



Changes in stroke mortality trends and premature mortality due to stroke in Serbia, 1992–2013

Zana Dolicanin · Dragan Bogdanovic · Konstansa Lazarevic

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Abstract

Objectives To determine mortality trends and premature mortality due to stroke in Serbia in 1992–2013 period.

Methods We obtained mortality database from the Statistical Office of Serbia.

Results From 1992 to 2005, age-standardized mortality rates (ASRs) per 100,000 for all stroke increased, with annual percentage change (APC) of 1.01 % in men and 1.05 % in women. From 2005 to 2013, ASRs decreased, with APC of –4.93 % in men, and –5.63 % in women. In men, years of life lost (YLLs) for all stroke deaths were 21,710 in 1992; 22,193 in 2003 and 17,464 in 2013, with average years of life lost (AYLLs) of 3.46, 2.89 and 3.00, respectively. In women, YLLs were 33,508 in 1992; 35,130 in 2003 and 21,676 in 2013, with AYLLs of 4.65; 3.57 and 2.97.

Conclusions From 1992 to 2013, ASRs and YLLs for all stroke showed two segment trends in Serbia, with increase in the first, and decrease in the second period. Due to the shorter AYLLs and longer life tables, in 2013 stroke deaths occurred at >4 years older age in both sexes than in 1992.

Keywords Stroke · Mortality · Years of life lost · Joinpoint regression

Introduction

Worldwide, aging and growth of populations have led to an increase in the total number of deaths for most of the leading non-communicable diseases between 1990 and 2013, but age-standardized mortality rates (ASRs) have fallen. Global ASR per 100,000 population for stroke has fallen by more than one-fifth, from 142 in 1990 to 110 in 2013, however, stroke remains the second most common cause of death, after ischaemic heart disease, and the third cause of years of life lost (YLLs), after ischaemic heart disease and lower respiratory infections (GBD 2013).

There are significant international differences in stroke mortality, with highest ASRs in the countries of Eastern Europe (Feigin et al. 2003; Truelsen et al. 2003). The distinctions between countries and regions are related to differences in key risk factors (hypertension, diabetes, lipids, tobacco use, alcohol consumption, physical inactivity) population level and control (Ghayour-Mobarhan et al. 2015; Feigin et al. 2003; Furie et al. 2011; Sarti et al. 2000), but can also be related to social and economic conditions (Folyovich et al. 2015; Brown et al. 2013; Lindmark et al. 2014; Jaja et al. 2013; Maruthappu et al. 2015).

There are a number of potential mechanisms by which low socioeconomic status may result in increased risk of cerebrovascular deaths. In the short term, lower socioeconomic status has been associated with a lower chance of receiving optimal treatment of acute stroke (Huang et al. 2013; Langagergaard et al. 2011). In the long term, these mechanisms include traditional cardiovascular risk factors such as poor diet, psychological disturbances, and smoking (Shinton and Beevers 1989; Lazzarino et al. 2013; Mejean et al. 2013).

Serbia has passed through a period of great political and economic changes from the 1990s. After the dissolution of

Z. Dolicanin · D. Bogdanovic (✉) · K. Lazarevic
Department of Biomedical Sciences, State University of Novi Pazar, Vuka Karadžića bb, 36300 Novi Pazar, Serbia
e-mail: draganbogdanovic@gmail.com

Z. Dolicanin
e-mail: zdolicanin@np.ac.rs

K. Lazarevic
e-mail: koni33@hotmail.com

Socialist Federal Republic of Yugoslavia in 1992, Serbia and Montenegro, two of six republics of the former country, formed the Federal Republic of Yugoslavia. In 2003, the name of the state was changed to Serbia and Montenegro. In 2006, Serbia and Montenegro formally dissolved into two states. Dramatic economic changes have followed and per capita gross domestic product decreased from 4099 US dollars in 1990 to 1161 US dollars in 2000, and then increased to 5315 US dollars in 2012 (The Department of Economic and Social Affairs of the United Nations Secretariat 2014). Demographic trends in Serbia are negative in the past few decades, and have three main characteristics: negative natural growth from 1993, intensive aging process, and migratory movements—population exodus (Petric et al. 2012). The Serbian population decreased from 7.8 million people in 1991 to 7.5 million in 2002, and 7.2 million in 2011. The average age of population increased from 36.4 in men and 38.4 in women in 1990 to 41.0 in men and 43.7 in women in 2013 (Statistical Office of the Republic of Serbia 2014).

