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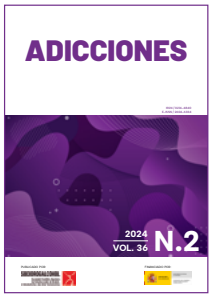

ORIGINAL

Impact of alcohol control policy on hemorrhagic and ischemic stroke mortality rates in Lithuania: An interrupted time series analysis

Impacto de políticas de control de alcohol en las tasas de mortalidad por ictus hemorrágico e isquémico en Lituania: Análisis de series temporales interrumpidas

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Abstract

Given the causal impact of alcohol use on stroke, alcohol control policies should presumably reduce stroke mortality rates. This study aimed to test the impact of three major Lithuanian alcohol control policies implemented in 2008, 2017 and 2018 on sex- and stroke subtype-specific mortality rates, among individuals 15+ years-old. Joinpoint regression analyses were performed for each sex- and stroke subtype-specific group to identify timepoints corresponding with significant changes in mortality rate trends. To estimate the impact of each policy, interrupted time series analyses using a generalized additive mixed model were performed on monthly sex- and stroke subtype-specific age-standardized mortality rates from January 2001-December 2018. Significant average annual percent decreases were found for all sex- and stroke subtype-specific mortality rate trends. The alcohol control policies were most impactful on ischemic stroke mortality rates among women. The 2008 policy was followed by a positive level change of 4,498 ischemic stroke deaths per 100,000 women and a negative monthly slope change of -0.048 ischemic stroke deaths per 100,000 women. Both the 2017 and 2018 policy enactment timepoints coincided with a significant negative level change for ischemic stroke mortality rates among women, at -0.901 deaths and -1.431 deaths per 100,000 population, respectively. Hemorrhagic stroke mortality among men was not affected by any of the policies, and hemorrhagic stroke mortality among women and ischemic stroke mortality among men were only associated with the 2008 policy. Our study findings suggest that the impact of alcohol control policies on stroke mortality may vary by sex and subtype.
Keywords: alcohol, stroke, mortality, health policy, Lithuania

Resumen

Dado el impacto del alcohol en los ictus, las políticas de control de alcohol deberían reducir las tasas de mortalidad. Nuestro objetivo fue demostrar el impacto de tres importantes políticas lituanas implementadas en 2008, 2017 y 2018 en las tasas de mortalidad específicas por subtipo de ictus y sexo, en mayores de 15 años. Se realizaron análisis de regresión «joinpoint» para identificar los cambios de tendencia. Para estimar el impacto, se realizaron análisis de series temporales interrumpidas utilizando un modelo mixto aditivo generalizado en las tasas mensuales estandarizadas por edad, desde enero 2001 hasta diciembre 2018. Se encontraron disminuciones porcentuales anuales promedio significativas en ambos subtipos de ictus y por sexo. Las políticas tuvieron un mayor impacto en las tasas de mortalidad por ictus isquémico en mujeres. Posterior a la política del 2008, ocurrió un cambio positivo de 4,498 muertes por ictus isquémico por 100 000 mujeres y un cambio de pendiente mensual negativo de -0,048 muertes por ictus isquémico por 100 000 mujeres. Posterior a las políticas de 2017 y 2018, hubo un cambio de tendencia negativo significativo para la mortalidad por ictus isquémico en mujeres, de -0.901 muertes y -1.431 muertes por 100 000 habitantes, respectivamente. La mortalidad por ictus hemorrágico en hombres no se vio afectada, y la mortalidad por ictus hemorrágico en mujeres y por ictus isquémico en hombres solo se vio afectada por la política del 2008. Nuestros hallazgos sugieren que el impacto de las políticas en la mortalidad por ictus puede variar según sexo y subtipo.
Palabras clave: alcohol, ictus, mortalidad, política sanitaria, Lituania

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Hemorrhagic and ischemic stroke are cardiovascular diseases caused by reduced blood supply to the brain and are among the most important disease categories causally affected by alcohol (Rehm et al., 2017). Age-standardized stroke mortality rates per 100,000 population have declined globally between 1990 and 2019, but stroke has remained the second greatest specific cause of death worldwide (GBD 2019 Stroke Collaborators, 2021). Specifically, age-standardized stroke mortality rates within Central Europe, Eastern Europe, and Central Asia have fluctuated around 200 deaths per 100,000 population between 1990 and 2002, followed by a decrease from approximately 205 deaths per 100,000 population to 120 deaths per 100,000 population between 2002 and 2017, and have plateaued at around 120 deaths per 100,000 population between 2017 and 2019 (GBD 2019 Stroke Collaborators, 2021). While the relationship between alcohol consumption and stroke subtype-specific mortality risk is complex, excessive alcohol consumption is associated with an increased risk of mortality for both stroke subtypes (O'Donnell et al., 2016; Patra et al., 2010). A meta-analysis by Patra and colleagues (2010) found that the risk for hemorrhagic stroke for men and women who drank more than 12g of pure alcohol per day was 1.3- and 1.5-times greater, respectively, than that of lifetime abstainers, and that the risk for ischemic stroke among men and women who drank more than 36g of pure alcohol per day was 1.2- and 1.4-times greater, respectively.

