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ORIGINAL ARTICLE

Stroke Mimics on the Stroke Unit – Temporal trends 2008–2017 at a large Norwegian university hospital

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Objectives: The objective was to quantify temporal trends in stroke mimics (SM) admissions relative to cerebrovascular accidents (CVA), incidence of hospitalized SMs and characterize the SM case-mix at a general hospital's stroke unit (SU).

Materials & Methods: All SU admissions (n = 11240) of patients aged 15 or older to Haukeland University Hospital between 2008–2017 were prospectively included and categorized as CVA or SM. Logistic regression was used to estimate time trends in the proportion of SMs among the admissions. Poisson regression was used to estimate time trends in age- and sex-dependent SM incidence.

Results: SMs were on average younger thaan CVA patients (68.3 vs. 71.4 years) and had a higher proportion of females (53.6% vs. 44.5%). The total proportion of SM admissions was 51.0%. There was an increasing time trend in the proportion of SM admissions, odds ratio 1.150 per year ($p < 0.001$), but this trend appears flattening, represented by a significant quadratic time-term, odds ratio 1.009 ($p < 0.001$). A higher SM proportion was also associated with the time period of a Mass Media Intervention (FAST campaign) in 2014. There was also an increasing trend in SM incidence, that remains after adjusting for age, sex, and population; also, for incidence the trend appears to be flattening.

Conclusions: SMs account for approximately half of the SU admissions, and the proportion has been increasing. A FAST campaign appears to have temporarily increased the SM proportion. The age- and sex-dependent incidence of SM has been increasing but appears to flatten out.

KEYWORDS
epidemiology, peripheral vertigo, stroke, stroke mimics, stroke unit

1 | INTRODUCTION

Stroke incidence and mortality is decreasing across the developed world, although the ageing of the population is offsetting some of the decline in age-adjusted incidence rates. Furthermore, stroke outcomes have seen substantial improvement since the introduction of thrombolytic treatment, and later endovascular thrombectomy. These novel treatment options have increased the emphasis on timely arrival to hospital and the stroke unit (SU) to ensure an optimal regime with the resulting improvement of prognosis – that *time is brain* has become doxa.[1] Moreover, health authorities in several countries have rolled out mass media information (MMI) campaigns

directed towards the general public, in particular Face-Arm-Speech-Time (FAST) campaigns, with the aim of educating citizens about stroke symptoms and the importance of admission without delay.[2–5] In brief, modern stroke treatment at a specialized SU[6,7] significantly benefits stroke patients,[7–10] but is demanding on limited resources.[6,9,11,12]

Stroke mimics (SMs) are defined as symptoms that are mistaken for acute stroke as the admission diagnosis, and which later are revised to a definite or more probable alternative diagnosis. Several studies have reported on the number of patients that ultimately were identified with SMs, but the settings and figures vary substantially between studies.[13,14] Peripheral vertigo, migraine and other headaches, epilepsy, and a host of other conditions are regularly initially misidentified as acute stroke or transient ischaemic attack (TIA).[15–17] Additionally, studies specifically addressing SMs have focused on the case-mix of SMs,[15,18] the safety of thrombolysis in these cases,[19-23] the difficulties in determining if symptoms were a TIA or not,[24] and some studies also highlight that admitting SMs to the SU is costly.[17,25] A recent study specifically aimed at looking at the economic burden of stroke mimics also published several extrapolated scenarios on the number of stroke mimics in the years to come.[17] The difficulty of distinguishing SMs from stroke symptoms and TIAs has attracted sustained attention.[23,26–29]

However, to our best knowledge, no study has hitherto analysed temporal trends as the main outcome with time series of SM admissions,[30] although Terrin et al. did correlate date of publication with share of SM reported.[31] To address this knowledge gap we analysed a data set of 5 720 SM admissions to the SU of a large Norwegian university hospital during a 10-year period. The aim of this study is to investigate temporal trends in the period 2008–2017 in the relative share of patients admitted to SUs with SMs, and to estimate incidence rates for SU admission of SMs.

2 | MATERIALS & METHODS

The present study is based on data from a prospective, single-centre study undertaken at Haukeland University Hospital (HUS), Bergen, Norway. The data underlying the analysis comprises all patients aged 15 or older admitted to the comprehensive SU at HUS with suspected acute stroke or TIA, and includes first-ever, recurrent, fatal, and non-fatal cases: the unit of analysis is '*admittance to the SU, after initial assessment by neurologist in the ED*. Data from the 10-year period 2008–2017 was analysed. Throughout this period, the use of MRI for this patient group has been close to 90% at HUS[32]; most patients were assessed by 1.5T, and only a minority have had 3T examination. It is not registered in our data whether 1.5T or 3T examination were used, but there has been no systematic change in the use of 1.5T or 3T during the study period. There has been no change in the medical competence at the ward: the senior physicians have been largely the same individuals, with many remaining throughout the whole period, and all included patients were assessed in the ED by a receiving physician. A chief physician, usually

TABLE 1 Descriptive statistics by year, and stratified by All admissions, Stroke mimic admissions and cerebrovascular accident admissions

Statistic	Year										All years
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2008–2017
N	834	787	918	1132	1225	1157	1216	1309	1369	1293	11 240
N_{SM}	356	333	424	573	654	580	705	703	729	675	5 732
N_{CVA}	478	454	494	559	571	577	511	606	640	618	5 508
$\overline{Age}$	70.58	69.04	69.43	67.22	68.39	68.94	68.03	68.12	67.00	67.44	68.28
$\overline{Age}_{SM}$	68.96	65.47	67.16	64.38	65.19	66.06	65.76	65.54	63.11	63.65	65.26
$\overline{Age}_{CVA}$	71.78	71.65	71.39	70.13	72.07	71.92	71.17	71.12	71.44	71.58	71.42
%Males	53.24	55.65	52.51	49.03	52.00	51.77	48.93	51.11	50.77	50.89	51.35
%$Males_{SM}$	47.19	53.15	46.70	42.93	46.64	46.72	46.81	45.52	46.09	45.63	46.39
%$Males_{CVA}$	57.74	57.49	57.49	55.28	58.14	56.85	51.86	57.59	56.09	56.63	56.52
%*SM*	42.69	42.31	46.19	50.62	53.39	50.22	57.98	53.71	53.25	52.20	51.00

$\overline{Age}$ = mean age.

