Changes in ischemic stroke occurrence following Daylight saving time transitions

Jussi O.T. Sipilä[1,2,3], Jori O. Ruuskanen[2,3], Päivi Rautava[4,5], Ville Kytö MD[6,7]

[1] Department of Neurology, North Karelia Central Hospital, Joensuu, Finland;

[2] Neurology, University of Turku, Turku, Finland;

[3] Division of Clinical Neurosciences, Turku University Hospital, Turku, Finland;

[4] Clinical Research Center, Turku University Hospital, Turku, Finland;

[5] Department of Public Health, University of Turku, Turku, Finland;

[6] Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland;

[7] Heart Center, Turku University Hospital, Turku, Finland.

Corresponding author: Jussi Sipilä, M.D.

Department of Neurology, North Karelia Central Hospital

Tikkamäentie 16

FI-80210 Joensuu, Finland

e-mail jussi.sipila@utu.fi

tel: +358-50 43 23 893

Abstract

Background

Circadian rhythm disruption has been associated with increased risk of ischemic stroke (IS). Daylight saving time (DST) transitions disrupt circadian rhythms and shifts the pattern of diurnal variation in stroke onset, but effects on the incidence of IS are unknown.

Methods

Effects of 2004-2013 DST transitions on IS hospitalizations and in-hospital mortality were studied nationwide in Finland. Hospitalizations during the week following DST transition (study group, n = 3 033) were compared to expected hospitalizations (control group, n = 11 801), calculated as the mean occurrence during two weeks prior to and two weeks after the index week.

Results

Hospitalizations for IS increased during the first two days (Relative Risk 1.08; CI 1.01-1.15, P=0.020) after transition, but difference was diluted when observing the whole week (RR 1.03; 0.99-1.06; P=0.069). Weekday-specific increase was observed on second day (Monday; RR 1.09; CI 1.00-1.90; P=0.023) and fifth day (Thursday; RR 1.11; CI 1.01-1.21; P=0.016) after transition. Women were more susceptible than men to temporal changes during the week after DST transitions. Advanced age (>65 years) (RR 1.20; CI 1.04-1.38; P=0.020) was associated with increased risk during the first two days, and malignancy (RR 1.25; CI 1.00-1.56; P=0.047) during the week after DST transition.

Conclusions

DST transitions appear to be associated with an increase in IS hospitalizations during the first two days after transitions but not during the entire following week. Susceptibility to effects of DST

transitions on occurrence of ischemic stroke may be modulated by gender, age and malignant comorbidities.

Key words: cerebrovascular disease, chronobiology, circadian rhythm, circadian rhythm misalignment, circadian rhythm disturbance

Introduction

Ischemic stroke (IS) is the second leading cause of death worldwide and a significant source of disability. Despite advances in primary prevention and treatment of IS, as reflected by decreases in age-standardized incidence and case-fatality during recent decades,[1,2] the absolute number of IS victims continues to increase because of population growth and ageing.[3] Traditional vascular risk factors have become better controlled in high-income countries but further efforts are still needed.[4,5] New ways of preventing cerebrovascular disease and IS should also be sought.

Similar to myocardial infarction (MI), IS shows a clear circadian rhythmicity with peaking incidence in the morning hours,[6,7] and even the safety and efficacy of thrombolytic therapy for non-lacunar IS has been reported to be associated with circadian factors.[8] Occurrence of MI has been shown to be affected by transitions to and from Daylight saving time (DST),[9-14] which disrupt circadian rhythms and beget sleep deprivation.[15] Circadian disruption associated with rotating night shift work[16] as well as aberrant sleep duration [17,18] have been associated with increased risk of IS. DST transitions shift the pattern of diurnal variation in stroke onset.[7] Effects of DST transitions to stroke incidence and severity are however unknown. We studied the effects of DST transitions on stroke hospitalizations and in-hospital mortality in a multihospital, nationwide setting.

Methods

Study patients

We studied all patients aged ≥15 years admitted to participating hospitals with IS as the primary discharge diagnosis (ICD-10 code I63) during 2004-2013. Patients admitted two weeks prior and three weeks after DST transition were included in the current study (see exceptions caused by Easter below). Data were collected from the 20 hospitals that provide care for patients with acute IS in Finland by using the Finnish Care Register for Health Care (CRHC), an obligatory, nationwide, and automatically collected database. This covers virtually all acute stroke hospitalizations in Finland, the population of which grew from 5.2 to 5.4 million during the study period. The manuscript does not contain clinical studies and involved no contact with patients. Therefore no approval of an ethics committee was needed. Anonymized patient data were collected retrospectively from patient records with the approval of the National Institute of Health and Welfare (permission THL/143/5.05.00/2015).