Despite being the only World Health Organization (WHO) region to report a decrease in total alcohol per capita consumption in the most recent Global Status Report (from 12.1 litres in 2000 to 9.8 litres in 2016), the European Region has consistently ranked the highest globally for alcohol consumption levels (World Health Organization, 2018). In addition, the highest alcohol-attributable mortality rates have been reported among certain Eastern European countries including Lithuania, where it was found to be 163.7 deaths per 100,000 population in 2016 (Shield et al., 2020). In an attempt to reduce alcohol-related harms, various alcohol control policies have been introduced in Lithuania since 2008 (Miščikienė et al., 2020), including the WHO's "best buys" – i.e., alcohol control policies that are evidence-based and highly cost effective (Chisholm et al., 2018; World Health Organization, 2017). Among the various policies implemented, the policies enacted in January 2008, March 2017, and January 2018, encompassed either a price increase, reduced availability of alcohol, or both (Miščikienė et al., 2020). These policies are believed to have had an immediate effect on alcohol consumption, thereby immediately reducing attributable harms (Rehm et al., 2021). In fact, Lhachimi et al. (2012) analyzed alcohol consumption data from 11 European Union-member states to model the effects of increased alcohol prices on stroke mortality and estimated that approximately 65,800 less men and 23,500 less women would experience a stroke over a ten-year period if all 11 countries were to increase the price of alcohol to that of Finland's, where at the time of the study, the price level index of alcohol was the highest within the European Union. However, to the best of our knowledge, there is currently no study that has empirically examined the impact of alcohol control policies on stroke mortality rates by subtype (i.e., hemorrhagic and ischemic stroke).

It is reasonable to hypothesize that the impact of alcohol control policies may differ by stroke subtype and sex, as the shape of the dose-response curves for alcohol consumption and the relative risks of hemorrhagic and ischemic stroke mortality appear to be sex specific. Specifically, there exists a linearly increasing dose-response relationship among men who drink any level of alcohol, so that they are at an increased relative risk of hemorrhagic stroke mortality compared to lifetime abstainers (Patra et al., 2010). On the other hand, hemorrhagic stroke mortality among women and ischemic stroke mortality for both men and women present a J-shaped dose-response curve, meaning that low-to-moderate levels of alcohol consumption have been associated with a protective effect against mortality risk while high consumption levels can cause harm (Patra et al., 2010). If alcohol control policies reduce consumption levels across the population and especially among heavy drinkers (Chisholm et al., 2018), the proportion of heavy drinkers in the population would decrease while the proportion low-to-moderate drinkers would increase. This increase in the population proportion of low-to-moderate drinkers may reduce stroke mortality differently among J-shaped and linear dose-response relationships. That is, the consequent increase in the proportion of low to moderate drinkers within a J-shaped dose-response relationship may increase the population proportion with lower risk for stroke mortality and thus decrease stroke mortality rates, while in the context of a linear dose-response relationship, the increased proportion of low to moderate drinkers would still possess a higher relative risk of mortality compared to lifetime abstainers resulting in less of a change. Therefore, in the current paper, we aimed to investigate the impact of the 2008, 2017 and 2018 alcohol control policies implemented in Lithuania on sex-specific hemorrhagic and ischemic mortality rates. We tested the hypothesis that the respective alcohol control policy enactments resulted in a reduction in both hemorrhagic stroke and ischemic stroke mortality rates, but that relatively greater reductions would be found for J-shaped dose-response relationships compared to linear dose-response relationships.

