Seasonal patterns and associations in the incidence of acute ischemic stroke requiring mechanical thrombectomy

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ABSTRACT

Background: In order to identify risk periods with an increased demand in technical and human resources we tried to determine patterns and associations in the incidence of acute ischemic stroke due to embolic large vessel occlusions (eLVO) requiring mechanical thrombectomy (MT).

Methods: We conducted a time series analysis over a nine-year period (2010-2018) based on observational data in order to detect seasonal patterns in the incidence of MT due to eLVO (n=2628 patients). In a series of sequential negative binominal regression models we aimed to detect further associations (e.g., temperature, atmospheric pressure, air pollution).

Results: There was a 6-month seasonal pattern in the incidence of MT due to eLVO (p=0.024) peaking in March and September. Colder overall temperature was associated with an increase in MT due to eLVO (Average Marginal Effect, [CI]: -0,15 [-0.30-0.0001]; p=0.05; per °C). A current increase in the average monthly temperature was associated with a higher incidence of MT due to eLVO (0.34 [0.11-0.56]; p=0.003). Atmospheric pressure was positively correlated with MT due to eLVO (0.38 [0.13-0.64]; p=0.003; per hpa). We could detect no causal correlation between air pollutants and MT due to eLVO.

Conclusions: Our data suggest a 6-month seasonal pattern in the incidence of MT due to eLVO peaking in spring and early autumn. This might be attributed to two different factors: (1) a current temperature rise (comparing the average monthly temperature in consecutive months); (2) colder overall temperature. These results could help to identify risk periods requiring an adaptation in local infrastructure.

INTRODUCTION

Evidence on a seasonal variation in stroke occurrence is broad but inconsistent. While different patterns with incidence rates peaking in spring, summer, autumn or winter are reported, other data indicate that there is no fluctuation at all (1-10). However, validity is often limited, e.g. due to a short observation period (3, 4, 9, 10). Parts of this inconsistency is also believed to be attributed to specific geographical or climate factors as the manifestation of seasons can vary depending on altitude, climate zone or distance to the equator. Differences between ischemic and hemorrhagic stroke are well-known (1-3). In contrast, specific ischemic stroke subtypes (e.g., atherosclerosis, cardiac embolism, small vessel disease) have rarely been addressed (10-12). Embolic stroke (e.g., cardiac embolism, atherosclerosis, dissection, paraneoplastic coagulopathy) frequently requires endovascular stroke therapy (mechanical thrombectomy [MT]) (13). Following an expansion of indication, the number of patients in need of MT is growing (14). MT is limited by both personal and technical resources and can be time-consuming. This requires a constant adaptation in infrastructure and resource management. To our knowledge, there is no data on specific (seasonal) patterns or associations influencing incidence rates of acute ischemic stroke caused by an embolic large vessel occlusion (eLVO).

Based on the frequency of endovascular stroke therapy we report data on seasonal variations in the incidence of acute ischemic stroke due to eLVO requiring MT. In additional analyses, we tried to detect influences of potential environmental and climate factors such as temperature, atmospheric pressure and air pollution.

METHODS

Study population

From our ongoing retrospective single-center stroke registry, ischemic stroke patients undergoing MT were identified. To evaluate incidence rates of embolic stroke requiring MT, other stroke etiologies were excluded. We considered consecutive patients treated with MT between January 2010 and December 2018. Patients were either seen in the emergency department of our neurovascular center or secondarily transferred from surrounding primary stroke centers (15). As there is an established cooperation network, MT for all ischemic stroke patients within the city of Stuttgart and a predefined number of surrounding districts (Esslingen [Neckar], Boeblingen, Rems-Murr district, Ostalb district) is exclusively carried out in our institution. Therefore, we believe that this is a robust dataset depicting the incidence and the development of MT in acute ischemic stroke caused by LVO in a pre-specified region covering approximately 2.3 million people (16). The structure of the population in this region remains stable during the course of a year. Unlike other regions in Europe, there is no particular tourist season (e.g., skiing season in winter, beach holidays in summer) leading to an increase in local population numbers. Overnight stays do not differ considerably (data from 2018 [source: state statistical office of Baden-Württemberg]): the lowest numbers of overnight stays are in January (634,305) and December (665,826), the most busy months are October (870,900) and July (856,782). The main vacation periods for people living in the area are during the summer holidays (July to September) and the end of December (Christmas).