Analysis

Association between IS and DST transitions was measured by calculating relative risks (RR) of observed hospitalizations following DST transition (study group) to expected hospitalization (control group) calculated as the mean occurrence during control weeks prior to DST and two weeks after DST transition. Hospitalizations following DST transition were analyzed during first two and seven days after transition as well as by weekdays. In Finland, DST starts on the last Sunday of March and ends on the last Sunday of October. Since Monday following Easter Sunday

is a national holiday in Finland, years with DST spring transition on Easter Sunday were excluded from the analysis (2005 and 2013) to avoid confounding. In addition, occurrence of Easter Sunday within two weeks prior or after DST transition was adjusted by not including the week following Easter as control, but selecting prior or following week. Shortening of Sunday after transition into DST was adjusted with multiplying the number of IS hospitalizations by 24/23, and lengthening of Sunday after transition out of DST with multiplying by 24/25.[9,10] Confidence intervals (95%) (CI) were calculated by using SAS CINV function and tested as previously described [19] with Bonferroni corrections applied as appropriate.

Modified Poisson regression with robust error variances was used to analyze associations of patient features and IS occurring during the week after DST transition. Models were adjusted for study year and spring/autumn period.[20,21] In-hospital mortality was analyzed using Cox's proportional hazards regression stratified for study year. Variable selection to Cox's regression model was performed by using augmented backwards elimination procedure with significance threshold α=0.2 and change-in-estimate threshold τ=0.05.[22] Age, gender and occurrence of IS during seven days after DST transition were forced into the Cox´s model. Results of regression analyses are given as RR or hazard ratio (HR) as appropriate. Statistical significance was inferred at $P<0.05$. SAS for windows v. 9.4. was used for analyses (SAS Institute, Cary, NC, USA).

Results

Total study population included 14834 patients with IS (age 71.3 SD 12.7; 54.2% men) of whom 3033 (20.5%) were admitted during 7 days following DST transition and 11801 (79.6%) during control weeks. DST transition was followed by an increase in IS hospitalizations during the first two days (RR 1.08; CI 1.01-1.15, P=0.020) after transition. When observing the whole week after transition, trend for increase persisted, but was not statistically significant (RR 1.03; 0.99-1.06; P=0.069). Weekday-specific increase in hospitalizations was observed on second day (Monday; RR 1.09; CI 1.00-1.90; P=0.023) and fifth day (Thursday; RR 1.11; CI 1.01-1.21; P=0.016) after transition (Figure 1).Of all study patients 6464 (43.6%) were admitted in spring and 8370 (56.4%) in autumn. There were no weekday-specific differences in relative risk of IS after DST transitions between spring and autumn periods, nor were the differences during the first two (RR 1.07; CI 0.95-1.21; P=0.552) or seven days (RR 0.99; CI 0.95-1.06; P=0.757) after transition (Figure 2).

Women were more susceptible to temporal changes after DST transitions compared to men (Figure 3). Compared to men, relative risk of IS was higher among women on second day after DST (RR 1.18; CI 1.02-1.38; P=0.031), but lower on sixth day after transition (RR 0.83; CI 0.69-1.00; P=0.045). Relative risk for IS between genders did not differ during the whole week after transition (RR 1.02; CI 0.95-1.08; P=0.625).

Variation in risk of IS was detected also with regard to age. Older patients (>65 years of age) had higher risk of IS than younger patients on the second day (RR 1.23; CI 1.03-1.47; P=0.021) as well as on the first two days (RR 1.20; CI 1.04-1.38; P=0.020) after DST transition (Figure 4), but risk during the whole week after transition was similar to that in younger patients (RR 1.02; CI 0.95-1.10; P=0.580).

Co-morbidity distribution of IS patients did not differ between patients admitted during the week after DST transition or the control weeks, with the exception of malignancy that was more common in IS patients during the week after DST transition (Table 1). Use of thrombolysis or duration of hospital admissions were not altered by DST transition. In-hospital mortality was 3.1% in the total study population. Daylight saving time transition did not affect in-hospital mortality in univariate (HR 1.02; CI 0.82-1.28; P=0.848) or multivariate model (HR 1.02; CI 0.81-1.28; P=0.870). Increasing age, spring period, malignancy, atrial fibrillation and heart failure/cardiomyopathy were associated with increased mortality (Table 2).

