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Title: The Burden of Stroke in Europe: An analysis of the Global Burden of Disease study findings from 2010 to 2019

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ABSTRACT (max. 300 words)

Background: While most European Regions perform well in global comparisons, large discrepancies within stroke epidemiological parameters exist across Europe. The objective of this analysis was to evaluate stroke burden across European regions and countries in 2019, and its difference to 2010.

Methods: GBD 2019 analytical tools were used to evaluate regional and country-specific estimates of incidence, prevalence, deaths and disability-adjusted life-years (DALYs) of stroke for the 53 countries making up the WHO European Region (EU-53) and for EU-28, between 2010 and 2019. Results were analysed at a regional, subregional and country level.

Results: In EU-53, the absolute number of incident and prevalent strokes increased by 2% (UI, 0 to 4%), from 1,767,280 to 1,802,559, and by 4% (UI, 3 to 5%) between 2010 and 2019, from 10,731,496 to 11,245,368, respectively. While the absolute number of incident strokes remained stable in EU-28, the absolute number of prevalent strokes and stroke-related deaths increased by 4% (UI, 2 to 5%), from 5,775,590 to 5,989,161, and by 7%, from 354,658 to 370,467 (UI, 2 to 12%), respectively. All-stroke age-standardized mortality rates, however, decreased by 18% (UI, -22 to -14%), from 82 to 67/100,000 people in EU-53, and by 15% (UI, -18 to -11%), from 49.3 to 42.0/100,000 people, in EU-28. Despite most countries presenting age-adjusted incidence, prevalence, mortality and DALY rate reductions, these were 1.4x, 1.2x, 1.6x and 1.7x higher in EU-53 in comparison to EU-28. There was significant variation between countries, with the largest discrepancies observed across age-standardized death rates (e.g. 206.6/100,000 in Montenegro versus 21.8/100,000 in Switzerland).

Conclusion: EU-53 showed a 2% increase in incident strokes, while they remained stable in EU-28. Age-standardized rates were consistently lower for all stroke-burden parameters in

EU-28 in comparison to EU-53, and huge discrepancies in incidence, prevalence, mortality and DALY rates were observed between individual countries.

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Introduction

Although substantial efforts have been made in primary stroke prevention, treatment and tertiary prevention strategies, stroke remains the second-leading cause of death and third-leading cause of burden of disease worldwide (1). The Global Burden of Disease, Injuries, and Risk Factors Study (GBD) 2019 stroke analysis reported a sharp decrease in age-standardised stroke mortality rates between 1990 to 2019 (2). However, despite reductions in age-standardised rates, absolute numbers of incident, prevalent and mortality cases secondary to strokes have increased by 70%, 85% and by 43%, between 1990 and 2019 worldwide (2).

In the European Union, stroke is the second most frequent cause of death and the leading cause of adult disability, with thirty-year projections of absolute numbers of incidence, prevalence, deaths and DALYs estimating a 27% increase by 2047 (3). In 2006, the Helsingborg Declaration on European Stroke Strategies was adopted (4). One of their aims was for all stroke patients in Europe to have access to a stroke unit by 2015, however, the 2020 Stroke Alliance for Europe Report found that only 30% of stroke patients across Europe currently have access to acute stroke unit care (4,5,6). They also found high discrepancies in stroke burden exist across Europe, with age-standardized death rates in Bulgaria, Romania, Serbia, Latvia, Lithuania, Croatia, Hungary, and Slovakia 7x times higher than in France, Spain, Luxembourg, Austria, and Belgium (6).

The European Stroke Organisation (ESO) and the Stroke Alliance for Europe (SAFE) created the European Stroke Action Plan (ESAP) for the years 2018 to 2030 (7,8). Their pursued targets for 2030 are *i)* reduction of absolute number of strokes in Europe by 10%, *ii)*

treatment of at least 90% of stroke patients in dedicated stroke units as the first level of care, *iii)* implementation of national plans for stroke management, and *iv)* implementation of national strategies for multisector public health interventions (7). Implementation of ESO guidelines and 2018-2030 ESAP strategies across all European countries could lead to standardization of stroke care across Europe, improving and homogenising the burden of stroke across different European countries (7-10). However, studies analysing the burden of stroke throughout Europe, considering both the European Union (EU-28), as well as Europe according to the 2019 World Health Organisation definition (EU-53) are lacking.

The aim of this study was to compare the burden of stroke during the last 10 years in EU-28 (the 27 member countries of the EU plus the UK) and in EU-53, including a regional and country-specific analysis.

Methods

Global Burden of Disease 2019: The GBD 2019 study effort has quantified the burden of 369 diseases and injuries in 204 countries and territories worldwide, analysing data from 3686 vital registration sources, 147 verbal autopsy sources, 368 incidence sources, 117 prevalence sources, 229 excess mortality sources, 7753 risk factor exposure sources, and 2733 risk factor relative risk sources (see http://ghdx.healthdata.org/for further details) (1, 11-16). It is a landmark effort, updated annually, designed to allow for consistent comparison over time starting from 1990 to 2019, by age and sex, socio-demographic index, World Bank country income, and across locations. (1,11) It produces standard epidemiological measures such as incidence, prevalence, and death rates as well as summary measures of health, including DALYs (1, 11), reported in compliance with Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) guidelines (17). All of their results are publically available, and can be found using the GBD Results Tool and GBD Compare website (1, 10, 11).

The GBD classifies causes into four levels, from the broadest (Level 1; eg, non-communicable diseases), to the most specific (Level 4; eg, ischaemic stroke [IS]). Stroke is categorized as a level 3 cause, and has 3 level 4 subtypes. Definitions and International Classification of Diseases codes used categorization are described in **Supplementary Table 1** (18, 19). Vital registration and verbal autopsy data are used as inputs into the Cause of Death Ensemble modelling (CODEm) framework to estimate deaths due to stroke and stroke subtypes (1,2). CODEm is a flexible modelling tool that utilises geospatial relationships and information from covariates to produce estimates of death for all locations across the time series (1990–2019). Deaths from vital registration systems coded to impossible or intermediate causes of death or unspecified stroke are reassigned using statistical methods (1,2,20,21). Methods used for assigning cause of death to stroke and stroke subtypes in regions where neuroimaging is not available have been previously described in detail (1,11-13).

Study Design: This study has analysed the burden of stroke using GBD data for all countries included in EU-53 (WHO definition of Europe), its three subregions (Central, Eastern and Western Europe), EU-28 (countries included in the European Union in 2019 plus the United Kingdom) and all 53 individual countries making up EU-53 for both 2019 and 2010 (**Supplementary Table 2**). Epidemiological estimates for incidence, prevalence, deaths, DALYs, YYLs and YLD for *i)* all stroke, *ii)* ischemic stroke (IS), *iii)* intracerebral haemorrhage (ICH) and *iv)* subarachnoid haemorrhage (SAH) were calculated and analysed. Standard life expectancy of the individual countries has been obtained using the lowest observed age-specific rates of mortality among populations in the world greater than 5 million. (1, 16, 20, 21) Absolute numbers, age-standardized rates per 100,000 population/year, age-standardized rates by gender, rates for the population under the age of 70 years of age and for the population ≥ 70 years of age (70+) for incidence, prevalence, death and DALYs for the years 2010 and 2019 have been presented, as well as the difference

between 2010 to 2019, given as percentage. Stroke-deaths attributable to risk factors for countries included in EU-53 and EU-28 were extracted from the GBD results tool and provided for both 2010 and 2019 in visual form. The exact methodology of how this was performed has been explained in detail previously (22). All estimates are given with a 95% uncertainty interval (UI), derived from the 25^{th} and 975^{th} ordinals of 1000 draws of the posterior distribution at each step of the burden estimation process (1). An increase in the absolute number or rate from 2010 to 2019 has been defined as a positive change between 2010 and 2019, wherein 0 can be in the limits of the UI interval, but cannot be included inside the UI interval (ie. [UI, 0 to +13%] has been considered a significant increase, but [UI, -3 to +13%] would not be considered a significant increase). Similarly, a decrease in the absolute number or rate between 2010 and 2019 is considered as any negative change between 2010 and 2019, in which the UI does not cross the zero line. Negative changes between 2010 and 2019 have been represented throughout the tables with a (-) sign.

Results

1. Incidence (Figure 1)

- ***EU-53:*** There was a 2% (95% UI, 0 to 4%) increase in the total number of incident strokes between 2010 and 2019, from 1,767,280 to 1,802,560 total incident strokes in 2019, 70% of which were attributable to IS **(Figure 1A, Supplementary Table 3).** Absolute numbers of IS and SAH increased by 3%, while ICH decreased by 4% (**Supplementary Table 4**). Age-adjusted incidence rates, however, decreased by 10% (UI, -12 to -8%) from 132.3 to 118.7 per 100,000 people, with consistent reductions in all stroke subtypes **(Figure 1B).** Despite a higher total number of incident strokes in women (1,029,427 vs. 773,133 in men, 2019), both genders presented similar age-adjusted incidence rates (116.9 in women vs. 118.8 in men, per 100,000, 2019) (**Figures 1A and 1B**). Between 2010 and 2019, all EU-53 countries showed

either stability or reduction of age-standarized incidence rates, with the largest reductions observed in Norway, Austria and Israel (**Figure 1C**). The lowest age-standardized incidence rate was observed in Switzerland, with 58.9 new cases per 100,000 (**Figure 1D**). Other countries with incidence rates under 65 included Ireland, France, Luxembourgh and the UK. Overall, however, there were large discrepancies, with multiple countries presenting incidence rates higher than 230 per 100,000, including Turkmenistan, Montenegro and Bulgaria. Of EU-53 countries, Northern Macedonia presented the highest age-adjusted incidence rate, at 259.3 per 100,000, 4.4x times higher than Switzerland **(Figure 1D).** An 8% (UI, -11 to -5%) reduction in incidence rates was observed in the population 70+, whilst remaining stable in those < 70 (**Figure 1E**). Finally, when analysing EU-53 by subregions, Eastern Europe reported the highest absolute number of incident strokes (629,928), followed by Western and Central Europe, with stable rates between 2010 and 2019 in all subregions (**Supplementary Table 5**)**.** Age-standardized incidence rates, however, decreased consistently across all subregions (**Figure 1F**), expect for those <70 in Eastern and Central Europe, were they remained stable. The highest age-standardised incidence rate was observed in Eastern Europe, which was 2.75x higher than in Western Europe, despite all subregions presenting significant rate reductions over the last 10 years.