TABLE 2 Crude counts of admissions within stroke/mimic subtypes (percentage of admissions in given year in parentheses)

Stroke/ mimic subcategory	Year											Associations		
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	All Years	Sex	t	Age
Ischaemic stroke	386 (46.3)	357 (45.4)	396 (43.1)	423 (37.4)	440 (35.9)	433 (37.4)	403 (33.1)	451 (34.5)	472 (34.5)	471 (36.4)	4 232 (37.7)	M		+
Transient ischaemic attack	36 (4.3)	30 (3.8)	34 (3.7)	47 (4.2)	64 (5.2)	63 (5.4)	41 (3.4)	52 (4.0)	59 (4.3)	50 (3.9)	476 (4.2)	M		+
Intracerebral haemorrhage	47 (5.6)	54 (6.9)	41 (4.5)	61 (5.4)	51 (4.2)	61 (5.3)	54 (4.4)	65 (5.0)	60 (4.4)	64 (4.9)	558 (5.0)	M		+
Other cerebrovascular diseases	9 (1.1)	13 (1.7)	23 (2.5)	28 (2.5)	16 (1.3)	20 (1.7)	13 (1.1)	38 (2.9)	49 (3.6)	33 (2.6)	242 (2.2)	M	+	+
ECH	6 (0.7)	4 (0.5)	4 (0.4)	6 (0.5)	13 (1.1)	7 (0.6)	10 (0.8)	9 (0.7)	11 (0.8)	11 (0.9)	81 (0.7)	M		+
CVA Sequela	22 (2.6)	23 (2.9)	35 (3.8)	35 (3.1)	25 (2.0)	15 (1.3)	18 (1.5)	27 (2.1)	18 (1.3)	30 (2.3)	248 (2.2)	M		+
Diseases of the circulatory system, incl. syncope	33 (4.0)	18 (2.3)	28 (3.1)	34 (3.0)	23 (1.9)	27 (2.3)	28 (2.3)	35 (2.7)	29 (2.1)	22 (1.7)	277 (2.5)			+
Cognitive impairment, incl. TGA	6 (0.7)	12 (1.5)	3 (0.3)	4 (0.4)	4 (0.3)	7 (0.6)	5 (0.4)	4 (0.3)	3 (0.2)	1 (0.1)	49 (0.4)			+
Epilepsy or seizures	19 (2.3)	18 (2.3)	13 (1.4)	19 (1.7)	34 (2.8)	23 (2.0)	36 (3.0)	40 (3.1)	44 (3.2)	32 (2.5)	278 (2.5)	M	+	+
Eye disease	2 (0.2)	4 (0.5)	4 (0.4)	3 (0.3)	2 (0.2)	7 (0.6)	9 (0.7)	5 (0.4)	2 (0.1)	3 (0.2)	41 (0.4)			+
Metabolic disorders	6 (0.7)	4 (0.5)	7 (0.8)	3 (0.3)	5 (0.4)	7 (0.6)	9 (0.7)	6 (0.5)	6 (0.4)	2 (0.2)	55 (0.5)			+
Injury, incl. commotio	21 (2.5)	14 (1.8)	18 (2.0)	20 (1.8)	18 (1.5)	23 (2.0)	24 (2.0)	33 (2.5)	26 (1.9)	30 (2.3)	227 (2.0)			+
Neoplasms	11 (1.3)	15 (1.9)	10 (1.1)	24 (2.1)	29 (2.4)	15 (1.3)	15 (1.2)	14 (1.1)	17 (1.2)	21 (1.6)	171 (1.5)			+
Infections	32 (3.8)	28 (3.6)	31 (3.4)	37 (3.3)	46 (3.8)	35 (3.0)	57 (4.7)	62 (4.7)	74 (5.4)	29 (2.2)	431 (3.8)			+
Other neurological conditions	10 (1.2)	8 (1.0)	14 (1.5)	9 (0.8)	16 (1.3)	22 (1.9)	12 (1.0)	17 (1.3)	11 (0.8)	10 (0.8)	129 (1.1)			+
Headaches incl. Migraine	43 (5.2)	50 (6.4)	75 (8.2)	135 (11.9)	138 (11.3)	110 (9.5)	123 (10.1)	120 (9.2)	143 (10.4)	136 (10.5)	1073 (9.5)	F	+	+
Musculoskeletal disorders	3 (0.4)	2 (0.3)	7 (0.8)	10 (0.9)	7 (0.6)	4 (0.3)	5 (0.4)	9 (0.7)	4 (0.3)	2 (0.2)	53 (0.5)			+
Peripheral vertigo	45 (5.4)	31 (3.9)	38 (4.1)	75 (6.6)	105 (8.6)	84 (7.3)	100 (8.2)	108 (8.3)	173 (12.6)	126 (9.7)	885 (7.9)		+	+

(Continues)

TABLE 2 (Continued)

Stroke/ mimic subcategory	Year										Associations		
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	All Years	Sex	t	Age
Diseases of the peripheral nervous system	18 (2.2)	15 (1.9)	24 (2.6)	17 (1.5)	21 (1.7)	25 (2.2)	19 (1.6)	32 (2.4)	17 (1.2)	12 (0.9)	200 (1.8)			+
Symptoms involving the nervous system	24 (2.9)	16 (2.0)	18 (2.0)	23 (2.0)	24 (2.0)	13 (1.1)	22 (1.8)	38 (2.9)	45 (3.3)	46 (3.6)	269 (2.4)		+	+
Observation for suspected nervous system disorder	10 (1.2)	18 (2.3)	22 (2.4)	35 (3.1)	67 (5.5)	97 (8.4)	161 (13.2)	76 (5.8)	52 (3.8)	88 (6.8)	626 (5.6)		+	+
Psychiatric disorders	10 (1.2)	10 (1.3)	6 (0.7)	8 (0.7)	10 (0.8)	5 (0.4)a	5 (0.4)	9 (0.7)	2 (0.1)	11 (0.9)	76 (0.7)			+
Intoxications	4 (0.5)	6 (0.8)	5 (0.5)	8 (0.7)	12 (1.0)	8 (0.7)	9 (0.7)	11 (0.8)	10 (0.7)	3 (0.2)	76 (0.7)	M		+
Other diagnoses	31 (3.7)	37 (4.7)	62 (6.8)	68 (6.0)	55 (4.5)	46 (4.0)	38 (3.1)	48 (3.7)	42 (3.1)	60 (4.6)	487 (4.3)			+

Note: The sex column indicates if male (M) or female (F) sex was Bonferroni significantly ($p < 0.00104$) associated with incidence for SU admissions for the relevant SM sub type. The *t*, sex, and age columns indicate if there was a significant $p < 0.001$positive (+) or negative (−) association for the subcategory. Detailed regression outputs are presented in Appendix II, tables 4A and 5A.

a stroke neurologist, was consulted in cases of doubt prior to admission to the SU. An inexperienced junior doctor will consult with a senior physician prior to all SU admittances.

