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## **Running title: Trend in RA mortality**

### **Title: Rheumatoid arthritis as underlying cause of death in 31 countries, 1987-2011: trend analysis of WHO mortality database**

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## **Abstract**

**Objective** To examine trends in rheumatoid arthritis (RA) as an underlying cause of death (UCD) in 31 countries across the globe during 1987-2011.

**Methods** Data on mortality and population were collected from the World Health Organization mortality database and the United Nations. Age-standardized mortality rates (ASMR) were calculated by means of direct standardization. We applied joinpoint regression analysis for trend analysis. Between-country disparities were examined using between-country variance, and Gini coefficient. Due to low numbers of deaths, we smoothed our ASMR using a three-year moving average. The changes in number of RA deaths between 1987 and 2011 were decomposed using two counterfactual scenarios.

**Results** The absolute number of deaths with RA registered as UCD declined from 9281 (0.12% of all-cause deaths) in 1987 to 8428 in 2011 (0.09% of all-cause deaths). The mean ASMR declined from 7.1/million person-years in 1987-89 to 3.7 in 2009-11 (48.2% reduction). Reduction of 25% or more in ASMR occurred in 21 countries while a corresponding increase was observed in 3 countries. There was a persistent reduction in RA mortality and, on average, the ASMR declined by 3.0% per year. The absolute and relative between-country disparities declined over the study period.

**Conclusion:** Mortality rates attributable to RA have declined globally. However, there were substantial between-country disparities in RA mortality, though the disparities decreased over time. Population aging combined with fall in RA mortality may lead to an increase in the economic burden of disease that should be taken into consideration in policy-making.

Rheumatoid arthritis (RA) affects about 0.5% to 1.0% of the adult population in most developed countries (1). The global prevalence of RA is reported to be somewhat lower, approximately 0.24%, with a three times higher prevalence in women than men (2). RA is associated with reduced mobility, disability, poor quality of life and mortality. Globally RA accounted for 0.49% of years lived with disability and 0.19% of disability-adjusted life years in 2010 (2). About one-fourth of RA patients are reported to be work-disabled within 3 years of diagnosis, and around 35% work-disabled with 10 years disease duration (3).

It is well recognized that people with RA have a higher risk of mortality compared with the general population, with lifespan shortened by 4-10 years (4). A recent meta-analysis reported a standardized mortality ratio of 1.5 for RA patients compared with the general population and this was stable over time (5). Several studies have investigated RA as the underlying cause of death (UCD) and among these, the proportion of RA deaths from all-cause deaths ranged from 0.03% in Sao Paulo Brazil (6) to 0.17% in Sweden (7).

Studies reported a stable or declining trend over time in RA mortality. However, previous studies were conducted in a single state/country. One meta-analysis combined data from different single era studies and suggested that the trend showed a decline (5). But there has been no comprehensive assessment of mortality trends in RA over time using repeated data from the same countries. The aim of the current study was to address the knowledge gap regarding potential cross-country differences in RA mortality as an UCD and whether RA mortality has been changing in different countries.

## **Materials and Methods**

### *Data sources*

Data on UCD were obtained from the World Health Organization (WHO) mortality database ([http://www.who.int/healthinfo/mortality\\_data/en/](http://www.who.int/healthinfo/mortality_data/en/)). This database contains country-level data on deaths by sex, age, and UCD submitted annually by WHO member states from their civil registration systems and includes only the medically-certified deaths. The data completeness and quality is assessed annually

according to the Health Facility Data Quality Report Card (DQRC). International Classification of Diseases (ICD) codes were used to extract data on deaths with RA registered as UCD (ICD-9 codes 714, and ICD-10 codes M05 and M06). Based on data available from the database and excluding the countries with no RA deaths for most years of the study period, a total of 31 countries from Europe, North America, and Australasia were included (England & Wales, Northern Ireland, and Scotland were included separately). All countries but Singapore and Greece applied both ICD-9 and ICD-10 revisions during the study period (Table 1 in supplement).

Data for years 2004-2005 in Italy and 1997-1998 in Poland were missing and were replaced by the mean of 10 imputed values using Poisson regression adjusted for year, sex, age group, and ICD revision with population as exposure. Population data by sex and age were obtained from the United Nations Population Prospects database (<http://esa.un.org/unpd/wpp/>).

#### *Trend analysis*

We computed age-standardized mortality rates per million population for each country-year by means of direct standardization using the WHO Reference Population (8). Due to low number of RA deaths, we smoothed these age-standardized rates by three-year moving averages and used the midpoint of each three-year period as the time-point in our analysis (i.e. the year 1988 for 1987-89, the year 1989 for 1988-90, and so on). We computed the overall percent change as the difference between 1988 and 2010 rates divided by the rate of 1988.

We used the Joinpoint Regression Program version 4.2.0.2 from the Surveillance Research Program of the US National Cancer Institute (<http://surveillance.cancer.gov/joinpoint>) for temporal trend analysis. Joinpoint regression identifies points with a significant change in trend (“joinpoints”) and determined linear trends between joinpoints (9). For each joinpoint, an annual percentage change (APC) is estimated by fitting a regression line to the natural logarithm of the age-standardized rates, using calendar year as a predictor. The average annual percent change (AAPC) as the weighted average of APCs was computed to provide a summary measure of the trend for the whole time period.