Discussion

In this nationwide study we found weekday-specific alterations of ischemic stroke hospitalizations during the week following Daylight saving time transition and increased number of hospitalizations during the first two days after transitions. The frequency of hospitalizations during the entire week following DST transitions, however, did not differ from that in control weeks. It therefore appears that, similarly to the situation in Finland considering myocardial infarctions [14], DST transitions appear to affect the temporal pattern of IS events.

Effects of DST transitions on occurrence of IS have not, to the best of our knowledge, been previously studied. Our findings are however well in line with previous knowledge on circadian distribution and stroke as DST transitions have been shown to be followed by immediate shifts in the time pattern of stroke onset.[7] Circadian misalignment has been associated with increased cardiovascular risk [23] and aberrant sleep duration, either long or short, has been associated with an increased risk of stroke.[17,18] Spring and autumn DST transitions have both been associated with decreased sleep efficiency, increased sleep fragmentation and cumulative sleep loss during the following week.[15] Women and elderly appear to have increased susceptibility to these effects of DST transitions but this is not reflected in the overall occurrence of IS.

We observed DST transitions to be followed by changes in the temporal distribution of IS hospitalizations mainly in women. One possible explanation for this might lie with gender differences in chronotype distribution. Finnish women are more often of the evening chronotype compared to men [24] and women and evening type persons have been found to have more sleep difficulties, insomnia and insufficient sleep.[24-27] Therefore women might be more vulnerable to the immediate effects of sleep disruption following DST transitions. Unfortunately we do not have

chronotype data to study this. We also found elderly people to be at increased risk of IS following DST transitions. The physiological basis of this vulnerability may be related to age-associated changes in sleep architecture and become apparent in the frailest old people with most risk factors who live in institutions or depend on home care, subject to staff schedules.

Traditional vascular risk factors are more prevalent in men [5] However, no association was found between IS hospitalizations after DST transition and vascular risk factors or male gender. This suggests that non-traditional risk factors primarily mediate the effect of DST transition on stroke risk. Curiously, our results indicate an association between malignancy and influence of DST on stroke risk. Cancer is a well-established risk factor of stroke and predicts a poorer prognosis.[28] Recent studies have associated mutations or dysfunction in a number of genes regulating circadian cycle and cancer with dysregulation of the immune system [29,30] which is also associated with increased risk of stroke.[31,32] Furthermore, circadian variation of pain episodes in cancer patients [33] and disruption of normal diurnal blood-pressure variability by catecholamine-producing tumors [34] suggests other potential mechanisms for association between circadian distraction and IS. Further research on the subject is however needed.

The potential effect of DST transitions on the occurrence of IS have not been studied previously. Studies of myocardial infarction with regard to DST transitions have reported conflicting results: some show increased MI incidence after transition into DST [10,11] whereas others show no change,[12-14] and while most studies show no change in MI incidence after transition out of DST,[9,12-14] one study has reported an increased incidence in the first four days following the transition.[11] Although DST transitions are not associated with changes in the total amount of IS or MI hospitalizations during the following week in Finland, the temporal effects still slightly differ

in the same population.[14] In the current study, we found IS hospitalizations to increase on Monday and Thursday after transition while occurrence of MI conversely decreases on Monday after transition out of DST, followed by rebound-increase on Thursday.[14] Interplay of circadian disruption and risk factor differences between IS and MI [34] appear as possible causes for different effects of DST transitions, for instance diabetes appears to modulate effects of DST transitions on MI risk [34] while no such association with IS risk was observed in the current study. Increased rate of ischemic events on fifth day after DST transitions suggests presence of yet unclear delayed mechanisms related to chronobiological disturbance. Severity or phenotype of stroke as measured by in-hospital mortality, duration of admission and administration of thrombolysis was not affected by DST transitions, although more subtle changes cannot be excluded.