HUS is the primary acute hospital for inhabitants in 24 municipalities in Vestland County, corresponding a catchment area of 4.7% of the Norwegian *person years* (PYs) for the period under study. The total population increased from 216 335 to 248 023 during the study period, and accounts for a total of 2.3 M PYs. In Norway, all non-elective inpatient admissions – including suspected strokes/TIAs – are handled by the public health care system, and there is choice of hospital of admittance: which hospital a patient is sent to is defined exclusively by suspected diagnosis and the patient's location at the time the need for medical attention arise. As such, there is no self-selection present in the data, and a patient with suspected stroke is always taken to the nearest hospital. In addition to residents of HUS's catchment area, HUS also admits patients who are candidates for thrombectomy from the surrounding Vestland county, in addition to lodging individuals (eg staying at a hotel or with family). Similarly, patients resident in HUS's catchment area who experience a (suspected) stroke while travelling will be admitted to the local hospital at the location of lodging.

The discharge diagnoses were first dichotomized into either *cerebrovascular accident (CVA)* – comprising *ischaemic stroke (IS)*, *intracerebral haemorrhage (ICH)*, *transient ischaemic attack (TIA)*, and *other cerebrovascular events (OCE*; *including spinal infarctions*, *amaurosis*, *and unspecified stroke)* – or, as *stroke mimics* (*SMs).*

All SM diagnoses were set by the same neurologist (HN), who also classified all CVA diagnoses. KWF independently sub-classified the SMs into 20 categories (See Table 2) based on previous literature, in order to facilitate comparisons.[13,17,18,25,29,30,33,34]

To conduct the analyses, three different data sets were used: (i) The NORSTROKE registry has prospectively registered all admissions to Haukeland University Hospital's SU since 2008 until the present. All SU admission for TIAs and strokes between 2008 and 2017 were used for the present analyses..[35] Variables extracted were: age at admission, sex, month and year of admission, diagnosis; (ii) data for the admissions resulting in a non-stroke diagnosis – the SMs of interest here – were only available on paper forms. These were entered into a separate data base for this study. Variables extracted were age at admission, sex, month and year of admission, and diagnosis. (iii) from Statistics Norway we extracted the number of inhabitants of age ≥ 15 within HUS' catchment area (by age and sex).

Detailed information on handling of missing data (year of admission for some SM's had not been entered at the forms) is described in an appendix (Appendix I).

In addition to descriptive statistics,[36] we analysed the time trend in the relative share of SMs in the SU and the time trend in the incidence of SM admissions to the SU.

The time trend of the relative share of SM admissions was analysed with a binary logistic regression model, which estimates the probability that an admission is a SM, given the calendar time of the event. The primary predictor was the time in years (*t*) since the

beginning of the study period (2008). In addition, we included a quadratic time-term (t^2) to represent changes to the time trend over the period.

Lastly, we hypothesized that an MMI campaign in May 2014 could have increased admittances for SMs, and therefore included an indicator dummy for this effect. We based the selection of this dummy on Advani et al.'s finding that the campaign's effect on decreased prehospital delay was noticeable for 6 month.[4] The campaign was described as '*with a precampaign month, priming the treatment chain and raising in-hospital awareness*[,]' so we coded this variable to indicate the months April–September 2014.

While the SM share model estimates the frequency of SM admission relatively to the total frequency of admissions to the SU, the incidence model estimates the number of SM admissions relative to the number of people in the hospital's catchment area. For this we used Poisson regression,[37] which estimates the number of SM admissions through year t from a population $P_{a,s,t}$ of patients with age a and sex s. With the predictors age (a), sex (s) and year (t), the functional form of the expected number of admissions is given by:

$$SM_{a,s,t} = \exp(\beta_0 + \beta_a a + \beta_s s + \beta_t t) P_{a,s,t}.$$

Here, β_t is the main coefficient of interest, which represents the time trend. Note that the exponential function ensures positive estimates and that the $P_{a,s,t}$ term ensures proportionality with the population size. The basic regression formula above was expanded by the inclusion of a quadratic year-term ($\beta_{t^2} t^2$), a quadratic age-term ($\beta_{a^2} a^2$), and interaction terms of sex with all the other predictors (effectively estimating separate models for each sex).

About 5% of the admissions in the data set pertained to individuals not residing in HUS' catchment area. The purpose of the incidence analysis was to estimate the number of admissions that can be expected from a population of a given size. While some non-HUS-area residents present with SM at HUS, some HUS-area residents will surely be hospitalized with SMs at other hospitals. Since we have no reason to assume that either group is larger, we decided to include the non-HUS patients in our incidence estimates.

To perform further sub-analyses, we conducted an explorative analysis on the SM subcategories, looking for evidence for temporal trends in age- and sex-adjusted incidence rates, with a particular focus on *peripheral vertigo*, *headaches including migraine*, and *symptoms involving the nervous system*, as these diagnoses are known to dominate amongst the stroke mimics.[16] The use of the diagnoses *observation for suspected nervous system disorder* (ICD-10: Z03.3) and *sequela after stroke* (ICD-10: I69.1 and I69.3) were also considered in more detail. As the use of *observation for suspected nervous system disorder* can represent any of the other mimics,[17] it is important to consider the temporal trends in its use to mitigate spurious trends in other mimics. For example, a decrease in the use of Z0.03 could explain an increase in other mimics.

We assessed the models with standard fitness statistics (R^2, AIC/BIC, and cross-validation routines).

All analyses were performed with the statistical software R (version 4.0.2) in the RStudio environment (version 1.2.5001),[38] relying on the Plotly, sjPlot, and Stargazer packages for graphing rendering and tabulating regression outputs.

3 | RESULTS

There was a total of 11 240 SU admissions recorded during the study period: 5 732 SM admissions (51.0%) and 5 508 CVA admissions

