N I Harlianto BSc), Institute for Risk Assessment Sciences (IRAS) (E Traini MSc), Utrecht University, Utrecht, Netherlands; Department of Radiology (N I Harlianto BSc), University Medical Center Utrecht, Utrecht, Netherlands; Research Unit (J M Haro MD), University of Barcelona, Barcelona, Spain; Biomedical Research Networking Center for Mental Health Network (CiberSAM), Barcelona, Spain (J M Haro MD); Sekolah Tinggi Ilmu Kesehatan Indonesia Maju (Indonesian Advanced College of Health Sciences) (R K Hartono MPH), Institution of Public Health Sciences, Jakarta, Indonesia; Department of Public Health (S Hasan PhD), German University Bangladesh, Dhaka, Bangladesh; Daffodil International University, Dhaka, Bangladesh (S Hasan PhD); Ophthalmology (H Hasani MD), IUMS, Karaj, Iran; Institute of Pharmaceutical Sciences (K Hayat MS), University of Veterinary and Animal Sciences, Lahore, Pakistan; Department of Pharmacy Administration and Clinical Pharmacy (K Hayat MS), Xian Jiaotong University, Xian, China; Independent Consultant, Santa Clara, CA, USA (G Heidari MD); Research Center (Z Heidarymeybodi MD), Department of Biostatistics and Epidemiology (M Taheri Soodejani PhD), Shahid Sadoughi University of Medical Sciences, Yazd, Iran; Departamento de Salud Oral (Department of Oral Health) (B Y Herrera-Serna PhD), Universidad Autónoma de Manizales (Autonomous University of Manizales), Manizales, Colombia; School of Business (Prof C Herteliu PhD), London South Bank University, London, UK; Department of Applied Microbiology (K Hezam PhD), Taiz University, Taiz, Yemen; Department of Microbiology (K Hezam PhD), Nankai University, Tianjin, China; Division for Health Service Promotion (Y Hiraike PhD), University of Tokyo, Tokyo, Japan; Kasturba Medical College, Mangalore (R Holla MD, A Kamath MD), Department of Community Medicine (S D Mallya MD, C R Rao MD, R S Shetty MD), Department of Nephrology (Prof S Nagaraju DM), Manipal College of Dental Sciences, Manipal (Prof A I Narayana PhD), Manipal College of Dental Sciences (Prof R A Radhakrishnan PhD), Manipal Academy of Higher Education, Manipal, India (A Kamath MD); Epidemiology & Public Health Research Dept (M Holm PhD), International Vaccine Institute, Seoul, South Korea; Department of Pulmonology (N Horita PhD), Yokohama City University, Yokohama, Japan; National Human Genome Research Institute (NHGRI) (N Horita PhD), National Institutes of Health, Bethesda, MD, USA; Social and Environmental Health Research

Department (M Hossain MPH), Nature Study Society of Bangladesh, Khulna, Bangladesh; Department of Health Promotion and Community Health Sciences (M Hossain MPH), Texas A&M University, College Station, TX, USA; Clinical Legal Medicine Department (S Hostiuic PhD), National Institute of Legal Medicine Mina Minovici, Bucharest, Romania; College of Science and Engineering (Prof M Househ PhD), Hamad Bin Khalifa University, Doha, Qatar; Department of Public Health and Community Medicine (Prof A Humayun PhD), Shaikh Khalifa Bin Zayed Al-Nahyan Medical College, Lahore, Pakistan; Czech National Centre for Evidence-Based Healthcare and Knowledge Translation (S Hussain PhD, M Klugar PhD, J Klugarová PhD), Institute of Biostatistics and Analyses (S Hussain PhD), Department of Public Health (A Riad DDS), Czech National Centre for Evidence-based Healthcare and Knowledge Translation (A Riad DDS), Masaryk University, Brno, Czech Republic; Department of Biomolecular Sciences (N R Hussein PhD), University of Zakho, Zakho, Iraq; Department of Occupational Safety and Health (Prof B Hwang PhD), China Medical University, Taichung, Taiwan; Department of Health Policy and Management (P M Iftikhar MD), City University of New York, New York, NY, USA; Department of Community Medicine (O S Ilesanmi PhD), Department of Medicine (A S Oguntade MSc), Department of Total Quality Management (O F Owopetu 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), University of Kragujevac, Kragujevac, Serbia; Department of Epidemiology and Biostatistics (K Innos PhD), National Institute for Health Development, Tallinn, Estonia; Faculty of Pharmacy (L M Irham BPharm), University of Ahmad Dahlan, Yogyakarta, Indonesia; Department of Nutrition Research (M Islam MSc), Institute of Public Health Nutrition, Dhaka, Bangladesh; Department of Epidemiology and Preventive Medicine (R M Islam PhD), Monash University, Melbourne, VIC, Australia; Surveillance and Health Services Research (F Islami PhD), American Cancer Society, Atlanta, GA, USA; Department of Clinical Pharmacy (Prof N Ismail PhD), MAHSA University, Bandar Saujana Putra, Malaysia; Department of Health Services Research (M Iwagami PhD), University of Tsukuba, Tsukuba, Japan; Department of Non-communicable Disease Epidemiology (M Iwagami PhD), Department of Health Services Research and Policy (Prof M McKee DSc), Medical Statistics Department (S Shivalli MD), London School of Hygiene & Tropical Medicine, London, UK; Department of Orthodontics & Dentofacial Orthopedics (L J BDS), Dr D Y Patil University, Pune, India; Centre for Community Medicine (A Jaiswal MD), Department of Preventive Oncology (J K Meena MD), All India Institute of Medical Sciences, New Delhi, India; Institute of Advanced Manufacturing Technologies (Prof M Jakovljevic PhD), Peter the Great St Petersburg Polytechnic University, St Petersburg, Russia; Institute of Comparative Economic Studies (Prof M Jakovljevic PhD), Hosei University, Tokyo, Japan; Department of Microbiology (M Jalili MSc), Hamadan University of Medical Sciences, hamadan, Iran; Division of Pulmonary Medicine (E Jamshidi PharmD), Lausanne University Hospital (CHUV), Lausanne, Switzerland; Department of Preventive Medicine (Prof S Jang PhD), Yonsei University College of Medicine (S Park BEng), Yonsei University, Seodaemun-gu, South Korea; Department of Internal Medicine (C T Jani MD), Harvard University, Cambridge, MA, USA; Postgraduate Institute of Medicine (U U Jayarajah MD), Department of Pharmacology (P Ranasinghe PhD), University of Colombo, Colombo, Sri Lanka; Department of Surgery (U U Jayarajah MD), National Hospital, Colombo, Sri Lanka; Department of Biochemistry (Prof S Jayaram MD), Government Medical College, Mysuru, India; Urology Department (S Jazayeri MD), University of Florida, Jacksonville, FL, USA; Department of Anesthesiology (B Jemal MSc), School of Public Health (G G Kanno MSc, M F Shaka MPH), Pediatrics and Child Health Nursing (M M Sibhat MSc), Dilla University, Dilla, Ethiopia; Department of Public Health (W Jeong PhD), Graduate School of Public Health (H Kang BPharm), Department of Preventive Medicine (Prof E Park PhD), Institute of Health Services Research (Prof E Park PhD), Yonsei University, Seoul, South Korea; Department of Community Medicine (R P Jha MSc), Dr Baba Saheb Ambedkar Medical College & Hospital, Delhi, India; Department of