### *Between-country disparity*

The absolute between-country disparity was measured using between-country variance which is equal to the squared differences in country age-standardized mortality rate from the pooled rate of all countries and weighted by country's proportion of the total population of all countries (10). The relative between-country disparity was measured by Gini coefficient based on the Lorenz curve plotting the cumulative share of population ranked by RA mortality rate, in increasing order, against the cumulative share of the RA mortality (10). The Gini coefficient is equal to twice the area between the Lorenz curve and diagonal. Its value ranges from 0 (perfect equality) to one (maximum possible inequality).

### *Decomposition analysis*

The drivers of changes in the number of RA deaths between 1987 and 2011 were decomposed into three components (i.e. population growth, population aging, and epidemiologic changes) (11). The expected number of RA deaths in 2011 was computed using two counterfactual scenarios: 1) population growth scenario where the size of the population in 2011 was considered to have the same age- and sex structure and RA death rates as in 1987, 2) population growth and aging scenario where the size of the population in 2011 had the actual age-sex structure of 2011, but RA death rates were the same as in 1987. The difference between the actual number of deaths in 1987 and the expected number from scenario 1 is change due to *population growth*. The difference between the expected number of deaths from scenarios 1 and 2 is change due to *population aging*. The difference between the actual number of deaths in 2011 and the expected number from scenario 2 is change due to *epidemiologic changes*. The epidemiologic changes are changes in the age-, sex-, and cause-specific rates of death and include all changes in mortality that cannot be explained by population growth and aging (11). The actual change in the number of deaths is equal to the net change of these components.

## Results

### *Number of deaths*

During 1987–2011, a total of 219,189 people died with RA registered as UCD in 31 countries. These represent 22.2 of total deaths attributed to musculoskeletal disorders (MSK) and 0.1% of all-cause deaths (Figure 1 in supplement). The number of deaths decreased from 9,281 in 1987 to 8,428 in 2011, representing a 9.2% reduction. The proportion of RA deaths from MSK deaths (all-cause deaths) declined from 30% (0.12%) in 1987 to 17.7% (0.09%) in 2011 (Figure 1). The proportion of RA deaths from MSK deaths (all-cause deaths) increased in 5 (13) countries between 1987 and 2011 (Table 2 in supplement).

### *Age-standardized mortality rate*

The mean age-standardized RA mortality rate, on average for all countries over the entire time period, was 5.2 per million person-years (3.0 for men and 6.7 for women, corresponding to a women-to-men rate ratio [95% CI] of 2.25 [2.23 to 2.26]). Singapore and Finland had the lowest and the highest mean age-standardized RA mortality rates, respectively (Figure 2). Women-to-men rate ratios were higher than 1 in all countries, ranging from 1.79 in Belgium to 3.38 in Czech Republic (Table 3 in supplement).

The mean age-standardized RA mortality rate declined from 7.1 per million person-years in 1987–89 to 3.7 in 2009–11, representing a 48.2% reduction (Table 1). Reductions of 25% or more were observed in 21 countries, while corresponding increases were seen only in Israel, Croatia, and Slovenia. In absolute terms, the greatest reduction in age-standardized RA mortality rate was observed in Finland (20.6 less deaths per million person-years) and the greatest increase was seen in Croatia (3.7 more deaths per million person-years). While the women-to-men age-standardized RA mortality rate ratio slightly declined from 2.28 in 1987–89 to 2.19 in 2009–11, the absolute difference declined from 5.1 to 2.6 deaths per million person-years.

Age-specific RA mortality rates declined in all age groups with the greatest reduction among the youngest and the smallest reduction in oldest age groups (Figure 2 in supplement). However, there were between-

country variations in age-specific RA mortality rates, particularly in older age groups (e.g., age-specific RA mortality rates for two oldest age groups increased in 10 countries).

### *Joinpoint Regression analysis*

The Joinpoint regression analyses (Figure 3 and Table 4 in supplement) demonstrated that, on average for all countries, the mean age-standardized RA mortality rate declined by 3.2% per year up to 1998 and then it was stable for four years and again declined by 4.2% per year thereafter, resulting in an average annual reduction of 3.0% for the whole study period. Although the magnitude and shape of temporal trends varied between countries, RA mortality declined in most countries over the study period. While there was no joinpoint (i.e., a constant linear trend) in Czech Republic and Singapore, in 26 out of 31 countries there were at least two joinpoints over the study period. During the most recent decade, RA mortality declined in all countries but Croatia and Slovenia.

### *Between-country disparities*

The between-country variance declined from 16 deaths per million person-years in 1987-89 to 1.8 deaths per million person-years in 2009-11 and Gini coefficient declined from 0.31 to 0.19 at the same time (Figure 4 in supplement), both reflecting declined between-country disparity over time.

### *Decomposition analysis*

Despite population growth and population aging, the number of RA deaths declined in 2011 compared with 1987 because of a large reduction due to epidemiologic changes (Table 5 in supplement). In 23 countries the number of RA deaths increased due to population growth and population aging and decreased due to epidemiologic changes. In 15 of these countries, this combination led to decline in the number of RA deaths. In 5 countries, the number of deaths due to all three components increased. In Bulgaria, Hungary, and Croatia the number of deaths due to population growth declined but only in the two former countries, this reduction was accompanied by declines due to epidemiologic changes which led to actual decreases in the number of RA deaths.



## Discussion

In the current study, the first cross-country analysis of mortality with RA as the UCD has been conducted. On average, the number of RA deaths, its proportion relative to MSK- and all-cause deaths, and also age-standardized RA mortality rates declined over the study period. However, there were substantial between-country disparities in the magnitude and temporal trend of RA deaths, though the disparities decreased over time.