Method

Measures

The mortality diagnoses included in this analysis were hemorrhagic stroke (International Classification of Diseases, 10th revision [ICD-10] codes: I60-I62.9, I67.0-I67.1, I69.0-I69.298) and ischemic stroke (ICD-10 codes: G45-G46.8, I63-I63.9, I65-I66.9, I67.2-I67.848, I69.3), according to the Institute for Health Metrics and Evaluation Global Burden of Disease Study 2019 definitions (IHME, 2020). The response variables in the current study were age-standardized sex- and stroke subtype-specific mortality rates per 100,000 population. The monthly number of deaths by stroke subtype and yearly population data from 2001 to 2018 were obtained from the Lithuanian Department of Statistics (Lithuanian Department of Statistics, n.d.) and the Lithuanian University of Health Sciences to calculate monthly sex- and stroke subtype-specific crude mortality rates per 100,000 population from January 2001 to December 2018, for a total of 216 monthly data points. Yearly population data was linearly interpolated to obtain monthly data. The crude mortality rates were determined by dividing the total number of deaths among individuals aged 15+ years of age by the respective population size. This value was then multiplied by 100,000 to obtain the crude mortality rate per 100,000 population. Finally, the sex- and stroke subtype-specific crude mortality rates were directly standardized to the 2011 to 2030 European standard population (Eurostat, 2013).

As specified above, the three policies tested were implemented on January 1, 2008 (Policy 1), March 1, 2017 (Policy 2) and January 1, 2018 (Policy 3), and have been previously described as policies likely to have an immediate impact on alcohol consumption and thus, alcohol-attributable harms (Rehm et al., 2021). For specific details on the policies see the paper by Miščikienė et al. (2020). The policy enactments were coded as dummy variables with values ranging from 0 to 1, according to the lag structure described in the following paragraph.

Lag effect of alcohol control policy on stroke mortality

In setting up time-series models for chronic disease conditions, there is always the question of whether a lag-time should be modelled between, in this case, the change in alcohol consumption and the potential change in chronic disease. While chronic diseases often develop over time, changes in alcohol consumption on the population level may have immediate effects. Take liver cirrhosis as an example, where abrupt changes in availability of alcohol had almost immediate effects on liver cirrhosis mortality (e.g., the Gorbachev reform, prohibition, or the German invasion of Paris; see (Zatoński et al., 2010)). For stroke, the lag-time in times series analyses has been handled similarly, with most or all of the effects being modelled immediately after a change of consumption (Lee, Liao, Peng & Lin, 2019; Pun et al., 2013; Razvodovsky, 2014). While Pun et al. (2013) did not explicitly test for any lag structure, Lee et al. (2019) and Razvodovsky (2014) tested different lag structures.

Given that both types of stroke are chronic diseases with some excepted lag effects (Holmes, Meier, Booth, Guo & Brennan, 2012) and that the stroke mortality data reflects population-level observations, we incorporated a lag structure into the time-series analyses to ensure the full effect was captured. Specifically, the cumulative geometric distribution structure of the lag structure was equal to

$$F(X = k) = 1 - (1 - p)^{k+1}$$

where p = 20% is the probability that the policy was effective in each month, and F (X = k) is the probability that the policy was effective after k months (Devroye, 1986). This resulted in a lag structure that had a 20% probability of an immediate effect, 36% after 1 month, 49% after 2 months, and approximately 100% at 24 months. The shape of the cumulative geometric distribution was taken from Holmes and colleagues (Holmes et al., 2012), and the overall lag-time of 24 months was based on an overall integration of the literature (Holmes et al., 2012; Lee et al., 2019; Pun et al., 2013; Razvodovsky, 2014), which tended to indicate relative short lag times (see (Razvodovsky, 2014) for a test of different lag-times).

Covariates

The underlying mechanisms of alcohol attributable harms are complex and are believed to be partly driven by economic factors that reflect the price and affordability of alcohol (Schmidt, Mäkelä, Rehm & Room, 2010; Stuckler, Meissner & King, 2008). Therefore, additional covariates, including gross domestic product *per capita* (GDP), consumer price index of alcoholic beverages compared to the December of the previous year (CPI), and sex-specific unemployment rates were considered for inclusion in the final model. Quarterly GDP, monthly CPI and monthly unemployment rate data were obtained from the Lithuanian Department of Statistics (Lithuanian Department of Statistics, 2020a, 2020b, 2021). Quarterly values were linearly interpolated to obtain monthly data.

Statistical analysis

Joinpoint regression analysis

The joinpoint regression is a segmented regression technique which identifies points of inflection in the data, fits linear segments between the identified inflection points and estimates changes in slope across a time series (i.e., annual percent change (APC) and average APC (AAPC)). Using the grid-search method and a permutation test procedure, the fewest number of linear segments such that an additional joinpoint does not add a statistically

significant linear trend is selected. The maximum number of joinpoints was set at five, which is standard for joinpoint analyses of 30 or more data points (Kim, Fay, Feuer & Midthune, 2000). The joinpoint regression analyses were conducted using the Joinpoint Regression Program version 4.8.0.1 (Statistical Methodology and Applications Branch, Surveillance Research Program, 2020).