- ***EU-28***: In contrast to EU-53, the absolute number of incident strokes in EU-28 remained stable during this period (**Figure 1A**), with a total of 844,239 incident strokes in 2019. Age-adjusted incidence rates for all-stroke decreased by 12% (UI, -14 to -10%) between 2010 and 2019, from 95.4 to 83.9 per 100,000. In 2019, these were 0.71x lower in EU-28 in comparison to EU-53 (**Figure 1C**). In EU-28, age-standardarized rates for women and men showed an 11% (UI, -14 to -8%) and a 13% (UI, -16 to -11%) reduction for all-stroke. In contrast to EU-53, all-stroke in EU-28 showed a reduction of rates not only for the 70+ population (-11 reduction, UI -14 to -7), but also for the population < 70 (-3% reduction, UI -7 to 0%) (**Figure**

1E). Except Switzerland, countries presenting lowest incidence rates were part of EU-28. In EU-28, countries with the highest age-standardized incidence rates were Bulgaria, with 236.24 new cases per 100,000, Romania (184.4) and Latvia (183.6) (**Figure 2**).

2. Prevalence (Figure 3):

- ***EU-53*:** The total number of prevalent strokes increased by 4% (UI, 3 to 5%) between 2010 and 2019, from 13,701,815 to 14,261,365 total prevalent cases in 2019 (**Figure 3A**). Ischemic strokes accounted for 78.9% of prevalent strokes, while ICH accounted for 14.4% and SAH for 10.6%. The largest increase in absolute prevelance numbers was observed for IS (**Supplementary Table 4**). Age-adjusted prevalence rates, however, decreased by 6% (UI, -7 to -5%) for all-stroke between 2010 and 2019, from 1,056 to 989 per 100,000 people, a decrease that was consistent for all stroke subtypes and for both men and women (**Figure 3B**). Women presented both significantly larger absolute prevalence numbers, but also 1.2 - 1.3x higher age-adjusted prevalence rates for all-stroke (1,067.6 vs 899.2), IS (831.6 vs 689.6), and for SAH (129.8 vs 97.2). All EU-53 countries showed either stability or reduction of the age-standarized prevalence rates, with the most significant reductions between 2010 and 2019 observed in Denmark, Kyrgyzstan and Kazakhstan **(Figure 3C).** Switzerland presented the lowest age-standardized prevalence rate in 2019, with 608 prevalent cases / 100,000 people. Other countries with age-standardized prevalence rates below 650 were Italy, France and Ireland. In contrast, Northern Macedonia and Bulgaria had the highest age-adjusted prevalence rates, both over 1,600 per 100,000 people (**Figure 3D**). Stroke prevalent cases in the population 70+ showed an 8% (UI, -10 to -6%) decrease. However, in the population <70, in contrast to incidence rates, they increased by 4% (UI, 2 to 5%) (**Figure 3E**). Finally, when analysing EU-53 by subregions, absolute prevalence numbers increased in Western and

Central Europe, while remaining stable in Eastern Europe. Overall, age-standardized prevalence rates decreased for all subgroups (**Figure 3F**). However, there was a 4 and 5% increase in age-standardized prevalence rates for the population <70 in Eastern and Central Europe. The highest age-standardised prevalence rate was observed in Eastern Europe, which was 1.89x higher than in Western Europe.

- ***EU-28***: The absolute prevalence also increased by 4% (UI, 2 - 5%) between 2010-2019, from 7,099,527 to 7,350,739 prevalent cases in 2019 (**Figure 3A**). IS and SAH absolute prevalent cases increased by 4% (UI, 2-6%) and 6% (UI, 4 – 8%), respectively, while ICH cases decreased by -2% (UI, -3 – 0%). Age-standardized prevalence rates, however, decreased by 6% (UI, -8 to -5), from 848 to 795 per 100,000 (**Figure 3B**). Although both EU-53 and EU-28 showed significant decreases in age-standardised prevalence rates, these were 0.80x, 0.82x, 0.68x and 0.87x times lower for all-stroke, IS, ICH and SAH in EU-28. Similar to EU-53, prevalent cases in the population < 70 also increased (2%, UI, 0 to 4%). Finally, the majority of countries with low prevalence rates were part of EU-28. Here, countries with the highest age-standardized incidence rates were Bulgaria, with 1605.2 prevalent cases per 100,000, Romania (1327.7) and Hungary (1236.6) (**Figure 2**).

Age-standardized incidence and prevalence rates for each of the 53 countries included in EU-53, for both sexes, men and women can be found in **Supplementary Table 6**.

3. Deaths (Figure 4):

- EU-53: The total number of all-stroke deaths remained stable between 2010 and 2019 (**Figure 4A**), with 1,176,328 deaths due to stroke registered in 2019. Of these, 70%, 24.5% and 5.5% were accounted for by IS, ICH and SAH, respectively (**Supplementary Table 4**). Age-standardized mortality rates saw a significant reduction, decreasing by 18%

(95% UI, -22 to -14%) between 2010 and 2019, from 81.5 to 66.8 per 100,000 (**Figure 4B**). Despite a higher absolute number of deaths in women, age-adjusted mortality rates were 0.87x lower in women than in men (61.9 vs. 71.3). In 2019, stroke was the leading cause of death in Montenegro, North Macedonia and Portugal **(Supplementary Figures 1)**. Countries presenting the largest reductions in age-adjusted mortality rates between 2010 and 2019 were Luxembourg, Armenia and Kyrgyzstan (**Figure 4C**). In 2019, Switzerland, Iceland and Andorra presented the lowest age-adjusted mortality rate, with < 25 deaths per 100,000; while Northern Macedonia and Montenegro had the highest rates, with > 200 deaths per 100,000 people **(Figure 4D).** Death rates in Montenegro were 12.5x higher than in Switzerland. In this regard, significant discrepancy in stroke-deaths attributable to risk factors exist throughout EU-53 (**Figure 5A and B**). Death rates in the population 70+, similarly to incidence rates, decreased by 11% (UI, -15 to -7%), whilst remaining stable in those <70 years (**Figure 4E**). Finally, when looking at the three subregions, the absolute number of stroke-related deaths increased by 9% (UI, 6-12%) in Western Europe, while remaining stable in Eastern and Central Europe. The highest age-adjusted mortality rate, but also biggest decrease between 2010 and 2019, was observed in Eastern Europe (167 to 131, 21% decrease [95% UI, -28 to -15%]), followed by Central Europe (116 to 95, 18% decrease [95% UI, -26 to -9%]) and lastly by Western Europe (37 to 32, 13% decrease [95% UI, -15 to -10%]) (**Figure 4F**)**.**

- ***EU-28***: In contrast to EU-53, a 6% (UI, 1 to 10%) increase in the number of stroke-related deaths was observed in EU-28, from 507,628 to a535,742 deaths in 2019, mainly attributable to a 7% increase of deaths caused by IS and SAH (UI: 2-12% for IS, and 1-12% for SAH) (**Figure 4A**). Age-adjusted mortality rates, however, decreased by 15% (95% UI, -18 to -11%) from 49 to 42 per 100,000 (**Figure 4B**), with the greatest reduction observed for ICH mortality (from 13 to 11, -16% decrease [95% UI, -20 to -12%]). Although the age-adjusted mortality rate reduction was smaller for EU-28 in comparison to EU-53, age-adjusted mortality rates for all stroke, IS, ICH and SAH were 0.62, 0.61, 0.64 and 0.76 lower in EU-28

than in EU-53, respectively. Reduction of age-adjusted rates was similar in both women and men. In contrast to EU-53, mortality rates in the population <70 in EU-28 also showed a 9% reduction (UI, -16 to -3%) between 2010 and 2019 (**Figure 4E**). In EU-28, the country with the lowest age-standardized mortality rates was France, with 24.54 deaths per 100,000, whilst the country with the highest rate, 7.8x higher than France, was Bulgaria, with 191.54 deaths per 100,000 (**Figure 2**). Although there is also significant discrepancy in stroke-deaths attributable to risk factors, its distribution is more consistent than in EU-53 (**Figure 5B**), with Bulgaria and Romania passing 250 deaths per 100,000 attributable to risk-factors. In the majority of countries, however, this rate was under 100. The rate of stroke-deaths attributatble to risk factors for 2010 can be found in **Supplementary Figures 2 and** 3.