We included patients with an acute ischemic stroke caused by an embolic occlusion of the internal carotid artery, the carotid-T, the M1 and M2-branch of the middle cerebral artery (MCA), the vertebral artery and the basilar artery. The diagnosis of an eLVO was established after initial imaging (vessel occlusion in CT-angiography or MRI-angiography) and later confirmed in digital subtraction angiography (prior to endovascular treatment). We did not differentiate specific sources of embolism (e.g., cardiac embolism due to atrial fibrillation, atherosclerosis, paraneoplastic coagulation disorder, dissection; all potential sources of embolism leading to a large vessel occlusion were included). Cases of an eLVO (based on initial imaging) that were found recanalized during angiography (spontaneously or as an effect of intravenous thrombolysis) were suitable for further analysis. Distal occlusions (e.g., M3 branch of the MCA) or an occlusion of the anterior or posterior cerebral artery could not be analyzed (as they were not treated on a regular basis but only as part of individual healing attempts). We excluded patients undergoing primary stenting (percutaneous transluminal angioplasty) due to extra- or intracranial stenosis (without an embolic vessel occlusion in initial imaging or angiography) as well as patients that were initially considered for MT but eventually did not undergo treatment (e.g., no vessel occlusion in initial imaging, chronic vessel occlusion). The STROBE guidelines were used to ensure the reporting of this observational study (17). There is a local institutional review board approval for patient data assessment and analysis (ethics committee: LÄK BW). We conducted the study in accordance with the declaration of Helsinki.

To detect influences of climate and environmental factors we analyzed specific features such as temperature, temperature change, atmospheric pressure, atmospheric pressure change and air pollution. The respective information was drawn from a local meteorological station which is located at the Stuttgart airport in Filderstadt (Deutscher Wetterdienst [DWD], station 4931). The city of Stuttgart is located in the southern part of Germany (altitude: 250m above sea level). The city center is concentrated in a basin. Outer districts and the area surrounding the city are located slightly higher (approximately 400m above sea level). There is a continental climate with cold winters (average temperature: 1.5°C in January) and moderately warm summers (average temperature: 19.9°C in July). Information on air pollution was drawn from the state office for the environment (Landesamt für Umwelt Baden-Württemberg; station 4452 [Stuttgart – Bad Cannstatt] provided data on ozone [O3]; station 55006 [Stuttgart – Arnulf-Klett-Platz] data on particulate matter with aerodynamic diameter <10µm [PM10], nitrogen dioxide [NO_2] and carbon monoxide [CO]).

Statistical analysis

As the total number of days per month differs within the 108-month observation period, frequencies were standardized and re-calculated for a 30-day period. The occurrence of eLVO was defined as MT due to eLVO within 30 days. Median-spline plots were used for a general description of the incidence.

A time series analysis aims to identify trends, seasonal patterns, cycles or coincidence in time. It is recommended to include more than 50 observations in a minimum of five consecutive years. Otherwise, an uncertainty remains as to whether an interference across the years indicates a real association (18). We used a time series analysis to identify possible seasonal patterns in the occurrence of MT due to eLVO during a 9-year time-period. The models are based on frequency domain analyses. Frequency domain analysis is reported to be an appropriate statistical method for a time series analysis (18). In addition to a general trend, cosinor functions for seasonal and cycle patterns (e.g., 6 months, 12 months, 24 months) and environmental factors (temperature, atmospheric pressure, air pollution) were used to explain the development of the incidence per 30 days. We used negative binominal regression models for calculation.