The present study has some limitations. Although misdiagnoses and coding errors in registry data are possible, the used registry has been proven valid [35] and the significance of random errors is diluted by the large sample size. Moreover, it is unlikely that these would occur at significantly different rates in study and control periods employed here. The timing of stroke symptom onset was not available to us, and analysis was thus limited to admission time, as in previous studies investigating the impact of DST transitions on MI incidence.[9, 10,13,14] It is however unlikely that this would significantly bias our results. It is also possible that larger sample sizes could uncover more subtle changes in respect to the 7-day end-point.

In conclusion, DST transitions seem to be associated with an increase in hospitalizations for IS during the first two days after the transition but no change was found when observing the week following DST transitions as a whole. Susceptibility to effects of DST transitions on occurrence of

IS may be modulated by gender, age and malignant comorbidities. The mechanisms by which these effects are conveyed needs to be further studied.

Funding:

This work was supported by governmental VTR-funding of the hospital district of Southwestern Finland and grant funding of the Finnish Cardiac Society. The funding sources had no role in in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Conflicts of interest:

Jussi O.T. Sipilä has received travel grants and congress fee covering (Orion Corporation, Abbvie, Lundbeck, Merck Serono, Sanquin) and holds shares (Orion Corporation).

Jori Ruuskanen, Päivi Rautava and Ville Kytö: None.

References

1. Bennett DA, Krishnamurti RV, Barker-Collo S, Forouzanfar MH, Naghavi M, Connor M, et al. The global burden of ischemic stroke: findings of the GBD 2010 study. Glob Heart 2014 9:107-112. doi: 10.1016/j.gheart.2014.01.001.
2. Meretoja A, Kaste M, Roine RO, Juntunen M, Linna M, Hillbom M, Marttila R, Erilä T, Rissanen A, Sivenius J, Häkkinen U. Trends in treatment and outcome of stroke patients in Finland from 1999 to 2007. PERFECT Stroke, a nationwide register study. Ann Med 2011 43 Suppl 1:S22-30. doi: 10.3109/07853890.2011.586361.
3. Feigin VL, Krishnamurti RV, Parmar P, Norrving B, Mensah GA, Bennett DA, et al. Update on the Global Burden of Ischemic and Hemorrhagic Stroke in 1990-2013: The GBD 2013 Study. Neuroepidemiology 2015 45:161-176. doi: 10.1159/000441085.
4. Fryar CD, Chen TC, Li X: Prevalence of uncontrolled risk factors for cardiovascular disease: United States, 1999-2010. NCHS Data Brief. 2012 Aug;(103):1-8.
5. Vartiainen E, Laatikainen T, Peltonen M, Juolevi A, Männistö S, Sundvall J, Jousilahti P, Salomaa V, Valsta L, Puska P. Thirty-five-year trends in cardiovascular risk factors in Finland. Int J Epidemiol 2010 39:504-518. doi: 10.1093/ije/dyp330
6. Elliott WJ. Circadian variation in the timing of stroke onset: a meta-analysis. Stroke 1998 29:992-996.
7. Foerch C, Korf HW, Steinmetz H, Sitzer M; Arbeitsgruppe Schlaganfall Hessen. Abrupt shift of the pattern of diurnal variation in stroke onset with daylight saving time transitions. Circulation 2008 118:284-290. doi: 10.1161/CIRCULATIONAHA.108.771246
8. Cappellari M, Bovi P, Moretto G. Circadian variation in the effect of intravenous thrombolysis after non-lacunar stroke. J Thromb Thrombolysis. 2014 38:253-259. doi: 10.1007/s11239-013-1041-6.