It has been suggested that changes in the management of RA toward early and aggressive treatment with disease-modifying anti-rheumatic drugs and subsequent biologic therapies has led to better health status and lower mortality for most people with RA over time (4, 5). In addition, it has been suggested that RA may be becoming a milder disease in general (12). Furthermore, large reductions in prevalence of smoking in people with RA over recent decades, improvements in diagnosis, increased public awareness of RA, and general improvements in cardiovascular mortality might also partially explain the observed declining trend in our study. Comparing RA mortality with all-cause mortality for 29 countries with full data in our study (i.e. excluding Italy and Poland) suggested that RA mortality rate declined in a higher pace than all-cause mortality over the study period (3.1% vs. 1.7% annual reduction). A recent study using data from the UK has indicated a greater degree of improvement in RA mortality rates than that of the general UK population between 1999 and 2014 (13). The findings from the Global Burden of Disease Study (<http://vizhub.healthdata.org/epi/>) suggests that in high income countries RA prevalence and incidence increased in both sexes during 1990-2011. These findings alongside aging of the population and fall in mortality may lead to an increase in the number of people with RA. Given that it appears that people with RA are now living longer, increase in burden of RA on health care systems is expected and policy-makers should be made aware about to appropriately plan for this anticipated increase.

The magnitude and temporal trend of RA mortality varied across countries. We found that countries in northern Europe, on average, had a higher mortality rate compared with other regions. Higher incidence and prevalence rates of RA in northern European and North American countries compared with southern European and developing countries has been previously reported (14) and might partially explain our

finding. Moreover, differences in genetic, epidemiologic, and clinical profile of RA, distribution of RA risk factors including environmental exposures, and socioeconomic status might also partially explain our findings (14). Between-country disparities in the validity and use of the RA diagnosis and access to treatments including disease-modifying anti-rheumatic drugs might be other potential reasons for the observed disparity in RA mortality. Moreover, the impact of differences in cause of death coding practices including time of the introduction of ICD-10 revision cannot be ruled out, although this cannot explain the observed disparities in the most recent decade since most countries were applying the ICD-10 revision during this time period. Furthermore, although most countries included in our study have a vital registration with satisfactory quality (15), differences in quality of cause-of-death registration might still be another potential reason for the observed disparities in RA mortality.

Several limitations of this study should be considered in interpreting the findings. We considered RA deaths to be those listed as the UCD on death certificates which is known to be underreported (4). The registration, reporting and analysis of contributory causes of death would have alleviated this problem, but such data are unfortunately not available at present. In addition, cause-of-death registrations suffer from errors and incompleteness. Variations in attribution of causes of death, underreporting and inaccuracy across countries and over time are of concern. Change in ICD revision might produce discontinuities in mortality data and can bias mortality trends. However, in many countries RA mortality rates started to decline prior to the introduction of ICD-10 implying that the observed declining trend is not artificial. Most of the countries included in this study are high income countries implying that generalizability of the results to low and middle income countries is limited. The small number of RA deaths might limit the power of joinpoint model to detect significant joinpoints. In addition, the wide confidence intervals for average annual percentage change in some countries and also sensitivity of our between-country disparity measures to outliers call for caution in interpreting the results. This is a descriptive aggregate-level analysis and all given explanations for mortality trends are speculative and no causal inference can be made.

## **Conclusion**

We report here the first cross-country analysis of mortality with RA as UCD, strongly suggesting that RA mortality declined in many countries over a 25-year period. There were substantial but declining disparities in RA mortality, with countries in northern Europe having the highest RA mortality rates. Increase in the number of people with RA due to population aging combined with fall in RA mortality imply that the burden of disease will rise in coming decade and this should be taken into consideration in policy-making by international and national health authorities.

## **Author's contributions**

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. AAK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design:** AAK

**Acquisition of data:** AAK

**Analysis and interpretation of data:** AAK, DTF, TN, ME.

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**Table 1. Changes in rheumatoid arthritis age-standardized mortality rate per million person-years 1987-2011.**