Analysis of stroke mortality in Belgrade, the capital of Serbia, during the 1989–2003 period showed that, in contrast to the global trend, ASRs of all stroke in Belgrade during the 1989–2003 period increased. The average ASRs per 100,000 for all stroke were 90.8 overall, 98.0 for men, and 82.4 for women (Pekmezovic et al. 2008). To our knowledge, the most recent study that has analyzed stroke mortality in the region (Redon et al. 2011) showed upward trend in stroke mortality from 1990 to 2006 in Serbia and Montenegro, Albania, Bulgaria, Romania, and Hungary, while the trend in Greece was downward.

Taking into account the significant social, economic and demographic changes in Serbia in the last few decades, and their possible impact on public health, the aim of this study was to analyze trends in mortality from stroke and its subtypes at the national level during the 22-year period from 1992 to 2013. Additionally, we estimated YLLs and average years of life lost (AYLLs) due to stroke for the years 1992, 2003 and 2013 in Serbia.

Methods

The research included the population of Central Serbia and the Province of Vojvodina, excluding the Province of Kosovo and Metohija. The national electronic mortality database in Serbia holds records for deaths from 1992. We obtained the mortality database for the 1992–2013 period from the Statistical Office of the Republic of Serbia. The underlying cause of death from stroke was determined using the International Classification of Diseases and Injuries (ICD), 9th Revision (ICD-9) codes 430–438 for the 1992–1996 period, and ICD-10 codes I60–69 for the

1997–2013 period. For analysis of stroke subtypes, subarachnoid hemorrhage (SAH) was coded as 430 (ICD-9) and I60, I69.0 (ICD-10); intracerebral hemorrhage (ICH) as 431–432 (ICD-9) and I61, I69.1 (ICD-10) and cerebral infarction (CI) as 433–434, 437.0 (ICD-9) and I63, I69.3 (ICD-10). The remaining codes were classified as undetermined stroke (UND).

ASRs per 100,000 persons for each year during the 1992–2013 period were calculated using the direct method according to the WHO World Standard Population (Ahmad et al. 2001). Population denominator data were obtained from the 1991, 2002 and 2011 national censuses by interpolation (Statistical Office of the Republic of Serbia 2012).

We estimated YLLs and AYLLs for the years 1992 (the first year of the examined period), 2003 (year with the most stroke deaths and with the highest ASRs values) and 2013 (the most recent available data). YLL for each person is calculated by subtracting the person's age at death from the reference age (Gardner and Sanborn 1990) which was life expectancy at birth according to the national life tables (Statistical Office of the Republic of Serbia 2014). Life expectancy at birth in these life tables was 68.48 years for men and 74.27 years for women in 1992; 69.61 and 74.96 years, respectively, in 2003; and 72.46 and 77.68 years, respectively, in 2013. If a person was older than the reference age at the time of their death, that person's YLL was set to zero (i.e., there are no "negative" YLLs). In effect, only those who die before the reference age are included in the calculation. To calculate the YLLs for male and female population in a particular year, we summed the individual YLLs for all individuals in that population who died in that year. AYLLs were then estimated dividing total YLLs by the number of stroke deaths (Pham et al. 2011). In the present data, we identified only 158 (0.05 %) deaths of unknown age, so the ASRs as well as YLLs have not been corrected for deaths of unknown age.

The trends in ASRs were analyzed using the joinpoint regression model (Kim et al. 2000). This analysis fits a series of straight lines (time periods) on a log scale to the ASRs, and detect the points in time (calendar years) where significant changes in trend occur. Annual percentage change (APC) in ASRs and the corresponding 95 % confidence interval are computed for each defined time period using generalized linear model assuming a Poisson distribution. We used ASR as the dependent variable and calendar year as the independent variable. The optimal number of joinpoints was identified using the Monte Carlo permutation method. Joinpoint analyses were performed using the Joinpoint Regression Program version 4.2.0.2 (Statistical Methodology and Applications Branch, Surveillance Research Program, US National Cancer Institute).