We developed a series of sequential models (R). R1 depicts the overall trend (per month), R2 – R4 the function of a time-period of 6 (R2), 12 (R3) and 24 (R4) months. In further models, we added functions for the average temperature per month (°C), the change in the average temperature per month (compared to the month before; °C; R5a), the average atmospheric pressure (hpa) and the change in the average atmospheric pressure per month compared to the prior month (hpa; R5b) as well as data on air pollution (R6). R7 combines all parameters of the prior models. We used the AIC (Akaike's information criterion) to compare the validity of the various models. The lower the AIC, the better the predictive power of the model. Average marginal effects (AME) were calculated for temperature, atmospheric pressure and month (MT due to eLVO within 30 days). The AME shows the estimated change in the incidence per 30 days. All statistical tests are two-sided, a p-value of 0.05 was considered statistically significant.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Between January 2010 and December 2018 n=2948 acute ischemic stroke patients received endovascular treatment. N=320 patients did not meet the inclusion criteria and had to be removed from further analysis (Fig. 1). We could eventually analyze n=2628 patients. In the anterior circulation, n=181 (6.9%) had an occlusion of the internal carotid artery, n=469 (17.8%) of the Carotid-T, n=1318 (50.2%) of the M1 and n=315 (12.0%) of the M2. In the posterior circulation, the vertebral artery was occluded in n=67 patients (2.5%), the basilar artery in n=276 (10.5%). In n=2 patients the site of the vessel occlusion could not be determined (insufficient image storing).

The observed average monthly incidence of MT due to eLVO is shown in table 1. Fig. 2a illustrates the development of the incidence per 30 days (actual incidence and median-spline plot). There was an overall increase of 0.28 cases per month (AME: 0.28 [0.24-0.32], see table 2). N=105 patients have been treated in 2010 compared to n=434 in 2018. Over the course of a year, we observed a variation of 36.2% in the incidence of MT due to eLVO. On average, 21.3 patients received endovascular therapy (as defined in our inclusion criteria) in January compared to 29.0 patients in March (table 1).

Via negative binominal regression models, we tried to detect patterns and associations in our data (Fig. 2b, table 2). We could determine a 6-month pattern in the occurrence of MT due to eLVO with estimated peaks in March and September. Comparing the 6-month seasonal pattern (R2) to other possible patterns (R3, R4), the 6-month pattern seems to be the most robust throughout the entire analysis reaching statistical significance (R2: p=0.075; R3: p=0.073; R4: p=0.105; R5a: p=0.048; R7: p=0.024). The estimated incidence of the 6-month seasonal pattern and the observed incidence are shown in Fig. 2b. Other estimated patterns (R3, R4) did not show any association (see table 2 for details). The function of the 6-month pattern peaks in March and September with higher estimated incidences in winter (months with lower overall average temperature) when compared to summer (see table 2).

Data on temperature and atmospheric pressure are shown in table 3. In general, the average air temperature is static in winter (mean air temperature; Dec.: 2.7°C, Jan.: 1.5°C, Feb.: 1.5°C) and summer (Jun.: 17.9°C, Jul.: 19.9°C, Aug.: 19.3°C). In spring and autumn, the monthly mean of the average air temperature is changing considerably compared to the month before. (see table 3). R5a and R7 show an estimated effect of temperature (R5a: p = 0.091; AME (95% CI): -0.13 [-0.29-0.02]; R7: p = 0.050; -0.15 [-0.30-0.001]). R5a did not show a significant effect. R7 indicates a potential temperature dependent decrease in the incidence of MT due to eLVO. The higher the overall temperature the lower the incidence (R7: -0.15 cases per °C, table 2). We did find an association between temperature change and MT due to eLVO. As the (average) temperature rose (meaning the average temperature of the current month was higher compared to the average temperature the month before) there was an increase in embolic stroke and MT (R5a: p=0.042; 0.24 [-0.01-0.48]; R7: p=0.003; 0.34 [0.11-0.05]). Solely looking at the AIC, R5a (adding the influence of temperature and temperature change) was superior (AIC: 662.0) to the remaining models.