9. Janszky I, Ljung R. Shifts to and from daylight saving time and incidence of myocardial infarction. New Engl J Med 2008 359:1966-1968. doi: 10.1056/NEJMc0807104.
10. Janszky I, Ahnve S, Ljung R, Mukamal KJ, Gautam S, Wallentin L, Stenestrand U. Daylight saving time shifts and incidence of acute myocardial infarction--Swedish Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA). Sleep Med 2012 13:237-242. doi: 10.1016/j.sleep.2011.07.019.
11. Čulić V. Daylight saving time transitions and acute myocardial infarction. Chronobiol Int 2013 30:662-668. doi: 10.3109/07420528.2013.775144.
12. Sandhu A, Seth M, Gurm HS. Daylight savings time and myocardial infarction. Open Heart 2014 1:e000019. doi: 10.1136/openhrt-2013-000019.
13. Jiddou MR, Pica M, Boura J, Qu L, Franklin BA. Incidence of myocardial infarction with shifts to and from daylight savings time. Am J Cardiol 2013 111:631-635. doi: 10.1016/j.amjcard.2012.11.010.
14. Sipilä JOT, Rautava P, Kytö V. Association of Daylight Saving Time transitions with incidence and in-hospital mortality of myocardial infarction in Finland. Ann Med 2016 48:10-16. doi: 10.3109/07853890.2015.1119302.
15. Harrison Y. The impact of daylight saving time on sleep and related behaviours. Sleep Med Rev 2013 17:285-292. doi: 10.1016/j.smrv.2012.10.001.
16. Brown DL, Feskanich D, Sánchez BN, Rexrode KM, Schernhammer ES, Lisabeth LD. Rotating night shift work and the risk of ischemic stroke. Am J Epidemiol 2009 169:1370-1377. doi: 10.1093/aje/kwp056
17. Leng Y, Cappuccio FP, Wainwright NW, Surtees PG, Luben R, Brayne C, Khaw KT. Sleep duration and risk of fatal and nonfatal stroke: a prospective study and meta-analysis. Neurology 2015 84:1072-1079. doi: 10.1212/WNL.0000000000001371.

18. Patyar S, Patyar RR. Correlation between Sleep Duration and Risk of Stroke. J Stroke Cerebrovasc Dis 2015 24:905-911. doi: 10.1016/j.jstrokecerebrovasdis.2014.12.038
19. Sun J, Ono Y and Takeuchi Y. A Simple Method for Calculation the Exact Confidence Interval of the Standardized Mortality Ratio with an SAS Function. J Occupat Health 1996 38:196-197.
20. Zou G. A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004 159:702–706.
21. Kytö V, Sipilä J, Rautava P. Clinical profile and influences on outcomes in patients hospitalized for acute pericarditis. Circulation 2014 130:1601-1606. doi: 10.1161/CIRCULATIONAHA.114.010376
22. Dunkler D, Plischke M, Leffondré K, Heinze G. Augmented backward elimination: a pragmatic and purposeful way to develop statistical models. PLoS One 2014;21;9:e113677. doi: 10.1371/journal.pone.0113677
23. Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. Proc Natl Acad Sci U S A. 2009 106:4453-4458. doi: 10.1073/pnas.0808180106.
24. Merikanto I, Kronholm E, Peltonen M, Laatikainen T, Lahti T, Partonen T. Relation of Chronotype to Sleep Complaints in the General Finnish Population. Chronobiol Int 2012 29:311-317. doi: 10.3109/07420528.2012.655870.
25. Nowakowski S, Meers J, Heimbach E. Sleep and Women's Health. Sleep Med Res 2013 4:1-22.
26. Singareddy R, Vgontzas AN, Fernandez-Mendoza J, Liao D, Calhoun S, Shaffer ML. Risk factors for incident chronic insomnia: a general population prospective study. Sleep Med 2012 13:346-353. doi: 10.1016/j.sleep.2011.10.033

27. Lindberg E, Janson C, Gislason T, Björnsson E, Hetta J, Boman G. Sleep disturbances in a young adult population: can gender differences be explained by differences in psychological status? Sleep 1997 20:381-387.

28. Qureshi AI, Malik AA, Saeed O, Adil MM, Rodriguez GJ, Suri MF. Incident cancer in a cohort of 3,247 cancer diagnosis free ischemic stroke patients. Cerebrovasc Dis 2015 39:262-268. doi: 10.1159/000375154.

29. Kettner NM, Katchy CA, Fu L. Circadian gene variants in cancer. Ann Med 2014 46:208-220. doi: 10.3109/07853890.2014.914808

30. Cermakian N, Lange T, Golombek D, Sarkar D, Nakao A, Shibata S, Mazzoccoli G. Crosstalk between the circadian clock circuitry and the immune system. Chronobiol Int 2013 30:870-888. doi: 10.3109/07420528.2013.782315.

31. Zöller B, Li X, Sundquist J, Sundquist K. Risk of subsequent ischemic and hemorrhagic stroke in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden. BMC Neurol 2012 12:41. doi: 10.1186/1471-2377-12-41.

32. Saini A, Tucci M, Tampellini M, Maina D, Bouraouia K, Giuliano PL, Termine A, Castellano M, Campagna S, Laciura P, Berruti A. Circadian variation of breakthrough pain in cancer patients. Eur J Pain. 2013; 17: 264-270. doi: 10.1002/j.1532-2149.2012.00184.x.