Results

We observed that stroke was responsible for 348,422 deaths in Serbia in 1992–2013 period, and it accounted for 16 % of all deaths. The median age of death caused by stroke was 74 years in men and 76 years in women. The number of deaths from stroke and its subtypes, ASRs, YLLs and AYLLs values for the years 1992, 2003 and 2013 are shown in Table 1.

In male population, the total number of stroke deaths increased from 6272 in 1992 to 7685 in 2003, and then decreased to 5821 in 2013. YLLs for all stroke deaths were 21,710 in 1992, increased to 22,193 in 2003, and then decreased to 17,464 in 2013. AYLLs for all stroke deaths decreased from 3.46 in 1992 to 2.89 in 2003, and increased to 3.00 in 2013.

In female population, the total number of stroke deaths increased from 7202 in 1992 to 9827 in 2003, and then decreased to 7291 in 2013. YLLs for all stroke deaths were 33,508 in 1992, increased to 35,130 in 2003, and then decreased to 21,676 in 2013. AYLLs for all stroke deaths decreased from 4.65 in 1992 to 3.57 in 2003, and to 2.97 in 2013.

Undetermined stroke group was the most frequent in both sexes in 1992 and 2003. It accounted for 49 % of all stroke in men, and 51 % in women. In 2003, the percentage of undetermined stroke increased to 62 % in men, and 65 % in women. In 2013, the percentage of undetermined stroke group decreased to 27 % in men, and 28 % in women. Cerebral infarction was the most frequent subtype of stroke in 2013, and it accounted for 58 % of all stroke in men, and 60 % in women.

AYLLs for subarachnoid hemorrhage deaths had the highest values during the 1992–2013 period. They decreased from 12.79 in 1992 to 10.90 in 2013 in men, and from 17.15 to 14.22 in women. AYLLs for intracerebral hemorrhage decreased from 12.79 in 1992 to 10.90 in 2013 in men, and from 17.15 to 14.22 in women.

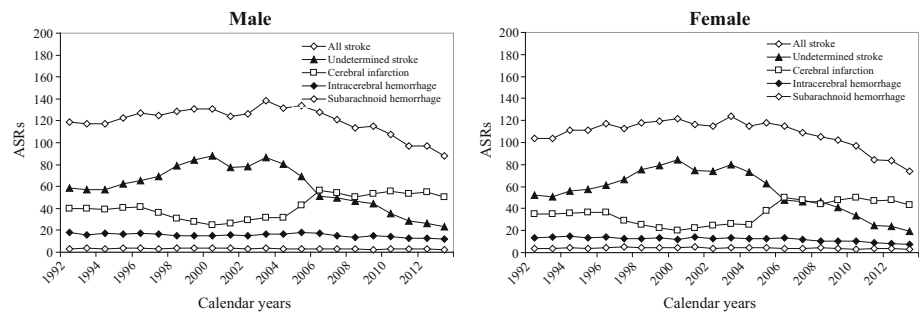
Changes in ASRs of stroke mortality by year are shown in Fig. 1. The ASRs for total stroke and all subtypes had similar trends in both sexes. During the whole 1992–2013 period, the ASRs for subarachnoid hemorrhage were higher in women, while ASRs for all other subtypes and for total stroke were higher in men.

From 1992 to 2013, ASRs for all stroke declined from 118.64 per 100,000 persons to 87.66 in men, and from 104.01 to 73.56 in women (Table 2). The ASRs for all stroke showed two segment calendar trends. The first period, from 1992 to 2005, showed a significant increase in ASRs, with APC value of 1.01 % in men, and 1.05 % in women. In the second period, from 2005 to 2013, ASRs for all stroke significantly decreased, with APC of -4.93 % in men, and -5.63 % in women.

