

1 **Title: The Burden of Stroke in Europe: An analysis of the Global Burden of Disease study**

2 **findings from 1990 to 2019**

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4 From Carlota F. Prendes, on behalf of the GBD Collaborators

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Research in Context:

Evidence before this study

To evaluate the potential novelty of this study, we performed a comprehensive review of published literature in MEDLINE, Scopus, Google Scholar, and PubMed for relevant reports published up to February 2021, using a combination of search terms that included stroke, cerebral infarction, intracerebral h(a)emorrhage, or subarachnoid h(a)emorrhage, AND incidence, prevalence, mortality, risk factor(s), or disability-adjusted life-year(s) (DALYs), AND Europe or European region.

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) produces the most comprehensive estimates of global, regional, and country-specific burden due to stroke up to now, including all stroke, subdivided into cerebral infarction, intracerebral h(a)emorrhage and subarachnoid h(a)emorrhage. Although the 2019 GBD Collaborator Network stroke paper is currently under development, the most recent paper by the GBD Collaborators dates back to

47 2016, and concluded that the decrease in global age-standardised incidence rates from 1990 to
48 2016 was minimal and that the burden of stroke was likely to remain high well into the future.

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50 **Added value of this study**

51 As part of GBD 2019, this study provides updated estimates of the burden of overall stroke,
52 ischaemic stroke (IS), intracerebral haemorrhage (ICH), and subarachnoid haemorrhage (SAH),
53 specifically targeting countries in the European region (as defined by the WHO), and also
54 looking into trends observed in Eastern, Central and Western Europe during the last decade,
55 contextualizing them in view of the most updated European guidelines and contrasting them with
56 trends observed in Europe during the last 30 years.

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58 **Implications of all the available evidence**

59 Wide variations in policy, management and number of available stroke units exist across Europe.
60 This study helps to show-cast the important disparities that exist between European countries in
61 terms of overall stroke burden, incidence and prevalence, gender differences, age-groups and
62 changes that have occurred during the last 10 years.

63 **Abstract:**

64 **Background:** Stroke was the second-leading cause of death in 2019. While most European
65 Regions appear to perform well in global comparisons, large discrepancies exist within Europe.
66 The objective of this analysis aims to take a more detailed view of the impact of stroke and its
67 subtypes in Europe during the last ten years.

68

69 **Methods:** The GBD 2019 analytical tools were used to evaluate regional and country-specific
70 estimates of incidence, prevalence, deaths and disability-adjusted life-years (DALYs) for the 53
71 countries making up the European Region between 2010 and 2019. Total numbers and age-
72 adjusted rates were collected for ischaemic stroke (IS), intracerebral haemorrhage (ICH),
73 subarachnoid haemorrhage (SAH), and all strokes combined. Results were analysed by specific
74 country, Western, Eastern and Central Europe, the European Union and Europe as defined by the
75 WHO.

76
77 **Findings:** *Total numbers:* From 2010 to 2019, the WHO European region saw an increase in
78 both the incidence (1,767,280 new cases to 1,802,559) and prevalence of total numbers of
79 strokes, while deaths and DALYs decreased by 2 and 7% (UI, -6 to 3%; UI, -12 to -3%),
80 respectively. However, in EU28 and Western Europe, the absolute number of deaths increased
81 by 6% (UI, 1-10%) and 9% (UI, 6-12%), respectively. Ischemic stroke accounted for 70.1% of
82 all stroke-related-deaths (825,184 deaths in 2019, with a 1% decrease since 2010 [UI, -6 to 4%]),
83 intracerebral stroke for 24.5% of deaths (4% decrease [UI, -9 to 0%]) and intracerebral stroke for
84 5.4% (3% increase [UI, -2 to 9%]). *Age-Standardized Rates: Mortality* rates decreased by 18%
85 (UI, -22 to -14%) between 2010 (82 per 100,000 people) and 2019 (67 per 100,000 people) for
86 all-stroke in the WHO European region, with the highest mortality rate, but also biggest decrease
87 observed in Eastern Europe (21% decrease [UI, -28 to -15%]). Age-standardized mortality was
88 most significantly reduced for ischemic strokes in the WHO European region (-19% [UI, -23 to -
89 15%]), while the greatest reduction in the EU28 was observed for intracerebral stroke mortality
90 (-16% decrease [UI, -20 to -12]). Switzerland (22 deaths per 100,000 people, UI, 18 - 25),
91 Iceland (22 deaths per 100,000 people, UI 19 to 25) and Andorra (23 deaths per 100,000 people,

92 UI 18 to 29) had the lowest age-adjusted mortality rates, while Northern Macedonia (274 deaths
93 per 100,000 people, UI 231 to 320), Montenegro (207 deaths per 100,000 people, UI 175 to 135)
94 and Bulgaria (192 deaths per 100,000 people, UI 159 to 227) had the highest – with mortality
95 rates 10-12x higher.