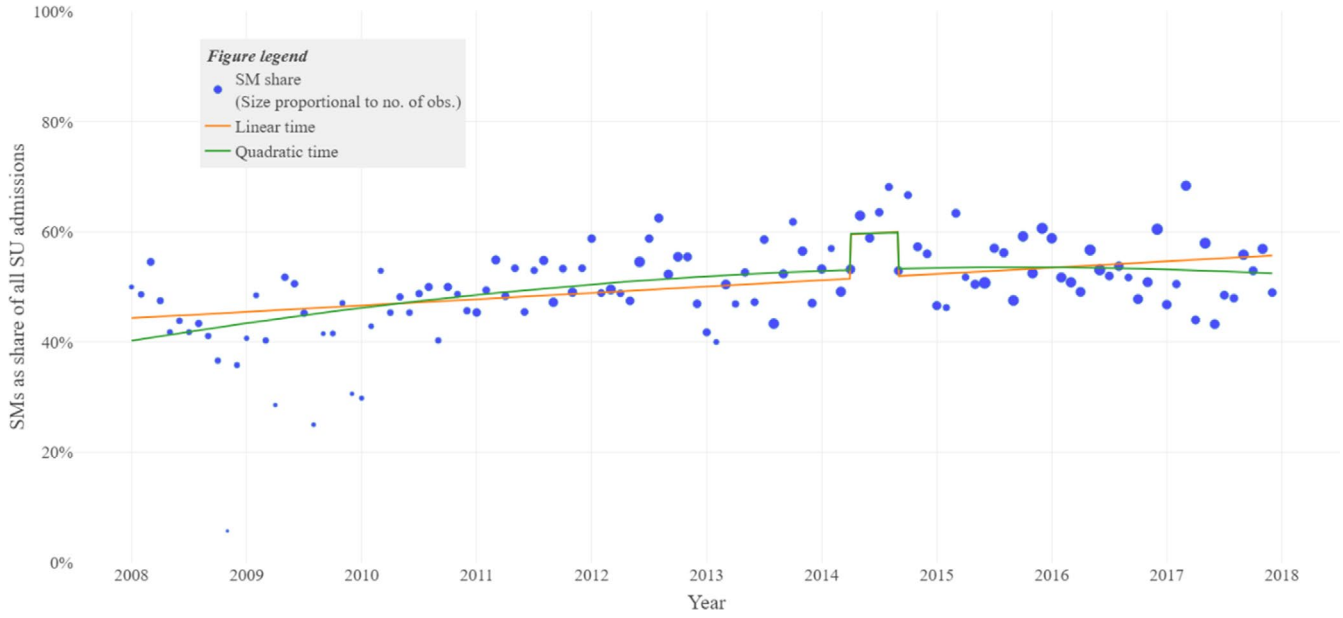

FIGURE 1 Plot of the share of admissions resulting in a mimic diagnosis, by month 2008–2017. The sizes of the markers are proportional to the number of admissions it represents. Traces correspond to the predictions by binary logistic regression models (2) and (4) (Table 4) and includes the effect of the MMI (visible as an elevated plateau April–September 2014)

TABLE 3 Regression results. Each model is a binary logistic regression of a dummy for SM status (SM = 1, CVA = 0) against an intercept (*intercept*) and time (*t*)

	Dependent variable:			
	SM			
Model	(1)	(2)	(3)	(4)
Variable	Regression coefficients[a]			
Intercept	−0.222***	−0.227***	−0.422***	−0.395***
(95%CI)	(−0.303, −0.141)	(−0.308, −0.146)	(−0.547, −0.297)	(−0.521, −0.269)
t	0.048***	0.046***	0.159***	0.140***
(95%CI)	(0.035, 0.062)	(0.033, 0.059)	(0.105, 0.213)	(0.085, 0.195)
MMI		0.325***		0.266**
(95%CI)		(0.160, 0.491)		(0.097, 0.435)
t^2			−0.011***	−0.009***
(95%CI)			(−0.016, −0.006)	(−0.014, −0.004)
Observations	11 240	11 240	11 240	11 240
AIC	15 530	15 517	15 515	15 507

A dummy *MMI*coding for an hypothesized 6-month effect from the Mass Media Intervention in May 2014 for stroke awareness described in Advani et al. (coded as 1 for April–September 2014) is included in models (2) and (4). A squared time-term (t^2) is included in models (3) and (4) to account for a dampening or acceleration of the temporal term. (95%CI) is the confidence interval for the regression coefficients of the coefficient.

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

[a]To obtain ORs, exponentiate the regression coefficients.

(49.0%). Descriptive statistics for the full sample of SU admissions (including CVAs) are provided in Table 1.

The number of SU admissions increased by 55.0% between 2008 and 2017, and the increase was higher for SMs (89.6%) than for CVAs (29.3%). Much of the absolute increase in SU admissions can be explained by both an increase and an ageing of HUS's catchment area (please see the subsection on incidence modelling below). The mean age of patients with CVAs appeared stable, while it decreased for patients with SMs.

Table 2 provides a break-down of the admissions by year and SM subcategories. The most common subcategories were *headaches including migraine* (18.7%), *peripheral vertigo* (15.4%) and *observation for suspected nervous system disorder* (10.9%). Table 2 also reports information about evidence for temporal trends for the SM subcategories (see also the section on regression modelling below).

3.1 | Mimics admissions' share of total SU admissions

Aggregating the admission counts (*AC*) for each of the 120 months in the 10-year period results in month-specific total, SM and CVA admission, and is plotted by month in Figure 1. We observe markedly more variance in the number of SM admissions than for CVA admissions: the range of mimic admissions in a given month is 2–80, while CVA admissions are in the range 28–68.

The main regression models that test if there is a significant temporal trend in the share of mimic admissions are presented in Table 3. Several specifications were tested: With and without a quadratic time-term, and with and without the MMI-dummy. The best fits were specifications which account for the regional MMI in May 2014. The regression analysis finds strong evidence for an increasing trend in the share of SMs. The share of SMs predicted by the models that include the MMI-dummy–models (2) and (4) – are plotted in Figure 1.

The share of SM admissions within each 10-year age bracket, for each year, is provided in a Table in an appendix (Table S3). For all age brackets below 65–74, the number of SMs exceeds the number of CVAs. Furthermore, an *ad hoc* regression analysis predicting share of SMs by year for each of the age brackets, suggests that the increase is most pronounced in the middle brackets 35–74, *except* 45–54.

3.2 | Incidence modelling

In Table 4 we give sex-specific, observed incidence rates (per 100k PY) for SU admissions and broken down into SM admissions and CVA admissions.

The regression modelling of incidence found no temporal trend in overall CVA incidence, but the expected highly significant effect of age and sex was observed (see Table S4). Regarding the incidence model for SM admissions, there was no significant difference in the temporal trends between the sexes (indicated by the nonsignificant sex-time interactions). The coefficients on both time and time squared were highly significant and exhibit the same pattern as for the share of all admissions that were due to SMs: a highly significant increasing temporal trend with additional evidence for that

TABLE 4 Observed age-specific incidences of SU admissions, CVA admissions, and SM admissions for the period 2008–2017