4. DALYs

- ***EU-53*:** The total number of DALYs decreased by 7% (UI, -12 to -3%), from 22,043,161 to 20,501,446 in 2019, of which 62.3%, 29% and 8.1% were accounted by IS, ICH and SAH, respectively (**Figure 6A, Supplementary Table 3 and 4**). Of all age-adjusted rates evaluated in EU-53, DALYs showed the largest reduction, with a 19% decrease between 2010 and 2019 (**Figure 6B**). IS was the stroke subtype with the largest reduction (-23%, UI, -19 to -16%). Despite higher absolute numbers of stroke DALYs in women, age-adjusted rates were 0.79x, 0.88x, 0.63x and 0.86 lower in women than men, for all-stroke, IS, ICH and SAH, respectively. Countries with the largest decrease in age-standardized DALYs between 2010 and 2019 were the Republic of Moldova and Kyrgyzstan, followed by Luxembourg and Armenia (**Figure 6C**). In 2019, Switzerland presented the lowest DALY rates, at 372 per 100,000 people. Other countries with rates below 450, were Iceland and Andorra. In contrast, Northern Macedonia, Uzbekistan and Turkmenistan presented rates of over 3500 DALYs/100,000 people (**Figure 6D**). Stroke was the leading cause of death and DALYs in

Montenegro, North Macedonia and Portugal. Regarding EU-53 subregions, the absolute number of DALYs remained stable in Central and Eastern Europe, while it decreased by 15% (UI, -22 to -7) in Eastern Europe. Despite larger reductions observed in Eastern and Central Europe age-adjusted DALY rates, significant discrepancies exist between regions, with rates being 4.5x higher in Eastern Europe in comparison to Western Europe (**Figure 6F**). Interestingly, despite Eastern Europe presenting the highest incidence, prevalence, death and DALY age-standardized rates of the three European subregions, Central-Europe presented the highest stroke prevalence rate in the population 70+.

- ***EU-28***: In comparison, the total number of DALYs remained stable, with 8,155,623 DALYs attributable to stroke in 2019 (**Figure 6A**). Here, too, age-standardized DALYs showed the biggest reduction in EU-28 of all evaluated parameters (16% decrease; 95% UI, -19 to -12%) (**Figure 6B**). Although the age-adjusted DALY rate reduction was smaller for EU-28 in comparison to EU-53, age-adjusted DALYs for all stroke, IS, ICH and SAH were 0.58, 0.57, 0.55 and 0.74 lower in EU-28 than in EU-53, respectively. Reduction of age-adjusted rates was similar in both women and men, with women having an age-adjusted DALY rate 0.90x, 0.87x, 0.63x lower than men for all-stroke, IS and ICH in 2019, respectively. In EU-28, the country with the lowest age-standardized DALY rates was France, with 453.6 DALYs per 100,000, whilst the country with the highest rate, 7.5x higher than France, was Bulgaria, with 3390.2 DALYs per 100,000 (**Figure 2**).

Age-standardized death and DALY rates for each of the 53 countries included in EU-53, for both sexes, men and women can be found in **Supplementary Table 7**.

Discussion

This study reflects significant geographic variations in the burden of stroke across EU-53, EU-28, Western, Central and Eastern Europe, as well as between individual countries.

While similar general trends were observed across EU-53 and EU-28, there were considerable discrepancies between individual countries. Comparison of age-adjusted mortality and DALY rates in countries with the lowest versus highest stroke burden showed some countries presenting rates up to 12x higher. These differences were more evident across EU-53 countries, however, relevant discrepancies were also observed across EU-28 countries, with Bulgaria, Hungary, Latvia, Lithuania, Romania and Slovakia presenting the highest incidence and prevalence rates. Interestingly, while Bulgaria, Latvia and Romania presented equiparable death and DALY rates, Hungary, Lithuania and Slovakia had death and DALY rates similar to the rest of EU-28 countries **(Figure 2).**

Absolute numbers of first-ever-in-a-lifetime-strokes and stroke prevalence increased throughout Europe, with the highest increase in EU-28 and Western Europe. These findings may be explained by the long life-expectancy in these countries, alongside a rising incidence of age-related diseases. Europe's population is also continuously growing, with an estimated 930 million people living in EU-53 in 2019, 35 million more than in 2010 (3.7% increase) (23). Most EU-53 countries saw a population increase (**Supplementary Figure 4**), with Tajikistan, Luxembough and Kyrgyzstan presenting the largest population growth (24%, 21% and 18%, respectively) between 2010 and 2019 (23). Eighteen countries, however, presented a population decline, with Latvia and Lithuania suffering the largest reductions (- 10 and -11%, respectively). During the same period, the estimated population in EU-28 grew only by 1.9%, from 503 to 512 million in 2019 (23) (**Supplementary Table 8**). Despite a lower population growth in EU-28, the median age was higher (41.9 vs. 38.6 years in EU-28 and EU-53, respectively). (23). In order to achieve a 10% reduction in the absolute number of strokes by 2030 and reach the target proposed by the European Stroke Action Plan (7), approximately 84,000 strokes would need to be prevented over 2020-2029 in EU-28. The population in EU-28 is projected to remain relatively stable, with estimates suggesting 512.48

million people in 2027 (3). Asuming this, an annual 0.08% reduction in stroke incidence would be necessary to achieve a total number 760,000 of strokes in 2030.

In contrast to absolute numbers, age-adjusted incidence, prevalence, death and DALY stroke rates, have decreased consistently in both EU-53 and EU-28, and European subregions. However, although EU-53, and especially Eastern Europe showed considerable improvements in stroke burden within the last decade, its rates remain considerably higher than other European subregions. Interestingly, Kyrgyzstan was one of the countries with the largest reductions in age-adjusted prevalence, death and DALY rates between 2010-2019. Similar to previous publications, more than 90% of the stroke burden remains attributable to modifiable risk factors, especially high blood pressure. **(Figure 5)** (1, 24-26). Here, again, there are significant discrepancies between countries, with Bulgaria and Romania showing very high rates of high blood pressure, dietary risks and tabacco consumption, similar to other Central and Eastern European countries which are not part of EU-28 (**Figure 5**).

Finally, alongside risk-factor prevention, nationwide implementation of stroke units could substantially improve acute stroke management and post-stroke rehabilitation. Unfortunately, there is no Europewide accepted definition of what a “stroke unit” should actually be, and here again, large disparities can be observed between countries (6). For example, although significant improvement have been made in the amount of resource allocation for stroke unit creation in Spain, stroke units tend to be concentrated in highly populated areas, so that autonomous regions like Madrid, Catalunya and the Vasque Country have significantly more stroke units, while poorer but more extensive areas, such as Andalucia have less stroke units, making access for the population in this area more difficult (27). French data indicates that only 50% of stroke patients are treated in stroke units (28), while 73% of Finnish patients that live within a specific catchment area of a stroke unit are treated in stroke units, compared to only 9% of patients treated in stroke units when they live outside a catchment area (29). These findings suggest large within-country and national variations in the quality and

accessibility of stroke treatment. Similarly, there are also significant variations regarding intravenous thrombolysis (IVT) and endovascular therapy (EVT) (30, 31). Country-level data shows that access to and delivery of acute stroke care are poor or totally lacking in many countries (32), with under 20% of patients with acute ischaemic stroke being provided with IVT, and an overall rate of IVT in incident IS of only 7.3% (29).

Limitations of this study: This study has chosen to focus on the epidemiological burden of stroke, looking specifically at differences observed between different European definitions, regions and country. However, an analysis of risk-factor prevalence and causalities have not been performed, so causative conclusions cannot be drawn from this analysis. Stroke unit accessibility and treatments used have also not been investigated, so that a deeper understanding into stroke treatment and mortality cannot be made. Lastly, it is possible that reporting quality is not the same for all 53 included countries, so that direct comparisons between e.g. Sweden, which has a nation-wide stroke register and Tajikistan may be susceptible to reporting errors.

Conclusion

Although a substantial effort has been made regarding stroke management in Europe, this analysis shows increasing absolute numbers of first-ever-in-a-lifetime-strokes and stroke prevalence in the last 10 years. Furthermore, the disparity of stroke burden across individual European countries, subregions and EU definitions (EU-28 vs EU-53) is significant and warrants further analysis.

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FIGURE LEGENDS AND TABLE TITLES:

Figure 1: Changes in stroke incidence rates in EU-53 and EU-28. Trend-diagrams of the (A) absolute numbers and (B) age-standardized rates of incident strokes. (C) Heatmap of age-standardized annual percentage difference in stroke-incidence rates between 2010 and 2019. (D) Age-standardized incidence rates in 2019 in all EU-53 countries. Trend-diagrams of incident stroke rates in (E) the population 70+ and <70 and (F) by EU-53 subregion.

Figure 2: Age-standardized (A) incidence, (B) prevalence, (C) death and (D) DALY rates for all 28 countries included in EU-28 in 2019, per 100,000 and for both sexes.

Figure 3: Changes in stroke prevalence rates in EU-53 and EU-28. Trend-diagrams of the (A) absolute numbers and (B) age-standardized rates of prevalent stroke cases. (C) Heatmap of the age-standardized annual percentage difference in stroke-prevalence rates between 2010 and 2019. (D) Age-standardized prevalence rates in 2019 in all EU-53 countries. (E). Trend-diagrams of prevalent stroke rates in (E) the population 70+ and <70 and (F) by EU-53 subregion.

Figure 4: Changes in stroke deaths rates in EU-53 and EU-28. Trend-diagrams of the (A) absolute numbers and (B) age-standardized rates of stroke deaths. (C) Heatmap of the age-standardized annual percentage difference in stroke-death rates between 2010 and 2019. (D) Age-standardized death rates in 2019 in all EU-53 countries. (E). Trend-diagrams of death rates in (E) the population 70+ and <70 and (F) by EU-53 subregion.

Figure 5: Stroke-deaths attributable to risk factors in 2019, age-standardized and for both sexes, for (A) the 25 countries in the EU-53, which are not part of EU-28, and (B) the 28 countries included in the EU-28. Note the difference in scales (600 per 100,000 in panel A and 400 per 100,000 in panel B).

Figure 6: Changes in stroke DALYs in EU-53 and EU-28. Trend-diagrams of (A) absolute numbers and (B) age-standardized DALY stroke rates. (C) Heatmap of the age-standardized annual percentage difference in stroke-DALY rates between 2010 and 2019. (D) Age-standardized DALYs in 2019 in all EU-53 countries (E). Trend-diagrams of age-standardized DALY rates in (E) the population 70+ and <70 and (F) by EU-53 subregion.

SUPPLEMENTARY MATERIAL:

Supplementary Table 1: Definitions, level causes and international classification codes used for categorization of stroke and its subtypes by the GBD and in this study.