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97 **Interpretation:** Wide variations exist across WHO European member countries, Central,
98 Eastern and Western Europe, as well as within the EU28 member states. Efforts coordinating
99 stroke-prevention strategies, stroke-unit care and IVT, and epidemiological measures may help
100 guide development of country-specific goals.

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102 **Funding:** Bill & Melinda Gates Foundation

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Introduction

Although substantial efforts have been made worldwide in stroke prevention strategies and therapy, stroke has remained the second-leading cause of death and third-leading cause of death and disability in 2019 (1). The Global Burden of Disease, Injuries, and Risk Factors Study (GBD) 2016 stroke analysis reported that age-standardised stroke mortality rates decreased sharply from 1990 to 2016; however, the decrease in age-standardised incidence was significantly less pronounced, suggesting that prevention efforts have been less successful than treatment efforts (2). Results from GBD 2016 have also demonstrated that almost 88% of ischaemic stroke (IS) DALYs (disability adjusted life years) and 90% of haemorrhagic stroke DALYs were attributable to modifiable risk factors, highlighting the importance of risk-factor modification and control to minimize the burden of stroke (2).

When taking a closer look at Europe, the latest Eurostat cardiovascular disease statistics (data extracted in October 2016) report stroke mortality figures showing the highest standardised death rates for stroke in Bulgaria, Romania, Serbia, Latvia, Lithuania, Croatia, Hungary, and Slovakia, while the lowest rates were reported for France, Spain, Luxembourg, Austria, and

138 Belgium, with rates being 7x higher in Bulgaria as compared to France, and with high
139 discrepancies between countries and regions (3). Additionally, there is currently no Europe-wide
140 standardised, nationally collected data on stroke, leading to a significant level of uncertainty, as
141 seen by the widely differing estimates derived from population-based registers and hospital data
142 sets (3).

143 In 2006, the 2nd Helsingborg Declaration stated that one of their main goals was that all
144 patients in Europe suffering from stroke should have access to a stroke unit in the acute phase by
145 2015 (4). The Stroke Alliance for Europe 2020 report, however, that only about 30% of stroke
146 patients across Europe receive stroke unit care, with only 5% of hospitals providing facilities
147 meeting the standards of comprehensive stroke centres (5). Additionally, 51% of participating
148 European hospitals (caring for 42% of all European stroke patients) did not meet minimum
149 standards in stroke care (5). Due to this broad disparity of stroke care in Europe, the European
150 Stroke Organisation (ESO) prepared a European Stroke Action Plan (ESAP) for the years 2018 to
151 2030 in cooperation with the Stroke Alliance for Europe (SAFE), with seven main domains in
152 stroke care: primary prevention, organisation of stroke services, management of acute stroke,
153 secondary prevention, rehabilitation, evaluation of stroke outcome and quality assessment and life
154 after stroke. The pursued targets for 2030 are (1) reduction of absolute number of strokes in Europe
155 by 10%, (2) treatment of at least 90% of stroke patients in a dedicated stroke unit as the first level
156 of care, (3) implementation of national plans for stroke management, (3) and implementation of
157 national strategies for multisector public health interventions (6). This should lead to a
158 harmonisation of stroke care and thereby improvement of outcomes across Europe.

159 Finally, the European Stroke Organization published its guidelines for management of
160 ischemic stroke and transient ischemic attack in 2008, with important differences to prior stroke-

161 management recommendations (7). Since then, although they have published guidelines for the
162 management of intracranial aneurysms and subarachnoid haemorrhage, for the establishment of
163 stroke units and stroke centres, recommendations on best medical treatment of ischemic stroke
164 have not substantially differed, with their newest transient ischemic attack guidelines being
165 published very recently, in February 2021 (8).

166 Considering the optimization of best-medical treatment, updated recommendations and
167 increasing efforts put into the constructions of stroke units in Europe for prevention and treatment
168 during the last ten years, as well as the high discrepancies regarding stroke burden across European
169 countries, we aimed to compare the burden of stroke in the EU28 (the 27 member countries of the
170 EU plus the UK) and WHO European region (53 member countries in 2019), focusing on the
171 differences between 2010 and 2019 and comparing them to reported differences between 1990 and
172 2010.