Community Medicine (R P Jha MSc), Banaras Hindu University, Varanasi, India; National Health System Resource Centre (H Jindal MD), Ministry of Health & Family Welfare, New Delhi, India; Institute of Molecular and Clinical Ophthalmology Basel, Basel, Switzerland (Prof J B Jonas MD); Department of Ophthalmology (Prof J B Jonas MD), Heidelberg University, Mannheim, Germany; Department of Family Medicine and Public Health (J J Jozwiak PhD), University of Opole, Opole, Poland; Institute of Family Medicine and Public Health (M Jürisson PhD, H Orru PhD), University of Tartu, Tartu, Estonia; Department of Medicine (S Kacimi MD), University of Tlemcen, Tlemcen, Algeria; Department of Oral Pathology and Microbiology, Forensic Odontology (V Kadashetti MDS), Krishna Institute of Medical Sciences deemed-to-be-university, Karad, India; Independent Consultant, Pune, India (P V Kakodkar MDS); Social Determinants of Health Research Center (L R Kalankesh PhD), Department of Anatomy (J Majidpoor PhD), Gonabad University of Medical Sciences, Gonabad, Iran; Institute for Prevention of Non-communicable Diseases (R Kalhor PhD), Health Services Management Department (R Kalhor PhD), Qazvin University of Medical Sciences, Qazvin, Iran; Division of Epidemiology and Biostatistics (V K Kamal PhD), National Institute of Epidemiology, Chennai, India, India; Department of Biology (Prof F Kamangar MD), Morgan State University, Baltimore, MD, USA; Department of Periodontology (E Kandaswamy MS), Louisiana State University Health Sciences Center, New Orleans, LA, USA; Sydney Eye Hospital (H Kandel PhD), South Eastern Sydney Local Health District, Sydney, NSW, Australia; Department of Preventive & Social Medicine (Prof S S Kar MD), Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India; School of Health Professions and Human Services (I M Karaye MD), Hofstra University, Hempstead, NY, USA; Institute for Epidemiology and Social Medicine (A Karch MD), University of Münster, Münster, Germany; Centre for Tropical Diseases and Global Health (P D Katoto PhD), Catholic University of Bukavu, Bukavu, Democratic Republic of the Congo; Department of Global Health (P D Katoto PhD), Stellenbosch University, Cape Town, South Africa; 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 Surgery (P M Kemp Bohan MD), Brooke Army Medical Center, San Antonio, TX, USA; Amity Institute of Forensic Sciences (H Khajuria PhD, B P Nayak PhD), Amity University, Noida, India; Bioinformatics and Biostatistics (A Khan PhD), Bio-X Institute (A K Khan MS), Department of Bioinformatics and Biostatistics (A U Rehman PhD), Shanghai jiao Tong University, Shanghai, China; Department of Animal Sciences (A K Khan MS), Quaid-i-Azam University, Islamabad, Islamabad, Pakistan; Department of Epidemiology and Biostatistics (E A Khan MPH), Department of Public Health (Z Z Piracha PhD), Health Services Academy, Islamabad, Pakistan; Department of Population Science (M Khan PhD), Jatiya Kabi Kazi Nazrul Islam University, Mymensingh, Bangladesh; Primary Care Department (M A Khan MSc), NHS North West London, London, UK; Faculty of Health and Wellbeing (K Khatab PhD), Sheffield Hallam University, Sheffield, UK; College of Arts and Sciences (K Khatab PhD), Ohio University, Zanesville, OH, USA; Basic Medical Sciences (M M Khatatbeh PhD), Yarmouk University, Irbid, Jordan; Global Evidence Synthesis Initiative (Prof M Khatib PhD), Department of Community Medicine (Prof Z Quazi Syed PhD), Datta Meghe Institute of Medical Sciences, Wardha, India; The Iranian Academy of Medical Sciences, Tehran, Iran (M Khayamzadeh MD); Department of Medicine (M Khazeei Tabari MD), Department of Immunology (Prof A Rafiei PhD), Molecular and Cell Biology Research Center (Prof A Rafiei PhD), Department of Medical-Surgical Nursing (S Shorofi PhD), Department of Environmental Health (Prof Z Yousefi PhD), Mazandaran University of Medical Sciences, Sari, Iran; MAZUMS Office (M Khazeei Tabari MD), Universal Scientific Education and Research Network, Tehran, Iran; Department of Epidemiology (M Khodadost PhD, M Khodadost PhD), Department of Public Health (F Sarvi PhD), Larestan University of Medical Sciences, Larestan, Iran; 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 Traditional Chinese Medicine (Y Kim PhD), Xiamen University Malaysia, Sepang, Malaysia; 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), Department of Medicine (M F Qadir PhD), Tulane University, New Orleans, LA, USA; Department of Nursing and Health Promotion (S Kisa PhD), Oslo Metropolitan University, Oslo, Norway; Institute for Health Information and Statistics of the Czech Republic, Prague, Czech Republic (M Klugar PhD); Faculty of Health and Medical Sciences (J Klugarová PhD), Adelaide Medical School (L Yadav PhD), University of Adelaide, Adelaide, SA, Australia; Institute for Allergy (P Kolkhir MD), Charité Medical University Berlin, Berlin, Germany (Prof T Pischon MD); Division of Immune-mediated Skin Diseases (P Kolkhir MD), First Moscow State Medical University (Sechenov University), Moscow, Russia; Department of Internal and Pulmonary Medicine (Prof P A Koul MD), Sheri