Supplementary Table 2: List of included countries in EU-53 region, European subregions and EU-28.

Supplementary Table 3: Absolute and relative measures of the burden of stroke in EU-53 and EU-28 for all stroke in 2010, 2019 and the difference between 2010 and 2019.

Supplementary Table 4: Absolute and relative measures of the burden of stroke in EU-53 and EU-28 for stroke subtypes in 2010, 2019 and the difference between 2010 and 2019.

Supplementary Table 5: Absolute and relative measures of the burden of stroke in the three EU-53 European subregions for all stroke in 2010, 2019 and the difference between 2010 and 2019.

Supplementary Table 6: Age standardized incidence and prevalence rates for all stroke.

Supplementary Table 7: Age standardized death and DALY rates for all stroke.

Supplementary Table 8: Population estimates for 2010 and 2019 for all EU-53 countries.

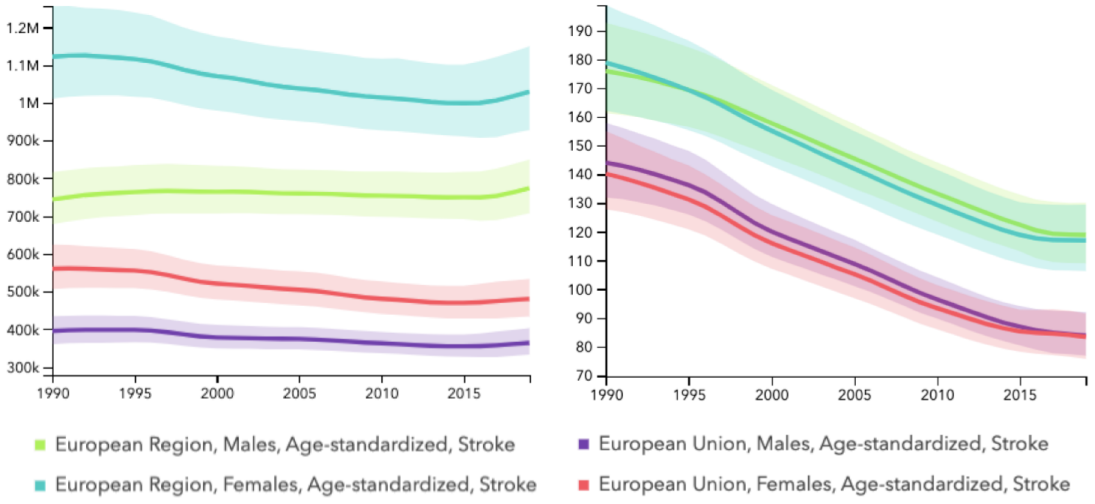
Supplementary Figure 1: Heat diagram showing the distribution of level 3 causes of death in 2019, for both sexes and all ages, for EU-53 countries.

Supplementary Figure 2: Stroke-deaths attributable to risk factors in 2010, age-standardized and for both sexes, for the 25 countries in EU-53, which are not part of EU-28.

Supplementary Figure 3: Stroke-deaths attributable to risk factors in 2019, age-standardized and for both sexes, for EU-28 countries.

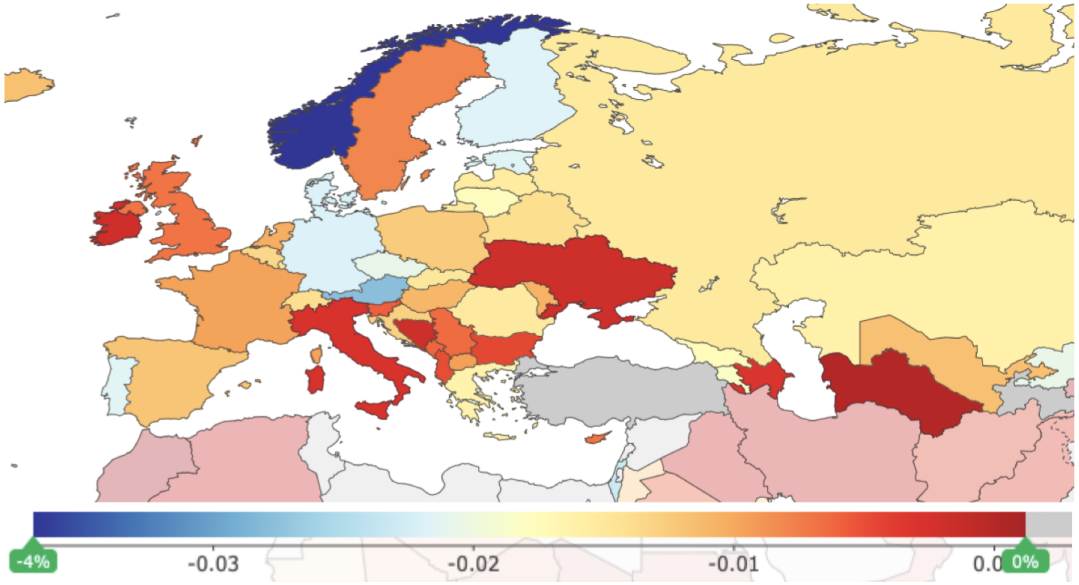
Supplementary Figure 4: Population change (%) between 2010 and 2019 in EU-53 countries.

A. Absolute incident cases, by gender

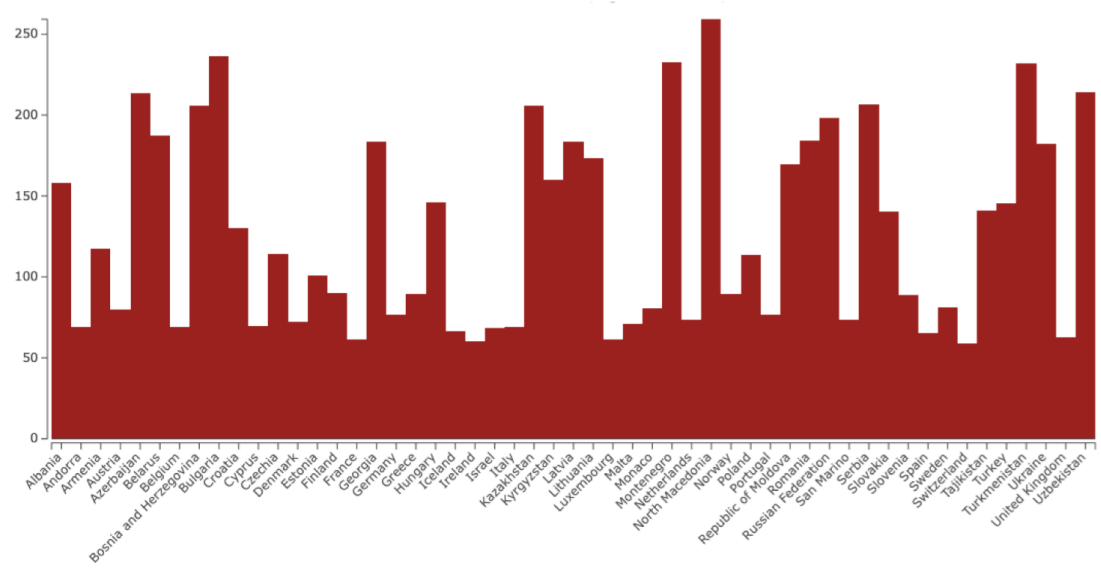


B. Age-standardized incident rates, by gender

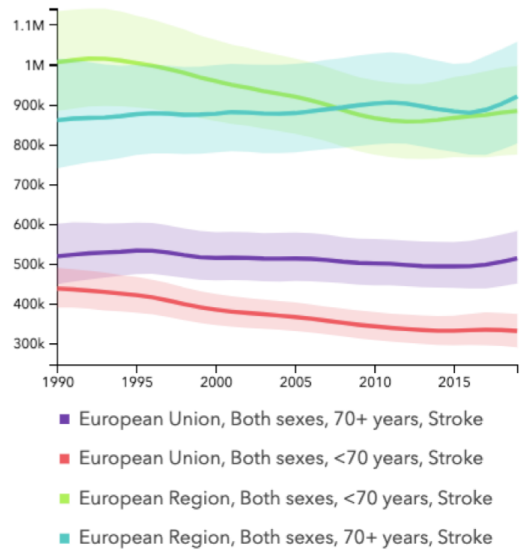
C. Age-standardized incidence annual % difference between 2010-2019



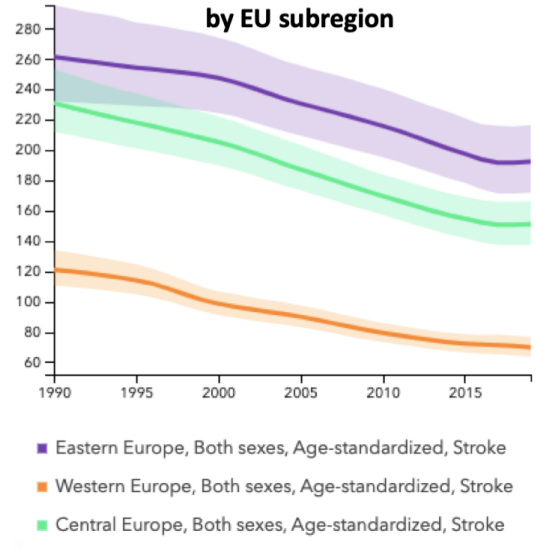
D. Age-standardized incidence rates per 100,000 in 2019, for both sexes, per country