Table 1 Population at risk, number of deaths, ASRs, YLLs, and AYLLs due to stroke in Serbia, in 1992, 2003 and 2013. ASRs age-standardized mortality rates per 100,000 persons. YLLs years of life lost. AYLLs average years of life lost

	Population at risk						Number of deaths (%)			ASRs			YLLs			AYLLs		
	1992		2003		2013		1992	2003	2013	1992	2003	2013	1992	2003	2013	1992	2003	2013
	1992	2003	1992	2003	1992	2003	2003	2003	2013	1992	2003	2013	1992	2003	2013	1992	2003	2013
Male	3,820,273	3,637,789	3,488,466															
Subarachnoid hemorrhage				146 (2)	183 (2)	145 (2)	3.0	3.5	2.5	1867	2282	1580	12.8	12.5	10.9			
Intracerebral hemorrhage				919 (15)	909 (12)	745 (13)	17.7	16.4	12.1	6429	5781	5316	7.0	6.4	7.1			
Cerebral infarction				2105 (34)	1820 (24)	3371 (58)	39.5	31.6	50.1	5360	4045	7917	2.5	2.2	2.3			
Undetermined stroke				3102 (49)	4773 (62)	1560 (27)	58.4	86.6	23.0	8054	10,086	2650	2.6	2.1	1.7			
All stroke				6272 (100)	7685 (100)	5821 (100)	118.6	138.2	87.7	21,710	22,193	17,464	3.5	2.9	3.0			
Female	3,991,464	3,842,802	3,675,666															
Subarachnoid hemorrhage				194 (3)	289 (3)	213 (3)	3.5	4.7	3.2	3326	4366	3029	17.1	15.1	14.2			
Intracerebral hemorrhage				886 (12)	979 (10)	644 (9)	13.6	13.6	7.6	7491	7840	4489	8.4	8.0	7.0			
Cerebral infarction				2448 (34)	2159 (22)	4393 (60)	34.8	26.3	43.0	9474	6538	10177	3.9	3.0	2.3			
Undetermined stroke				3674 (51)	6400 (65)	2041 (28)	52.1	79.5	19.8	13,217	16,386	3981	3.6	2.6	1.9			
All stroke				7202 (100)	9827 (100)	7291 (100)	104.0	124.2	73.6	33,508	35,130	21,676	4.6	3.6	3.0			

Fig. 1 Trend in age-standardized rates (ASRs) per 100,000 persons for all stroke and its subtypes during 1992–2013 period in Serbia



Subarachnoid hemorrhage mortality had similar patterns to all stroke mortality, showing two segment trends. The first period, from 1992 to 2000, showed a significant increase in ASRs in women, and an insignificant increase in men. In the second period, from 2000 to 2013, ASRs for subarachnoid hemorrhage significantly decreased in both sexes.

Values of ASRs for intracerebral hemorrhage had three segment trends. The first period, from 1992 to 2000, showed a significant decrease in ASRs in men, and an insignificant decrease in women. In the second period, from 2000 to 2005, ASRs insignificantly increased in both sexes. In the third period, from 2005 to 2013, ASRs values for intracerebral hemorrhage significantly decreased in both sexes.

The ASRs for cerebral infarction had three segment trends. The first period, from 1992 to 2002, showed a significant decrease in ASRs, with APC value of -5.20% in men, and -6.13% in women. In the second period, from 2002 to 2006, ASRs significantly increased, with APC value of 19.99% in men, and 22.51% in women. In the third period, from 2006 to 2013, ASRs values for cerebral infarction insignificantly varied in both sexes.

The ASRs for undetermined stroke had two segment trends. The first period, from 1992 to 2003, showed a significant increase in ASRs, with APC value of 4.15% in men, and 4.48% in women. In the second period, from 2003 to 2013, ASRs significantly decreased, with APC value of -12.65% in men, and -13.18% in women.