Kashmir Institute of Medical Sciences, Srinagar, India; Kasturba Medical College, Udupi, India (S Koulmane Laxminarayana MD); 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 Anthropology (Prof K Krishan PhD), Panjab University, Chandigarh, India; Community Medicine (Y Krishnamoorthy MD), Employees' State Insurance Model Hospital, Chennai, India; Faculty of Medicine (B Kucuk Bicer PhD), Gazi University, Ankara, Turkey; University of Environment and Sustainable Development, Somanya, Ghana (N Kugbey PhD); Health Research Institute (M Kulimbet MSc), Al Farabi Kazakh National University, Almaty, Kazakhstan; Cardiothoracic Surgery (A Kumar MD), UN Mehta Institute of Cardiology and Research Center, Ahmedabad, India; Department of Cardiothoracic Surgery (A Kumar MD), Medanta Hospital, Gurugram, India; Department of Orthopaedics (Prof N Kumar MS), Medanta Hospital, Lucknow, India; Faculty of Health and Life Sciences (O P Kurmi PhD), Coventry University, Coventry, UK; Department of Medicine (O P Kurmi PhD), 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 Nephrology (A Kuttikkattu MD), Usha Hospital, Chengannur, India; Department of Clinical Sciences and Community Health (Prof C La Vecchia MD), University of Milan, Milan, Italy; Dr B C Roy Multi Speciality Medical Research Centre (A Lahiri MD), Indian Institute of Technology Kharagpur, Kharagpur, India; NEVES Society for Patient Safety, Budapest, Hungary (J Lám PhD); Division of Cancer Epidemiology and Genetics (Q Lan PhD), National Cancer Institute, Rockville, MD, USA; 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); Department of Otorhinolaryngology (S Lasrado MS), Father Muller Medical College, Mangalore, India; Department of Surgery (J Lau MPH, K Tan PhD), National University of Singapore, Singapore, Singapore; International Society Doctors for the Environment, Arezzo, Italy (P Lauriola MD); Pattern Recognition and Machine Learning Lab (Prof S Lee PhD), Gachon University, Seongnam, South Korea; School of Pharmacy (S W H Lee PhD), Monash University, Bandar Sunway, Malaysia; School of Pharmacy (S W H Lee PhD), Taylor's University Lakeside Campus, Subang Jaya, Malaysia; The Office of Health Policy & Legislative Affairs (W Lee PhD), Department of Pathology (V Y Tat BS), 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; Department of Preventive Medicine (Y Lee PhD), Korea University, Suwon-si, South Korea; Knowledge Translation Directorate (S M Legesse PhD), Environmental Health and Noninfectious Disease Research team (S D Mengesha MSc), Ethiopian Public Health Institute, Addis Ababa, Ethiopia; Faculty of Science (E Leong PhD), Universiti Brunei Darussalam (University of Brunei Darussalam), Bandar Seri Begawan, Brunei; Department of Health Promotion and Health Education (M Li PhD), National Taiwan Normal University, Taipei, Taiwan; School of Life Sciences (G Liu PhD), University of Technology Sydney, Ultimo, NSW, Australia; Centre for Inflammation (G Liu PhD), Centenary Institute, Camperdown, NSW, Australia; Department of Epidemiology and Biostatistics (Prof J Liu PhD), Peking University, Beijing, China; Department of Internal Medicine (C Lo MD), Kirk Kerkorian School of Medicine at UNLV, Las Vegas, NV, USA; Department of Public Health (A Lohiya MD), Kalyan Singh Super Specialty Cancer Institute, Lucknow, India; Department of Health Economics (L Lorenzovici MSc), Syreon Research Romania, Targu Mures, Romania; Department of Doctoral Studies (L Lorenzovici MSc), George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Tirgu Mures, Tirgu Mures, Romania; 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), Institute of Population Health Sciences (M R Mathur PhD), University of Liverpool, Liverpool, UK; Department of Biostatistics and Epidemiology (F Madadzadeh PhD), Yazd University of Medical Sciences, Yazd, Iran; Proteomics and Metabolomics Unit (Prof S Magdeldin PhD), Children's Cancer Hospital Egypt, Cairo, Egypt; Cellular and Molecular Biology Research Center (Prof S Mahjoub PhD), Department of Clinical Biochemistry (Prof S Mahjoub PhD, A Mospour PhD), Babol University of Medical Sciences, Babol, Iran; Radiology and Precision Health Program (M Mahmoudi PhD), Michigan State University, East Lansing, MI, USA; Department of Biostatistics and Epidemiology (M Mahmoudimanes PhD), Management and Leadership in Medical Education Research Center (S Mousavi PhD), Department of Immunology (M Razeghinia MSc), Kerman University of Medical Sciences, Kerman, Iran; Department of Primary Care and Public Health (Prof A Majeed MD, Prof S Rawaf MD), National Heart & Lung Institute (Prof D Munblit PhD), WHO Collaborating Centre for Public Health Education and Training (D L Rawaf MD), Imperial College London, London, UK; Cyprus International Institute for Environmental and Public Health (K C Makris PhD), Cyprus University of Technology, Limassol, Cyprus; Clinical Pharmacy Department (T Mallhi PhD), Jouf University, Sakaka, Saudi Arabia; Department of Epidemiology (M A Mamun HSC), CHINTA Research Bangladesh, Dhaka, Bangladesh; Department of Public Health and Informatics (M A Mamun HSC), Jahangirnagar University, Dhaka, Bangladesh; General Surgery Department I (A Manda MD), Emergency University Hospital Bucharest, Bucharest, Romania; 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; Faculty of Public Health (S Martini PhD), Universitas Airlangga (Airlangga University), Surabaya, Indonesia; Indonesian Public Health Association, Surabaya, Indonesia (S Martini PhD); Department of Nutrition and Dietetics (M Martorell PhD), University of Concepcion, Concepción, Chile; Centre for Healthy Living (M Martorell PhD), University of Concepción, Concepción, Chile; Board of Directors (C N Matei PhD), Association of Resident Physicians, Bucharest, Romania; Department of Public Health and Community Medicine (E Mathews PhD), Central University of Kerala, Kasaragod, India; Department of Orthopedic Surgery (V Mathur MD), Massachusetts General Hospital, Boston, MA, USA; School