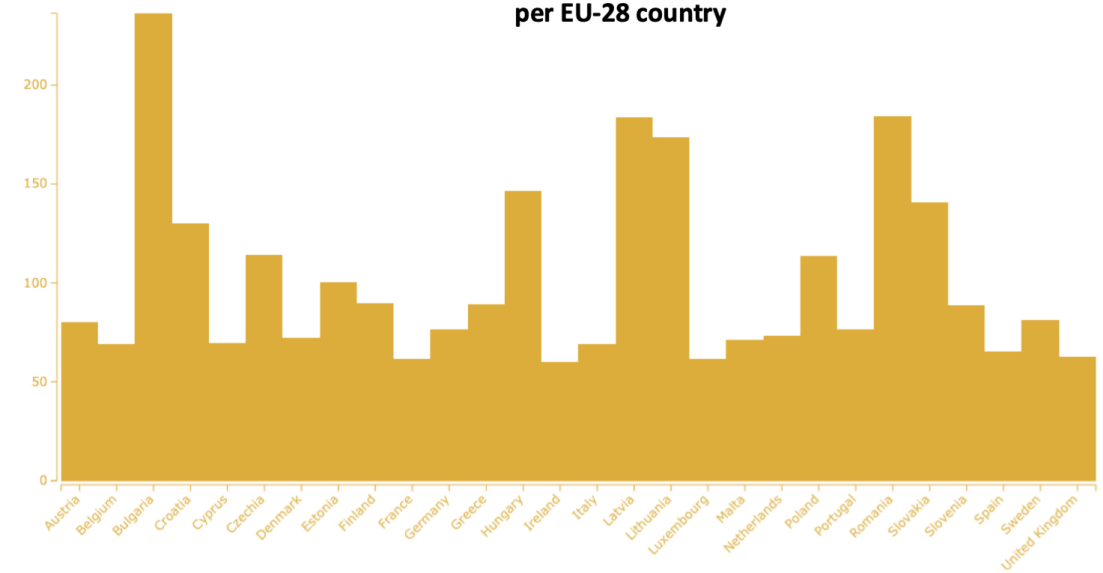
E. Incident cases, by age (70+ and <70)



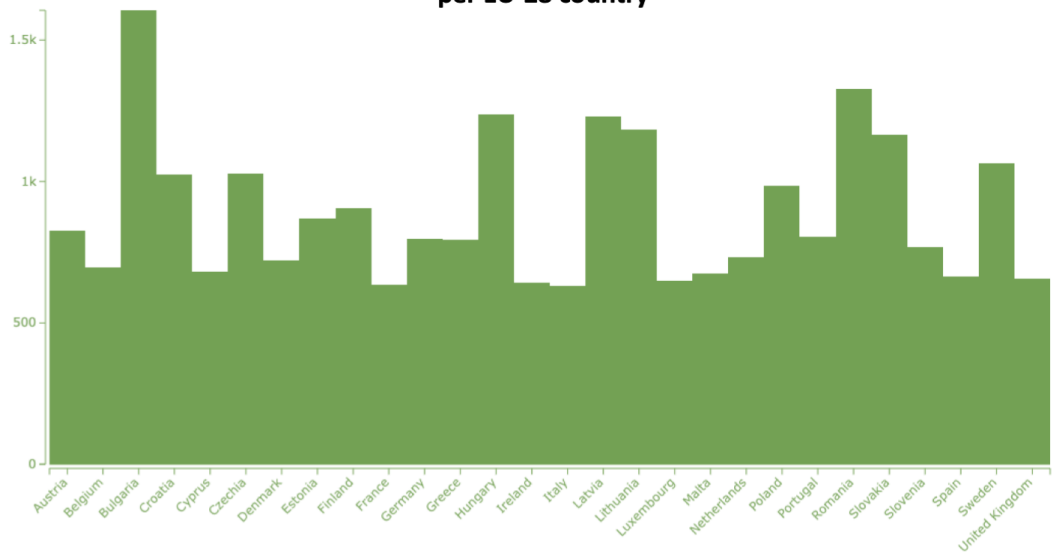
F. Age-standardized incidence rates, by EU subregion



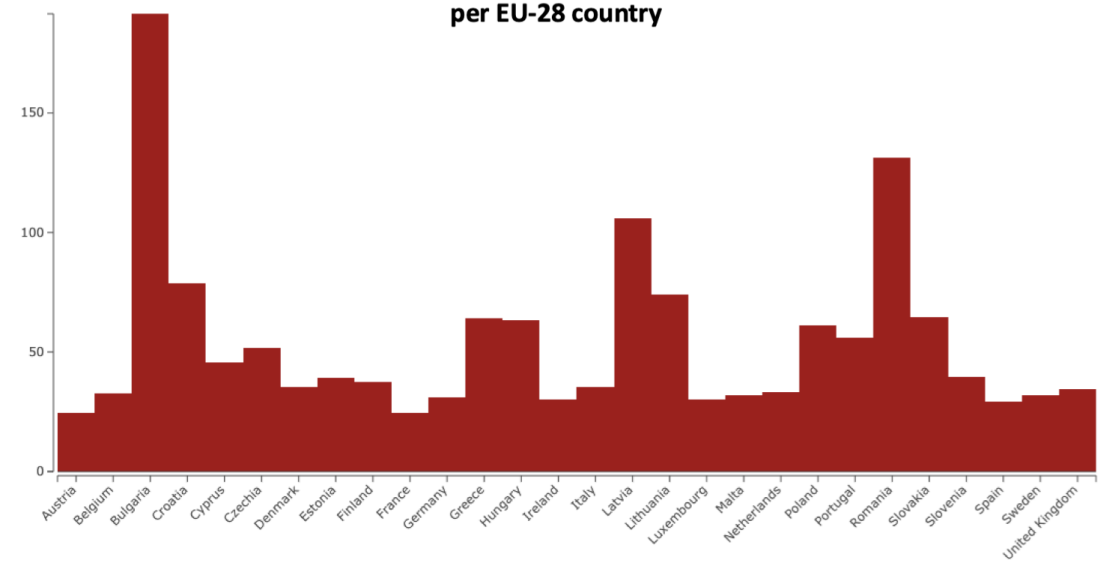
A. Age-standardized incidence rates per 100,000 in 2019, for both sexes, per EU-28 country



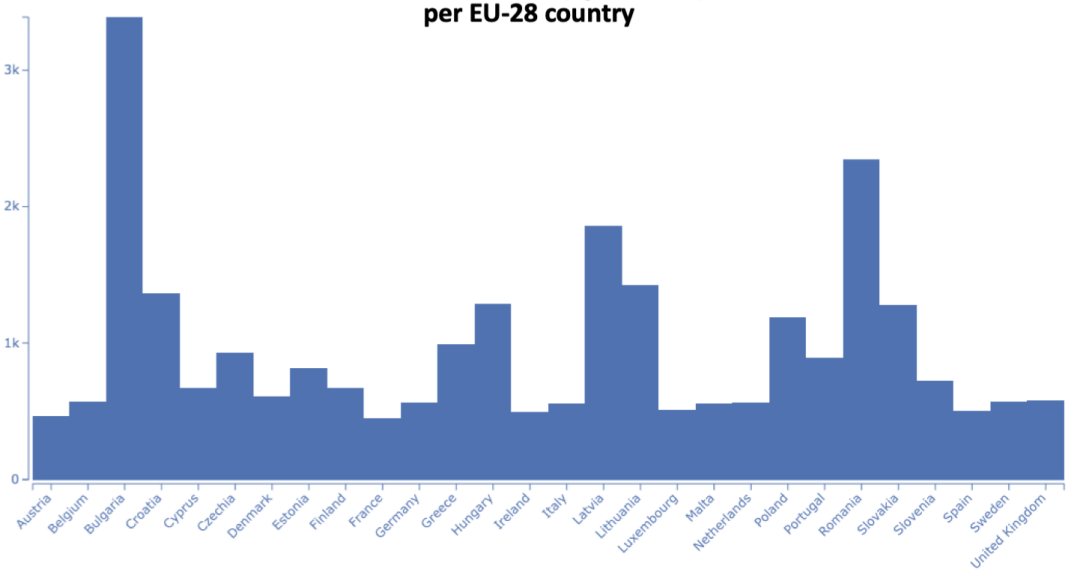
B. Age-standardized prevalence rates per 100,000 in 2019, for both sexes, per EU-28 country



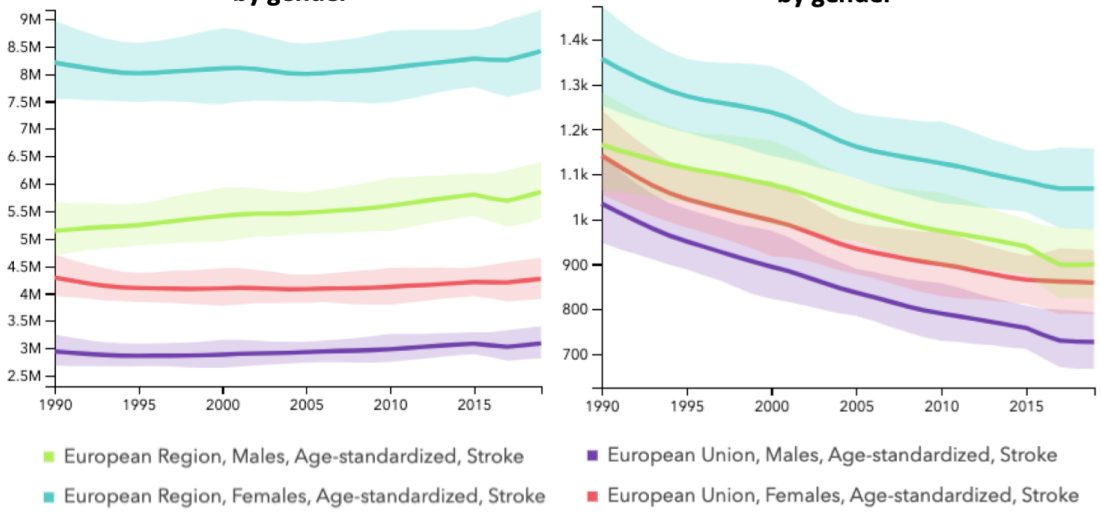
C. Age-standardized death rates per 100,000 in 2019, for both sexes, per EU-28 country



