Global, regional and national estimates of influenza-attributable ischemic heart disease mortality

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Summary

Background Influenza virus infection is associated with incident ischemic heart disease (IHD) events. Here, we estimate the global, regional, and national IHD mortality burden attributable to influenza.

Methods We used vital registration data from deaths in adults ≥50 years (13.2 million IHD deaths as underlying cause) to assess the relationship between influenza activity and IHD mortality in a non-linear meta-regression framework from 2010 to 2019. This derived relationship was then used to estimate the global influenza attributable IHD mortality. We estimated the population attributable fraction (PAF) of influenza for IHD deaths based on the relative risk associated with a given level of weekly influenza test positivity rate and multiplied PAFs by IHD mortality from the Global Burden of Disease study.

Findings Influenza activity was associated with increased risk of IHD mortality across all countries analyzed. The mean PAF of influenza for IHD mortality was 3.9% (95% uncertainty interval [UI] 2.5–5.3%), ranging from <1% to 10%, depending on country and year. Globally, 299,858 IHD deaths (95% UI 191,216–406,809) in adults ≥50 years could be attributed to influenza, with the highest rates per 100,000 population in the Central Europe, Eastern Europe and Central Asia Region (32.3; 95% UI 20.6–43.8), and in the North Africa and Middle East Region (26.7; 95% UI 17–36.2).

Interpretation Influenza may contribute substantially to the burden of IHD. Our results suggest that if there were no influenza, an average of 4% of IHD deaths globally would not occur.

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Keywords: Influenza; Ischemic heart disease; Mortality; Cardiovascular; Global disease burden

Introduction

Ischemic heart disease (IHD) is the leading cause of death worldwide.[1] Studies have shown a significant and clinically important association between influenza and major cardiovascular events,[2–5] highlighted by a study describing patients six times more likely to experience a heart attack the week after influenza virus infection than at any other point during the year before or after that infection.[5] Experimental and observational reports found that influenza virus infection can cause direct cardiac changes, and the host's response to influenza virus infection can increase circulation of inflammatory

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Research in context

Evidence before this study
Associations between influenza epidemics and cardiovascular deaths, including from acute cardiac events, were first reported in the early 20th century following observations of synchronous influenza activity and excess mortality. Since then, an increasing body of literature has confirmed these associations using population- and individual-level studies of increasing complexity and quality. We conducted a search using PubMed and Embase databases on 20th June 2022 including terms for influenza and heart diseases and identified approximately 90 publications describing relationships between influenza and cardiocirculatory disease from specified geographies and timepoints using heterogeneous effect measures and metrics of limited comparability. None used cause-specific mortality data from multiple countries and continents to understand influenza-attributable ischemic heart disease mortality burden and the variation in its association due to differences in influenza virus circulation and underlying characteristics of populations at the global level.

Added value of this study
This study provides the first global estimates of influenza-attributable ischemic heart disease mortality, using a harmonized approach generating exposure–response relationships in countries of differing geographical location,

hemisphere and socio-economic status. These relationships were extrapolated globally and converted to readily interpretable units for policymaking. We found that, globally, 3–5% of the total number of ischemic heart disease deaths could be attributed to influenza, corresponding to 200,000–400,000 ischemic heart disease deaths annually. Whilst global modeling approaches are imperfect, the study provides country-specific estimates allowing policymakers to prioritize influenza prevention in context of this additional public health impact, and provides a benchmark for replication using other exposures, outcomes, and methods.

Implications of all the available evidence
Influenza virus infection is an important trigger for cardiac events and may be responsible for 3–5% of ischemic heart disease deaths, annually. Ischemic heart disease is the leading cause of global mortality. If influenza exposure could be removed, a substantial number of ischemic heart disease deaths would be prevented. Policymakers should consider the benefit of influenza vaccination, especially in people at risk for cardiovascular events and complications. Additional research may be required to quantify the vaccine-preventable fraction of ischemic heart disease burden in different countries with varying influenza seasonality and prevalence of underlying risk factors for cardiovascular diseases.

mediators and activate immune cells that can induce damage throughout the body, not just locally within the respiratory tract.[6] Nonetheless, the contribution of influenza virus infection to IHD mortality is not well quantified and the impact of influenza vaccination as part of routine care to prevent IHD morbidity and mortality remains uncertain.[7–9]

Historically, studies evaluating influenza-associated cardiovascular deaths have used time series approaches to estimate influenza-attributable events and have been limited to settings where vital statistics records are available,[10–14] with no global estimates reported previously. In those time-series analyses, baseline mortality was usually estimated using multi-year averages, and influenza-attributable mortality defined as excess mortality above expected baselines during an influenza season. The variation in background rates in all-cause or cause-specific mortality time series may mask influenza signals, revealing only high-intensity peaks and potentially missing epidemics that span longer periods at lower influenza incidence (as can occur in tropical areas).[15]