		Observed incidence per 100k PYs			
Age	Sex	SU admissions	SM admissions	CVA admissions	PYs
15–24	Male	27.59	19.98	7.61	210,247
15–24	Female	44.59	36.26	8.33	204,071
15–24	All	35.96	28.00	7.96	414,318
25–34	Male	64.52	45.33	19.19	244,892
25–34	Female	97.32	83.10	14.22	225,039
25–34	All	80.22	63.41	16.81	469,931
35–44	Male	140.71	96.88	43.84	228,127
35–44	Female	148.80	112.44	36.36	209,004
35–44	All	144.58	104.32	40.26	437,131
45–54	Male	338.91	185.17	153.74	203,596
45–54	Female	261.24	184.96	76.28	191,392
45–54	All	301.27	185.07	116.21	394,988
55–64	Male	745.24	337.38	407.86	146,128
55–64	Female	450.94	285.43	165.51	142,590
55–64	All	599.89	311.72	288.17	288,718
65–74	Male	1618.05	650.58	967.47	83,310
65–74	Female	1096.04	595.06	500.98	91,420
65–74	All	1344.93	621.53	723.40	174,730
75–84	Male	3073.09	1244.82	1828.26	44,906
75–84	Female	2247.10	1083.11	1163.99	63,059
75–84	All	2590.65	1150.37	1440.28	107,965
85–94	Male	4624.39	1966.85	2657.55	15,202
85–94	Female	3690.81	1728.80	1962.00	32,161
85–94	All	3990.46	1805.21	2185.25	47,363
95–105+	Male	3869.05	2232.14	1636.90	672
95–105+	Female	3417.90	1162.79	2255.11	2838
95–105+	All	3504.27	1367.52	2136.75	3510
15–105+	Male	490.45	225.90	264.55	1,177,080
15–105+	Female	470.65	264.55	206.10	1,161,574
15–105+	All	480.62	245.10	235.52	2,338,654

this trend has either peaked or is flattening. Unlike for CVAs, males appear to start out with a lower SM-admission rate than females – negative sex-coefficient – but the sex-difference diminishes with age, and changes sign between 54 and 55 years of age, after which females have a lower age-adjusted admission rate for SMs.

The model's predictions are plotted in Figure 2.

3.3 | Subcategories

We next fitted Poisson regression models for each of the 24 subcategories of diagnoses (four CVA subcategories and the 20 SM subcategories; see Table 2) both without and with a quadratic temporal trend. For the interpretation of the regression results there are therefore several caveats. Due to the high number of tests (48), we employed Bonferroni-correction when interpreting the results,[39] using $p < \frac{0.05}{48} = 0.0010$ as the significance level.

With this correction in place, we still found a significant, increasing, temporal trend for the following SM subcategories: *peripheral vertigo*, *headaches including migraine*, *epilepsy or seizures*, *symptoms involving the nervous system*, *diseases of the peripheral nervous system*, and observation *for suspected nervous system disorder*. Among these, the trends for headache- and for the observation diagnoses displayed evidence for a flattening of the trend (negative coefficient for the quadratic time-term,) but the increase in the remaining appear to be ongoing. Furthermore, age was positively associated with admission for all categories. Among the SMs, male sex was positively associated only with SU admission for *intoxications*, *extra cranial haemorrhages*, *epilepsy and seizures*, and *CVA sequela*; female sex was associated with SU admission for *headaches including migraine*. Due

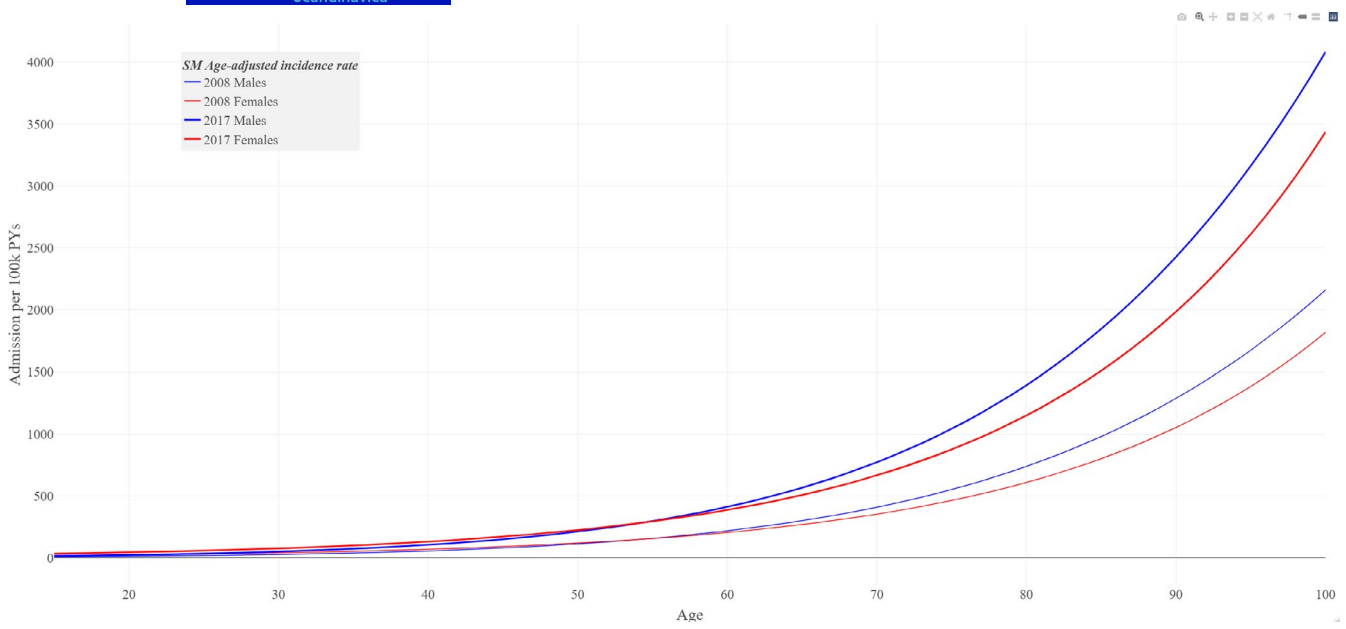

FIGURE 2 The plots show Poisson regression estimates for incidence rates for males (blue) and females (red) for stroke mimics; 2008, thin lines; 2017, thicker lines. We see that male risk for SM overtakes female risk for SM by the age of 54. (Plot based on regression omitting nonsignificant sex-year interactions, for model output, see supplementary Table S4.)

to the problem with multiple testing, and the fact that some of the SM subcategories had a low number of admissions, we did not conduct further explorations (eg an age sex interaction) as was done for the full model (Table S4). See supplementary Appendix II for more detailed regression output for the subcategory analyses (Tables S5 and S6).

4 | DISCUSSION

In this study, we have found strong evidence for a substantial and significant increase in the SMs' share of the SU case-mix at a large Norwegian university hospital: from just below 43% in 2008 and up to 52% in 2017. Furthermore, we can assert that this increase is not due to changing demographics between SM and CVA: as the incidence of SU admission for SMs increase adjusted for age and sex, and the age profile for incidences are similar between SMs and CVAs. We cannot conclude that this increase is set to continue, as we find evidence that this trend might have peaked.