of Atmospheric Physics (K Mehmod PhD), Nanjing University of Information Science and Technology, Nanjing, China; Peru Country Office (W Mendoza MD), United Nations Population Fund (UNFPA), Lima, Peru; Eunice Kennedy Shriver National Institute of Child Health and Human Development (L G Mensah MD), National Institute of Health, Bethesda, MD, USA; University Research Institute (A A Mentis MD), National and Kapodistrian University of Athens, Athens, Greece; CES University, Medellín, Colombia (A Y M Mera-Mamián MSc); Cauca University, Popayan, Colombia (A Y M Mera-Mamián MSc); Breast Surgery Unit (T J Meretoja MD), Helsinki University Hospital, Helsinki, Finland; University of Helsinki, Helsinki, Finland (T J Meretoja MD); Department of Epidemiology and Biostatistics (M W Merid MPH), University of Gondar, Addis Ababa, Ethiopia; School of Medicine and Public Health (A G Mersha MD), Department of Public Health and Medicine (D N Tollosa PhD), University of Newcastle, Newcastle, NSW, Australia; Midwifery

Department (Prof B T Meselu MSc), Debre Markos University, Debre Markos, Ethiopia; 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; Department of Propeudetics of Internal Diseases & Arterial Hypertension (Prof T Miazgowski MD), Pomeranian Medical University, Szczecin, Poland; Woman-Mother-Child Department (I Michalek PhD), Lausanne University Hospital, Lausanne, Switzerland; Department of Nursing (G F W Mijena MSc), Haramaya University, Harar, Ethiopia; Pacific Institute for Research & Evaluation, Calverton, MD, USA (T R Miller PhD); School of Public Health (T R Miller PhD), Curtin University, Perth, WA, Australia; College of Applied Medical Sciences (S A Mir PhD), Majmaah University, Riyadh, Saudi Arabia; Social Determinants of Health Center (M Mirza-Aghazadeh-Attari MD), Urmia University of Medical Science, Urmia, Iran; Department of Biology (K A Mohammad PhD), Salahaddin University-Erbil, Erbil, Iraq; Department of Information Technology (M Mohammadi PhD), Lebanese French University, Erbil, Iraq; Department of Biology (A Mohammed PhD), University of Jeddah, Jeddah, Saudi Arabia; Health Systems and Policy Research Unit (S Mohammed PhD), Department of Community Medicine (M B Sufiyan MD), Ahmadu Bello University, Zaria, Nigeria; Department of Health Care Management (S Mohammed PhD), Technical University of Berlin, Berlin, Germany; School of Helath Sciences (S Mohan PhD), University of Petroleum and Energy Studies, Dehradun, India; Health Services Management (M Mohseni PhD), Iran University of Medical Sciences, Iran, Iran; Oncology Department (N Moka MD), Appalachian Regional Healthcare, Hazard, KY, USA; Department of Internal Medicine (N Moka MD), University of Kentucky, Lexington, KY, USA; School of Nursing (Prof A Molassiotis PhD), Department of Land Surveying and Geo-Informatics (Y Song PhD), Hong Kong Polytechnic University, Hong Kong, China; Clinical Epidemiology and Public Health Research Unit (L Monasta DSc, E Traini MSc), Burlo Garofolo Institute for Maternal and Child Health, Trieste, Italy; Faculty of Medicine and University Hospital Cologne (Prof U Mons PhD), University of Cologne, Cologne, Germany; Department of Medicine (A A Montasir FMD), TMSS Medical College, Bogura, Bangladesh; Department of Medicine (A A Montasir FMD), Sofia Ismail Memorial Medical Centre, Bogura, Bangladesh; Faculty of Veterinary Medicine and Zootechnics (Prof A Montero PhD), Autonomous University of Sinaloa, Culiacan, Mexico; Department of Molecular Medicine (M Moosavi PhD), National Institute of Genetic Engineering and Biotechnology, Tehran, Iran; School of Medicine (Prof A Moradi PhD), Department of Nutrition (M Raiesi PhD), Golestan Research Center of Gastroenterology and Hepatology (G Roshandel PhD), Infectious Diseases Research Center (H Shirzad-Aski PhD), Golestan University of Medical Sciences, Gorgan, Iran; Social Determinants of Health Research Center (Y Moradi PhD), Kurdistan University of Medical Sciences, Kurdistan, Iran; Computer, Electrical, and Mathematical Sciences and Engineering Division (P Moraga PhD), King Abdullah University of Science and Technology, Thuwal, Saudi Arabia; International Laboratory for Air Quality and Health (Prof L Morawska PhD), School of Public Health and Social Work (M T N Tran PhD, N Wang PhD), Queensland University of Technology, Brisbane, QLD, Australia; Department of Cardiology and Cardiac Surgery (J Morze PhD), University of Warmia and Mazury, Olsztyn, Poland; Department of Medicine (E Mostafavi PhD), Stanford Cardiovascular Institute (E Mostafavi PhD), Stanford University, Palo Alto, CA, USA; Department of Fruit and Vegetable Product Technology (Prof A Mousavi Khaneghah PhD), Prof Waclaw Dąbrowski Institute of Agricultural and Food Biotechnology State Research Institute, Warsaw, Poland; 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 Multita MD), General University Hospital of Patras, Patras, Greece; Medical School (F Multita MD), University of Thessaly, Larissa, Greece; Scientific Communications Department (S B Munro PhD), Invitae, Boulder, CO, USA; Family Medicine Unit 19 (E Murillo-Zamora PhD), Mexican Institute of Social Security, Colima, Mexico; Postgraduate in Medical Sciences (E Murillo-Zamora PhD), Universidad de Colima, Colima, Mexico; Knowledge Translation and Utilization (Prof A F Nabhan PhD), Egyptian Center for Evidence Based Medicine, Cairo, Egypt; Research