Country	Mortality rate			% Δ		AAPC (95% CI), %	
	1987 - 1989	2000- 2002	2009- 2011	1987 to 2011	2000 to 2011	1987–2011	2000-2011
<b>All countries (n=31)</b>	7.1	5.2	3.7	-48.2	-29.3	-3.0 (-3.5 to -2.5)	-3.9 (-4.6 to -3.2)
Australia	9.0	5.6	4.6	-49.3	-17.8	-3.0 (-3.9 to -2.1)	-2.4 (-3.2 to -1.6)
Austria	6.4	4.0	2.2	-65.2	-44.1	-4.9 (-6.4 to -3.3)	-7.1 (-9.5 to -4.7)
Belgium	5.7	3.8	1.9	-67.6	-51.6	-4.7 (-5.8 to -3.7)	-6.9 (-8.1 to -5.7)
Bulgaria	0.9	0.9	0.5	-41.6	-36.2	-2.6 (-6.4 to 1.4)	-4.5 (-12.5 to 4.2)
Canada	6.0	6.2	4.1	-32.2	-34.0	-1.7 (-2.5 to -0.8)	-4.5 (-5.1 to -3.9)
Croatia	1.6	1.9	5.3	226.4	170.7	7.4 (1.3 to 13.8)	9.9 (6.6 to 13.3)
Czech Republic	2.4	0.3	0.7	-69.6	174.3	-11.7 (-15.6 to -7.6)	11.8 (-16.8 to 50.1)
England & Wales	15.7	8.0	5.8	-63.4	-27.9	-4.8 (-6.1 to -3.5)	-4.6 (-5.5 to -3.7)
Finland	25.3	10.3	4.6	-81.6	-55.0	-7.2 (-8.2 to -6.3)	-7.2 (-8.5 to -5.9)
France	4.9	3.9	2.3	-53.9	-42.9	-3.4 (-4.1 to -2.7)	-6.2 (-7.4 to -5.0)
Germany	8.1	2.4	2.0	-75.5	-17.6	-6.4 (-7.2 to -5.5)	-1.8 (-4.1 to 0.5)
Greece	0.8	1.6	1.0	14.2	-38.1	1.4 (-6.2 to 9.6)	-6.0 (-9.3 to -2.5)
Hong Kong SAR	1.0	1.2	1.0	9.2	-11.8	-0.3 (-3.9 to 3.3)	-1.8 (-3.2 to -0.3)
Hungary	6.8	3.9	2.8	-58.8	-29.0	-3.7 (-4.4 to -3.0)	-3.1 (-4.4 to -1.8)
Ireland	16.3	9.8	7.3	-54.9	-25.5	-3.4 (-4.7 to -2.1)	-2.3 (-6.2 to 1.8)
Israel	0.7	2.2	1.5	108.5	-33.0	6.2 (2.1 to 10.4)	-4.9 (-8.3 to -1.4)
Italy	4.2	3.7	3.4	-18.8	-8.2	-0.7 (-1.2 to -0.3)	-1.2 (-1.8 to -0.6)
Japan	10.3	6.4	4.2	-59.1	-34.3	-4.2 (-4.5 to -3.8)	-4.4 (-4.9 to -3.9)
Netherlands	13.9	5.4	2.8	-79.5	-47.0	-7.4 (-8.5 to -6.2)	-7.7 (-8.7 to -6.6)
New Zealand	10.8	10.2	6.7	-38.2	-34.7	-2.8 (-4.4 to -1.2)	-5.3 (-6.9 to -3.8)
Northern Ireland	6.9	8.2	7.3	5.1	-10.9	-0.1 (-3.6 to 3.5)	-2.0 (-4.7 to 0.8)
Norway	14.2	7.6	4.5	-68.0	-40.1	-4.9 (-5.9 to -3.9)	-4.6 (-5.8 to -3.4)
Poland	11.4	5.5	4.2	-63.0	-22.8	-4.4 (-4.8 to -3.9)	-3.2 (-3.7 to -2.8)
Portugal	3.7	3.4	2.3	-38.4	-32.7	-3.6 (-7.5 to 0.5)	-8.2 (-12.6 to -3.7)
Republic of Korea	2.2	5.8	2.4	4.9	-59.6	-0.6 (-2.3 to 1.2)	-11.9 (-14.3 to -9.5)
Scotland	11.1	12.8	9.4	-15.1	-26.4	-0.4 (-2.4 to 1.7)	-2.5 (-3.9 to -1.0)
Singapore	3.1	0.7	0.2	-95.0	-78.9	-14.2 (-18.3 to -9.9)	-21.4 (-45.6 to 13.6)
Slovenia	5.5	3.8	6.9	25.7	83.2	0.9 (-1.6 to 3.5)	4.2 (-0.1 to 8.7)
Spain	3.4	3.3	2.3	-31.1	-29.7	-1.9 (-2.6 to -1.2)	-3.9 (-4.4 to -3.4)
Sweden	8.3	7.8	5.3	-36.1	-31.8	-1.8 (-3.2 to -0.4)	-3.7 (-4.5 to -2.8)
USA	4.5	5.9	4.4	-2.3	-25.6	-0.3 (-0.7 to 0.1)	-3.3 (-3.5 to -3.1)

AAPC: average annual percent change, CI: confidence interval.

## Figures

Figure 1. Changes in proportion of rheumatoid deaths from musculoskeletal disorders and all deaths, 1987-2011.