33. van Eps RG, van den Meiracker AH, Boomsma F, Man in't Veld AJ, Schalekamp MA. Diurnal variation of blood pressure in patients with catecholamine-producing tumors. Am J Hypertens 1994 7:492-497.

34. Fisher M, Folland E. Acute ischemic coronary artery disease and ischemic stroke: similarities and differences. Am J Ther 2008 15:137-149. doi: 10.1097/MJT.0b013e31816a61bb.

35. Sund R. Quality of the Finnish Hospital Discharge Register: a systematic review. Scand J Public Health 2012 40 505-515. doi: 10.1177/1403494812456637

Figure Titles and Legends

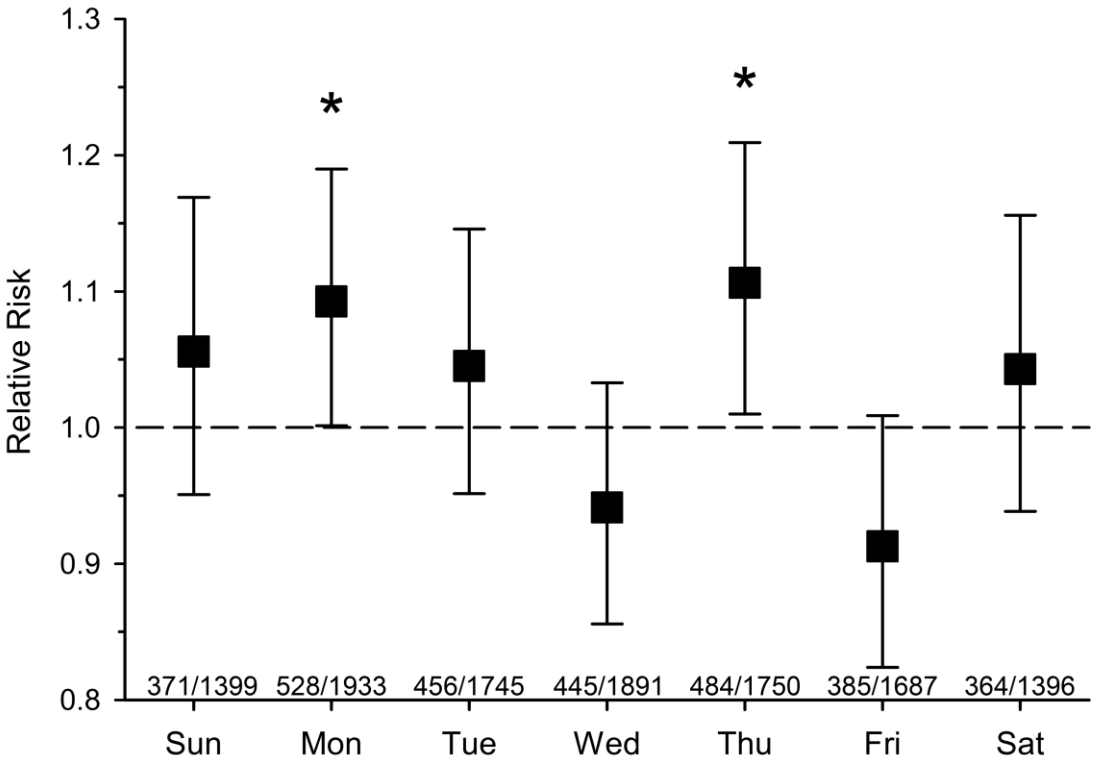

Figure 1. Overall occurrence of ischemic stroke hospitalizations after DST transitions.

Relative risk of ischemic stroke hospitalizations in the week following daylight savings time transition compared to control weeks. Both spring and autumn transitions are included. The total number of hospitalizations for each day during the study weeks and the control weeks is presented above the horizontal axis. Error bars represent 95% confidence interval. * = $P<0.05$.