and Analytics Department (A J Nagarajan MTEch), Initiative for Financing Health and Human Development, Chennai, India; Department of Research and Analytics (A J Nagarajan MTEch), Bioinsilico Technologies, Chennai, India; Institute of Epidemiology and Medical Biometry (Prof G Nagel PhD), Ulm University, Ulm, Germany; Laboratory of Public Health Indicators Analysis and Health Digitalization (M Naimzada MD, S S Otstavnov PhD), Department of Information Technologies and Management (S K Vladimirov PhD), Moscow Institute of Physics and Technology, Dolgoprudny, Russia; Experimental Surgery and Oncology Laboratory (M Naimzada MD), Kursk State Medical University, Kursk, Russia; Health Workforce Department (T S Nair MD), World Health Organisation, Geneva, Switzerland; School of Pharmacy (A Naqvi PhD), University of Reading, Reading, UK; Mysore Medical College and Research Institute (Prof S Narasimha Swamy MD), Government Medical College, Mysore, India; Department of Disease Control and Environmental Health (R Ndejjo MSc), Makerere University, Kampala, Uganda; School of Pharmacy (S O Nduaguba PhD), West Virginia University, Morgantown, WV, USA; Department of Nursing (W W Negash MSc), Madda Walabu University, Ginnir, Ethiopia; Pharmaceutical Sciences Research Center (K Nejadi PhD), Ardabil University of Medical Science, Ardabil, Iran; Estia Health Blakehurst (S Neupane Kandel BSN), Estia Health, Sydney, NSW, Australia; Health Innovation and Transformation Centre (H V N Nguyen PhD), Federation University Australia, Brisbane, QLD, Australia; Department of Population and Quantitative Health Sciences (H V N Nguyen PhD), University of Massachusetts Medical School, Worcester, MA, USA; International Islamic University Islamabad, Islamabad, Pakistan (R K Niazi PhD); 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; Center of Excellence in Reproductive Health Innovation (CERHI) (C I Nzopotam MPH), University of Benin, Benin City, Nigeria; Department of Physiology (O J Nzopotam PhD), University of Benin, Edo, Nigeria; Department of Physiology (O J Nzopotam PhD), Benson Idahosa University, Benin City, Nigeria; Administrative and Economic Sciences Department (Prof B Oancea PhD), Department of Statistics and Cybernetics (Prof M Paun 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), Department of Medical Oncology (N Sayegh MD), University of Utah, Salt Lake City, UT, USA; Department of Preventive Medicine (I Oh PhD), Kyung Hee University, Dongdaemun-gu, South Korea; Department of Food and Nutrition (A P Okekunle PhD), Seoul National University, Seoul, South Korea; Department of Psychiatry (A T Olagunju MD), University of Lagos, Lagos, Nigeria; Community Prevention and Care Services (B O Olakunde PhD), National AIDS Control Committee, Abuja, Nigeria; Mass Communication Department (E Omer PhD), Ajman University, Dubai, United Arab Emirates; Department of Anatomic Pathology (A E E Omonisi FWACP), Ekiti State University, Ado- Ekiti, Nigeria; Department of Anatomic Pathology (A E E Omonisi FWACP), Ekiti State University Teaching Hospital, Ado- Ekiti, 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; Department of Pharmacology and Therapeutics (Prof O E Onwujekwe PhD), University of Nigeria Nsukka, Enugu, Nigeria; Section of Sustainable Health (H Orru PhD), Umeå University, Umeå, Sweden; Department of Project Management (S S Otstavnov PhD), Department of Health Care Administration and Economics (Prof V Vlassov MD), National Research University Higher School of Economics, Moscow, Russia; Department of Biochemistry (B E Oyinloye PhD), Afe Babalola University, Ado Ekiti, Nigeria; Department of Biochemistry and Microbiology (B E Oyinloye PhD), University of Zululand, Kwadlangezwa, South Africa; Department of Respiratory Medicine (Prof M P A DNB), Jagadguru Sri Shivarathreeswara Academy of Health Education and Research, Mysore, India; National School of Public Health (A Padron-Monedero PhD), Institute of Health Carlos III, Madrid, Spain; Department of Forensic

Medicine and Toxicology (J Padubidri MD), Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal, India, Mangalore, India; Department of Food Safety (B Pakbin PhD), Qazvin University of Medical Sciences, Medical Microbiology Research Center, Iran; Department of Epidemiology (R Pakzad PhD), Ilam University of Medical Sciences, Ilam, Iran; Hungarian Health Management Association (T Palicz MD), Hungarian Health Management Association, Budapest, Hungary; Department of Health Metrics (A Pana MD), Center for Health Outcomes & Evaluation, Bucharest, Romania; Research Department (A Pandey MPH), Public Health Research Society Nepal, Kathmandu, Nepal; Vision and Eye Research Institute (Prof S Pardhan PhD), Anglia Ruskin University, Cambridge, UK; Department of Medical Humanities and Social Medicine (Prof E Park PhD), Kosin University, Busan, South Korea; Global Health Governance Programme (J Patel), Centre for Medical Informatics (Prof A Sheikh MD), University of Edinburgh, Edinburgh, UK; School of Dentistry (J Patel), University of Leeds, Leeds, UK; Skills Innovation and Academic Network (SIAN) Institute (S Pati PhD), Association for Biodiversity Conservation and Research (ABC), Odisha, India; Central Department of Public Health (R Paudel MPH), Faculty of Humanities and Social Sciences (U Paudel PhD), Tribhuvan University, Kathmandu, Nepal; Department of Bioinformatics and Biostatistics (Prof M Paun PhD), National Institute of Research and Development for Biological Sciences, Bucharest, Romania; Department of Infection Control (M Peng MPH), Taihe Hospital, Shiyang, China; The First Clinical College (M Peng MPH), School of Public Health and Management (Y Yu MS), Hubei University of Medicine, Shiyang, China; Department of Orthopedics (J Pereira MS), Yenepoya Medical College, Mangalore, India; Department of Biology (Prof S Perna PhD), University of Bahrain, Sakir, Bahrain; Department of Zoology (Prof N Perumalsamy PhD), Yadava College, Madurai, India; Department of Zoology (Prof N Perumalsamy PhD), Annai Fathima College, Madurai, 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 Medicine (R Pezzani PhD), University of Padova, Padova, Italy; Associazione Italiana Ricerca Oncologica di Base AIROB (Italian Association of Basic Research Oncology), Padova, Italy (R Pezzani PhD); SSD Epidemiology Screening (C Piccinelli MS), City of Health and Science University Hospital of Turin, Turin, Italy; Basic Medical Sciences Department (J D Pillay PhD), Durban University of Technology, Durban, South Africa; Molecular Epidemiology Research Group (Prof T Pischon