Interrupted time series analysis using generalized additive mixed models (GAMM)

To test the hypothesis that the three policy enactments had a relatively greater impact on reducing sex-specific hemorrhagic stroke mortality than ischemic stroke mortality, an interrupted time series analysis using a generalized additive mixed model (GAMM) (Beard et al., 2019) was performed for each policy, in RStudio version 1.3.1073 (RStudio Team, 2020). Seasonality of the sex- and stroke subtype-specific mortality rates were accounted for in the GAMMs by the inclusion of a smoothing spline with 12 knots, to reflect each month. The correlation matrices and cross correlation functions between the sex- and stroke subtype-specific mortality rates and each covariate (i.e., GDP, CPI and sex-specific unemployment rates) were assessed to identify any significant lagged relationships. Analysis of variance (ANOVA) testing was performed at a 0.05 alpha level to determine the inclusion of an interaction term between the linear time variable (i.e., months variable) and the lagged policy effect, as well as to determine the inclusion of a quadratic effect of the months variable. The number of autoregressive (AR) and moving average (MA) terms of each sex- and stroke subtype-specific GAMM was determined using the auto.arima function from the forecast package in R and confirmed by examination of their respective autocorrelation function (ACF) and partial autocorrelation function (PACF) plots. AR and MA terms were included in the final model when it resulted in a better model fit, as indicated by greater R^2, and lower AIC or BIC values. Finally, the Shapiro-Wilk test (Shapiro & Wilk, 1965) and Q-Q plots were used to assess residual normality, and residual plots against linear predicted values were assessed to determine stationarity.

A *p*-value less than 0.05 was considered statistically significant for all analyses. The protocol for this study was registered to Open Science Framework Preregistration (DOI: 10.17605/OSF.IO/4MXCZ, submitted May 28, 2021).