Our data indicate an association of atmospheric pressure and frequency of MT due to embolic stroke (R5b: p=0.090; 0.26 [-0.04-0.57]; R7: p=0.003; 0.38 [-0.39-0.06]). An increase in atmospheric pressure might lead to an increase in the incidence of MT due to eLVO. The difference in atmospheric pressure (current period vs. the period before) seems to be without effect (see table 2).

The models adding data on air pollution (R6) did not show any correlation (O3: p=0.359; -0.05 [-0.14-0.05]; CO: p=0.059; 13.66 [-0.52-27.85]; NO2: p=0.701; 0.03 [-0.13-0.19]; PM10: p=0.348; -0.11 [-0.35-0.12]; data not shown). In our data, there was a strong correlation between temperature and CO (Bravais-Pearson correlation coefficient: -0.7507), PM10 (-0.6694) as well as O3 (0.7701). See table 4 for information on the raw data on air pollution parameters.

DISCUSSION

The main finding of this time series analysis is a seasonal 6-month pattern in the incidence of MT due to eLVO with peaks in March and September. To our knowledge, this is the first dataset analyzing seasonal fluctuations and patterns in embolic strokes requiring MT. Similar results have been reported for ischemic stroke overall (1, 4, 5). However, fluctuations in the incidence rate in ischemic stroke subtypes (e.g., embolic stroke) have rarely been investigated (10-12). One of the studies could not detect any seasonal predominance (10). Due to a one-year observation period, validity regarding a time series analysis is limited. Cardioembolic stroke and cervical artery dissection – both frequent causes of cerebral embolism – seem to peak in winter whereas other ischemic stroke subtypes such as atherosclerotic large vessel disease, small vessel disease or stroke due to undetermined source do not appear to follow any seasonal pattern (11, 12).

Seasonal fluctuation in acute ischemic stroke seems to be influenced by two different parameters: absolute temperature and temperature change when comparing consecutive months. There is evidence that (in ischemic stroke overall) ambient temperature correlates with stroke incidence (7, 19-21). The most common finding is an increase in ischemic stroke cases in colder months (7, 19-22). Likewise, we observed a temperature dependence in the incidence of MT due to eLVO: the lower the temperature, the higher the estimated incidence. The overall incidence was higher in winter when compared to summer. Besides the absolute temperature level, dynamic changes in the average air temperature might be crucial. Exposure to a short-term temperature variability leads to a higher risk of hospitalization due to ischemic stroke (23, 24). A substantial increase in the average monthly temperature in the current month compared to the month before was shown to be associated with ischemic stroke events (22). In our data, one of the main findings was that MT due to embolic large vessel occlusion was more frequent in months with a substantial change in the mean of the average air temperature. An augmentation in the average temperature seems to lead to an increase in embolic stroke. These changes are predominant in spring as well as late summer, when the average monthly temperature is rising.

Additional factors with a seasonal predominance such as air pollution and respiratory tract infections (e.g., influenza) can influence stroke incidences and hospitalization rates (25-28). Our model could not detect influences of air pollutants on the incidence of MT due to eLVO. However, there was a strong correlation between CO, PM10 and temperature. Both CO and PM10-concetrations peaked in colder months. Air pollutants might therefore contribute to the overall observation of higher incidence rates in low-temperature months. Similar results are reported for respiratory tract infections such as influenza (27, 28). In the covered region, influenza infections start to occur in October with incidence rates peaking in February and March followed by a subsequent decline until the end of influenza-season in May (29). In colder months, the number of infections is rising (28). In September (one of the two months with the highest incidence of MT due to eLVO in our model) hardly any influenza infections are reported (29). A seasonal pattern correlating MT due to eLVO with influenza incidences in the observed region could not be found.