173

174 **Methodology**

175 The GBD 2019 is a network producing estimates of the burden of 369 diseases and injuries
176 in 204 countries worldwide (1, 9-14). It is an ongoing effort, updated annually, designed to allow
177 for consistent comparison over time from 1990 to 2019, by age and sex, and across locations. (1,9)
178 It produces standard epidemiological measures such as incidence, prevalence, and death rates as
179 well as summary measures of health, such as DALYs (disability adjusted life years), YLD (years
180 of life lost to disability) and YLL (years of life lost) (1,9). All results are available using the GBD
181 Results Tool and GBD Compare website (1,9), and all input data is identified via the Global Health
182 Data Exchange website (10). The study is performed in compliance with Guidelines for Accurate

183 and Transparent Health Estimates Reporting (GATHER) guidelines for reporting health estimates
184 (1).

185 The GBD classifies causes into four levels, from the broadest (Level 1; eg, non-
186 communicable diseases), to the most specific (Level 4; eg, intracerebral haemorrhage). Stroke is a
187 Level 3 cause, while its subtypes are Level 4 causes (15). GBD uses the WHO definition of stroke
188 as “rapidly evolving clinical signs of disturbance of cerebral function lasting more than 24 hours
189 or leading to death” (15). Only first-ever-in-a-lifetime strokes are included in the GBD estimates.
190 Stroke (level 3 cause) is subdivided into *ischemic stroke* (IS), defined as an episode of neurological
191 dysfunction due to focal cerebral, spinal, or retinal infarction, *intracerebral haemorrhage* (ICH),
192 stroke with a focal collection of blood in the brain not due to trauma and *subarachnoid*
193 *haemorrhage* (SAH), non-traumatic stroke due to bleeding in the subarachnoid space (16). The
194 analyses in the current study follows the GBD methodology, which has been previously described
195 in detail, as have been described the methods used for assigning cause of death to stroke and stroke
196 subtypes in regions where neuroimaging is not available. (9-11) It uses vital registration (VR) and
197 verbal autopsy (VA) data as inputs into the Cause of Death Ensemble modelling (CODEm)
198 framework to estimate deaths due to overall stroke and stroke subtypes. (15) CODEm is a flexible
199 modelling tool that utilises geospatial relationships and information from covariates to produce
200 estimates of death for all locations across the time series (1990–2019). Deaths from VR systems
201 coded to impossible or intermediate causes of death or unspecified stroke are reassigned using
202 statistical methods (15,17,18). The GBD 2019 analysed data from 3686 VR sources, 147 VA
203 sources, 368 incidence sources, 117 162 prevalence sources, 229 excess mortality sources, 7753
204 risk factor exposure sources, and 2733 risk 163 factor relative risk sources (see
205 <http://ghdx.healthdata.org/>for further details) (15).

206 In this study, data on GBD outcomes from the countries included in the EU28 were isolated
207 and compared with the WHO European region. According to WHO, the European region includes,
208 in addition to the 28 European countries that were part of the EU28 in 2019, another 25 countries,
209 reaching a total of 53 member states (**Supplementary Table 1**). The WHO further divides the
210 European region into three subregions: western, central, and eastern Europe Estimates in this paper
211 are presented in absolute numbers and age-standardised rates per 100,000 population (with 95%
212 uncertainty intervals [UIs]) and are stratified by age, sex, and regions.

213 To compare deaths and non-fatal outcomes, DALYs were used, which are the sum of YLLs
214 and YLDs. YLLs are the product of the number of deaths multiplied by the standard life
215 expectancy at the age of death. Standard life expectancy is obtained from the lowest observed age-
216 specific rates of mortality among populations in the world greater than 5 million. (14, 17, 18)
217 YLDs are the product of the prevalence of individual sequelae of each disease multiplied by a
218 disability weight, quantifying the severity of a sequela as a number between 0 (representing full
219 health) and 1 (representing death).

220

221 **Results**

222 *Absolute Numbers (Tables 1 and 2):*

223 Between 2010 and 2019, the total number of incident strokes in the WHO European union
224 member states increased by 2% (UI, 0 to 4%), from 1,767,280 new cases in 2010 to 1,802,559 new
225 cases in 2019. Of these, 69.4% were ischemic strokes (1,250,175 new cases in 2019, with a 5%
226 increase [UI, 3 to 6%] since 2010), 18.7% were intracerebral strokes (337,789 incident cases in
227 2019, with a 4% decrease since 2010 [UI, -6 to -1%]) and 11.9% were caused by subarachnoid
228 haemorrhages (214,595 incident cases in 2019, with a 3% increase since 2010 [UI, -6 to -1%]).

229 Eastern Europe (629,928; 35%) had the highest total number of incident strokes, followed by
230 Western Europe (602,981; 33.5%) and finally, Central Europe (307,697; 17%). This increase was
231 not observed in the EU28, where the total number of incident strokes remained stable between
232 2019 and 2010 (843,359 in 2010 to 844,239 in 2019; 0% change [UI -3 to 3%]).