MD), Max Delbrueck Center for Molecular Medicine, Berlin, Germany; University Medical Center Groningen (Prof M J Postma PhD), School of Economics and Business (Prof M J Postma PhD), University of Groningen, Groningen, Netherlands; 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; Pohang University of Science and Technology, South Korea (N Rabiee PhD); College of Medicine (A Radfar MD), University of Central Florida, Orlando, FL, USA; Department of Medical Oncology (Prof V Radhakrishnan MD), Cancer Institute (WIA), Chennai, India; Department of Medicine (A Rafiee MSc), University of Alberta, Edmonton, AB, Canada; Pathology Department (N Raheem FMCPATH), Federal Medical Centre, Yola, Nigeria; Center for Surveillance, Immunization, and Epidemiologic Research (M Rahman PhD), National Institute of Infectious Diseases, Tokyo, Japan; Global Health Nursing (M Rahman PhD), St Luke's International University, Tokyo, Japan; Department of Population Science and Human Resource Development (M Rahman DrPH), University of Rajshahi, Rajshahi, Bangladesh; School of Nursing and Healthcare Professions (M Rahman PhD), Federation University Australia, Berwick, VIC, Australia; Future Technology Research Center (A Rahmani PhD), National Yunlin University of Science and Technology, Yunlin, Taiwan; Department of Community Medicine (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; Department of Epidemiology, Biostatistics and Occupational Health (J Rana MPH), McGill University, Montreal, QC, Canada; Research and Innovation Division (J Rana MPH), South Asian Institute for Social Transformation (SAIST), Dhaka, Bangladesh; 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; Department of Oral Pathology (S Rao MDS), Sharavathi Dental College and Hospital, Shimoga, India; Department of 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; Department of Biomedical Engineering (Z Ratan MSc), Khulna University of Engineering and Technology, Khulna, Bangladesh; School of Health and Society (Z Ratan MSc), University of Wollongong, Wollongong, NSW, Australia; University College London Hospitals, London, UK (D L Rawaf MD); Academic Public Health England (Prof S Rawaf MD), Public Health England, London, UK; School of Health, Medical and Applied Sciences (L Rawal PhD), CQ University, Sydney, NSW, Australia; Department of Immunology and Laboratory Sciences (M Razeghinia MSc), Medical Laboratory Sciences (M Sahebazzamani MSc), Sirjan School of Medical Sciences, Sirjan, Iran; Molecular Biology and Biochemistry (A U Rehman PhD), University of California Irvine, Irvine, CA, USA; Department of Pharmacy (I Rehman PhD), Biochemistry (Prof A W Wadood PhD), Abdul Wali Khan University Mardan, Mardan, Pakistan; 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; Institute of Diagnostic and Interventional Radiology and Neuroradiology (R Rikhtegar MD), Essen University Hospital, Essen, Germany; Dana-Farber Cancer Institute, Boston, MA, USA (T J Roberts MD); Center for Indigenous Health Research (P Rohloff MD), Wuqu' Kawoq Maya Health Alliance, Tecpan, Guatemala; Clinical and Epidemiological Research in Primary Care (GICEAP) (E Romero-Rodríguez PhD), Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Cordoba, Spain; Department of Internal Medicine (G M Rwegerera MD), University of Botswana, Gaborone, Botswana; Department of Oral and Maxillofacial Surgery (M S MDS), Jagadguru Sri Shivarathreeswara University, Mysore, India; Department of Medical Pharmacology (M M Saber-Ayad MD), Public Health and Community Medicine Department (M R Salem MD), Cairo University, Giza, Egypt; Independent Consultant, Gdansk, Poland (Prof M R Saeb PhD); 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; Department of Development Studies (H Sahoo PhD), International Institute for Population Sciences, Mumbai, India; Department of Statistics (M R Sajid PhD), University of Gujrat, Pakistan, Gujrat, Pakistan; Department of Health Policy and Management (H Salari PhD), Bushehr University of Medical Sciences, Bushehr, Iran; School of Public Health (Y L Samodra MPH), Taipei Medical University, Taipei, Taiwan; Department of Nutrition and Preventive Medicine (Prof J Sanabria MD), Department of Pediatrics (S Sankararaman MD), Division of Pediatric Gastroenterology (A Thavamani MD), Case Western Reserve University, Cleveland, OH, USA; Department of Pediatrics (S Sankararaman MD), A Thavamani MD), University Hospitals Rainbow Babies & Children's Hospital, Cleveland, OH, USA; Research Development Coordination Section (M N 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 Methodology and Innovation in Prevention (M Schwarzingler MD), University Hospital of Bordeaux, Bordeaux, France; University of Bordeaux (M Schwarzingler MD), Inserm, Bordeaux, France; Department of Medical Statistics (M Škerija PhD),

University of Zagreb, Zagreb, Croatia; Department of Epidemiology and Prevention of Chronic Noncommunicable Diseases (M Šekerija PhD), Croatian Institute of Public Health, Zagreb, Croatia; Emergency Department (S Senthilkumaran MD), Manian Medical Centre, Erode, India; National Heart, Lung, and Blood Institute (A Seylani BS), National Institute of Health, Rockville, MD, USA; Department of Midwifery (K Seyoum MSc), Madda Walabu University, Robe, Ethiopia; Center for Biomedical Information Technology (F Sha PhD), Shenzhen Institutes of Advanced Technology, Shenzhen, China; Infectious Diseases and Microbiology (P A Shah MBBS), Rajiv Gandhi University of Health Sciences, Bangalore, India; HepatoPancreatoBiliary Surgery and Liver Transplant (P A Shah MBBS), HealthCare Global Limited Cancer Care Hospital, Bangalore, India; Department of Internal Medicine (I Shahid MBBS), Ziauddin University, Karachi, Pakistan; Regenerative Medicine (M Shahrbaaf MD), Royan Institution, Tehran, Iran; Department of Chemistry (H Shahsavari PhD), Institute for Advanced Studies in Basic Sciences (IASBS), Zanjan, Iran; Independent Consultant, Karachi, Pakistan (M A Shaikh MD); Symbiosis