Atrial fibrillation is one of the main risk factors for acute ischemic stroke caused by eLVO. The frequency of paroxysmal atrial fibrillation also follows a seasonal pattern with higher observation and detection rates in colder months (30-32). Cold temperature might induce atrial fibrillation by enhancing the sympathetic function (up-regulation of hypothalamic mineralocorticoid receptors) or due to cold-induced hypertension (33, 34). In animal models, mild hypothermia triggers atrial fibrillation (35). Subsequently, atrial fibrillation might induce embolic stroke. Other physiological changes observed in colder months such as higher plasma fibrinogen levels, factor VII clotting activity and an increase in platelet count and blood viscosity appear to have additional effects (36, 37).

Evidence on the influence of atmospheric pressure is rare (22, 33). High-pressure days seem to be a risk factor for stroke (22). A recent meta-analysis did not detect any influence of atmospheric pressure on the occurrence of ischemic stroke overall (38). Focusing on mechanical thrombectomy in acute ischemic stroke, we observed an increase in high-pressure months. The pathophysiological background remains to be understood.

This study has several limitations. The retrospective design might lead to selection bias as we do not know the number of patients that were not considered for endovascular therapy. However, we believe that the percentage of people transferred for endovascular therapy did not change within the different institutions. As our hospital is the only center offering mechanical thrombectomy for a pre-defined region, it is guaranteed that only a few patients had been transferred to other external centers (outside our neurovascular network; due to capacity concerns). Between 2010 and 2018, there is a constant increase in the use of MT in our cohort. We believe that this is attributed to the growing popularity of endovascular stroke therapy after publication of the first successful randomized controlled trial together with a recent expansion of the indication (e.g., wake-up stroke) (13, 14). However, despite the increase in MT cases, the pattern with its supposed annual peaks did not change when looking at each year separately.

Conclusion

Our data suggest a 6-month pattern in the incidence of MT following embolic large vessel occlusion with peaks in spring and late summer. This pattern seems to be influenced by two independent parameters: (1) change in the average monthly temperature and (2) absolute temperature. An increase in the average temperature comparing consecutive months (prominent in spring and at the end of summer) might lead to an increase in the incidence of MT due to eLVO. A lower overall temperature seems to be associated with higher incidence rates (explaining the higher number of MT cases in winter). High atmospheric pressure appears to be an additional risk factor. Since MT following embolic stroke requires numerous human and technical resources, the identified pattern could be helpful in adapting local infrastructure and workflow during these risk periods.

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Table 1. Observed incidence of MT due to eLVO per month (2010-2018).

Month	mean (SD)	median (min-max)
January	21.3 (8.1)	25.0 (5-34)
February	23.0 (10.2)	21.0 (10-43)
March	29.0 (12.2)	29.0 (10-49)
April	24.7 (12.1)	24.0 (6-43)
May	22.4 (11.5)	21.0 (6-41)
June	22.8 (8.6)	24.0 (11-37)
July	25.0 (10.0)	27.0 (8-37)
August	22.7 (9.3)	22.0 (8-36)
September	24.4 (8.4)	23.0 (9-33)
October	26.3 (12.7)	25.0 (8-52)
November	23.2 (9.0)	23.0 (9-40)
December	27.1 (9.0)	28.0 (12-39)

MT, mechanical thrombectomy; eLVO, embolic large vessel occlusion; SD, standard deviation; min, minimum; max, maximum.

Table 2. Sequential models (R1-R5, R7) analyzing specific cycles, temperature, temperature change, atmospheric pressure and atmospheric pressure change.

	R1	R2	R3	R4	R5a	R5b	R7
Month	$p<0.001$	$p<0.001$	$p<0.001$	$p<0.001$	$p<0.001$	$p<0.001$	$p<0.001$
AME (95% CI)	0.28 (0.23-0.32)	0.28 (0.24-0.31)	0.27 (0.24-0.31)	0.28 (0.24-0.32)	0.28 (0.24-0.32)	0.27 (0.23-0.31)	0.27 (0.24-0.31)
6-month pattern		$p=0.075$	$p=0.073$	$p=0.105$	$p=0.048$	$p=0.061$	$p=0.024$
12-month pattern			$p=0.666$	$p=0.557$			
24-month pattern				$p=0.313$			
Temperature (average/month, per °C)					$p=0.091$		$p=0.050$
AME (95% CI)					-0.13 (-0.29-0.02)		-0.15 (-0.30-0.0001)
Temperature (difference to prior month; per °C)					$p=0.042$		$p=0.003$
AME (95% CI)					0.24 (-0.01-0.48)		0.34 (0.11-0.56)
Atmospheric pressure (average/month; per hpa)						$p=0.090$	$p=0.003$
AME (95% CI)						0.26 (-0.04-0.57)	0.38 (0.13-0.64)
Atmospheric pressure (difference to prior month; per hpa)						$p=0.374$	$p=0.150$
AME (95% CI)						-0.12 (-0.37-0.14)	-0.17 (-0.39-0.06)