Here, we estimate the global IHD mortality attributable to influenza from 2010 through 2019, before the emergence of the COVID-19 as a global pandemic. To extend previous excess mortality estimations we directly modeled a risk-response function between influenza activity and IHD deaths from vital registration data that was then applied to age and location-specific estimates of IHD mortality from the Global Burden of Disease (GBD) Study.[16,17]

Methods

Data sources and exposure modelling
A total of 13.2 million IHD diagnoses as underlying cause of deaths in adults ≥50 years were retrieved from vital registration systems from 10 countries (Brazil, Chile, China, Denmark, Guatemala, Italy, New Zealand, Mexico, South Africa, and United States), using International Classification of Diseases, 10th Revision (ICD-10) codes I20–I25. Additionally, we gathered weekly all-cause mortality data (119.5 million all-cause deaths) from Australia, Canada, France, Germany, Israel, Norway, Poland, Portugal, Spain and Sweden (Table S1 in the Supplementary Appendix – Section 1).

We used public health influenza surveillance data to quantify influenza activity, defined as the proportion of influenza positive samples tested weekly, from 2010 through 2019 and modelled location-specific weekly influenza exposure using RegMod,[18] a Bayesian Regression model developed for the GBD project.[16,17,19] The model was fit to influenza surveillance data obtained from the World Health Organization, the Brazilian Ministry of Health and the U.S. Centers for Disease Control and Prevention influenza surveillance

systems (Table S2), and adjusted by environmental covariates including time (year), seasonality (week), temperature, dewpoint, and population density (Table S3 – Section I). More detailed information about the exposure-modelling approach with RegMod is included in the Supplementary Material Section II. Because >50% influenza positivity rate was observed very rarely and mostly in weeks with small number of samples tested for influenza, we excluded these weeks from the analysis (Fig. S1, Supplementary Appendix – Section II modelling influenza activity). Influenza activity varied by country, region and calendar year (Fig. S2).

We filled missing data points within each country-specific time series and estimated data for countries without influenza surveillance by imputing information from surrounding locations and covariates (Table S4 shows the list of countries with missing data on weekly influenza surveillance). The average observed versus modeled influenza activity as well as the out-of-sample prediction error by GBD super-region[20] and year are presented in Table S5. To evaluate the predictive capacity of the model, we conducted an out-of-sample validation. We split the data set into training data (80%) to which we fit the model, and validation data (20%) which we used for validating the model. Table S6 in the Supplementary Material shows predicted values, measured values and root squared mean error (RSME) for the training data set by super region. The model performed best in high-income areas and worst in South Asia, North Africa and the Middle East.

Statistical analysis

We used generalized additive models with shape constraints (SCAMs) for individual locations to estimate the relationship between influenza activity and excess risk of IHD mortality in the ten countries with cause-specific mortality data. We calculated means of influenza activity across the same week of exposure and previous weeks. For instance, a lag of two weeks reflects the mean of the current week and 1 week prior. To avoid noise in the curves due to residual confounding or data quality issues, we constrained the curve to be monotonically increasing. The models considered weekly IHD deaths as outcome variables, and influenza activity, defined as the fraction of samples testing positive for influenza, as a predictor variable. Models were adjusted for trend, season, temperature, and dewpoint and explored temporal delay between exposure (influenza activity) and the occurrence of IHD deaths (Supplementary Appendix – Section III). For the US and Brazil, where subnational data were available, we incorporated a random effect by region.

The Meta-regression-Bayesian, Regularized, Trimmed (MR-BRT) tool[21] was used to meta-regress the country-specific exposure-response curves into a single relationship between influenza activity and the relative risk (RR) of IHD death. Initially we included all-cause and IHD exposure-response curves and indicated the mortality category through a covariate. This was done to a) assess whether there is a systematic difference between both mortality curve types and b) to include the all-cause curves in the uncertainty range estimations. Since there was no difference in both curve types (meaning the co-variate did not show to be significant – Fig. S3), we decided to only include IHD data in the final meta-regression and influenza attributable IHD burden estimations were exclusively based on the exposure-response curves that include only IHD-specific mortality data. The exposure-response curves from each country were normalized so that the lowest relative risk was zero when there was no positivity rate. The curves were then meta-regressed to fit a 3rd degree spline with a knot centered around 0.25. Though we included a number of covariates (population density, urbanicity, mean temperature, mean dewpoint temperature, air pollution [population-weighted mean PM2.5 and Ozone exposures], mean influenza positivity, temperature range, Healthcare Access and Quality Index [HAQI] and Socio-demographic index [SDI], Table S3) that could potentially explain the difference in country-specific exposure–response relationships, none were selected during the MR-BRT bias covariate selection process.[22] (Supplementary Appendix – Section IIIa and IIIb for details).