Discussion

The numbers of all stroke deaths increased in both sexes in the 1992–2003 period. The subsequent increase of YLLs values was not as high because the life expectancy values increased in the same period, and AYLLs values have decreased for 0.83 in men and 1.08 in women in the 1992–2003 period. The increase of mortality was observed in both sexes for all stroke, UND, and for SAH. ICH

mortality increased in women and slightly decreased in men. At the same time, the mortality for CI has decreased for both sexes. The increase in ASRs for stroke in the first half of the examined period can be attributed to worsening of the social and economic conditions which occurred in Serbia in 1990s, but the decrease of AYLLs values indicates that those conditions mostly influenced older people.

In the 2003–2013 period, the mortality and YLL and AYLL values for all stroke, SAH, ICH and UND have decreased to values even lower than the ones in 1992. ASRs values decreased from 1992 to 2013 for all stroke, SAH, ICH and UND, while ASRs for CI increased in the same period. For all stroke, SAH and CI values of ASRs showed two segment calendar trends with significant increase in the first, except for SAH in men, and significant decrease in the second period. For ICH and CI values of ASRs showed three segment calendar trends. In the first period, ASRs for ICH significantly decreased, in the second period they insignificantly increased, and in the third period they significantly decreased. ASRs for CI significantly decreased in the first, significantly increased in the second, and insignificantly decreased in the third period.

In the present study, we used YLLs and AYLLs to describe premature deaths due to stroke and to evaluate changes in the burden of stroke over the recent period at the national level in Serbia. Overall AYLLs of all stroke were considerably shorter at the end of this 22-year period, as its AYLLs decreased from 3.5 years to 3.0 in men and 4.6 years to 3.0 in women between 1992 and 2013. In other words, both men and women who died of stroke did so at an older age in 2013 than they did 22 years previously. It is important to note that the YLLs estimates in the present study were based on the respective life tables. Accordingly, life expectancy at birth for the year 1992 was 4.0 years shorter for men and 3.5 years shorter for women than those for 2013 (Statistical Office of the Republic of Serbia 2014). Therefore, although we observed close values of AYLLs in 1992 and 2013, AYLLs in 2013 had already benefited from the longer life expectancy. We observed a 0.5 years difference in AYLLs in men and 1.6 in women between 1992

Table 2 APCs in ASRs of stroke and its subtypes mortality in Serbia, 1992–2013, joinpoint regression analysis. ASRs age-standardized mortality rates per 100,000 persons. APC annual percentage change in age-standardized mortality rates. CI confidence interval

	ASRs		1st period trend			2nd period trend			3rd period trend		
	1992	2013	Period	APC (95 % CI)	p value	Period	APC (95 % CI)	p value	Period	APC (95 % CI)	p value
Male											
Subarachnoid hemorrhage	3.0	2.5	1992–2000	1.64 (−0.70 to 3.98)	0.189	2000–2013	−3.05 (−4.17 to −1.92)	<0.001	2005–2013	−4.42 (−5.73 to −3.11)	<0.001
Intracerebral hemorrhage	17.7	12.1	1992–2000	−2.05 (−3.36 to −0.74)	0.008	2000–2005	2.82 (−1.00 to 6.64)	0.172	2005–2013	0.03 (−3.14 to 3.19)	0.987
Cerebral infarction	39.5	50.1	1992–2002	−5.20 (−7.04 to −3.36)	<0.001	2002–2006	19.99 (7.88 to 32.10)	0.009	2006–2013		
Undetermined stroke	58.4	23.0	1992–2003	4.15 (2.77 to 5.54)	<0.001	2003–2013	−12.65 (−14.24 to −11.05)	<0.001			
All stroke	118.6	87.7	1992–2005	1.01 (0.59 to 1.44)	<0.001	2005–2013	−4.93 (−5.81 to −4.04)	<0.001			
Female											
Subarachnoid hemorrhage	3.5	3.2	1992–2000	4.31 (0.88 to 7.75)	0.026	2000–2013	−2.94 (−4.13 to −1.74)	<0.001			
Intracerebral hemorrhage	13.6	7.6	1992–2000	−1.55 (−3.57 to 0.46)	0.148	2000–2005	0.18 (−2.37 to 2.73)	0.893	2006–2013	−7.44 (−9.45 to −5.42)	<0.001
Cerebral infarction	34.8	43.0	1992–2002	−6.13 (−8.42 to −3.85)	<0.001	2002–2006	22.51 (7.37 to 37.66)	0.016	2006–2013	−0.11 (−4.05 to 3.82)	0.955
Undetermined stroke	52.1	19.8	1992–2003	4.48 (2.92 to 6.04)	<0.001	2003–2013	−13.18 (−14.98 to 11.38)	<0.001			
All stroke	104.0	73.6	1992–2005	1.05 (0.51 to 1.59)	0.001	2005–2013	−5.63 (−6.75 to −4.51)	<0.001			