D. Age-standardized DALY rates per 100,000 in 2019, for both sexes, per EU-28 country

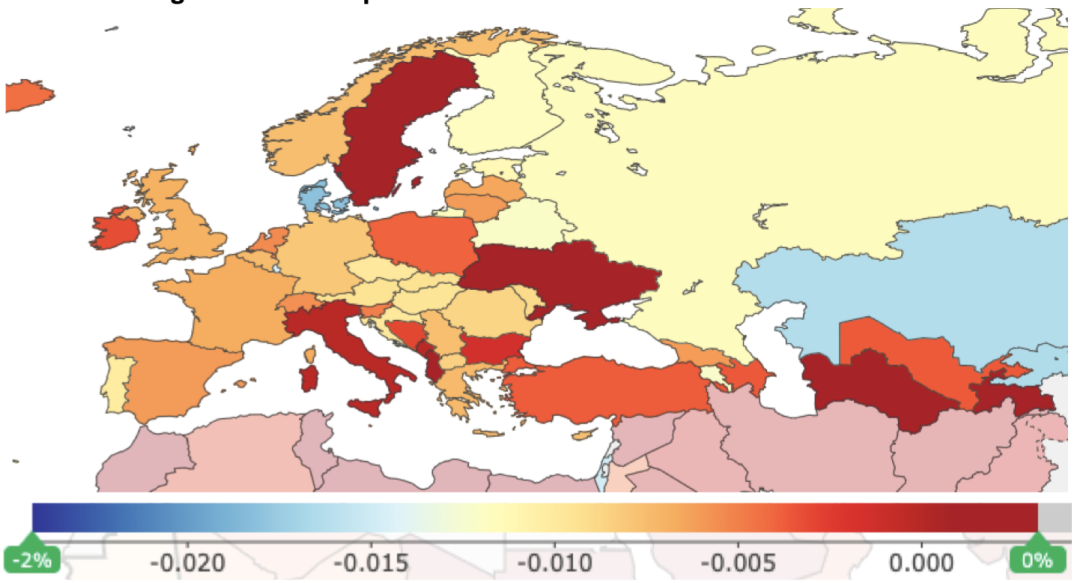


A. Absolute prevalent cases, by gender

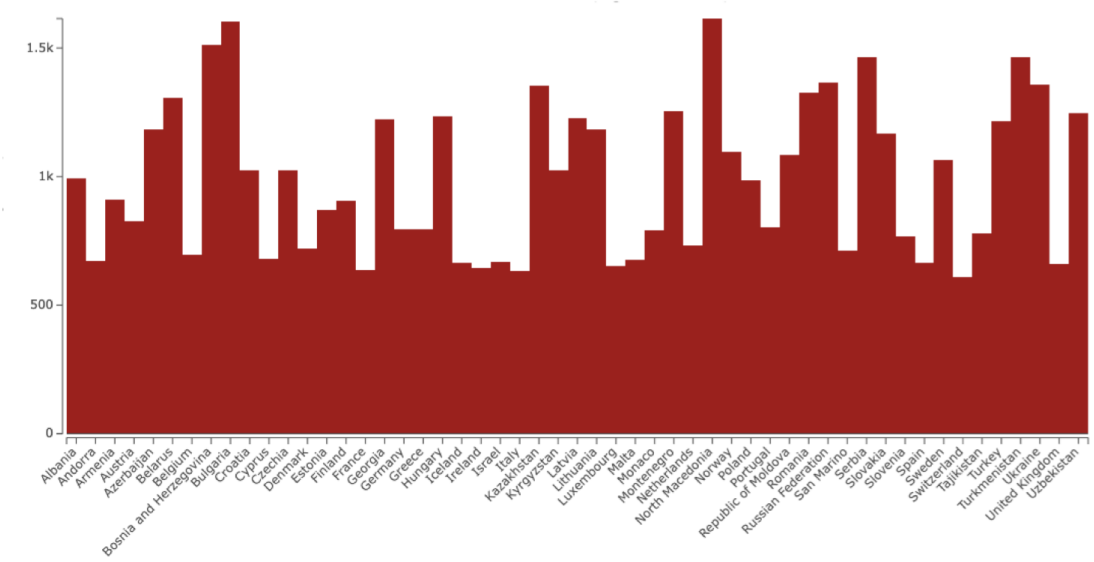


B. Age-standardized prevalence rates, by gender

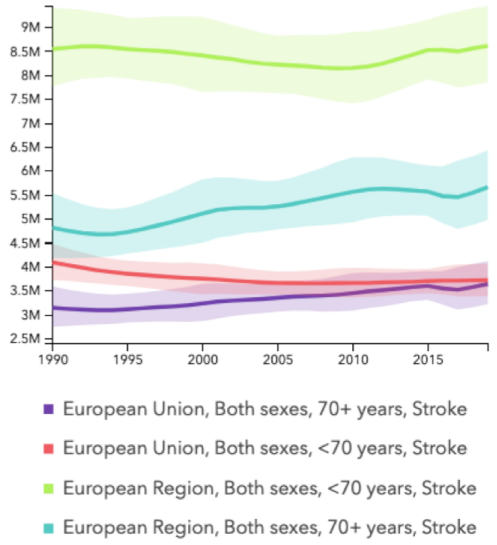
C. Age-standardized prevalence annual % difference between 2010-2019



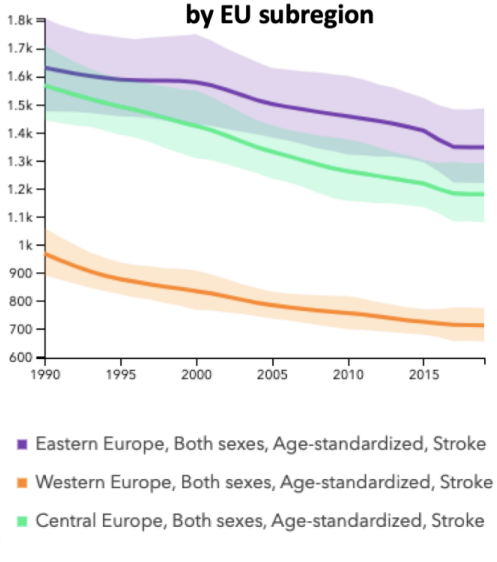
D. Age-standardized prevalence rates per 100,000 in 2019, for both sexes, per country



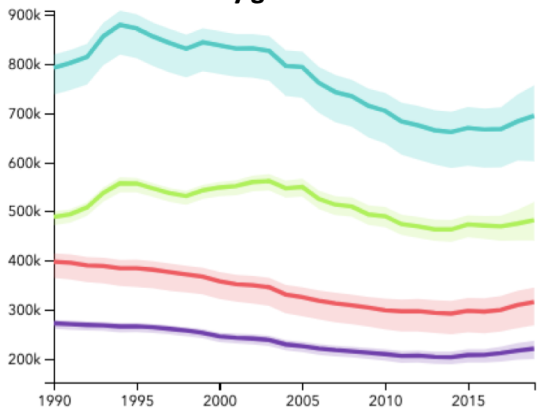
E. Prevalent cases, by age (70+ and <70)



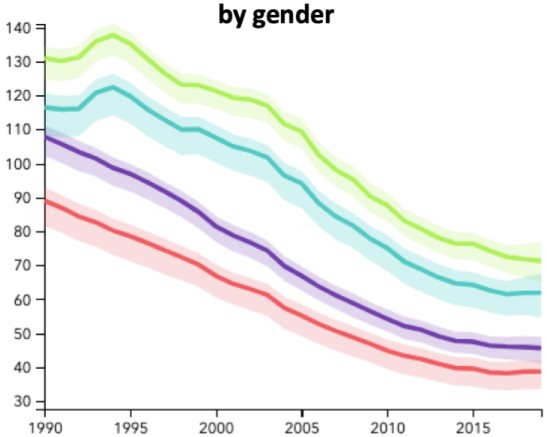
F. Age-standardized prevalence rates, by EU subregion