233
234 Prevalent strokes increased by 4% (UI, 3 to 5%), from 13,701,815 in 2010 to 14,261,365
235 in 2019 in the WHO European region. The greatest increase was observed in ischemic strokes,
236 which rose from 10,731,496 in 2010 to 11,245,368 in 2019 (5% increase, UI 3 to 6%), followed
237 by subarachnoid haemorrhages (4% increase, UI 2 to 6%). In contrast, the number of prevalent
238 intracerebral strokes decreased by 1% (UI, -2 to 1%) from 2,071,155 to 2,051,471. Western Europe
239 saw the biggest increase in prevalent cases (5%, UI, 3 to 7%), from 5,351,562 in 2010 to 5,595,567
240 in 2019, while Eastern Europe saw a 2% decrease (UI, -4 to 1%) from 4,386,982 to 4,319,081 total
241 stroke cases. A similar trend was observed in the EU28, with a 4% increase (UI, 2 to 5%) in
242 prevalent cases between 2010 and 2019 (from 7,099,527 to 7,350,739).

243
244 The total number of deaths in the WHO European region decreased by 2% (UI -6 to 3%)
245 between 2010 to 2019, from 1,194,838 to 1,176,328, with decreased numbers observed in Eastern
246 and Central Europe (505,800 in 2010 to 455,235 in 2019, 1% decrease [UI, -17 to 2) and 215,676
247 in 2010 to 214,399, 1% decrease (UI, -11 to 10), respectively]. In contrast, Western Europe saw a
248 9% increase (UI, 6 to 12%) during this time period, from 339,219 stroke deaths in 2010 to 370,209
249 in 2019. During the same time period, the EU28 saw a 6% (UI, 1 to 10%) increase in the total
250 number of deaths.

251 Seventy percent of stroke deaths were secondary to ischemic stroke (825,184 deaths in
252 2019, with a 1% decrease since 2010 [UI, -6 to 4%]), 24.5% were secondary to intracerebral stroke
253 (287,812 deaths in 2019, with a 4% decrease since 2010 [UI, -9 to 0%]) and 5.4% were secondary
254 to intracerebral stroke (63,332 deaths in 2019, with a 3% increase since 2010 [UI, -2 to 9%]).
255 Ischemic strokes were the leading cause of death (70.1% of all stroke-deaths). Western Europe
256 saw an 11% increase (UI, 1-14%) in ischemic-stroke related deaths, from 225,755 deaths in 2010
257 to 249,532 deaths in 2019, in contrast to a 9% decrease (UI, -17 to -2%) observed Eastern Europe
258 (388,613 in 2010 to 351,967 in 2019). During the same time period, the number of deaths from
259 stroke in EU28 increased from 507,628 in 2010 to 535,742 (6% increase, UI 1 to 10%), was mainly
260 due to a 7% rise in total ischemic and subarachnoid haemorrhage (UI, 2 to 12%; UI., 1 to 12%,
261 respectively) deaths. Of the 53 countries that constitute the WHO European Region, in 2019 stroke
262 constituted the leading-cause of death in Montenegro, North Macedonia and Portugal; the third-
263 leading cause of death in Estonia, Andorra, France, Iceland, Monaco, Netherlands and Switzerland
264 and the second-cause of death in all the other countries (**Figure 1**). In France, Iceland and
265 Switzerland stroke has gone from 2nd in 2010 to 3rd leading-cause currently.

266
267 Finally, DALYs decreased by 7% (UI -12 to -3%) between 2010 to 2019, from 22,043,161
268 to 20,501,446 in the WHO European region, with decreased numbers observed in Eastern and
269 Central Europe (9,935,368 in 2010 to 8,459,592 in 2019, 15% decrease [UI, -22 to -7]) and
270 3,959,055 in 2010 to 3,687,846, 7% decrease [UI, -16 to 3], respectively). In contrast, Western
271 Europe saw a 2% increase (UI, 0 to 4%) during this time period, from 5,166,657 to 5,280,690
272 DALYs attributable to stroke in 2019. In the EU28, a 2% decrease was observed, from 8,306,955
273 in 2010 to 8,155,623 in 2019. Of all stroke related DALYs in 2019, ischemic strokes contributed

274 to 62.3%, intracerebral strokes to 29% and subarachnoid haemorrhage to 8.1% (62.5%, 28.8% and
275 7.7% in 2010, respectively). Of the 53 countries that constitute the WHO European Region, in
276 2019 stroke constituted the leading-cause of DALYs in Montenegro, North Macedonia and
277 Portugal; while the lowest figures were observed in Iceland and Ireland (seventh level-3 leading
278 cause of DALYs) and Andorra (9th) (**Figure 2**).