We calculated the population attributable fraction (PAF) for each week and country, based on the RR associated solely on differences in influenza activity in a specific location and country. The PAF reflects the proportion of IHD deaths attributable to influenza. Equation 1 describes the calculation of weekly PAFs.

$$wPAF_{la} = \frac{RR_a - 1}{RR_a}$$

where l is the location, and a is the weekly influenza activity a given location. RR_a is the relative risk associated with influenza activity a.

$$PAF_l = \sum_{w=1}^{52} wPAF_{la}$$

Weekly PAFs were then aggregated for each year from 2010 to 2019. To generate higher level PAFs (i.e., for super regions) we calculated population weighted averages.

We used estimates from GBD 2019 for IHD mortality[16,17] and estimated the influenza-attributable IHD mortality for three age groups (50–64 years, 65–74 years and ≥75 years) as the product of the total IHD mortality and the corresponding PAF for each GBD location by year and age group. We provide a schematic of the analytical strategy used for the GBD IHD estimation in the Supplementary Material Section IIIc (Fig. S4).[16,17]

Our approach allowed for quantitative assessments of uncertainty that reflect data variance, model uncertainty, and stochastic effects. We propagated uncertainty from all components of the modelling chain using posterior simulation: for each quantity of interest, we pulled 1000 random draws from the posterior distribution of the estimate and performed all calculations at the draw level to estimate 95% uncertainty intervals (UI).

Ethics statement

Human subject review was not required for this study as only aggregate national data without personal identifiers were used in analyses. Data was aggregated by age group and week.

Role of funding source

Results

Regression results

We found a significant increase in IHD mortality related to increased influenza activity and observed the main effect for the same week of exposure, with no evidence of temporal delays in effects or mortality displacement. Fig. 1 shows meta-regression conducted for no lag (same week of exposure or week 0). The curves display a steeper slope at lower exposure levels before leveling off at higher exposures. In Supplementary Material (Fig. S5) we show the average of the influenza activity in the week of exposure and n previous weeks (up to a lag of 6 weeks).

Population attributable fraction and attributable mortality

The annual mean PAF, i.e., the percentage of IHD deaths that can be attributed to influenza exposure globally, was 3.9% (UI 2.5–5.3%), with slightly lower annual mean in Central Europe, Eastern Europe and Central Asia, high income and North Africa and Middle East Regions. Fig. 2 shows the annual mean PAF for each country considering all years (2010–2019). Country-specific mean PAF ranged from <1% to 8%, with some countries in Southeast Asia, Africa and South America showing ≥4% of IHD mortality attributed to influenza. Variation in country specific PAF estimates by year can be seen in Fig S6 (Panels A–J) and Table S7 in Supplementary Appendix section IV.

On average, from 2010 to 2019 approximately 299,858 IHD deaths (95% UI 191.216–406,809) or 18.4 deaths (95% UI 11.8, 25) per 100,000 adults ≥50 years could be attributed to influenza activity globally. The frequency of IHD deaths attributed to influenza activity increased by age, with 165,955 (95% CI
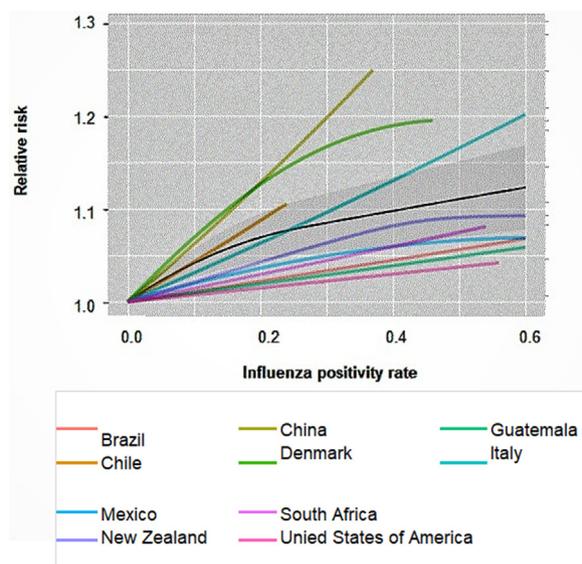
Fig. 1: Meta-regression exposure-response curves between ischemic heart disease death and influenza activity for individual countries for no lag derived from country-specific SCAMs. Black solid line depicts meta-regressed curve with grey areas displaying 95% confidence intervals. The area under the curve (AuC), the area under the meta-regressed curve, is an indicator of the effect magnitude for each lag and an evaluation of the potential temporal delays that could either imply lagged effects or harvesting. For the exposure in the same week the AuC is 0.649.