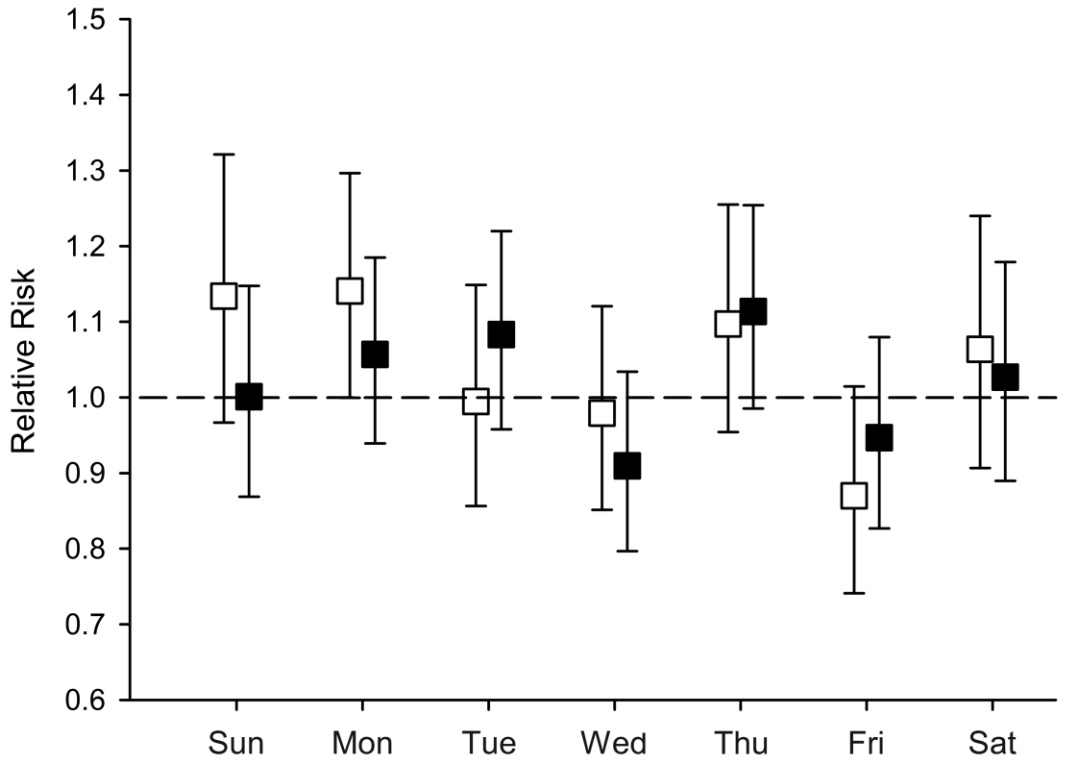

Figure 2. Occurrence of ischemic stroke hospitalizations after DST transition by season.

Relative risks of ischemic stroke in the week following daylight savings time transition compared to control weeks after spring (open squares) and autumn (filled squares) transitions. Error bars represent 95% confidence interval.