Results

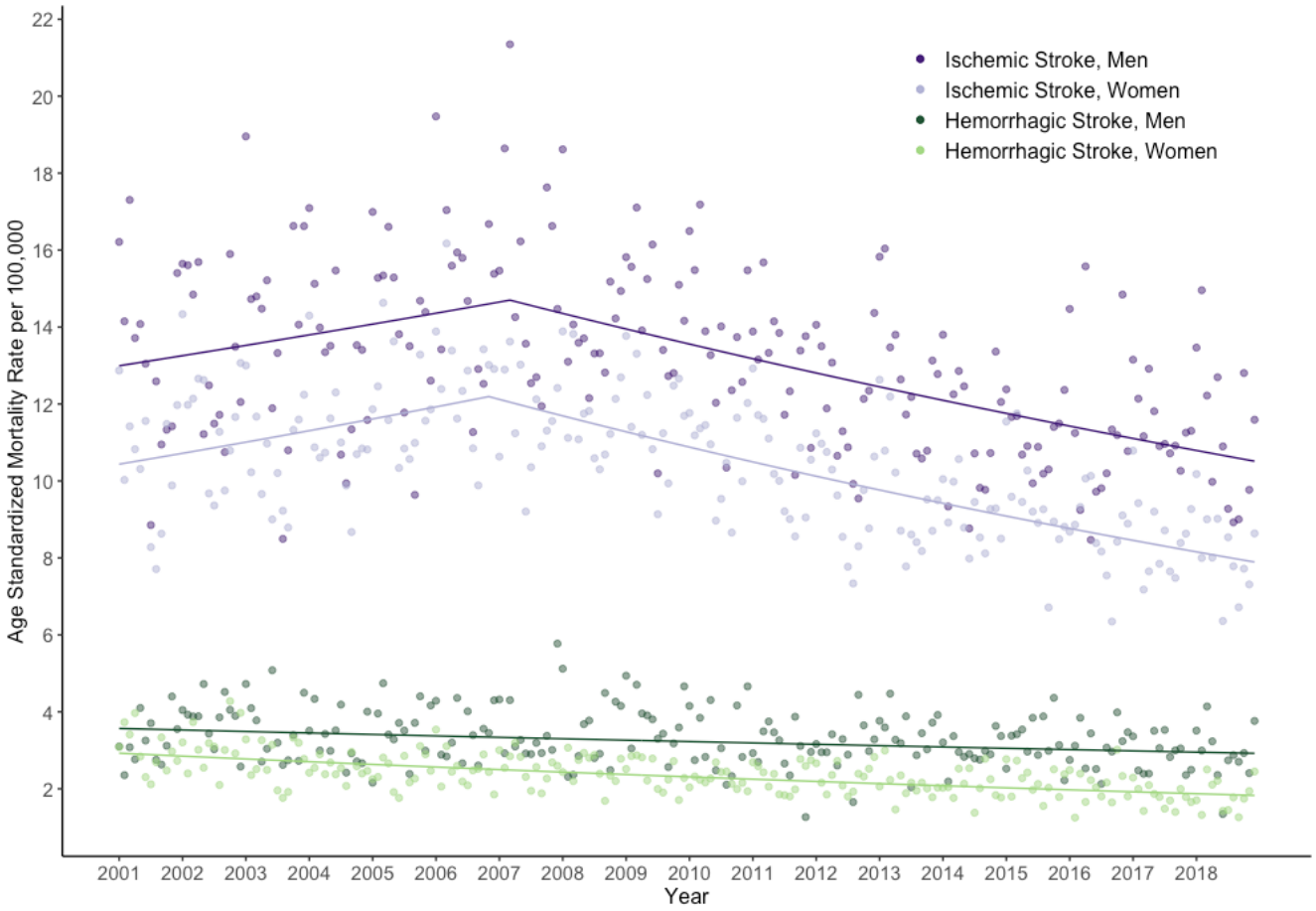
Joinpoint regression analysis

Overall, the age-standardized ischemic stroke mortality rates for both men and women were greater than that of hemorrhagic stroke, and stroke subtype-specific mortality rates among women were lower than those for men (Fig 1). The joinpoint regression analyses revealed that age-standardized mortality rates for both hemorrhagic and ischemic stroke significantly decreased between January 2001 and December 2018 among both sexes, with a greater rate of decline observed among women compared to men (Table 1). The AAPC for hemorrhagic and ischemic stroke mortality rate among men were -0.09% (95% confidence interval (CI): -0.14%, -0.05%; $p < 0.001$) and -0.10% (95% CI: -0.18%, -0.01%; $p = 0.02$), respectively. Whereas the hemorrhagic and ischemic stroke mortality rate AAPC among women were -0.22% (95% CI: -0.26%, -0.18%; $p < 0.001$) and -0.13% (95% CI: -0.21%, -0.05%; $p < 0.001$), respectively. No significant joinpoints were identified for hemorrhagic stroke mortality rates for either sex. However, one significant joinpoint was identified for ischemic stroke mortality rates for both men and women, in March 2007 and November 2006, respectively (Fig 1). The ischemic stroke mortality rate APC among men was 0.17% (95% CI: -0.03%, 0.37%; $p = 0.10$) until March 2007, after which the mortality rate significantly decreased each year by -0.24% (95% CI: -0.31%, -0.16%; $p < 0.001$). Similarly, the ischemic stroke mortality rate APC among women was 0.22% (95% CI: 0.03%, 0.42%; $p = 0.02$) up to November 2006, after which the mortality rate significantly decreased each year by -0.30% (95% CI: -0.36%, -0.23%; $p < 0.001$).

Interrupted times series analysis results for sex-specific hemorrhagic stroke mortality rates

The R^2 values for all the sex-specific hemorrhagic stroke mortality GAMMs were low, indicating a poor model fit (Table 2) and that other unknown factors are likely impacting the sex-specific hemorrhagic stroke mortality rate. None of the tested policies were found to have a significant effect on hemorrhagic stroke mortality rates among men, while Policy 1 was the only policy to have a significant effect among women. Specifically, the full effect of Policy 1 was associated with a slope change for hemorrhagic stroke mortality rates among women. The "months" term (ß = -0.016; 95% CI: -0.024, -0.008; $p < 0.001$) and interaction term (months*policy effect; ß = 0.007; 95% CI: 0.001, 0.013; $p = 0.020$) were found to be significant, and the coefficients of these two variables can be added to calculate the slope of hemorrhagic stroke mortality 24 months after Policy 1 enactment (i.e., timepoint at which the policy is assumed to have full effect); this was equal to a monthly decrease of -0.009 hemorrhagic stroke deaths per 100,000 population among women once Policy 1 was in full effect. Therefore, within the limitations of a low R^2 value for this model ($R^2 = 0.434$), it can be inferred that as compared to a monthly decrease of -0.016 deaths per 100,000 population prior to policy enactment, the full effect of Policy 1 coincided with a reduced rate of decline for hemorrhagic stroke mortality among women.