Increased emphasis on stroke as a medical emergency and the 'time is brain' paradigm after the breakthrough of intravenous thrombolytic therapy has likely resulted in a lower threshold for admissions to an SU for suspected strokes and TIAs. For example, TIAs were not routinely admitted to hospitals in Norway prior to 2011, and there is evidence that milder strokes (NIHHS at arrival) are hospitalized more often than two decades ago.[40] An almost inevitable consequence of such a medically desired intake policy is an increase in ED and SU admissions for patients who prove to have other conditions than acute stroke. Another way to view this is that if the health system's *sensitivity* for stroke increase, then the *specificity* must almost surely suffer somewhat. However, SU beds are resource consuming; hence, it is important to evaluate the use of SU beds and to monitor temporal trends. In this study, SMs outnumbered CVA admissions already in 2011 – and has not declined since – although we observe a flattening during the latter part of the 10-year period. We strongly suspect that the paradigm shift in acute stroke treatment needs to be followed up by diagnostic tools that have better specificity for stroke. This study indicates that an increased sensitivity of the Norwegian health care system to detect and admit stroke likely comes at the cost of a lowered specificity.

The overall CVA incidence rate was comparable to other data.[41] Interestingly, the SM incidence rate was about the same as the CVA incidence. By using Faiz et al.'s estimates for hospital length of stay (LOS) for TIA, IS, ICH and SM admissions, a 50% share of SM's translates into a 20% increase in the demand for SU beds, when considering that SM admissions have shorter LOS. The implication is that health authorities risk a serious discrepancy between SU-demand and SU capacity if hospitalization of stroke mimics are not factored into administrative estimates. Furthermore, SMs require assessment from physicians and allied health personnel and radiological investigations. Importantly, patients with SMs will potentially receive delayed diagnostic investigation and treatment for their actual condition, for example their infection, epileptic seizure or migraine attack. With limited MRI capacity, incidental imaging findings might lead to unnecessary control regimes and overtreatment.[42,43]

Several studies have focused on safety and cost burden in the hyperacute stroke setting regarding provision of intravenous thrombolytic therapy to patients with SMs.[20,22,25,44,45] With an ageing population over the next decades combined with improvements in disease prevention and treatment, stroke is one of the diseases that

has caused concern. One reason for this concern is that the absolute number of stroke events may increase due to demographic changes, despite a reduction in age- and sex-adjusted incidence rates, which eventually will require more resources and hospital capacity. A substantial part of this capacity is now occupied with patients with SMs.

Previous publications on SMs have highlighted a higher proportion of female and younger patients compared to patients with CVA.[13,14,30,31,33] Our study is consistent with such findings, but with several caveats, and our results nuances this picture. For example, we do observe a higher SM admission rate for female than male patients, but only among the younger patients. The sex-difference diminishes with age, and after the age of 50 years, males have the highest age-adjusted SM admission rate; just as for CVAs. While most patents with SMs are female in the lower and the upper age groups, for 44–65-year-olds only 47% of the are female. Furthermore, advanced age only weakly predicted CVA. Even among the 85+ year-olds, 4 out of 10 SU admissions were caused by SMs. This illustrates that SMs provide for a complicating factor on the SUs, where the conditional pre-diagnostic probabilities for SM versus CVA can be non-trivial to disentangle, and where conventional age- or sex-based intuitions may fail; indeed, we were surprised ourselves by some of our findings.

It is often challenging to compare SM proportions between studies because of different health care organization, including admission threshold, patient populations, time periods and SM definitions. In a recent study from Japan evaluating the 10-year period 2007–2016, 23.5% of the patients (348/1482) were diagnosed with stroke mimics (compared to our 51.0%),[46] but the study did not analyse temporal trends during the 10-year period. Another study evaluating a 10-year period (2001–2010) from the United States reported a SM proportion of 30.0% (2454/8187).[30] In the most recent systematic review, SM proportions varied between 3% and 64%.[14]

MMIs have previously been shown to have a substantial, but time-limited effect,[4] on stroke knowledge and prehospital delay. In our study, we had a predefined hypothesis that a specific MMI intervention in 2014 increased the SM proportion in the following six months. Our regression analyses confirmed this with an estimated substantial and statistically significantly ($p = 0.002$) increased share (about 10%) of SMs in the given time period.

Moreover, during the 10-year period presented in this study, new national stroke guidelines were published in 2011, that emphasized the hospitalization also of TIA patients. A national clinical stroke registry with various quality indicators was implemented in 2013, and in 2017 a national stroke pathway with additional quality indicators was introduced. In addition to a regional MMI in 2014, a national MMI on both linear media and social media was initiated in October 2016. Taken together, increased focus on acute stroke during this period, though guidelines, increased reporting of quality indicators such as prehospital delay, and MMIs, may be underlying drivers that have resulted in an increase in SM SU admissions as a side effect.[3,4,47] That these efforts may already have come into effect by the end of the period under study also fit with an initially steeper increase, and a levelling out towards the end.

Some studies have highlighted functional mimics as an important subgroup of the SMs.[33,48] In our study, only about 1% of the SMs were psychiatric disorders, but 15.6% of the SM admissions did not get an exact diagnosis, rather a symptom-based or an observational diagnosis. We suspect that a proportion of these patients could have functional SMs. Importantly, some of the mimic subgroups were stable during the 10-year period, while others, such as headaches, peripheral vertigo and epilepsy/seizures, increased significantly. This is consistent with the systematic reviews of SM case-mix when taking into account that we only find significant increasing incidence of SU admission for vertigo, headaches, symptoms involving the nervous system, and epilepsy.

We were also concerned with monitoring the possible shift between SM subcategories. For example, decline in the use of either *observation for suspected nervous system disorder* or *other diagnoses* could both explain an increase in other SM subcategories, say *peripheral vertigo*, and represent a welcomed result of more specific diagnosing. Instead, we observed that, by and large, there was no evidence that the incidence of the hospitalization of *any SM* subcategory were declining, and that admissions classified as *observation for suspected nervous system disorder* increased. (Appendix II).

TIA admission incidence also increased enough to suggest a possible increasing temporal trend, albeit not significant when applying the Bonferroni-correction for multiple testing ($p = 0.03$; Appendix II). Furthermore, if present, it seems to level out at the end of the period under study. This observation is consistent with an increased awareness of the importance of fast admission to an SU also for TIAs and milder strokes following the rTPA revolution of the early 2000s. The CVA sequela subcategory displayed the expected male sex association, consistent with male sex increased risk for CVAs. No discernible temporal trend for CVAs was observed, which is consistent with the stable or declining stroke incidence rates observed in Norway.[49,50]

Our study has several implications for SU physicians and for policy makers. In the clinical setting, the staff should be aware that despite improved diagnostics and imaging, SU intake appears to be less specific for stroke than ten years ago. An awareness of this phenomenon could help guide the work-up and target the patients with highest pre-test probability of presenting with mimics on the SU.