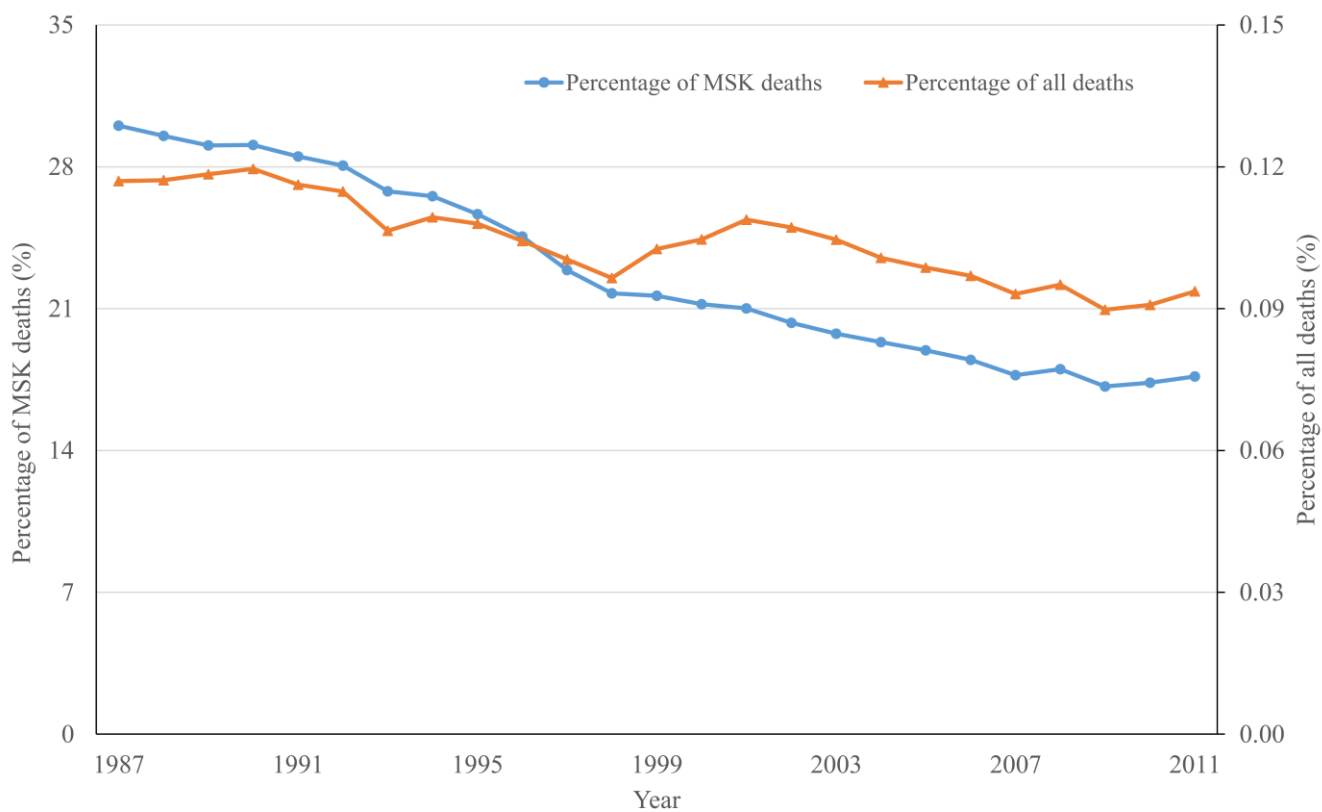
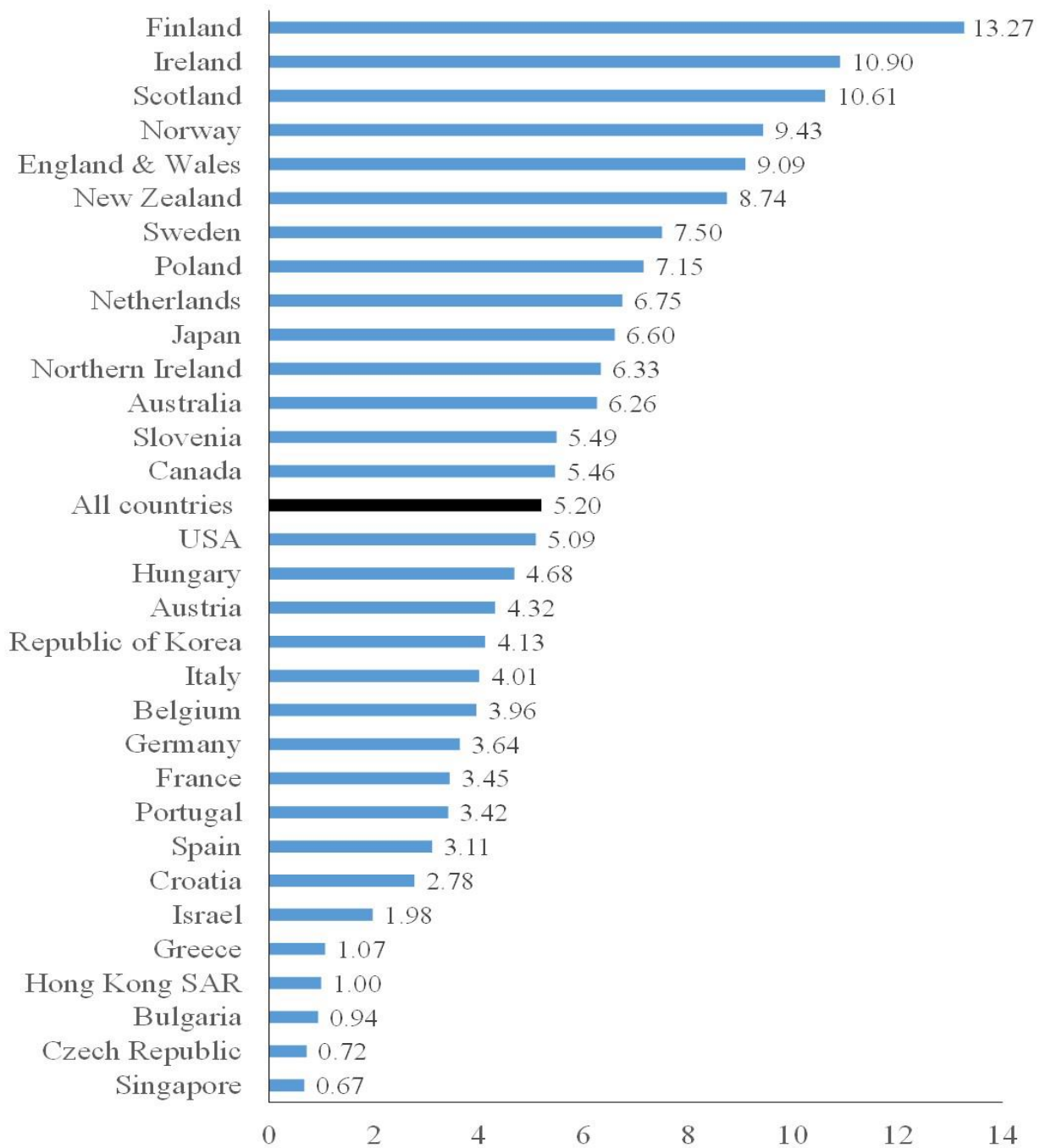


Figure 2. The mean age-standardized rheumatoid arthritis mortality rates per million person-years, 1987-2011.