Medical College for Women (M Shannawaz PhD), Symbiosis International University, Pune, India; Nahavand School of Allied Medical Sciences (A Sharifi PhD), Hamadan University of Medical Sciences, Hamadan, Nahavand, Iran; Facultad de Medicina (Faculty of Medicine) (J Sharifi-Rad PhD), Universidad del Azuay (University of Azuay), Cuenca, Ecuador; Department of Medical Oncology (P Sharma MD), Kent Hospital, Warwick, RI, USA; Genomic Epidemiology Branch (M Sheikh PhD), International Agency for Research on Cancer, Lyon, France; Health in Disasters and Emergencies (R Sheikh BHLthSci), Iran University of Medical Sciences, Shahrekord, Iran; Maurice Wilkins Centre for Biodiscovery, Auckland, New Zealand (Prof P R Shepherd PhD); Tokyo Foundation for Policy Research, Tokyo, Japan (Prof K Shibuya MD); Public Health Dentistry Department (Prof K M Shivakumar PhD), Krishna Institute of Medical Sciences deemed-to-be-university, Karad, India; Clinical Immunology and Hematology (V Shivarov PhD), Sofamed University Hospital, Sofia, Bulgaria; Department of Genetics (V Shivarov PhD), Sofia University "St Kliment Ohridski", Sofia, Bulgaria; School of Pharmacy (S Shrestha PharmD), Monash University, Selangor Darul Ehsan, Malaysia; Department of Hematology-Oncology (S K Siddappa Malleshappa MD), Baystate Medical Center, Springfield, MA, USA; Department of Health Science (Prof L M R Silva PhD), Polytechnic of Guarda, Guarda, Portugal; Department of Health Science (Prof L M R Silva PhD), University of Beira Interior, Covilhã, Portugal; Real World Insights (G Silva Julian MSc), IQVIA, São Paulo, Brazil; Department of Medical Oncology (N Silvestris MD), IRCCS Cancer Institute "Giovanni Paolo II", Bari, Italy; DIMO (N Silvestris MD), University of Bari, Bari, Italy; Department of Community Medicine (G Singh MD), Lady Hardinge Medical College, New Delhi, India; Department of Pulmonary and Critical Care Medicine (H Singh MD), Medical College of Wisconsin, Milwaukee, WI, USA; School of Medicine (Prof J A Singh MD), Department of Radiology (H Sotoudeh 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; Department of Community Medicine & Public Health (J Singh PhD), Tribhuvan University, Janakpur, Nepal; Department of Radiodiagnosis (P Singh MD), All India Institute of Medical Sciences, Bathinda, India; Department of Epidemiology (D N Sinha PhD), School of Preventive Oncology, Patna, India; Department of Epidemiology (D N Sinha PhD), Healis Sekhsaria Institute for Public Health, Mumbai, India; Program Services Unit (A H Sinke MD), Pathfinder International, Addis Ababa, Ethiopia; Maternal and Child Health Division (M Siraj MSc), International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh; Department of Chemistry (S S Siwal PhD), Maharishi Markandeshwar (deemed-to-be-university), Mullana- Ambala, India, Mullana, India; Department No16 (V Y Skryabin MD), Moscow Research and Practical Centre on Addictions, Moscow, Russia; Department of Infectious Diseases and Epidemiology (A A Skryabina MD), Pirogov Russian National Research Medical University, Moscow, Russia; Surgery (B Socea PhD), "Sf Pantelimon" Emergency Clinical Hospital Bucharest, Bucharest, Romania; Asbestos Diseases Research Institute, Sydney, NSW, Australia (M J Soeberg PhD); Cochrane Iran Associate Centre (A Sofi-Mahmudi DDS), Iranian Ministry of Health and Medical Education, Tehran, Iran; Department of Health Policy and Management (S Song PhD), University System of Georgia, Athens, GA, USA; Public Health Department (S Soshnikov PhD), Bukhara State Medical Institute, Bukhara, Uzbekistan; Laboratory of Public Health Indicators Analysis and Health Digitalization (S Soshnikov PhD), Moscow Institute of Physics and Technology, Moscow, Russia; Department of Epidemiology and Global Health (A Sowe MSc), Umeå University, Umeå, Sweden; Department of Management, Policy, and Community Health (R Suk PhD), The University of Texas Health Science Center at Houston, Houston, TX, USA; Center for Biotechnology and Microbiology (M Suleman PhD), University of Swat, Mingora, Swat, Pakistan; School of Life Sciences (M Suleman PhD), Xiamen University, Xiamen, China; National Institute of Epidemiology (R Suliankatchi Abdulkader MD), Indian Council of Medical Research, Chennai, India; Department of Maternal and Child Health (S Sultana MPH), Projahnmo Research Foundation, Dhaka, Bangladesh; Department of Medical Oncology (D Sur PhD), The Oncology Institute "Prof Dr Ion Chiricuță" Cluj-Napoca, Cluj-Napoca, Romania; Department of Medical Oncology (D Sur PhD), Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania; 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; Cancer Control Center (T Tabuchi MD), Osaka International Cancer Institute, Osaka, Japan; University of Western Australia, Sydney, NSW, Australia (Prof K Takahashi PhD); University of Occupational and Environmental Health, Japan (Prof K Takahashi PhD); Department of Dermato-Venereology (M Tampa PhD), Dr Victor Babes Clinical Hospital of Infectious Diseases and Tropical Diseases, Bucharest, Romania; Department of Economics (N Y Tat MS), Rice University, Houston, TX, USA; Research and Innovation (N Y Tat MS), Enventure Medical Innovation, Houston, TX, USA; Engineering Systems and Environment (A Tavakoli PhD), University of Virginia, Charlottesville, VA, USA; School of Public Health (F H Tesfay PhD), Mekelle University, Mekelle, Ethiopia; Department of Gastroenterology and Hepatology (V Thoguluva Chandrasekar MD), Mayo Clinic, Scottsdale, AZ, USA; Department of Gastroenterology (N K Thomas MD), PSG Institute of Medical Sciences and Research, Coimbatore, India; Faculty of Public Health (J H V Ticoalu MPH), Universitas Sam Ratulangi, Manado, Indonesia; Institute of Public Health (R Topor-Madry PhD), Jagiellonian University Medical College, Kraków, Poland; Agency for Health Technology Assessment and Tariff System, Warsaw, Poland (R Topor-Madry PhD); Nutritional Epidemiology Research Team EREN (M Touvier PhD), National Institute for