and 2013, but the actual AYLL value would be 4.5 years in men and 5.1 in women due to the shorter life tables in 1992 compared to that in 2013.

The share of UND in the total mortality from stroke climbed in both sexes from 1992 to 2003, which indicates insufficient stroke subtypes diagnosis and a very imprecise process of coding the cause of death during that period. The sharp decrease in proportion of UND and increase in proportion of CI from 2003 to 2013 indicate that many deaths from the UND group might have been from CI (Pham et al. 2011). Economic recovery and subsequently increased expenditure on health care in Serbia enabled widespread use of sophisticated diagnostic procedures (computed topography, magnetic resonance imaging, etc.) and more accurate stroke subtypes diagnosis in inpatient death cases. In cases of death for stroke which did not occur in hospitals, the coding of stroke subtypes is less accurate, and that might be a reason why the proportion of UND mortality is still very high, besides the decreasing trend. From 2005, a network of 24 Public health institutes was included in the control of the process of coding the causes of death in the Republic of Serbia. A significant decrease of the share of UND in the total mortality from stroke in 2003–2013 period might be a consequence of this measure. In support of this conclusion is also our finding that the share of cases with the main cause of death coded as some of the causes from the 18th ICD-10 group (R00–R99), symptoms, signs, and abnormal findings, rather than the conditions that caused them, in the total mortality in Serbia was 9.0 % in the 2000–2004 period, in 2005 decreased to 6.0 %, and in 2013 to 4.4 %.

The positive change in trend of stroke-related mortality, and decrease in ASRs, YLLs and AYLLs values can be attributed to improvement of social and economic conditions, as well as the numerous measures taken for improving the medical health care and public health in recent years in Serbia.

Total expenditure on health as percent of gross domestic product increased from 7.1 % in 2000 to 10.6 % in 2012. In the same period, the per capita government expenditure on health increased from 266 to 760 US dollars (GBD 2013).

Since 2001, the Ministry of Health of the Republic of Serbia has published over 40 guidelines for good clinical practice for diagnosis, therapy and prevention of the most important diseases and medical conditions, among them, the guidelines related to acute cerebral infarction, cerebrovascular diseases, diabetes, obesity, hypertension, lipid disorders, vein diseases, carotid arteries diseases, and alcoholism (Ministry of Health of the Republic of Serbia 2013).

Life expectancy on birth increased from 68.48 years for men and 74.27 years for women in 1992 to 72.46 and

77.68 years, respectively, in 2013 (Statistical Office of the Republic of Serbia 2014), but the lag compared to high-income countries (76 years for men and 82 years for women in 2013) (GBD 2013) is still significant.

This study has shown that mortality from stroke in the last decade in Serbia is beginning to decrease, but the ASRs values are still very high. Apart from the unfavorable financial situation, risk factor percentages for stroke in Serbia are still very high: the prevalence of raised blood pressure among adults aged ≥ 18 years in 2014 was 33.2 % in men, and 24.9 % in women; the prevalence of obesity among adults aged ≥ 18 years in 2014 was 18.6 % in men, and 20.5 % in women; per capita alcohol consumption (≥ 15 years) in 2010 was 12.6L; the prevalence of smoking any tobacco product among adults aged ≥ 15 years in 2012 was 45.5 % in men, and 39.8 % in women (World Health Organization 2015).

Despite its recent downward trend, stroke remains an important component of the total burden of disease in Serbia. Further increase of government expenditure on health, efficient programs of primary and secondary prevention, as well as the improvement of diagnostics and therapy could contribute to further reductions in stroke mortality and postpone many stroke-related deaths in Serbia.

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