## Figures in supplement

Figure 1. Proportion of rheumatoid arthritis deaths from musculoskeletal disorders and all deaths, 1987-2011.

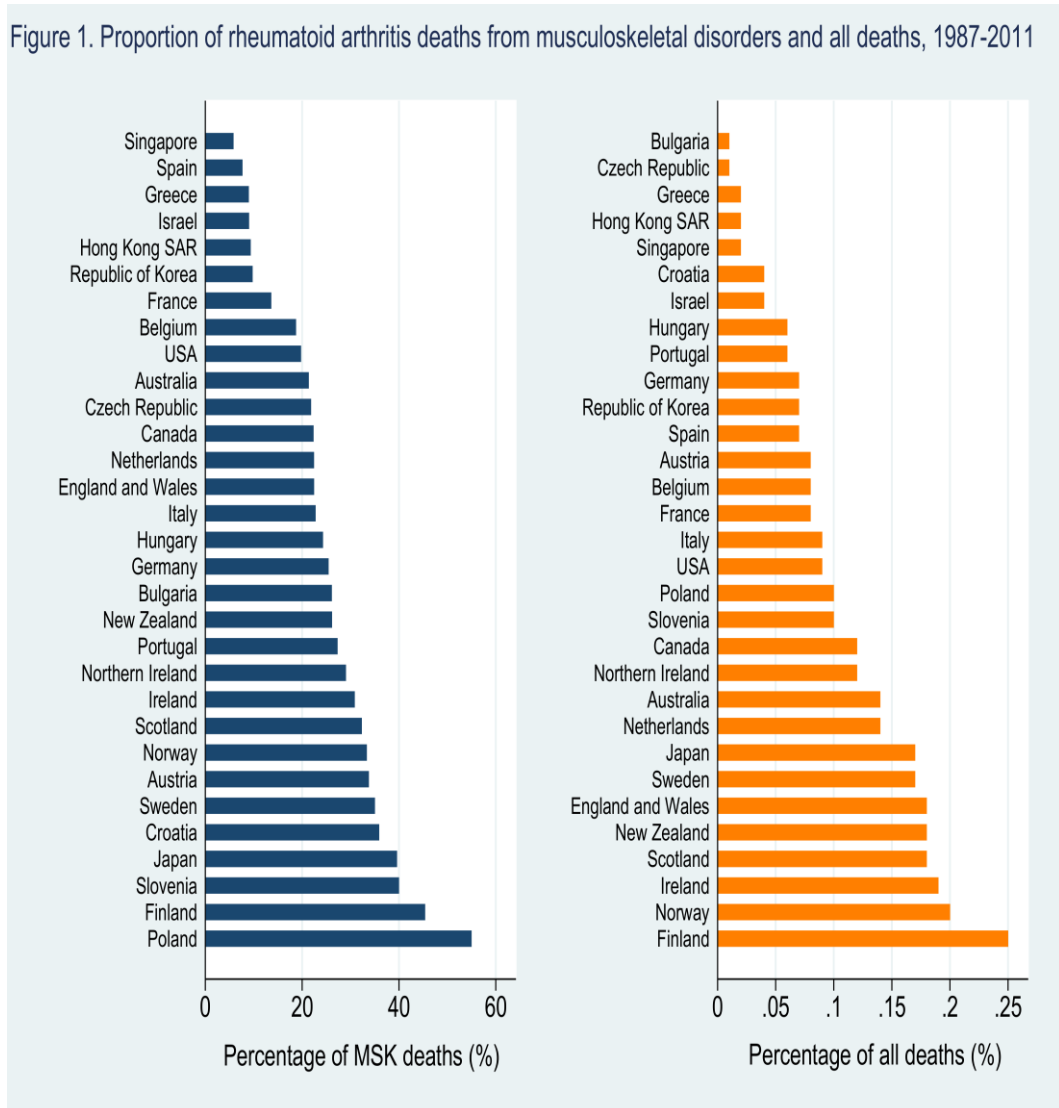




Figure 2. Percentage change in age-specific rheumatoid arthritis mortality rate between 1987-89 and 2009-11.

