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Multiple sleep-wake disturbances after stroke predict an increased risk of cardio-cerebrovascular events or death – a prospective cohort study

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ABSTRACT

Background

In the general population, sleep-wake disturbances (SWD) have been shown to increase the risk of cardio- and cerebrovascular events (CCE) including death. Systematic studies on the effect of SWD on the risk of CCE in patients with stroke are lacking.

Methods

Patients with acute ischemic stroke or transient ischemic attack (TIA) were prospectively recruited. Four SWD were analyzed: 1) sleep-disordered breathing (SDB) with respirography, 2) insomnia (by insomnia severity index, ISI), 3) restless legs syndrome (RLS, by International RLS Study Group rating scale) and 4) self-estimated sleep duration at 1 and 3 months. A "sleep burden index" as the mean of z-transformed values from assessments of these four SWD was created. The occurrence of CCE was recorded over a follow-up of 3.2±0.3 years (mean±standard deviation).

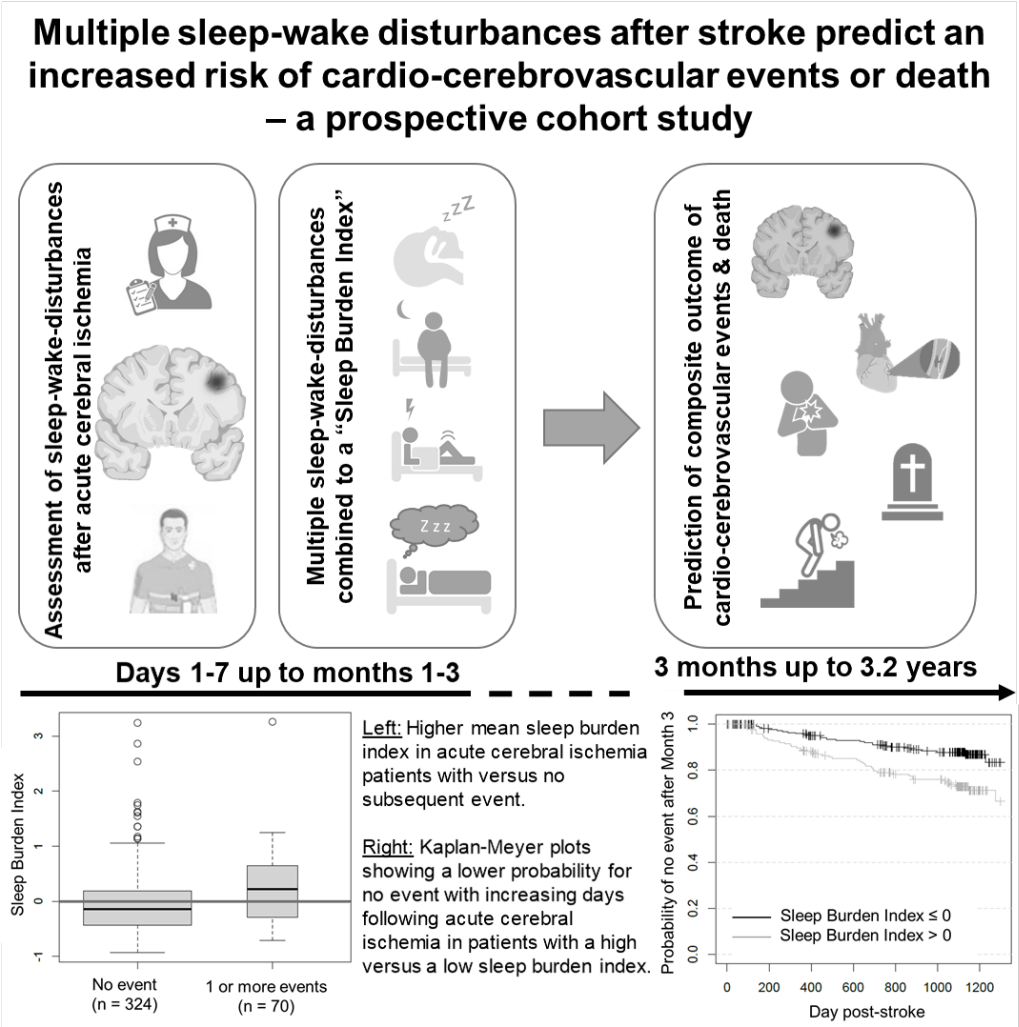
Results

We assessed 437 patients (87% ischemic stroke, 13% TIA, 64% males) with a mean age of 65.1±13.0 years. SDB (respiratory event index, REI≥5) was present in 66.2% thereof. Insomnia (ISI≥10), RLS and extreme sleep duration affected 26.2%, 6.4% and 13.7% of the patients 3-month post-stroke. Seventy out of the 437 (16%) had at least one CCE during the follow-up. The sleep burden index was associated with a higher risk for subsequent CCE including death (Odds Ratio = 1.80 per index unit, 95% CI: 1.19-2.72, p=0.0056).

Conclusion

The presence of multiple SWDs constitutes a risk for subsequent CCE (including death) within the first three years following stroke. Larger systematic studies should assess the sleep burden index' utility for patients' risk stratification in clinical practice.