279

280 *Age Standardized Rates (Tables 1, 2 and Supplementary Files):*

281 A 10% decrease in incident age-standardized rates was observed in the WHO European
282 Region (UI, -12 to -8%) between 2010 and 2019 (from 132.30 to 118.7 per 100,000 people) for
283 all-stroke, a 10% decrease (UI, -12 to -7%) (2010, 88.7 per 100,000 people; 2019, 80.1 per 100,000
284 people) for ischemic stroke, a 14% decrease (UI, -17 to -12%) (2010, 26.9 per 100,000 people;
285 2019, 23.1 per 100,000 people) for intracerebral stroke, and a 6% decrease (UI, -9 to -4%) (2010,
286 16.7 per 100,000 people; 2019, 15.6 per 100,000 people) for subarachnoid haemorrhage. The
287 greatest decrease was seen in Western Europe (-12%, UI -15 to -9%), followed by Eastern Europe
288 (-11%, UI -13 to -9%) and Central Europe (-11%, UI -14 to -8%). The EU28 followed a similar
289 trend, with a 12% (UI, -14 to -10%) decrease between 2010 and 2019 for all stroke (-14% [UI, -
290 17 to -12%] for intracerebral stroke, -13% [UI, -17 to -10%] for ischemic stroke and -4% [UI, -8
291 to 0%] for subarachnoid haemorrhage).

292 Switzerland had the lowest incidence rate in 2019, at 58.9 (UI, 52.9 to 64.8) per 100,000
293 people and was the only country with an incidence rate under 60. Other countries with rates
294 between 60-70/100,000 included Ireland (60.2 [UI, 55-65.5]), France (61.4 [UI, 55.8-67.4]),
295 Luxembourg (61.4 [UI, 55.6-67.7]), the United Kingdom (62.6 [UI, 56.1-69.6]), Spain (65.4 [UI,
296 58.9-72.5]), Iceland (66.6 [UI, 60-73.8]), Israel (68.3 [UI, 61.2-75.6]), Italy (68.9 [UI, 61.5-76.8]),

297 Belgium (69.3 [UI, 63.1-76.1]) and Andorra (69.3 [UI, 62.5-76.9]). The largest decreases between
298 2010 and 2019 were observed in Norway (from 125.1 to 89.7 per 100,000 population; -28%, UI -
299 31 to -25%), Austria (from 103.2 to 80.2 per 100,000 population; -22%, UI -27 to -17%), Israel
300 (from 61.7 to 68.3 per 100,000 population; -19%, UI -24 to -14%), Denmark (from 88.6 to 72.5
301 per 100,000 population; -18%, UI -23 to -13%), Germany (from 93.5 to 76.5 per 100,000
302 population; -18%, UI -23 to -13%), Finland (from 109.7 to 61.4 per 100,000 population; -18%, UI
303 -23 to -13%) and Portugal (from 93.1 to 76.6 per 100,000 population; -18%, UI -22 to -13%). In
304 contrast, the highest incidence rate observed in 2019 was in Northern Macedonia, with 259.3 age-
305 standardized incident cases per 100,000 people (UI, 234.8 – 285.7). Other countries with rates
306 above 230 new cases per 100,000 people included Turkmenistan (232.1 [UI, 213.5-252.6]),
307 Montenegro (232.7 [UI, 217.8-249.6]) and Bulgaria (236.2 [UI, 214.8-258.1]). Additionally,
308 countries with the smallest changes between 2010 and 2019 include Tajikistan (with a 1% increase,
309 UI -3 to 5%), Turkey (from 145 to 145.5 per 100,000 population; 0%, UI -4 to 6%), and Monaco
310 (from 80.8 to 80.7 per 100,000 population; 0%, UI -6 to 7%) (**Supplementary Table 2**). Overall,
311 the percentage change between 2010 and 2019 was larger in males, with an average of $-10.5 \pm$
312 7.3% (range, -32.5% in Norway to $+2.4\%$ in Tajikistan) in comparison to females, with an average
313 drop in incidence rates of $-9.9 \pm 6.9\%$ (range, -32.9% in Uzbekistan to 0% in Tajikistan) (**Figure**
314 **3**).

315 The prevalent age-standardized rates also decreased by 6% (UI, -7 to -5%) between 2010
316 (1,056 per 100,000 people) and 2019 (989 per 100,000 people) for all-stroke in the WHO European
317 region, with the highest prevalence, but also biggest decrease, observed in Eastern Europe (1,457
318 to 1,347 per 100,000 people, 8% decrease [UI, -9 to -6%]), followed by Central Europe (1,457 to
319 1,347 per 100,000 people, 8% decrease [UI, -9 to -6%]); a similar 6% decrease was observed in