4.1 | Strengths and limitations

This study is conducted at a large Norwegian university hospital with little self-selection (no private alternative). The data were collected prospectively, and longitudinal data for a relatively long time period (10 years) strengthens the results. In addition, we present the first time trend analysis of SM admissions to the SU. One important limitation is that the data are from a single-centre, external validity is therefore questionable. Different health care systems, guidelines, intake criteria, and referral practices might interact with the process of admission to an SU in different ways. We did not have additional information on SMs, such as types and degree of symptoms

and disability, or previous medical history including typical stroke risk factors, which prevents our study from contributing to more accurate discrimination between SMs and stroke. However, we do believe that our findings should be of interest, and that our results, viewed in conjunction with the recent surge in interest for SMs, indicate that the observed trend might not be specific to our centre or country.

5 | CONCLUSIONS

SMs' share of the case-mix of SU admissions appears to have seen a substantial and highly significant increase over the past decade in our stroke centre, and this finding cannot be explained by a demographic shift. The share of SMs has risen to above 50%. Our results are inconclusive as to whether the observed surge in SMs at the stroke unit is levelling out or continuing to climb, and we caution others to extrapolate our findings into the future. While male sex is a predictor for CVA-caused SU admissions, patients on the SU with SMs are more often female. However, older males have a higher risk of being admitted to an SU with an SM than females of the same age, although the sex-imbalance in the Norwegian population offsets this risk to the extent that most SMs are female. Young age at SU admissions is predictive of an SM diagnosis. In absolute terms, most SU admissions for SMs involve a patient of age 67 or older (50.5%). There is a substantial variation in the risk profiles, according to SM subcategory, and age. The observed increase in SMs—both incidences and proportion of SU admissions—is attributable mainly to *peripheral vertigo*, *headaches*, *epilepsy*, *nervous system symptoms*, and *observation diagnoses*. We venture to recommend that it would not be prudent to scale down on SU capacity based on declining CVA incidences alone. Further trends in SU capacity demand should be monitored closely by health care administrators and policy makers, and we encourage further investigation of SM incidences, as well as intensified research into more accurate initial diagnostics for suspected acute CVA to alleviate the SUs.

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CONFLICT OF INTERESTS

All authors state no conflict of interest.

AUTHOR CONTRIBUTIONS

MB conceived the study, designed and performed the analyses, collected data, and drafted the manuscript. **KWF** classified the mimics, suggested secondary analyses, and revised the manuscript. **FAD** aided with statistical design and critically revised the manuscript. **HN** helped design the study, collected data, classified the mimic diagnoses, suggested secondary analyses, and revised the manuscript.

ETHICAL APPROVAL

The NORSTROKE registry comprises all patients (including stroke mimics) admitted to the Stroke unit at Haukeland University Hospital. It was defined as a 'quality assurance database' and approved by the head of Department of Neurology, Haukeland University Hospital. Additional statistical analyses by NORSTROKE members, based on data either covered by previous Regional Ethical Committee approvals or the general purpose of the NORSTROKE data base (eg monitoring of SU activity) does not require a separate approval according to Norwegian law. No additional data (eg patient journal reviews) was collected for the herein presented analyses.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Saver JL. Time is brain—quantified. *Stroke*. 2006;*37*:263-266.
2. Wall HK, Beagan BM, O'Neill J, Foell KM, Boddie-Willis CL. Addressing stroke signs and symptoms through public education: the Stroke Heroes Act FAST campaign. *Prev Chronic Dis*. 2008;*5*:A49.
3. Wolters FJ, Paul NLM, Li L, Rothwell PM. Sustained impact of uk fast-test public education on response to stroke: a population-based time-series study. *Int J Stroke*. 2015;*10*:1108-1114.
4. Advani R, Naess H, Kurz M. Mass media intervention in western norway aimed at improving public recognition of stroke, emergency response, and acute treatment. *J Stroke Cerebrovasc Dis*. 2016;*25*:1467-1472.
5. Editorial. Stroke—acting FAST at all ages. *Lancet*. 2018;*391*(10120):514.
6. Govan L, Weir CJ, Langhorne P. Organized Inpatient (Stroke Unit) Care for Stroke. *Stroke*. 2008;*39*:2402-2403.
7. Chan DKY, Cordato D, O'Rourke F, et al. Comprehensive stroke units: a review of comparative evidence and experience. *Int J Stroke*. 2013;*8*:260-264.
8. Rønning OM, Guldvog B. Stroke units versus general medical wards, I: twelve- and eighteen-month survival: a randomized, controlled trial. *Stroke*. 1998;*29*:58-62.
9. Indredavik B. Stroke Units – the Norwegian experience. *CED*. 2003;*15*:19-20.
10. Stavem K, Rønning OM. Survival over 12 years following acute stroke: initial treatment in a stroke unit vs general medical wards. *Acta Neurol Scand*. 2011;*124*:429-433.
11. Dodel RC, Haacke C, Zamzow K, et al. Resource utilization and costs of stroke unit care in Germany. *Value in Health*. 2004;*7*:144-152.