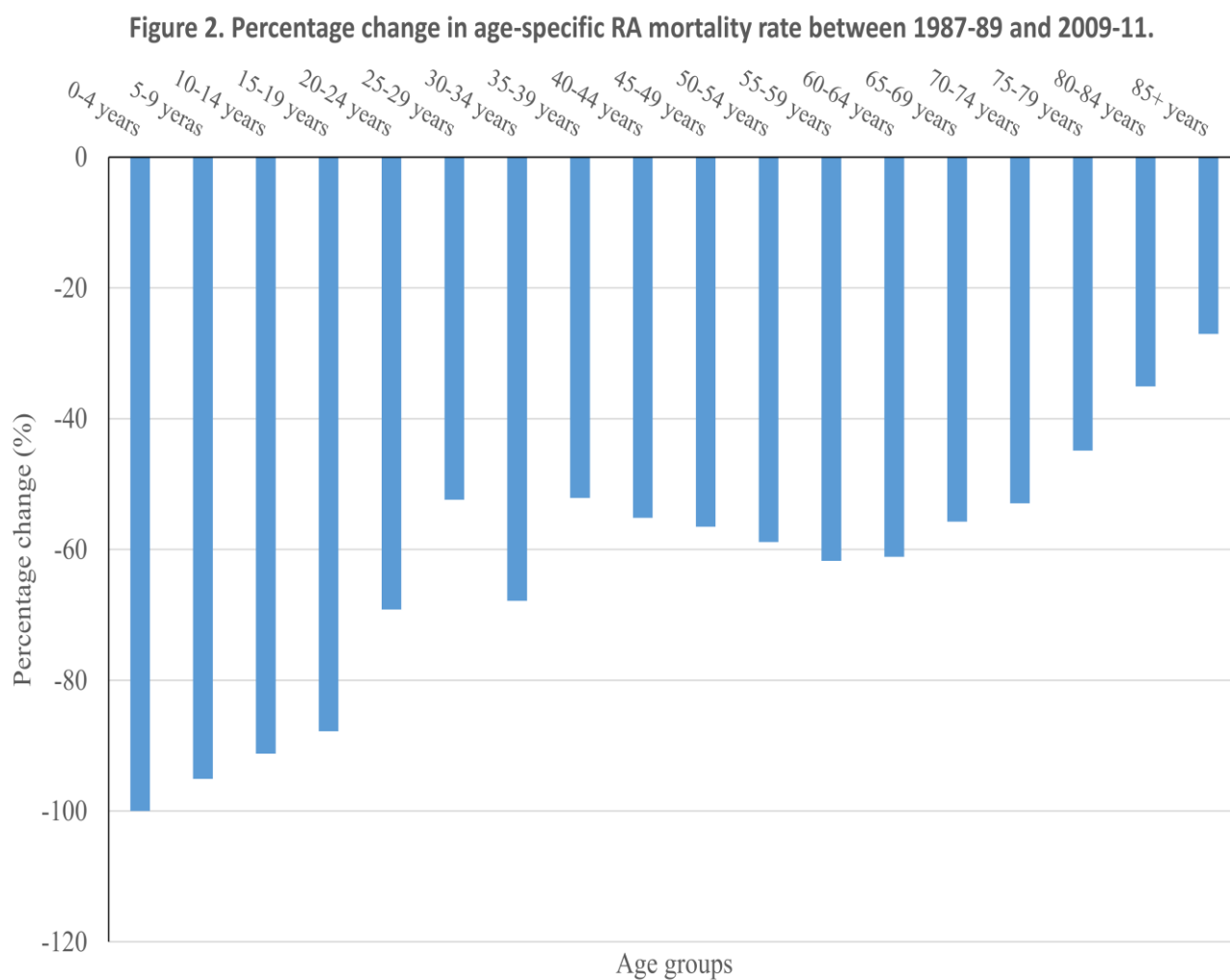


Figure 3. Temporal trend in age-standardized rheumatoid arthritis mortality rates across countries, 1987-2011. Footnote: Symbols display observed values and solid lines show fitted values from joinpoint regression. Red vertical line shows the year prior to the introduction of ICD-10 revision.