320 EU28 (848 to 795 per 100,000 people, 6% decrease [UI, -8 to -5%]). Intracerebral strokes had the
321 most significant decrease (WHO region: 173 to 158 per 100.000 people, -8% [UI, -10 to -7]. EU28:
322 117 to 107 per 100.000 people, -8% [UI, -9 to -6]), followed by ischemic strokes (WHO region:
323 816 to 766 per 100.000 people, -6% [UI, -7 to -5]. EU28: 677 to 633 per 100.000 people, -7% [UI,
324 -8 to -5]). Regarding individual countries, in 2019 Switzerland had the lowest prevalence rate, at
325 608 (UI, 562 - 662) cases per 100,000 people. Other countries with prevalence rates below 650
326 cases/100,000 included Italy (633 [UI, 569-703]), France (635 [UI, 584-687]) and Ireland (643
327 [UI, 581-722]). In contrast, Northern Macedonia (1,615 [UI, 1445-1817]), Bulgaria (1,605 [UI,
328 1447-1777]) and Bosnia (1,511 [UI, 1370-1656]) had the highest rates per 100,000 people. The
329 countries with the largest percentual decrease between 2010 and 2019 were Denmark (15%
330 decrease, UI – 19 to -11), Kyrgyzstan and Kazakhstan (14% decrease, UI – 18 to -10 and UI -18
331 to -9, respectively). The countries with the lowest change were Tajikistan (3% increase, UI-2 to
332 7%), Ukraine (2% increase, UI -4 to 7%) and Albania (2% increase, UI -2 to 6%) (**Supplementary**
333 **Table 2**).

334

335 Age-standardized mortality rates decreased by 18% (UI, -22 to -14%) between 2010 (82
336 per 100,000 people) and 2019 (67 per 100,000 people) for all-stroke in the WHO European region,
337 with the highest mortality rate, but also biggest decrease, observed in Eastern Europe (167 to 131
338 per 100,000 people, 21% decrease [UI, -28 to -15%]), followed by Central Europe (116 to 95 per
339 100,000 people, 18% decrease [UI, -26 to -9%]) and lastly in Western Europe (37 to 32 per 100,000
340 people, 13% decrease [UI, -15 to -10%]). In the EU28, mortality rates decreased by 15% (UI, -18
341 to -11%) from 49 to 42 per 100,000 people.

342 Regarding stroke type, age-standardized mortality was most significantly reduced for
343 ischemic strokes in the WHO region (56 to 45 per 100.000 people, -19% [UI, -23 to -15%]), while
344 the greatest reduction in the EU28 was observed for intracerebral stroke mortality (from 13 to 11
345 per 100,000, -16% decrease [UI, -20 to -12]). There were significant variations between percentual
346 changes and basal age-standardized mortality between regions for the different subtypes of stroke,
347 with the greatest difference existing between ischemic stroke mortality for Eastern Europe (100
348 per 100,000 people in 2019, with a 22% decrease [UI, -28 to -15%]) and Western Europe (21 per
349 100,000 people in 2019, with a 13% decrease [UI, -16 to -11%]). Overall, Switzerland (22 deaths
350 per 100,000 people, UI, 18 - 25), Iceland (22 deaths per 100,000 people, UI 19 to 25) and Andorra
351 (23 deaths per 100,000 people, UI 18 to 29) had the lowest age-adjusted mortality rates, while
352 Northern Macedonia (274 deaths per 100,000 people, UI 231 to 320), Montenegro (207 deaths per
353 100,000 people, UI 175 to 135) and Bulgaria (192 deaths per 100,000 people, UI 159 to 227) had
354 the highest. On the other hand, countries with the largest percentual decrease between 2010 and
355 2019 were Luxembourg (30% decrease, UI - 38 to -21), Armenia (29% decrease, UI -39 to -28%)
356 and Kyrgyzstan (29% decrease, UI - 37 to -21), while Albania (4% decrease, UI -23 to 18%),
357 Turkmenistan (4% decrease, UI -22 to 16%) and Andorra (5% decrease, UI -23 to 17%) presented
358 the lowest decrease in mortality rates (**Supplementary Table 3**). Overall, the decrease in age-
359 standardized rates was significantly higher in women, with an average decrease of $35.5 \pm 19.8\%$
360 (range, -72.9% in Estonia to 28% increase in Azerbaijan) in comparison to males, who presented
361 an average decrease of $-16.7 \pm 8\%$ (range, -40.2% in Cyprus to a 0.8% increase in Montenegro)
362 (**Figure 4**).