AIC		674.85	673.20	675.01	675.84	662.0	674.56	674.56
Incidence (estimated)								
	lowest	Jan 10	Jun / Dec	Jun / Dec	Jun / Dec			
	highest	Dec 18	Mar / Sep	Mar / Sep	Mar / Sep			

AME, average marginal effect; CI, confidence interval; ACI, Akaike's information criterion, hpa, hectopascals.

Table 3. Meteorological raw data on temperature and atmospheric pressure (2010-2018).

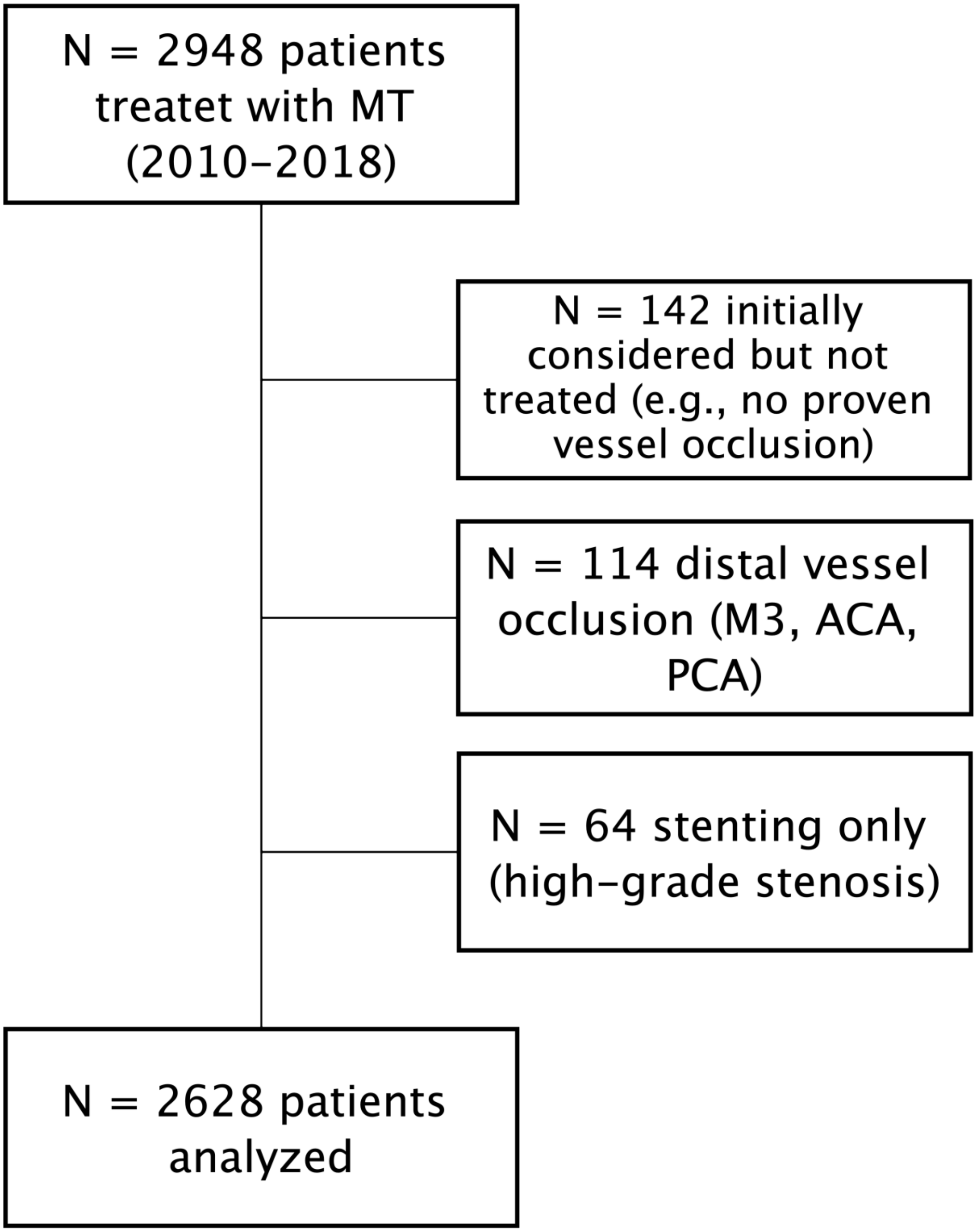
	Average air temperature per month (°C)		Average atmospheric pressure per month (hpa)	
	mean (SD)	**median (min-max)**	**mean (SD)**	**median (min-max)**
January	1.5 (2.5)	2.5 (-2.8-5.0)	970.1 (3.9)	968.4 (964.3-976.0)
February	1.5 (2.6)	1.2 (-2.4-4.6)	968.7 (5.7)	969.0 (958.9-979.5)
March	5.9 (2.1)	6.2 (2.2-4.6)	969.8 (6.5)	970.8 (958.5-979.8)
April	10.4 (1.8)	9.6 (8.6-13.8)	969.4 (4.2)	968.9 (960.8-974.2)
May	14.0 (1.7)	14.1 (11.6-16.4)	969.5 (2.2)	969.9 (965.8-973.0)
June	17.9 (0.9)	17.5 (16.9-19.9)	970.8 (1.5)	971.3 (969.2-973.3)
July	19.9 (1.6)	20.0 (16.8-22.0)	970.9 (1.8)	970.9 (968.2-973.8)
August	19.3 (1.5)	19.4 (16.6-21.2)	971.5 (1.6)	971.9 (969.4-974.3)
September	15.0 (1.6)	14.7 (12.9-17.4)	972.1 (1.6)	972.2 (970.6-975.4)
October	10.2 (1.3)	9.8 (8.3-12.3)	972.1 (2.6)	972.0 (967.7-975.3)
November	5.6 (1.2)	5.4 (4.4-7.8)	969.6 (4.6)	969.8 (961.4-975.1)
December	2.6 (2.1)	2.8 (-2.0-5.8)	973.4 (6.6)	973.4 (965.5-983.2)