A. Absolute stroke deaths, by gender

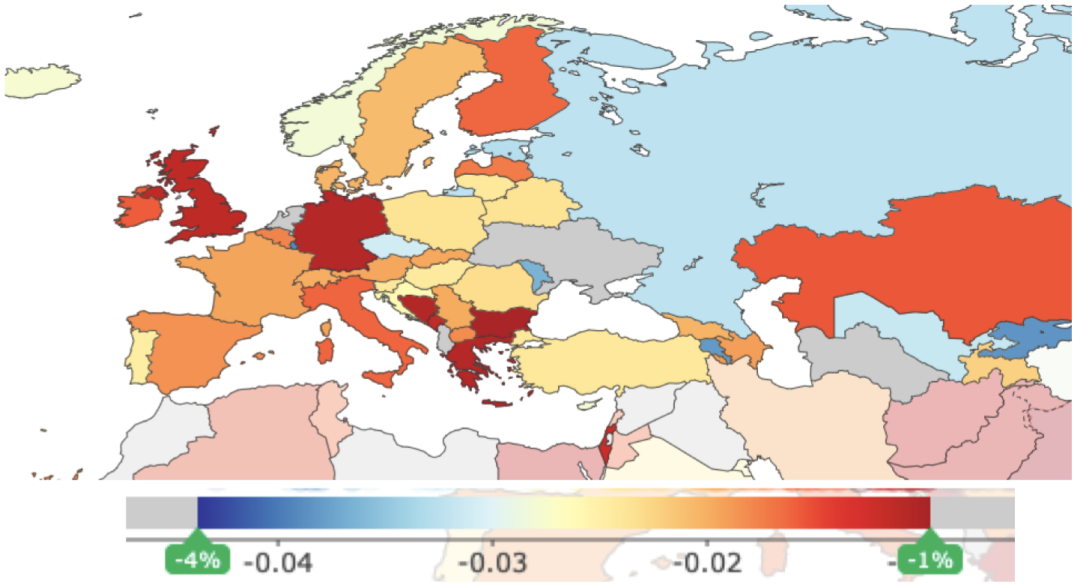


B. Age-standardized death rates, by gender

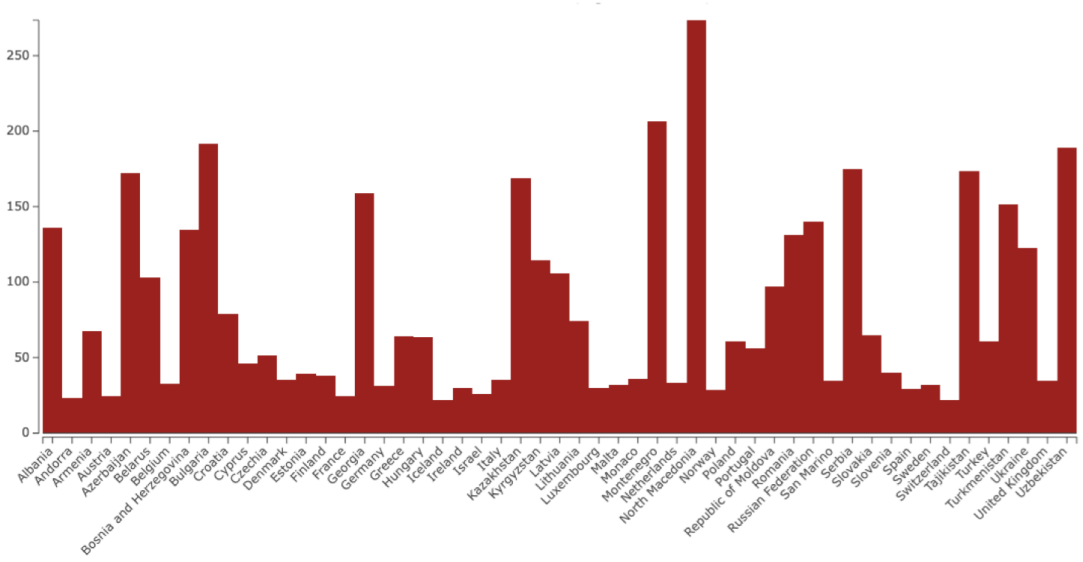


European Region, Males, Age-standardized, Stroke
European Region, Females, Age-standardized, Stroke
European Union, Males, Age-standardized, Stroke
European Union, Females, Age-standardized, Stroke

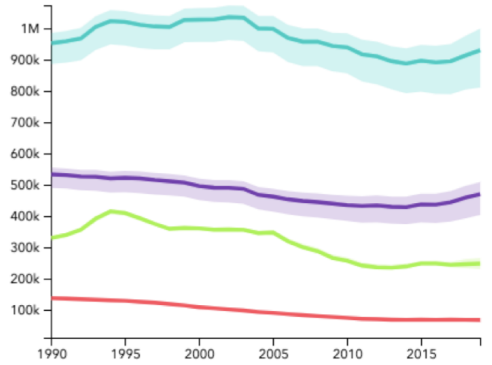
C. Age-standardized death annual % difference between 2010-2019



D. Age-standardized death rates per 100,000 in 2019, for both sexes, per country

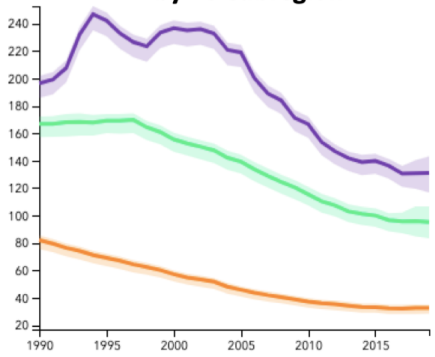


E. Deaths per 100,000, by age (70+ and <70)



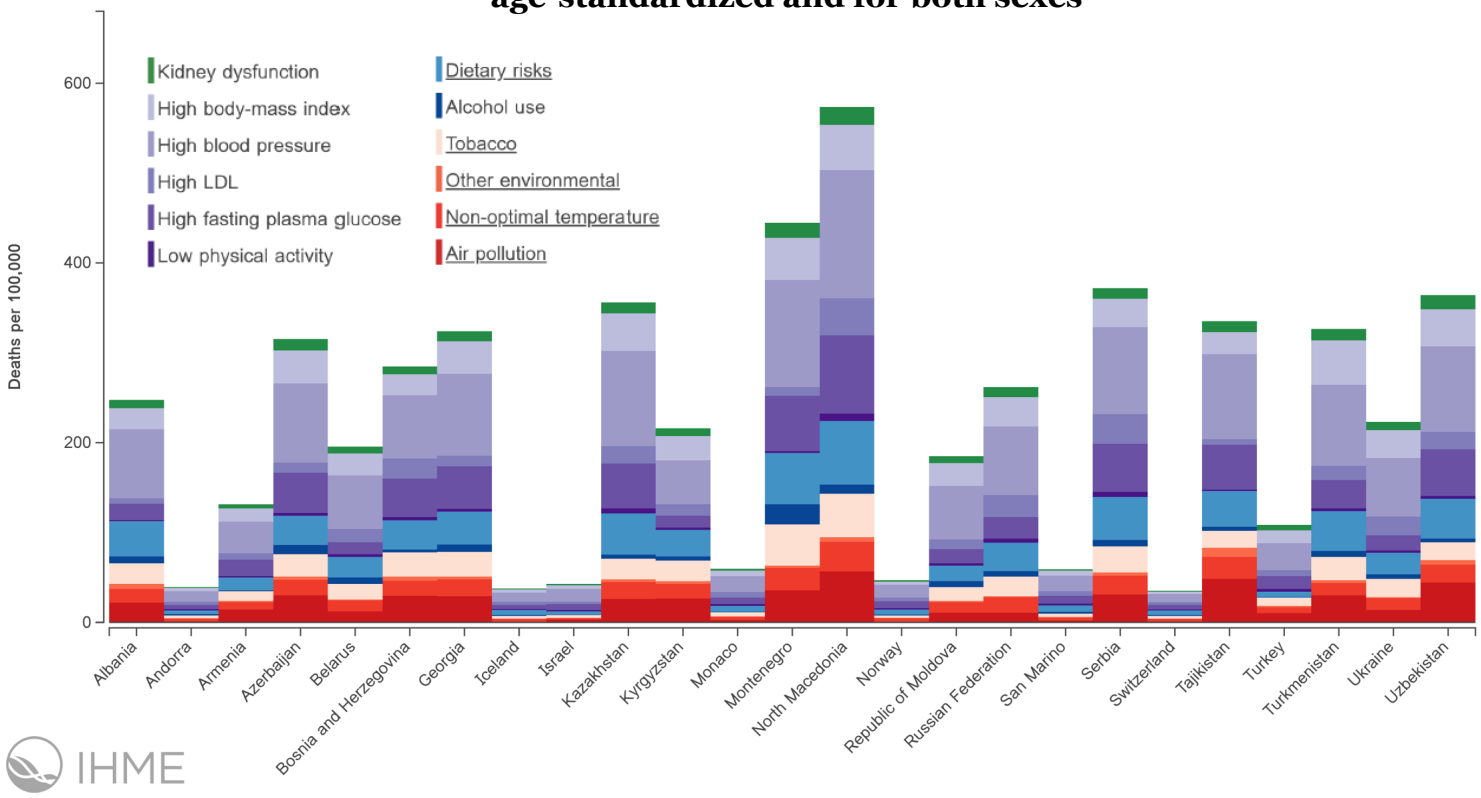
European Union, Both sexes, 70+ years, Stroke
European Union, Both sexes, <70 years, Stroke
European Region, Both sexes, <70 years, Stroke
European Region, Both sexes, 70+ years, Stroke