Health and Medical Research INSERM, Paris, France; Department of Health, Medicine and Human Biology (M Touvier PhD), Sorbonne Paris Nord University, Bobigny, France; Department of Pathology and Legal Medicine (M R Tovani-Palone PhD), University of São Paulo, Ribeirão Preto, Brazil; Modestum, London, UK (M R Tovani-Palone PhD); Health Informatics Department (M T N Tran PhD), Hanoi Medical University, Ha Noi, Vietnam; Department of Community Medicine (J P Tripathy MD), All India Institute of Medical Sciences, Nagpur, India; Department of Zoology (S Ullah PhD), Division of Science and Technology (S Ullah PhD), University of Education, Lahore, Lahore, 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; Velez Sarsfield Hospital, Buenos Aires, Argentina (Prof P R Valdez MEd); Laboratory of Toxicology (C Vardavas PhD), University of Crete, Heraklion, Greece; School of Mathematics and Statistics (Prof P J Villeneuve PhD), Carleton University, Ottawa, ON, Canada; Occupational Health Unit (Prof F S Violante MD), Sant'Orsola Malpighi Hospital, Bologna, Italy; Faculty of Information Technology (B Vo PhD), HUTECH University, Ho Chi Minh City, Vietnam; Foundation University Medical College (Prof Y Waheed PhD), Foundation University Islamabad, Islamabad, Pakistan; Department of Cultures, Societies and Global Studies (R G Wamai PhD), Northeastern University, Boston, MA, USA; School of Public Health (R G Wamai PhD), University of Nairobi, Nairobi, Kenya; Department of Medicine (C Wang MPH), Vanderbilt

University, Nashville, TN, USA; School of Public Health (F Wang PhD), Xuzhou Medical University, Xuzhou, China; National Center for Chronic and Non-communicable Disease Control and Prevention (N Wang PhD), Chinese Center for Disease Control and Prevention, Beijing, China; Department of Otolaryngology (Y Wang MD), Peking University Third Hospital, Beijing, China; Centre for Health Policy Research (Prof P Ward PhD), Torrens University Australia, Adelaide, SA, Australia; Department of Biomedical Sciences (A Waris MS), City University of Hong Kong, Hong Kong, China; Competence Center of Mortality-Follow-Up of the German National Cohort (R Westerman DSc), Federal Institute for Population Research, Wiesbaden, Germany; Department of Community Medicine (N D Wickramasinghe MD), Rajarata University of Sri Lanka, Anuradhapura, Sri Lanka; School of Public Health (H Xiao PhD), Zhejiang University, Zhejiang, China; Department of Public Health Science (H Xiao PhD), Fred Hutchinson Cancer Research Center, Seattle, WA, USA; Department of Endocrinology (Prof S Xu PhD), University of Science and Technology of China, Hefei, China; Department of Medicine (Prof S Xu PhD), University of Rochester, Rochester, NY, USA; Cardiovascular Program (X Xu PhD), The George Institute for Global Health, Sydney, NSW, Australia; Research and Development Division (L Yadav PhD), The George Institute for Global Health, New Delhi, India; 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; Department of Pharmacy (Y Yismaw MSc), Alkan Health Science, Business and Technology College, Bahir Dar, Ethiopia; Department of Neuropsychopharmacology (N Yonemoto PhD), National Center of Neurology and Psychiatry, Kodaira, Japan; Department of Public Health (N Yonemoto PhD), Juntendo University, Tokyo, Japan; Department of Health Policy and Management (Prof M Z Younis PhD), Jackson State University, Jackson, MS, USA; School of Business & Economics (Prof M Z Younis PhD), University Putra Maylisia, Kuala Lumpur, Malaysia; Department of Pharmacology (B A Zaman MSc), University of Duhok, Duhok, Iraq; Research and Development Department (I Zare BSc), Sina Medical Biochemistry Technologies, Shiraz, Iran; Department of Bioengineering and Therapeutic Sciences (Prof M S Zastrozhin PhD), University of California San Francisco, San Francisco, CA, USA; Addictology Department (Prof M S Zastrozhin PhD), Russian Medical Academy of Continuous Professional Education, Moscow, Russia; Victorian Comprehensive Cancer Centre, Melbourne, VIC, Australia (J Zhang MD); School of Public Health (Y Zhang PhD), Hubei Province Key Laboratory of Occupational Hazard Identification and Control (Y Zhang PhD), Wuhan University of Science and Technology, Wuhan, China; Bone Marrow Transplantation Center (L Zhou MD), Zhejiang University, Hangzhou, China.

Contributors

See appendix (pp 260–69) for detailed information about individual author contributions to the research, divided into the following categories: managing the overall research enterprise; writing the first draft of the manuscript; primary responsibility for applying analytical methods to produce estimates; primary responsibility for seeking, cataloguing, extracting, or cleaning data; designing or coding figures and tables; providing data or critical feedback on data sources; developing methods or computational machinery; providing critical feedback on methods or results; drafting the manuscript or revising it critically for important intellectual content; and managing the estimation or publications process. Members of the core research team for this topic area 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 the research evaluation process, which includes additional stages of formal review. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Data sharing

This paper summarises key findings from our analysis of GBD 2019 estimates. Citations for the data used in this study can be accessed from the Global Health Data Exchange data input sources tool (<http://ghdx.healthdata.org/gbd-2019/data-input-sources>). Files containing all GBD 2019 estimates are available on the Global Health Data Exchange website (<http://ghdx.healthdata.org/gbd-2019>) and can also be downloaded from the Global Health Data Exchange results tool (<http://healthdata.org/gbd-results-tool>). Additional results can be explored through online interactive visualisations (<https://vizhub.healthdata.org/gbd-compare/>).

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