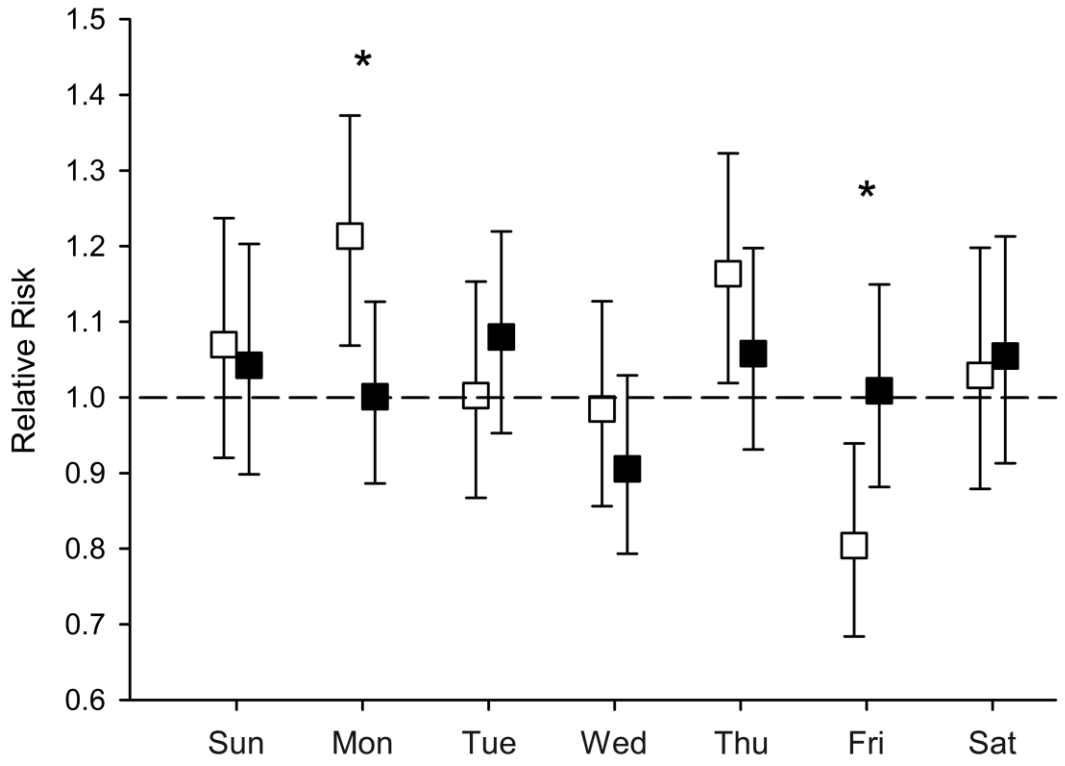

Figure 3. Occurrence of ischemic stroke hospitalizations after DST transition by gender.

Gender-based relative risks of ischemic stroke in the week following daylight savings time transition compared to control weeks. Both spring and autumn transitions are included. Open squares represent women and filled squares men. Error bars represent 95% confidence interval. P* <0.05 between genders.

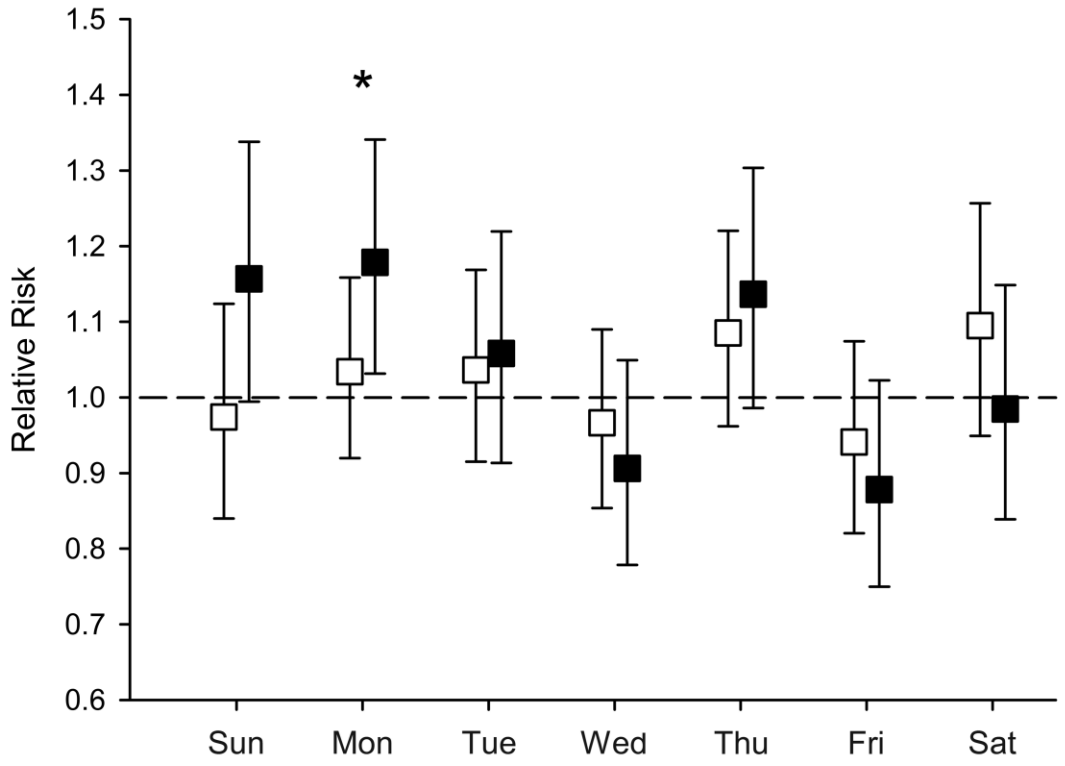

Figure 4. Occurrence of ischemic stroke hospitalizations after DST transition by age.

Age-dependent relative risks of ischemic stroke in the week following daylight savings time transition compared to control weeks. Open squares represent patients ≤65 year and filled squares patients >65 years of age. Both spring and autumn transitions are included. Error bars represent 95% confidence interval. P * <0.05 between age groups.