Figure 1
Age-standardized sex-specific hemorrhagic stroke (green) and ischemic stroke (purple) mortality rates and joinpoint trends in Lithuania among 15+ year-olds, from January 2001 to December 2018



Interrupted times series analysis results for sex-specific ischemic stroke mortality rates

Policy 1 was the only policy to have a significant effect on ischemic stroke mortality rates among men, while all three policies had a significant effect among women (Table 3). In the Policy 1 model for men, the "months" term (ß = 0.031; 95% CI: 0.003, 0.060; $p < 0.033$) and interaction term (months*policy effect; ß = -0.054; 95% CI: -0.075, -0.033; $p < 0.001$) were found to be significant. This indicated that the ischemic stroke mortality rate increased up until the enactment of Policy 1 and the rate of the increase began to decrease after Policy 1 enactment.

In the Policy 1 model for women, ischemic stroke mortality rates were stable prior to Policy 1 enactment, followed by a positive level change at the timepoint of Policy 1 enactment and a negative slope change after the policy reached its full effect. The policy effect (ß = 4.498; 95% CI: 3.163, 5.833; $p < 0.001$) and the interaction term (months*policy effect; ß = -0.048; 95% CI: -0.063, -0.032; $p < 0.001$) were significant, representing a positive level change (i.e., an immediate increase in ischemic stroke mortality rate after the policy 1 enactment timepoint) followed by a significant declining trend for ischemic stroke mortality rates among women. The coefficients for the policy effect and interaction term can be added to calculate the ischemic stroke mortality rate when the policy reached its full effect (that is, 24 months after its enactment). This would result in an ischemic stroke mortality rate equal to 3.35 (4.498 – 0.048*24) deaths per 100,000 population on January 1, 2010, followed by a monthly rate decrease of -0.048 for each month thereafter.

The months and policy effect terms were significant in both the Policy 2 model and Policy 3 model for ischemic stroke mortality rates among women. For Policy 2, the months term (ß = -0.030; 95% CI: -0.039, -0.022; $p < 0.001$) and policy effect term (ß = -0.901; 95%. CI: -1.715, -0.088; $p = 0.031$) were significant, indicating that ischemic mortality rates among women declined at a monthly rate of -0.030 deaths per 100,000 population from 2001 to 2018, with a significant negative level change of -0.901 deaths per 100,000 population once Policy 2 reached its full effect. For Policy 3, the months term (ß = -0.033; 95% CI: -0.041, -0.025; $p < 0.001$) and policy effect term (ß = -1.431; 95% CI: -2.609, -0.252; $p = 0.018$) were significant,

Table 1
Joinpoint analysis of age-standardized[a] hemorrhagic and ischemic stroke mortality rates (per 100,000 population) from 2001-2018, by sex

	Mortality Rate per 100,000 (Date)[a]				Period 1			Period 2		
	Min.	Max.	AAPC (95% CI)	*p*	Date	APC (95% CI)	*p*	Date	CPA IC 95%	*p*
Hemorrhagic stroke										
Men	1.27 (Nov. 2011)	5.77 (Dec. 2007)	-0.09 * (-0.14, -0.05)	<0.001	Jan. 2001 – Dec. 2018	0.09* (-0.14, -0.05)	<0.001	n/a	n/a	n/a
Women	1.25 (Feb. 2016)	4.28 (Oct. 2002)	-0.22* (-0.26, -0.18)	<0.001	Jan. 2001 – Dec. 2018	-0.22* (-0.26, -0.18)	<0.001	n/a	n/a	n/a
Ischemic stroke										
Men	8.47 (May 2016)	21.35 (Mar. 2007)	-0.10* (-0.18, -0.01)	0.02	Jan. 2001 – Mar. 2007	0.17 (-0.03, 0.37)	0.10	Mar. 2007 – Dec. 2018	-0.24* (-0.31, -0.16)	<0.001
Women	6.35 (Sep. 2016)	16.17 (Mar. 2006)	0.13* (-0.21, -0.05)	<0.001	Jan. 2001 – Nov. 2006	0.22* (0.03, 0.42)	0.02	Nov. 2006 – Dec. 2018	-0.30* (-0.36, -0.23)	<0.001

Note. AAPC, average annual percent change; APC, average percent change; 95% confidence interval; n/a, not applicable.
*$p < 0.05$.
[a]2011-2030 European standard population age-standardized mortality rate per 100,000 population.