A

PAFs
- < 1%
- 1% – 2%
- 2% – 3%
- 3% – 4%
- 4% – 5%
- 5% – 6%
- 6% – 7%
- 7% – 8%

B

Location	Mean	95% Uncertainty Interval	
		Lower	Upper
Global	4%	3%	5%
Southeast Asia, East Asia, and Oceania	4%	3%	6%
Central Europe, Eastern Europe, and Central Asia	3%	2%	4%
High-income	3%	2%	4%
Latin America and Caribbean	4%	3%	6%
North Africa and Middle East	3%	2%	5%
South Asia	4%	3%	6%
Sub-Saharan Africa	4%	2%	5%
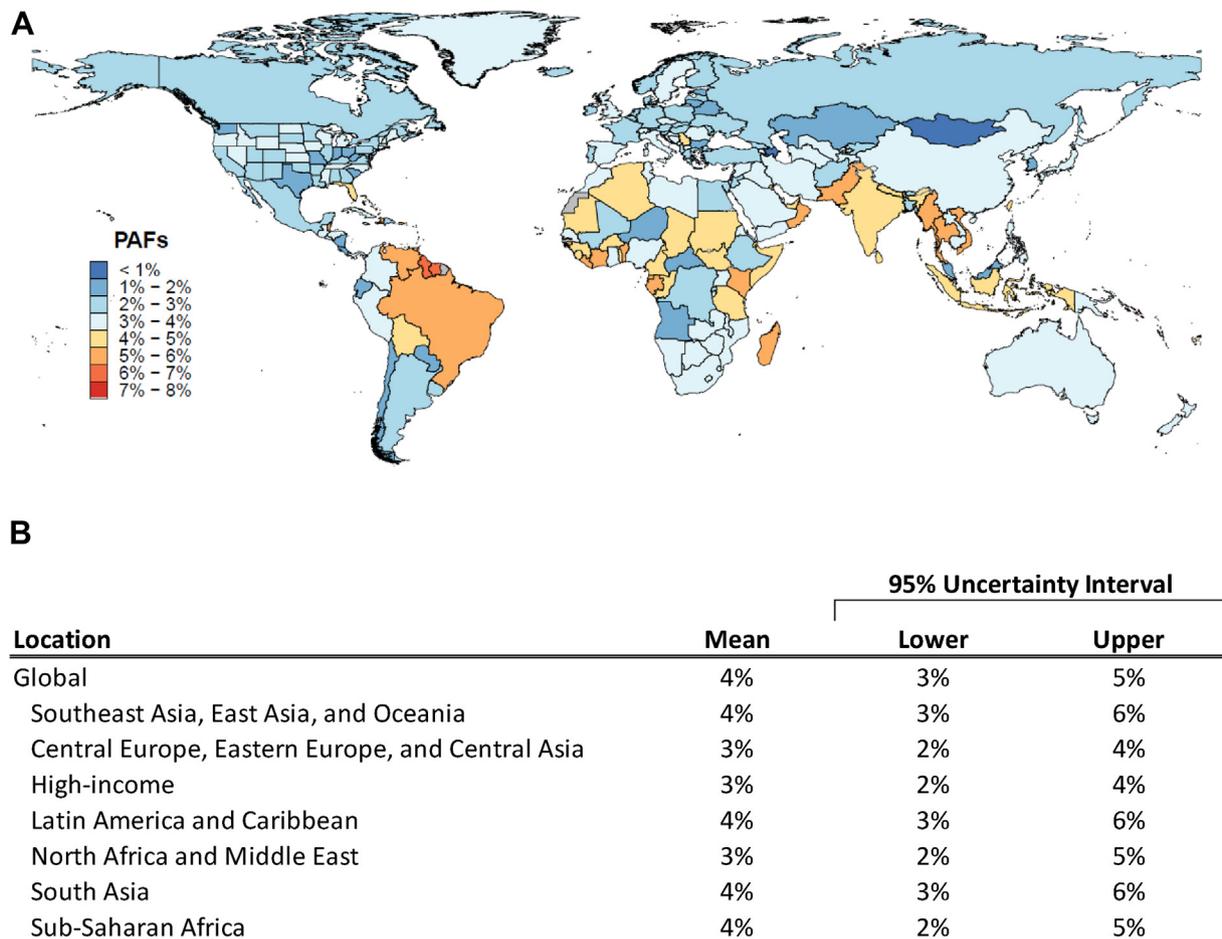
Fig. 2: The influenza-attributable fraction (PAF) of ischemic heart disease mortality by country and super regions. Panel A shows a map with each country's annual mean percentage of ischemic heart disease death attributed to influenza (population attributable fraction) among adults aged ≥50 years, from 2010 to 2019. Panel B shows table with annual mean population attributable fraction (in percentage) of ischemic heart disease deaths globally and by super regions, with 95% uncertainty interval.