363

364 Of all epidemiological parameters, age-standardized DALYs saw the biggest reduction
365 both in the WHO European Region (1,592 in 2010 to 1,296 in 2019 [19% decrease, UI -23% to -
366 15%]), as in EU28 (894 in 2010 to 754 in 2019 [16% decrease, UI -19% to -12%]). The biggest
367 decrease was observed in Eastern Europe (3,208 in 2010 to 2,507 in 2019 [22% decrease, UI -28%
368 to -15%]), followed by Central Europe (2,118 in 2010 to 1,732 in 2019 [18% decrease, UI -27%
369 to -9%]) and lastly, by Western Europe (642 in 2010 to 557 in 2019 [13% decrease, UI -15% to -
370 11%]). By stroke subtype, ischemic strokes were associated with the largest decrease in the WHO
371 European Region (952 to 768 per 100.000 people, -23% [UI, -19 to -16%]), while intracerebral
372 strokes were associated to the biggest reduction in EU28 (275 to 225 per 100.000 people, -18%
373 [UI, -23 to -14%]). In Eastern Europe there was a 23% decrease for both ischemic stroke related
374 DALYs (from 2154 to 1668, UI -28 to -26%) and intracerebral stroke related DALYs (from 827
375 to 639, UI -31 to -14%). In contrast, in Central and Western Europe, intracerebral stroke related
376 DALYs saw a greater decrease (-21%, UI -30 to -11%; -15%, UI -18 to -13%; respectively) than
377 ischemic stroke related DALYs (-18%, UI -25 to -9%; -13%, UI -15 to -11%; respectively).

378 Regarding individual countries, in 2019 Switzerland had the lowest stroke DALYs, at 372
379 (UI, 328 - 413) cases per 100,000 people. Other countries with rates below 450 cases/100,000
380 included Iceland (404 [UI, 357-449]) and Andorra (430 [UI, 347-532]). In contrast, Northern
381 Macedonia (4,296 [UI, 3,569 -5,054]), Uzbekistan (3,615 [UI, 3131 - 4140]) and Turkmenistan
382 (3,537 [UI, 2889 - 4268]) had the highest rates per 100,000 people. The countries with the largest
383 percentual decrease between 2010 and 2019 were the Republic of Moldova (31% decrease, UI –
384 38 to -22%) and Kyrgyzstan (29% decrease, UI – 37 to -20), followed by Luxembourg and
385 Armenia (28% decrease, UI -35 to -20% and UI -37 to -18%, respectively). The countries with the
386 lowest change were Ukraine (1% decrease, UI -13 to 14%), Albania (3% decrease, UI -22 to 18%),

387 followed by Turkmenistan and Andorra (4% decrease, UI -22 to 17% and UI -20 to 14%,
388 respectively (**Supplementary Table 3**). Overall, the decrease in age-standardized rates was
389 similar between both sexes, with an average decrease of $9.9 \pm 6.9\%$ (range, -32.9% in Uzbekistan
390 to 2.6% increase in Andorra) in females and an average reduction of $10.5 \pm 7.3\%$ (range, -32.5%
391 in Norway to a 2.4% increase in Tajikistan) in males (**Figure 5**).

392

393 **<70 vs. 70+:**

394 There has been a significant reduction in the incidence of stroke in the population 70+, from 947
395 cases to 871 new cases in 2019 (8% decrease, UI, -11 to -5) in the WHO European Region, a
396 reduction that has been observed in all regions except for Easter Europe, where numbers increased
397 from 1,358 to 1,375% (1% increase, UI, -4 to 6). Similarly, prevalent cases have also significantly
398 decrease, from 5,834 in 2010 to 5,361 in 2019 (-8% [UI, -10 to -6]). On the contrary, prevalent
399 cases in the population <70 have substantially increased, from 1,005 to 1,042 (4% increase [UI, 2
400 to 5%]). Overall, percentual changes between 2010 and 2019 have been significantly greater in
401 those 70+ (**Tables 1 and 2**).

402

403 **Discussion**

404 In 2019, stroke remained the second level-3 cause of death and the third level-3 cause of
405 death and disability worldwide, with an increase of absolute numbers and DALYs observed
406 between 1990 to 2019 (32% increase [UI, 22 to 42%] of years of full health lost due to death and
407 disability) (1, 19). This analysis of GBD in Europe demonstrated persisting geographic variations
408 in absolute stroke numbers and mortality, nevertheless confirming it to be within the first three-
409 leading causes of death in all 53 WHO European member states (**Figure 1**). Over the last years,

410 absolute numbers of first-ever-in-a-lifetime-strokes and stroke prevalence marginally increased all
411 over Europe, with the highest increased observed in Western Europe and EU28 (+1% and +5%:
412 and 0 and 4% increase, respectively); and although overall stroke mortality decreased in WHO
413 Europe countries, this was not observed in EU28 or in Western Europe. Furthermore, despite stable
414 incidence-rates of ischemic strokes in Western Europe between 2010 and 2019, absolute mortality
415 numbers significantly increased during the last decade (225,755 in 2010 vs 249,532 in 2019, +11%
416 [UI, 7-14%]).