SD, standard deviation; hpa, hectopascals; min, minimum; max, maximum.

Table 4. Average concentration of air pollutants (2010-2018).

	CO (mg/m^3)	PM 10 (ug/m^3)	Ozone (ug/m^3)
	mean (SD)	**mean (SD)**	**mean (SD)**
January	0.43 (0.07)	35.6 (9.9)	23.5 (4.9)
February	0.40 (0.07)	39.2 (8.6)	29.6 (5.7)
March	0.36 (0.09)	36.4 (7.8)	40 (4.9)
April	0.26 (0.05)	27.7 (3.9)	54.4 (3.7)
May	0.24 (0.05)	21.7 (2.3)	60.2 (8.9)
June	0.21 (0.06)	20.8 (2.6)	63.2 (8.2)
July	0.23 (0.05)	22.8 (2.7)	66.2 (9.9)
August	0.22 (0.04)	21.6 (1.1)	57.2 (6.3)
September	0.28 (0.04)	23.7 (2.7)	37.2 (6.3)
October	0.36 (0.05)	27.6 (4.2)	20.2 (4.5)
November	0.44 (0.11)	28.2 (5.2)	15.6 (7.0)
December	0.47 (0.12)	27.5 (7.7)	21.1 (7.4)

SD, standard deviation; CO, carbon monoxide; PM 10, particulate matter with aerodynamic diameter <10μm



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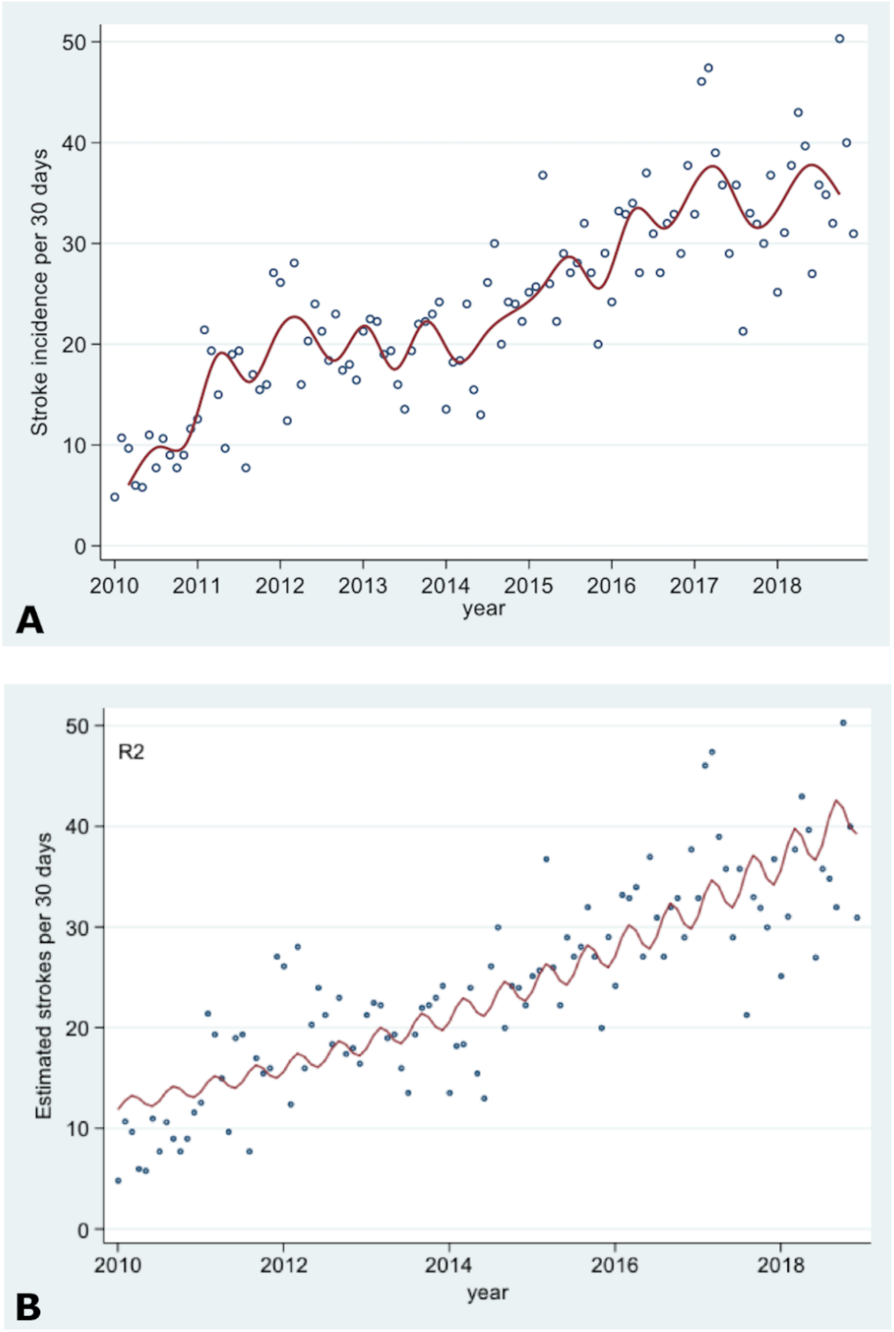

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