12. Stroke Unit Trialists Collaboration. Organised inpatient (stroke unit) care for stroke. Cochrane Database Syst Rev [Internet]. 2013 [cited 2019 Nov 8];2013. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6474318/
13. Gibson LM, Whiteley W. The differential diagnosis of suspected stroke: a systematic review. *J R Coll Physicians Edinb*. 2013;*43*:114-118.
14. McClelland G, Rodgers H, Flynn D, Price CI. The frequency, characteristics and aetiology of stroke mimic presentations: a narrative review. *Eur J Emerg Med*. 2019;*26*:2-8.
15. Dawson A, Cloud GC, Pereira AC, Moynihan BJ. Stroke mimic diagnoses presenting to a hyperacute stroke unit. *Clin Med*. 2016;*16*:423-426.
16. Quenardelle V, Lauer-Ober V, Zinchenko I, et al. Stroke mimics in a stroke care pathway based on MRI screening. *Cerebrovasc Dis*. 2016;*42*:205-212.
17. Faiz KW, Labberton AS, Thommessen B, Rønning OM, Dahl FA, Barra M. The burden of stroke mimics: present and future projections. *J Stroke Cerebrovasc Dis*. 2018;*27*(5):1288-1295. http://www.strokejournal.org/article/S1052-3057(17)30673-0/fulltext
18. Fernandes PM, Whiteley WN, Hart SR, Salman RA-S. Strokes: mimics and chameleons. *Pract Neurol*. 2013;*13*:21-28.
19. Chernyshev OY, Martin-Schild S, Albright KC, et al. Safety of tPA in stroke mimics and neuroimaging-negative cerebral ischemia(Podcast)(e–Pub ahead of print)(CME). *Neurology*. 2010;*74*:1340-1345.
20. Förster A, Griebe M, Wolf ME, Szabo K, Hennerici MG, Kern R. How to identify stroke mimics in patients eligible for intravenous thrombolysis? *J Neurol*. 2012;*259*:1347-1353.
21. Zinkstok SM, Engelter ST, Gensicke H, et al. Safety of thrombolysis in stroke mimics. *Stroke*. 2013;*44*:1080-1084.
22. Tsivgoulis G, Zand R, Katsanos AH, et al. Safety of intravenous thrombolysis in stroke mimics. *Stroke*. 2015;*46*:1281-1287.
23. Ali-Ahmed F, Federspiel JJ, Liang L, et al. Intravenous tissue plasminogen activator in stroke mimics: findings from the get with the guidelines-stroke registry. *Circ Cardiovasc Qual Outcomes*. 2019;*12*(8):e005609. 10.1161/CIRCOUTCOMES.119.005609
24. Amort M, Fluri F, Schäfer J, et al. Transient ischemic attack versus transient ischemic attack mimics: frequency, Clinical Characteristics and Outcome. *Cerebrovasc Dis*. 2011;*32*:57-64.
25. Goyal N, Male S, Al Wafai A, Bellamkonda S, Zand R. Cost burden of stroke mimics and transient ischemic attack after intravenous tissue plasminogen activator treatment. *J Stroke Cerebrovasc Dis*. 2015;*24*:828-833.
26. Nor AM, Davis J, Sen B, et al. The Recognition of Stroke in the Emergency Room (ROSIER) scale: development and validation of a stroke recognition instrument. *Lancet Neurol*. 2005;*4*:727-734.
27. Hand PJ, Kwan J, Lindley RI, Dennis MS, Wardlaw JM. Distinguishing between stroke and mimic at the bedside. *Stroke*. 2006;*37*:769-775.
28. Dassan P, Keir G, Jäger HR, Brown MM. Value of measuring serum vascular endothelial growth factor levels in diagnosing acute ischemic stroke. *Int J Stroke*. 2012;*7*:454-459.
29. Goyal N, Tsivgoulis G, Male S, et al. FABS: an intuitive tool for screening of stroke mimics in the emergency department. *Stroke*. 2016;*47*:2216-2220.
30. Merino JG, Luby M, Benson RT, et al. Predictors of acute stroke mimics in 8187 patients referred to a stroke service. *J Stroke Cerebrovasc Dis*. 2013;*22*:e397-e403.
31. Terrin A, Toldo G, Ermani M, Mainardi F, Maggioni F. When migraine mimics stroke: a systematic review. *Cephalalgia*. 2018;*38*:2068-2078.
32. Kvistad CE, Thomassen L, Waje-Andreassen U, Moen G, Logallo N, Naess H. Clinical implications of increased use of MRI in TIA. *Acta Neurol Scand*. 2013;*128*:32-38.
33. Gargalas S, Weeks R, Khan-Bourne N, et al. Incidence and outcome of functional stroke mimics admitted to a hyperacute stroke unit. *J Neurol Neurosurg Psychiatry*. 2015;*88*(1):2-6.
34. Khanevski AN, Kvistad CE, Novotny V, Næss H, Thomassen L, Logallo N, Bjerkreim AT. Incidence and etiologies of stroke mimics after incident stroke or transient ischemic attack. *Stroke*. 2019;*50*(10):2937-2940. 10.1161/STROKEAHA.119.026573
35. Thomassen L, Waje-Andreassen U, Broegger J, Næss H. Acute stroke centre – the changing focus of stroke unit care. The Bergen NORSTROKE Study. *Acta Neurol Scand*. 2012;*125*:410-415.
36. Feigin V, Vander HS. How to study stroke incidence. *Lancet*. 2004;*363*:1920-1921.
37. Tutz G. Poisson Regression. *International Encyclopedia of Stat Sci*. 2011;1075-1077.
38. R Core Team. *R: A Language and Environment for Statistical Computing [Internet]*. R Foundation for Statistical Computing; 2020. http://www.R-project.org/
39. Shaffer JP. Multiple hypothesis testing. *Annu Rev Psychol*. 1995;*46*:561-584.
40. Labberton AS, Rønning OM, Thommessen B, Barra M. Changes in survival and characteristics among older stroke unit patients—1994 versus 2012. *Brain and Behavior*. 2018;*9*:e01175.
41. Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet*. 2014;*383*:245-254.
42. Booth TC. Incidental findings on imaging. *BMJ*. 2018;*361*:k2611. https://www.bmj.com/content/361/bmj.k2611
43. Ganguli I, Simpkin AL, Lupo C, et al. Cascades of care after incidental findings in a US national survey of physicians. *JAMA Netw Open*. 2019;*2*:e1913325.
44. Garg R, Rech MA, Schneck M. Stroke mimics: an important source of bias in acute ischemic stroke research. *J Stroke Cerebrovasc Dis*. 2019;*28*:2475-2480.
45. Keselman B, Cooray C, Vanhooren G, et al. Intravenous thrombolysis in stroke mimics: results from the SITS International Stroke Thrombolysis Register. *Eur J Neurol*. 2019;*26*:1091-1097.
46. Suzuki J, Nakai N, Kondo N, et al. Ten-year evaluation of the TOYOTA prehospital stroke scale for tissue plasminogen activator intravenous therapy in the real world. *CED*. 2018;*46*:184-192.
47. Nordanstig A, Asplund K, Norrving B, Wahlgren N, Wester P, Rosengren L. Impact of the Swedish National Stroke Campaign on stroke awareness. *Acta Neurol Scand*. 2017;*136*:345-351.
48. Jones AT, O'Connell NK, David AS. Epidemiology of functional stroke mimic patients: a systematic review and meta-analysis. *Eur J Neurol*. 2019;n/a:1-9.
49. Rand K, Dahl FA, Viana J, Rønning OM, Faiz KW, Barra M. Fewer ischemic strokes, despite an ageing population: stroke models from observed incidence in Norway 2010–2015. *BMC Health Services Research*. 2019;*19*:705.
50. Barra M, Labberton AS, Faiz KW, et al. Stroke incidence in the young: evidence from a Norwegian register study. *J Neurol*. 2018;*266*:68-84. https://rdcu.be/cwvZg

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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