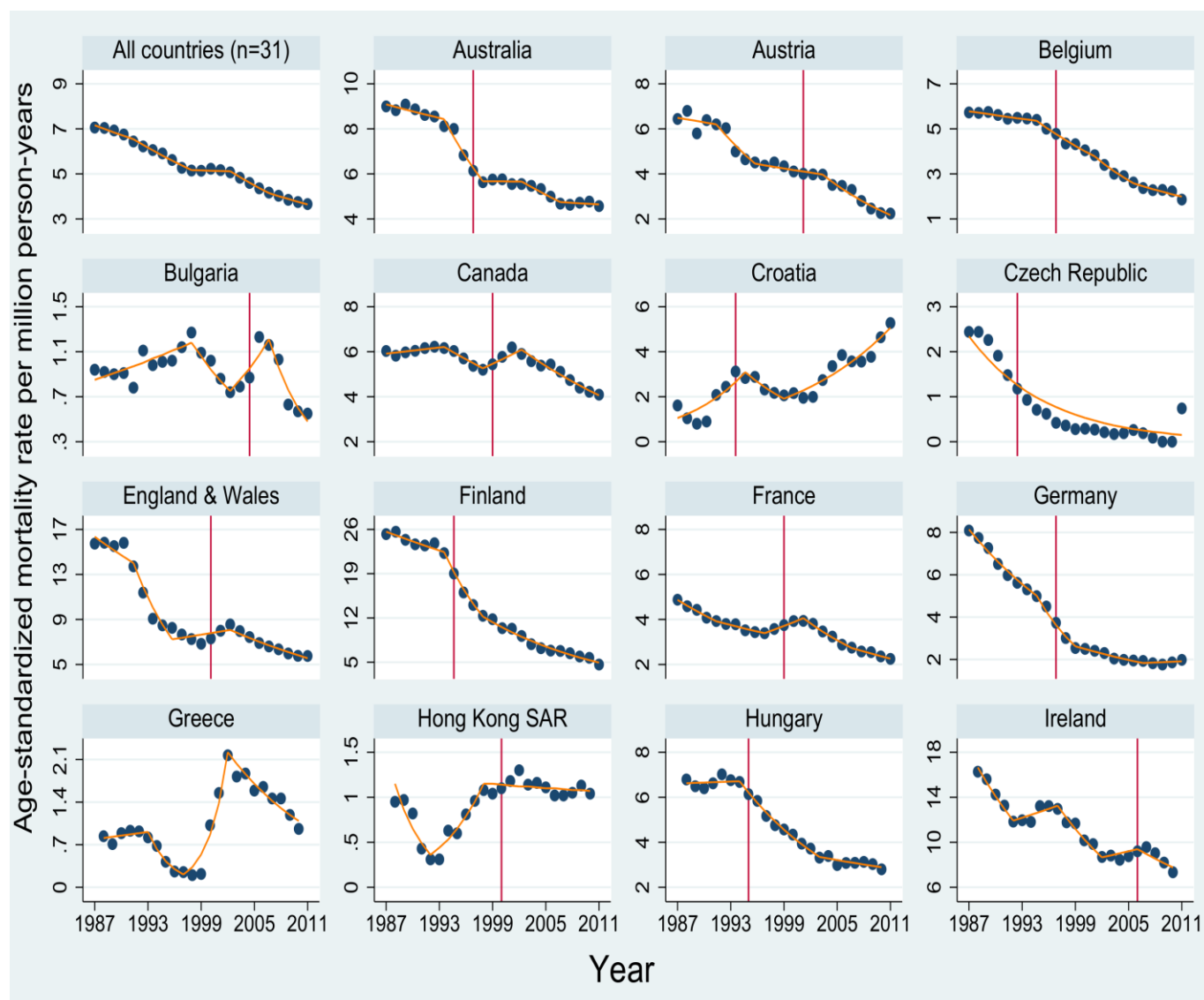


Figure 3. Continue

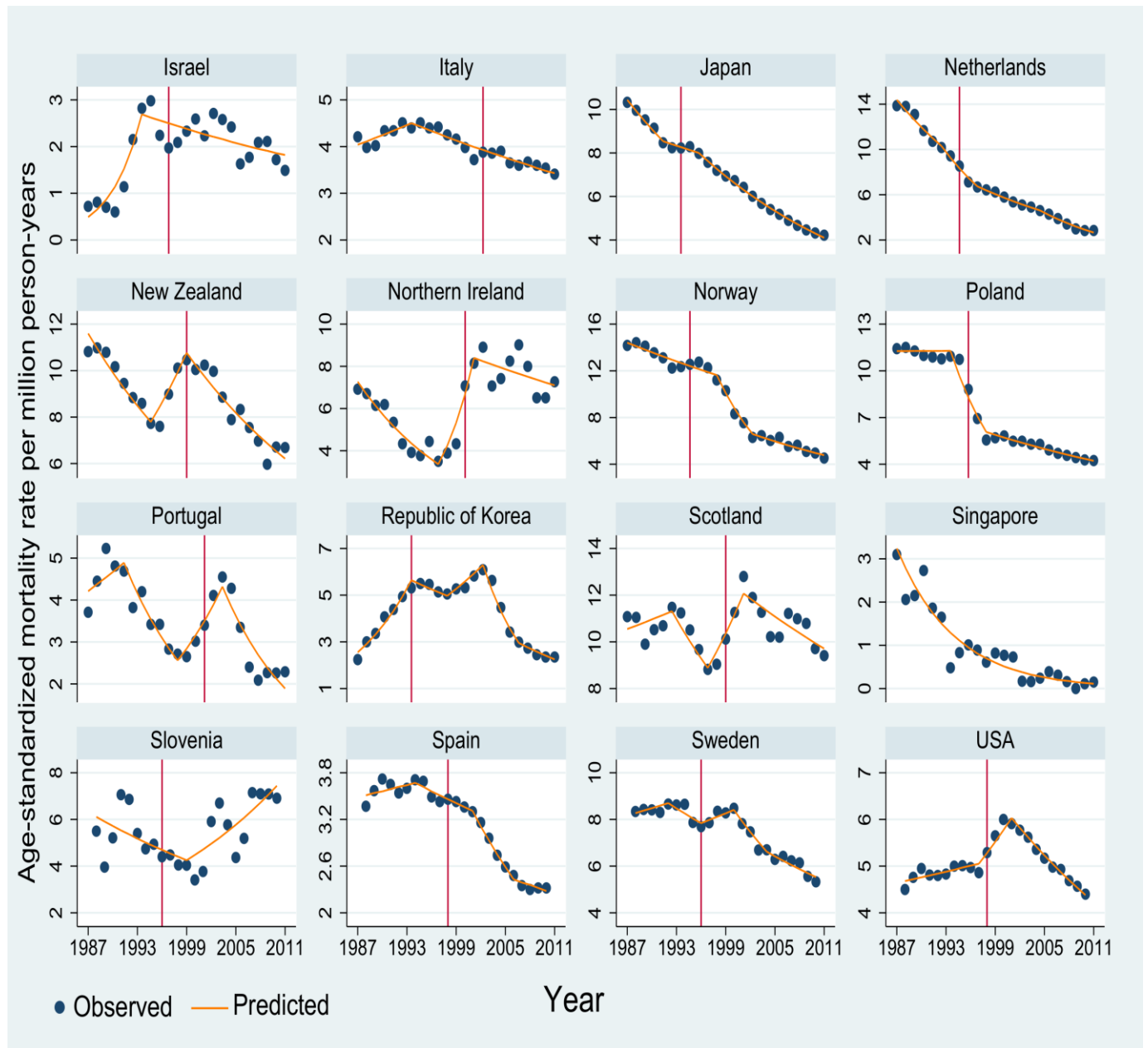


Figure 4. Changes in the absolute and relative between-country disparities in rheumatoid arthritis mortality rate, 1987-2011.