417 Eastern Europe saw considerable improvements in stroke burden within the last decade,
418 with absolute numbers of incidence, prevalence and mortality decreasing substantially.
419 Additionally, Eastern and Central Europe experienced a relevant decrease in stroke related DALYs
420 during the last decade. On the other hand, Western Europe reported higher numbers of overall-
421 stroke DALYS in 2019, with ischemic stroke being the largest contributor. Ischemic stroke was
422 also the leading cause of stroke-related DALYs in Central Europe, whereas subarachnoid
423 haemorrhage was the leading contributor in eastern Europe.

424 Overall, age-standardized rates (incidence, prevalence and death rates) decreased in the
425 WHO European Region and subregions (Eastern, Western and Central Europe), as did age-
426 standardized DALYs, with a most pronounced reduction of 15% amongst countries of Eastern
427 Europe. However, when looking individually at country-level-data, although decreasing age-
428 standarized incidence rates were observed for most WHO European member countries, Tajikistan,
429 Turkey and Monaco saw an increase in the incidence rates, and there was great disparity in the
430 observed percentual decrease between 2010 and 2019, from +1% at one extreme to -28% (Norway)
431 at the other end– as there was substantial disparity between female and male reductions (**Figures**
432 **3-5**), as well as when comparing the population below and above 70 years (**Tables 1 and 2**).

433 Similarly, decreasing prevalence rates were observed for most countries (except for Andorra
434 [stable], Monaco [stable], Tajikistan [+3], Turkmenistan [+1] and Ukraine [+2]). Again, significant
435 variations in reduction rates (Denmark -15%, Kyrgyzstan and Kazakhstan -14%) were observed
436 between countries.

437

438 **Impact of Stroke in DALYs**

439 The persisting relevant impact of stroke in DALYs, especially in western Europe, might be
440 explained by the long life-expectancy in these countries and, despite an overall decrease in age-
441 standardised rates, by the rising incidence of ageing-related diseases (20). Additionally, Europe's
442 population is continuously growing which could also be a reason for our findings. While 721
443 million people lived in Europe in 1990, in 2016 Europe counted 916 million inhabitants (21).

444 The significant reduction of all-age and age-standardised DALYs in Eastern Europe is an
445 important finding of this study. Preventive medicine with optimization of medical treatment and
446 lifestyle changes are the most likely explanations and highlight the beneficial effects of control of
447 preventable risk factors (blood pressure and diabetes control, optimization of cholesterol levels
448 and smoking cessation) affecting mainly the prevalence. Previous GBD publications showed that
449 more than 90% of the stroke burden was attributable to modifiable risk factors (1, 22-23).

450 In theory, nationwide implementation of stroke units will substantially improve acute
451 stroke management and post-stroke rehabilitation, however, there is no Europe-wide accepted
452 definition of what a "stroke unit" should actually be. Large disparities have been consistently
453 observed between countries, with only few European hospitals providing an optimal level of care
454 (5). In Estonia, France, Greece, and Portugal, for example, more than three quarters of participating
455 hospitals do not provide the minimum level of care; and only 5% of European hospitals have

456 facilities meeting the standards of comprehensive stroke centres (5). In Spain, for example, stroke
457 units are concentrated in the regions of Madrid and Barcelona and the ratio of stroke unit beds to
458 residents was found to range from 1/74,000 to 1/1,037,000 (24-25). French data indicate that only
459 33% of stroke patients are treated in stroke units (26). In contrast, 73% of Finnish patients living
460 within the catchment area of a stroke unit were treated in a stroke unit compared to 9% outside a
461 catchment area (27). Overall, these findings suggest large within-country and national variations.

462 Attached to stroke unit care is the supply of thrombolysis for patients with acute ischemic
463 stroke. Intravenous thrombolysis (IVT) and endovascular therapy (EVT) IVT have been shown to
464 improve the outcome of ischaemic stroke, although major disparities exist within European
465 countries (28, 29). Country-level data shows that access to and delivery of acute stroke care are
466 poor or totally lacking in many countries (28), with under 20% of patients with acute ischaemic
467 stroke being provided with IVT, and an overall rate of IVT in incident ischaemic stroke of 7.3%
468 (27).

469

470 **Conclusion**

471 Although a substantial effort has been made regarding stroke management in Europe, this
472 analysis shows increasing absolute numbers of first-ever-in-a-lifetime-strokes and stroke
473 prevalence rates in the last 10 years. The disparity in stroke prevention and stroke management
474 strategies and opportunities between, and even within countries, is considerable and may be a
475 fundamental cause in the observed geographic differences among EU regions. Further focus on
476 EU wide accepted recommendations on risk factor management and the implementation of stroke
477 units seem to be vital to making further progress in reducing stroke burden in European countries.

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