105,828–221,145) occurring in the population ≥75 years, 70,032 (95% CI 44,659–95,010) in those aged 65–74 years, and 63,870 (95% CI 40,729–86,653) in the age 50–64 years (Table 1). From 2010 to 2019, the mean annual influenza-attributable IHD mortality rate per 100,000 adults ≥50 years was the highest in Central Europe, Eastern Europe and Central Asia region (32.3 per 100,000 population; 95% UI 20.6–43.8), and in North Africa and Middle East region (26.7 per 100,000 population; 95% UI 17–36.2). Fig. 3 shows the mean rates (Panel A) and number of IHD deaths (Panel B) attributed to influenza activity by country.

The lowest global number of attributable deaths was observed in 2011 with 248,900 (95% UI 158,672–337,819) deaths and the highest in 2019 with 363,800 (95% UI 232,105–432,262) deaths (Table S8). We observed a variation in influenza attributable IHD mortality rates by super region, with the highest rate in 2016 observed in Central Europe, Eastern Europe and

Central Asia Region, while 2017 and 2018 were associated with higher mortality rates in South Asia. In Sub-Saharan Africa, influenza-attributable mortality was more equally distributed across years (Fig. 4; Table S8).

Discussion

Our analysis showed a consistent association between influenza activity and IHD deaths across different countries over a 9-year period. By applying this relationship to influenza activity measures globally, we estimated that an average of approximately 4% (95% UI 3–5%) of IHD deaths could be attributed to influenza activity, with some variations by year and country/region. The highest contribution of influenza to IHD deaths was seen in South Asia and parts of Africa and the Americas, with 5–7% of influenza attributable IHD deaths. The highest rates of influenza attributable IHD

Super region	Age (in years)	Mean number	95% Uncertainty interval	Mean rates per 100,000	95% Uncertainty interval
Global	≥50	2,99,858	1,91,216, 4,06,809	18.4	11.8, 25.0
	50–64	63,871	40,729, 86,653	6.4	4.1, 8.6
	65–74	70,032	44,659, 95,010	18.7	11.9, 25.3
	75+	1,65,955	1,05,828, 2,25,147	67.6	43.1, 91.7
Southeast Asia, East Asia, and Oceania	≥50	99,009	63,167, 1,34,270	18.2	11.6, 24.7
	50–64	18,591	11,861, 25,212	5.3	3.4, 7.1
	65–74	22,491	14,349, 30,500	18.5	11.8, 25.2
	75+	57,928	36,957, 78,558	85.0	54.2, 115.3
Central Europe, Eastern Europe, and Central Asia	≥50	42,483	27,091, 57,636	32.3	20.6, 43.8
	50–64	7093	4523, 9623	9.0	5.8, 12.3
	65–74	8724	5563, 11,837	29.3	18.7, 39.8
	75+	26,666	17,005, 36,177	114.6	73.1, 155.4
High-income	≥50	45,582	29,050, 61,869	11.7	7.4, 15.8
	50–64	5105	3253, 6929	2.5	1.6, 3.4
	65–74	6888	4390, 9349	7.0	4.4, 9.5
	75+	33,589	21,407, 45,591	38.9	24.8, 52.9
Latin America and Caribbean	≥50	17,751	11,319, 24,084	15.6	9.9, 21.1
	50–64	3812	2430, 5171	5.3	3.4, 7.2
	65–74	4143	2642, 5620	16.2	10.4, 22.0
	75+	9797	6247, 13,292	58.2	37.1, 78.9
North Africa and Middle East	≥50	22,564	14,382, 30,624	26.7	17.0, 36.2
	50–64	6039	3849, 8197	10.6	6.7, 14.3
	65–74	5853	3731, 7944	33.7	21.5, 45.7
	75+	10,671	6802, 14,483	106.5	67.9, 144.5
South Asia	≥50	61,093	38,952, 82,895	22.6	14.4, 30.6
	50–64	20,200	12,879, 27,409	11.5	7.4, 15.7
	65–74	18,586	11,850, 25,219	29.1	18.5, 39.5
	75+	22,307	14,222, 30,267	71.4	45.5, 96.9
Sub-Saharan Africa	≥50	11,375	7255, 15,432	12.7	8.1, 17.2
	50–64	3032	1933, 4113	4.9	3.1, 6.7
	65–74	3347	2135, 4541	17.9	11.4, 24.3
	75+	4997	3187, 6778	53.4	34.1, 72.5

Table 1: Mean number and rates of influenza attributable ischemic heart disease deaths by age groups and super region, 2010–2019.

mortality were seen in North Africa and Eastern Europe countries. The global annual average of IHD deaths attributed to influenza was approximately 300,000 (200,000–400,000).