F. Age-standardized death rates, by EU subregion

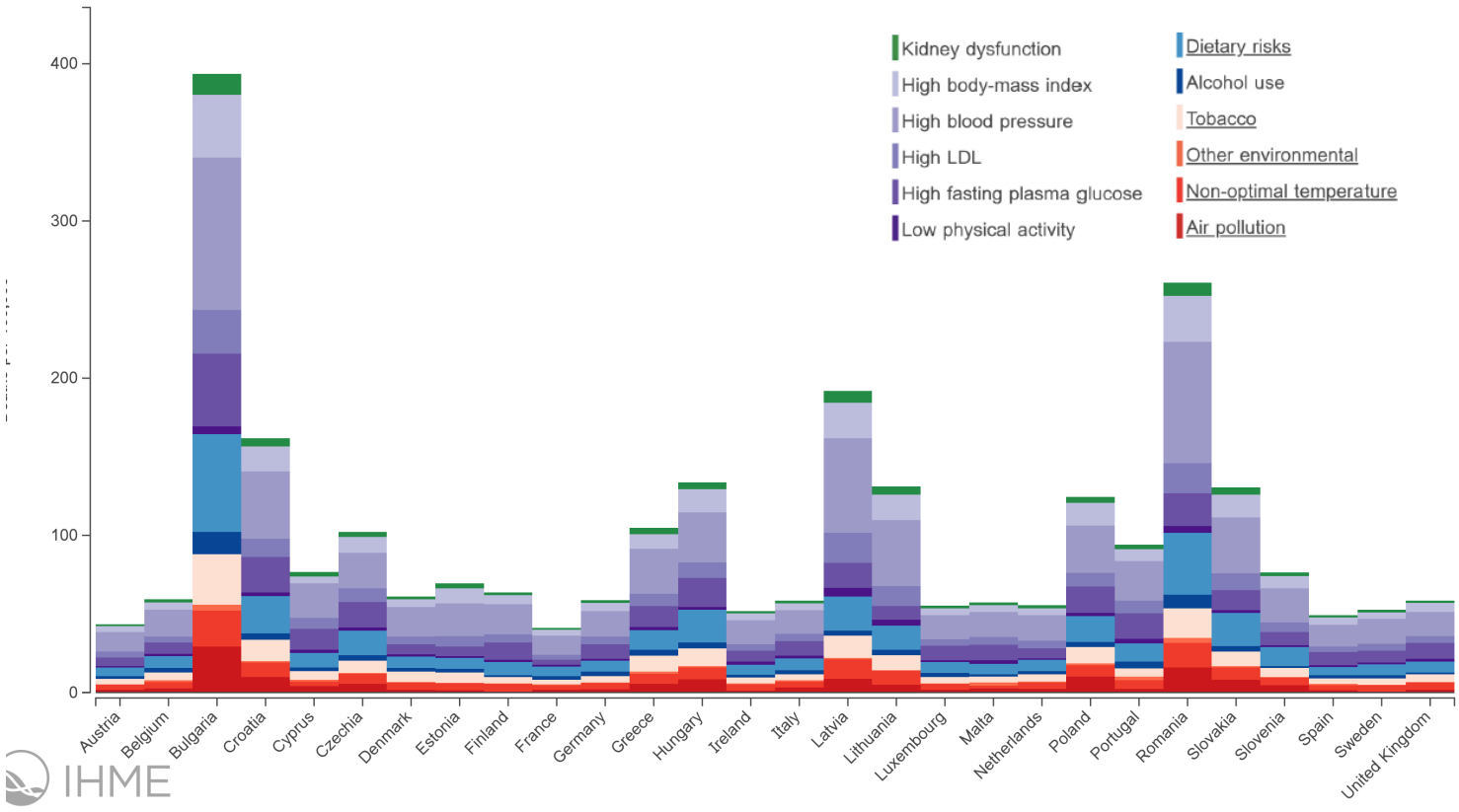


Eastern Europe, Both sexes, Age-standardized, Stroke
Western Europe, Both sexes, Age-standardized, Stroke
Central Europe, Both sexes, Age-standardized, Stroke

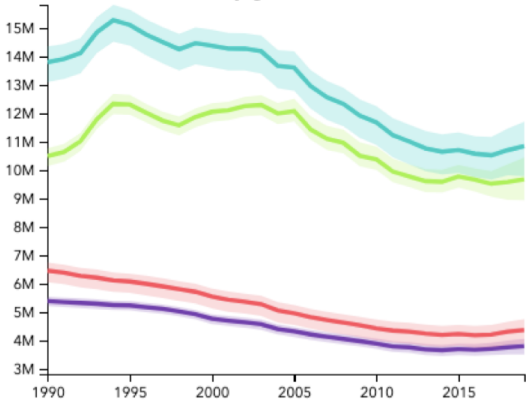
A. Stroke-deaths attributable to risk factors in 2019 for the 25 additional countries in the EU-53 (and not part of the EU-28), age-standardized and for both sexes



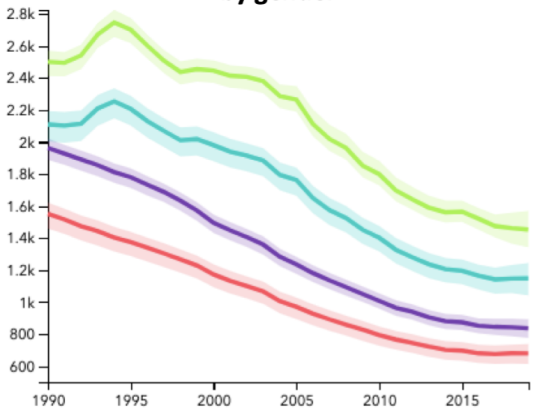
B. Stroke-deaths attributable to risk factors in 2019 for countries in EU-28, age-standardized and for both sexes



A. Absolute DALY cases, by gender

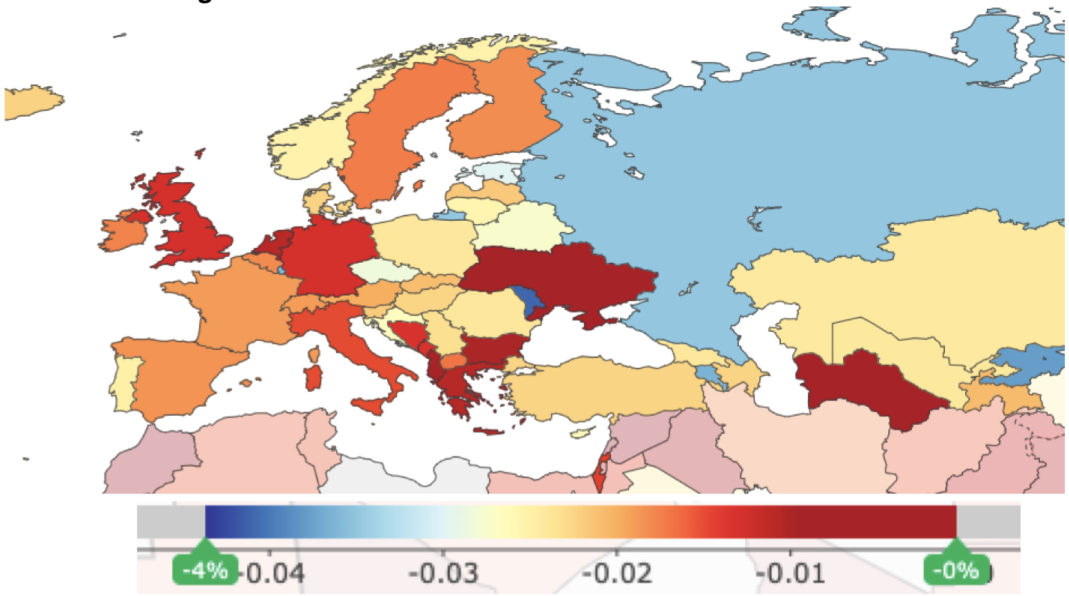


B. Age-standardized DALY rates, by gender

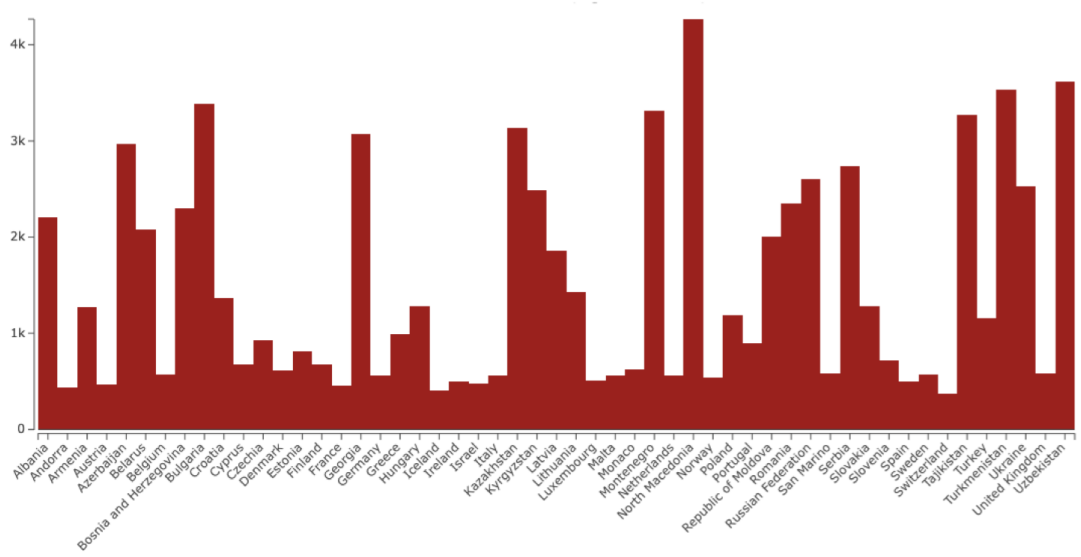


European Region, Males, Age-standardized, Stroke
European Region, Females, Age-standardized, Stroke
European Union, Males, Age-standardized, Stroke
European Union, Females, Age-standardized, Stroke

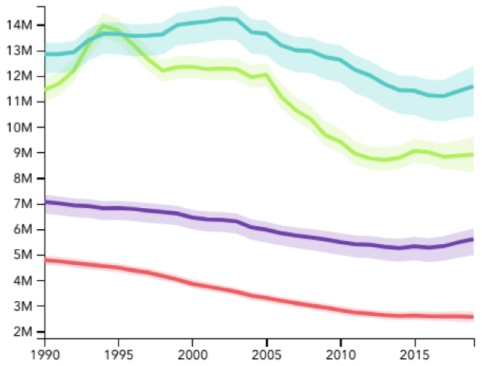
C. Age-standardized DALY annual % difference between 2010-2019



D. Age-standardized DALY rates per 100,000 in 2019, for both sexes, per country

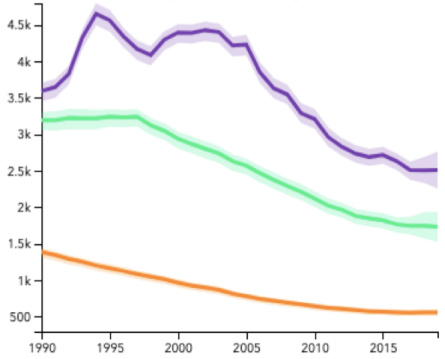


E. DALYs per 100,000, by age (70+ and <70)



European Union, Both sexes, 70+ years, Stroke
European Union, Both sexes, <70 years, Stroke
European Region, Both sexes, <70 years, Stroke
European Region, Both sexes, 70+ years, Stroke

F. Age-standardized DALY rates, by EU subregion



Eastern Europe, Both sexes, Age-standardized, Stroke
Western Europe, Both sexes, Age-standardized, Stroke
Central Europe, Both sexes, Age-standardized, Stroke