Table 2
Final sex-specific hemorrhagic stroke GAMM model regression coefficients (95% CI) and p-value (α = 0.05)

	Policy 1 (Jan. 1, 2008)		Policy 2 (Mar. 1, 2017)		Policy 3 (Jan. 1, 2018)	
	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*
Men						
Adjusted R^2	,110		0.098		0.102	
Intercept	4,035 (3,072, 4,998)	<0.001*	3.652 (3.178, 4.125)	<0.001*	3.638 (3.179, 4.096)	<0.001*
Months	0,001 (-0,011, 0,014)	0.852	-0.003 (-0.008, 0.001)	0.165	-0.004 (-0.008, 0.001)	0.093
Policy effect	0,918 (-0,012, 1,848)	0.054	2.358 (-14.327, 19.043)	0.782	-0.278 (-0.896, 0.340)	0.379
CPI	-0,001 (-0,027, 0,026)	0.967	0.002 (-0.029, 0.034)	0.886	0.0003 (-0.025, 0.026)	0.983
Unemployment rate	-0,023 (-0,066, 0,020)	0.303	-0.006 (-0.026, 0.014)	0.551	-0.006 (-0.025, 0.014)	0.579
GDP	-0,0002 (-0,0005, 0,0001)	0.253	0.00003 (-0.0002, 0.0003)	0.809	0.00005 (-0.0002, 0.0003)	0.709
Interaction term[a]	-0,006 (-0,015, 0,003)	0.214	-0.012 (-0.0921, 0.068)	0.763	n/a	n/a
Women						
Adjusted R^2	0.434		0.415		0.412	
Intercept	3.819 (3.094, 4.544)	<0.001*	2.971 (2.626, 3.316)	<0.001*	2.918 (2.579, 3.257)	<0.001*
Months	-0.016 (-0.024, -0.008)	<0.001*	-0.004 (-0.007, -0.001)	<0.004*	-0.005 (-0.008, -0.003)	<0.001*
Policy effect	0.099 (-0.400, 0.598)	0.697	-6.513 (-16.446, 3.420)	0.200	0.017 (-0.351, 0.385)	0.928
CPI	-0.015 (-0.033, 0.003)	0.106	0.008 (-0.011, 0.027)	0.423	-0.0003 (-0.016, 0.016)	0.975
Unemployment rate	-0.052 (-0.094, -0.010)	0.017*	-0.001 (-0.021, 0.019)	0.911	0.0003 (-0.020, 0.020)	0.980
GDP	0.00004 (-0.0002, 0.0002)	0.723	-0.00005 (-0.0002, 0.0001)	0.566	0.000003 (-0.0001, 0.0002)	0.966
Interaction term[a]	0.007 (0.001, 0.013)	0.020*	0.031 (-0.017, 0.078)	0.208	n/a	n/a

Note. GAMM, generalized additive mixed model; CPI, consumer price index; GDP, gross domestic product per capita; 95% confidence interval; n/a, interaction term not included in final model.
*$p < 0.05$.
[a]Between months and policy effect (dummy variable).

indicating that ischemic mortality rates among women declined at a monthly rate of -0.033 deaths per 100,000 population from 2001 to 2018, with a significant negative level change of -1.431 deaths per 100,000 population once Policy 3 reached its full effect.

Discussion

In the current study, we found that the age-standardized stroke subtype-specific mortality rates per 100,000 population significantly declined in Lithuania between 2001 and 2018. Larger annual rates of decline were observed among women than men, with overlapping confidence intervals for ischemic stroke but not for hemorrhagic stroke. The trends identified in the current study provide more recent sex- and stroke subtype-specific mortality rate trends, which largely contradict the trends described by Shah and colleagues (Shah et al., 2019), whom conducted joinpoint regression analyses to estimate the AAPC for sex- and stroke subtype-specific age-standardized mortality rates in Lithuania using WHO global mortality data from 1993 to 2016. While all sex- and stroke subtype-specific mortality rate trends declined between 1993 and 2016, the decline in hemorrhagic stroke mortality rates among women was the only trend found to be significant. Specifically, while no significant joinpoints were identified for hemorrhagic stroke mortality rates among women, the AAPC was equal to -2.5% ($p < 0.05$) for the time period of 1993 to 2016 (Shah et al., 2019). The divergent findings are likely due to the different observation time periods, data sources and populations standards used. Additional explanation is also provided by the significant changes that took place in the risk profile of circulatory diseases among the Lithuanian population between 2001 and 2018. In 2006, the National Program for the Prevention of Circulatory System Diseases in High-Risk Individuals was launched in Lithuania, and the prevalence of the certain risk factors for cardiovascular diseases (e.g., arterial hypertension, dyslipidemia, metabolic syndrome, and smoking (Kutkiene et al., 2018; Laucevičius et al., 2020; Rinkūnienė et al., 2019)) has since decreased.