Globally, influenza is associated with 290,000–650,000 annual deaths from respiratory causes alone.[23] The full range of influenza-associated mortality world-wide could be twice as high, as previous estimates did not account for non-respiratory deaths, such as those associated with cardiovascular disease (CVD).[4,23,24] A study among adults ≥65 years in New York City, which looked at excess IHD deaths during influenza epidemics, demonstrated differences in the timing and magnitude of the association as dependent on influenza activity and CVD outcome, with estimated influenza-associated IHD mortality varying from 2.4% to 6.9%.[10] Similarly, we found an annual average of 3% (95% UI 2–5%) in IHD deaths attributable to influenza in the United States (data in Table S5). Influenza-associated health effects can vary by season and depend on population immunity and other host factors, vaccine coverage and effectiveness, and virulence of the circulating influenza viruses.[12,25,26] Nonetheless, improving influenza surveillance worldwide and supporting global civil registration and vital statistics,[27] especially in low and middle income countries, could improve our attribution estimations, strengthening the evidence-base for clinical and health policy recommendations for the use of influenza vaccination.

A recent study estimated approximately 8 million global IHD deaths in 2019,[16] with an age standardized death rate increasing in many locations across South, East and Southeastern Asia since the 90s. More than 80% of IHD deaths are estimated to occur in low- and lower-middle-income countries.[28] In China, IHD mortality rates increased significantly (from 742 to 938 per
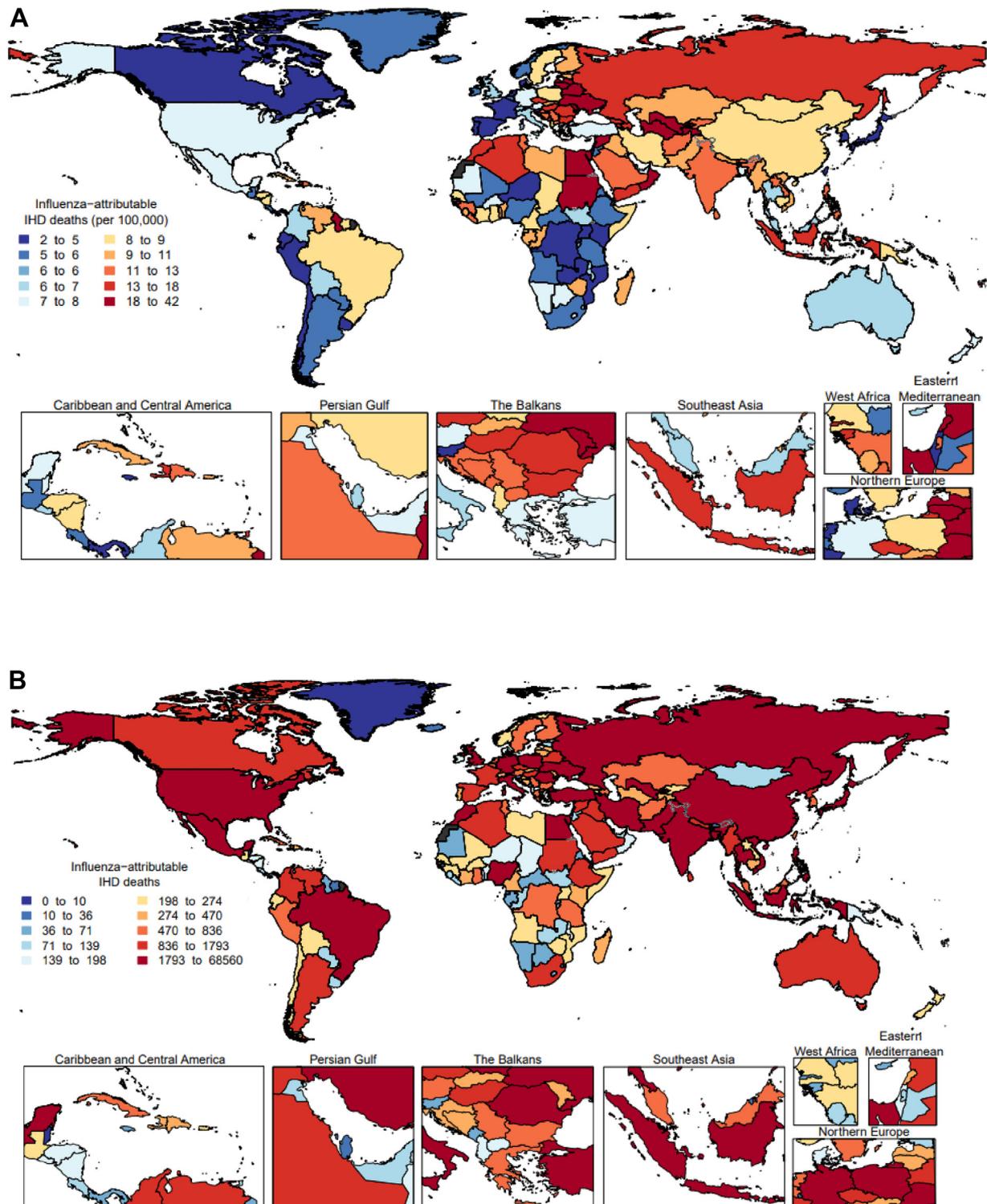
Fig. 3: Mean annual ischemic heart disease mortality rate per 100,000 population (A) and mean annual number of deaths (B) attributable to influenza among adults ≥50 years, 2010–2019.
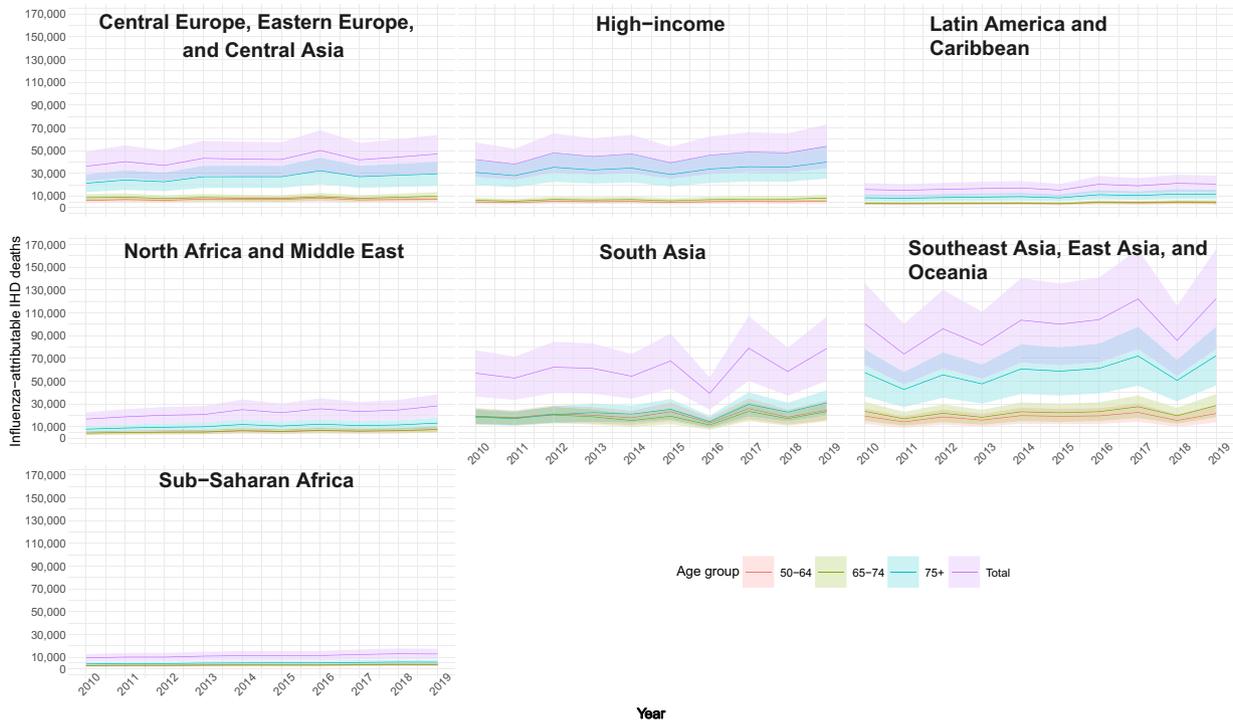
Fig. 4: Influenza-attributable ischemic heart disease (IHD) deaths by age group, super regions, and year, from 2010 through 2019. Shaded area indicates 95% uncertainty interval (UI).

100,000 population, p = 0.002) during 2011–2018.[29] International guidelines for CVD prevention focus on social determinants of health, particularly lifestyle changes (e.g., smoking cessation, diet, exercises) and medications to control elevated levels of cholesterol and blood pressure.[30,31] More recently, the European Society of Cardiology[32] and the American College of Cardiology[33] have recommended influenza vaccination for prevention of heart failure and IHD. Nonetheless, despite the growing evidence of the role of influenza virus infection as a trigger for cardiovascular events, the use of influenza vaccination is suboptimal. A study assessing the uptake of influenza vaccination among patients with heart failure found coverage ranging from 2.6% in Asia and 53% in North America.[34] Moreover, a survey done among the World Health Organization Member States found that only 6.4% of African Region countries, and 9.1% of South-East Asian Region countries reported having national influenza immunization programs for adults.[35] Efforts to increase access to influenza vaccines worldwide could have an important impact in reducing IHD mortality, especially in areas where access to healthcare may be limited.

We observed marked PAF variation among countries. This variation in attribution could not be explained by differences related to population density, urbanicity, temperature, air pollution, influenza positivity, health

care access or socio-demographics. Most importantly, we lacked information on other potential risk factors for IHD deaths such as diet, sedentarism, tobacco and alcohol consumption, or adherence to preventive measures for both IHD and influenza, which could partially explain some of the differences. Similarly, other potential disease modifiers at household level (e.g., in-house air-pollution) or individual level (e.g., frailty, adherence to treatments, impaired heart diseases) were not available. Moreover, we were unable to estimate the impact of influenza vaccination on IHD mortality in our study as influenza vaccine uptake data are not available for most countries. We did not find a strong time lag between influenza exposure and IHD mortality. Similar to our findings, a study in China, using a time series approach, found no apparent time lag for influenza virus activity and increased CVD, IHD and ischemic stroke mortality, with the strongest association being during or within the week of activity.[29] Some other studies have reported an association between influenza and myocardial infarction,[5,36] particularly in the first few days after infection and for up to 4 weeks.[4,37] Our analysis was at the week-level which may have reduced the modelling sensitivity to identify (at least short) time lags. Another contributing factor could be the fact that most surveillance for influenza world-wide is done in outpatient settings where children are over-represented, and

we know that children drive the influenza epidemic, with infection in older adults typically following.[38]

There are other limitations in our study that warrant discussion. Influenza ascertainment is limited by the lack of laboratory test confirmation, both in high-resource and low-resource settings.[39,40] Moreover, national influenza surveillance systems, for most countries, have limited geographic representativeness and many countries do not have monitoring systems in place,[41] limiting our assessment to certain countries where both influenza surveillance and vital statistics data sources were available. Death certificates may misclassify causes of death, and this may be different from country to country. Moreover, the quality of data from countries with limited resources was likely not as good as in some of the high-income countries since the former may rely on sample registration or verbal autopsy data instead of vital registry. This variation in diagnostic coding and cause of death classification compounded with limited (or absence) influenza surveillance data, may also explain some of the large variation observed in the association between influenza and IHD mortality. Moreover, because IHME GBD estimates are done using underlying cause of death, there may be events classified IHD as contributing causes that were not included. Another point to consider is that we used calendar year to investigate the association between influenza and IHD in the Northern Hemisphere countries where influenza circulation is seasonal, with peak activity varying from December through February and therefore spanning into two calendar years. This may have diluted the impact of influenza on IHD deaths in these countries. Future work should consider incorporating seasonal variations in the estimates, allowing influenza transmission in temperate countries to be assessed differently than tropical countries.

In conclusion, influenza may contribute substantially to the burden of IHD. Our study suggests that if there were no influenza, an average of 4% of IHD deaths globally would not occur. Estimates of influenza vaccination program impact on IHD mortality should be conducted to help understand the full public health value of influenza vaccination. Our study supports clinical practice guidelines recommending influenza vaccination as an important component IHD to preventive care.

Contributors
S.S.C.: conception, design, interpretation, writing. J.N.: conception, design, interpretation. K.G.B.: design, analysis, interpretation. D.M.: data access, analysis, interpretation. T.B.-S.: data access, analysis, interpretation. J.R.O.: interpretation; V.M.V.-T.: analysis; L.E.W.: analysis; G.R.: design, analysis, interpretation; C.M.: conception, design, interpretation; M.B.: design, analysis, interpretation. K.G.B., V.M.V.-T., L.E.W. and M.B. had direct access to and verified the data in the manuscript. All authors critically reviewed the manuscript and contributed to the decision to publish its final version.

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