Results from our time-series analyses support the hypothesis that the 2008, 2017 and 2018 alcohol control policies may have had a relatively greater impact on reducing sex- and stroke subtype-specific mortality rates that demonstrate a J-shaped relative risk dose-response relationship to increasing alcohol consumption levels, compared to those with a linear dose-response relationship. Hemorrhagic stroke mortality among men was the only sex- and stroke subtype-specific category with a linear dose-response relationship (Patra et al., 2010) and our analyses revealed it to be the only category that did not have a significant declining trend in mortality rates that coincided with a policy implementation.

The 2008 alcohol control policy (Policy 1), which involved a 20% excise tax increase for ethyl alcohol, wine, and intermediate products, and a 10% increase for beer, had a significant effect on all sex- and stroke subtype-specific mortality rates with a J-shaped dose-response relationship. However, it is important to acknowledge that the effect of Policy 1 (2008) on sex- and stroke subtype-mortality may have likely been augmented by the 2008 global economic crisis, in comparison to Policy 2 (2017) and Policy 3 (2018) which were implemented during a calm period of stable economic growth. In an interrupted time-series analysis study by Mackenbach et al. (2018), the authors combined census data from Western and Eastern European countries, from 1990 to 2015, to describe sex-specific trends in all-cause and cause-specific mortality rates, and to describe health inequalities in mortality trends. The authors found that among both men and women in Eastern European countries, including Lithuania, alcohol-related mortality rates increased until 2008 and decreased afterwards; albeit not significantly.

Ischemic stroke mortality rates among women were the only category to have declining mortality rates that coincided with all three policy implementation dates. This finding is in contrast to that presented by Štelemėkas et al. (2021) on the effect of Lithuania's alcohol control policies on adult all-cause mortality. The authors investigated the impact of the same three policy enactments investigated in the current study and found that while the alcohol control policies had no significant effects on all-cause mortality among women, Policy 1 and Policy 2 significantly reduced all-cause mortality among men. The results from these two studies suggests that while the investigated alcohol control policies may reduce mortality rates among men to a greater extent than women for most causes of mortality, mortality rates among women are reduced to a greater extent compared to men for stroke subtype-specific mortality. Sex differences in binge-drinking behaviour may provide some explanation as to why alcohol control policies impact stroke subtype-specific mortality rates among women more than men. In a cluster analysis study of Wave 1 and Wave 2 data from the National Epidemiologic Survey on Alcohol and Related Conditions, male drinkers reported a higher amount of average daily alcohol consumption compared to female drinkers (Jiang, Lange, Tran, Imtiaz & Rehm, 2021). It may be possible that alcohol control policies do not have an effect on reducing binge-drinking behaviour and therefore have a greater effect of reducing stroke subtype-specific mortality among women than men.

There are some limitations of the current study that should be acknowledged. First and foremost, the lag structure of alcohol consumption on stroke subtype-specific mortality is not yet established in the literature and as such, the lag structure included in our analysis was informed by a limited number of studies that incorporated

or tested various lag-times for alcohol consumption and stroke (Holmes et al., 2012; Lee et al., 2019; Pun et al., 2013; Razvodovsky, 2014; Zatoński et al., 2010). Therefore, there is a need for formal testing of various lag-times of alcohol consumption on the specific stroke subtypes to improve future time-series analyses. Second, the low to moderate adjusted R^2 values suggest the presence of one or more unknown factors driving the decreasing stroke subtype-specific mortality rates and as such, we encourage researchers to explore other potential explanations, such as binge-drinking behaviour and non-alcohol policy changes related to cardiovascular health, in the future. Third, our models would have benefited from the inclusion of important covariates, such as age to reveal in which age groups the reduction in mortality was most significant, and comorbidity which is an established risk factor for stroke mortality. Finally, the limited number of time points following the 2018 policy enactment could account for the finding that there was no relationship between the reduction in alcohol availability and stroke mortality due to limited power, especially given the suspected lag time for this chronic disease. The significant changes have been observed in a period of 2016 to 2018 during a stable period of economic growth while the alcohol consumption was declining at the same period. This suggests that the future analysis should concentrate on assessing the impact of alcohol control policies on stroke when more data points are available.

Our findings suggest that the effectiveness of alcohol control policies, particularly those targeting price, may differ by sex- and stroke subtype categories. Additionally, such policies may be more effective in reducing sex- and stroke subtype-specific mortality rates if applied in tandem with national health promotion programs aimed to improve cardiovascular health risk profiles but may be less effective in the presence of binge-drinking behaviour, as observed in men. This has implications for policy makers and other relevant stakeholders who are interested in reducing alcohol-related stroke mortality in a developed, high-income country.

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Conflict of interests

The authors declare no conflicts of interests.

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