Graphic Abstract



Nonstandard Abbreviations and Acronyms

AHI	Apnea-Hypopnea-Index
CBT-I	Cognitive Behavioural Therapy for Insomnia
CCE	Cardio-Cerebrovascular Events
ICSD-3	international classification system of sleep disorders, 3rd edition
IRLS	International Restless Legs Scale
ISI	Insomnia Severity Index
NIHSS	National Institute of Health stroke scale
REI	Respiratory Event Index
RLS	Restless Legs Syndrome
SDB	Sleep Disordered Breathing
SWD	Sleep-Wake-Disturbances
TIA	Transient Ischemic Attack

INTRODUCTION

Although the number of individuals dying from stroke has decreased over the last decade - especially in developed countries - stroke is still one of the leading causes of long-term disability in adults and imposes an enormous economic burden on society [1]. Any modifiable determinant to improve long-term stroke outcome and prevent subsequent cardio-cerebrovascular events is therefore of relevance. While normal sleep promotes body and brain health [2, 3], sleep loss and sleep-wake disturbances (SWD) are risk factors of brain disorders including stroke and also have a detrimental effect on their evolution and long-term outcome [4-6].

The frequency and impact of several SWD in stroke patients have been studied in the last 25 years. Two recent systematic reviews and meta-analyses including 89 and 132 studies, respectively, consistently report that about 2/3 of the stroke and transient ischemic attacks (TIA) patients suffer from at least mild (Apnea-Hypopnea-Index (AHI) derived from polysomnography and/or Respiratory Event Index (REI) derived from limited channel devices such as respirography > 5 /h) and 1/3 from severe sleep disordered breathing (SDB) (AHI/REI > 30/h) [7, 8]. Data on the frequency of insomnia and restless legs syndrome in stroke survivors are sparser and less consistent. Baylan and colleagues reported a pooled prevalence of post-stroke insomnia of 38% (95% Confidence Interval (CI) = 30-47%) summarizing 16 studies assessing insomnia at different time points following stroke [9]. Hasan and colleagues estimated pooled prevalence of post-stroke insomnia to be 41% (95% CI = 32-50, N = 12 studies) in acute stroke and TIA patients and 43% (95% CI = 32-54, N = 4 studies) and 36% (95% CI = 29-44, N = 15 studies) in the subacute and chronic phases, respectively [8]. Pooled prevalence of RLS following stroke or TIA was estimated to be 10% (95% CI = 6-16) in the acute phase and 14% (95% CI = 2-52) in the chronic phase following the event [8].

SDB not only doubles the risk of stroke if left untreated [4, 10, 11], but also increases the risk for recurrent strokes and TIA and all-cause mortality in stroke or ischemic heart disease survivors [12]. In prospective studies, no clear association with stroke risk was found selectively for insomnia [13, 14]. However, insomnia in combination with short sleep duration (≤ 5 h) was associated with an increased risk of cardio-cerebrovascular events including stroke [14], and, in one study, insomnia in stroke patients was associated with increased mortality during a 6-year follow-up [15]. Also long sleep duration is consistently found to increase the risk for stroke and stroke mortality, even to a higher extent than short sleep duration [16-19]. An expert consortium has recently evaluated the association of RLS with stroke risk and the impact of post-stroke RLS on stroke outcome as not conclusive [4]. It emphasizes the need for more studies investigating the association of SWD

with functional recovery and subsequent cardio-cerebrovascular events and death following stroke to draw solid conclusions on the impact of SWD on stroke outcome [4].

A few very recent studies have investigated the combined impact of different sleep facets (pooled self-reported information on chronotype, sleep duration, insomnia, snoring and excessive daytime sleepiness) on cardio-cerebrovascular health. These studies found that healthy sleep patterns are associated with lower risk for overall cardiovascular diseases, and separately for coronary heart disease and stroke [20]; for all-cause, cardiovascular and cancer-specific mortality [3]; as well as for incident heart failure [21]. Hence, good sleep may play an important role in prevention of cardio-cerebrovascular diseases and all-cause mortality.

To the best of our knowledge, however, no studies have so far investigated the effect of the multiple SWD on subsequent cardio-cerebrovascular events following an ischemic stroke or TIA. We hypothesized that looking at the combined burden of SWD, instead considering single SWD on their own, may be more useful in determining cardio-cerebrovascular risk since SWD are frequently comorbid and share common features (such as sleep fragmentation and impairment of daytime functioning).

METHODS

Study design, recruitment of participants and assessments

All data used for this exploratory investigation have been collected as part of the two-center prospective cohort study "Sleep Deficiency and Stroke Outcome" registered on clinicaltrials.gov (NCT02559739). The sample characteristics and the frequency and evolution of the sleep-wake-disturbances up to two years following the cerebral ischemia have been recently published [22].

Neurologists or study physicians at the Bern University Hospital (between 07/2015-01/2018) and the Neurocenter of Southern Switzerland (between 11/2015-07/2016) recruited patients with acute ischemic stroke or TIA consecutively admitted to their stroke centers (VISIT 1, day 1-7, mean (M) = 2.1 days, standard deviation (SD) = 1.5 days). Eligible patients were 18-85 years of age and able to give informed consent. Clinical unstable patients (e.g. coma/stupor, severe heart failure, persisting oxygen-dependency), patients with primary haemorrhagic stroke and drug/alcohol abuse were not eligible. An exclusion criterion for female participants was pregnancy. Patient demographics, medical history, stroke/TIA characteristics and severity at both hospital admission and discharge using the National Institute of Health Stroke Scale Stroke

(NIHSS) were collected. Following admission (the latest 7 days after acute stroke/TIA), a respirography was performed to assess SDB.

After discharge, 5 follow-up up visits were planned: at approximately 1 month (visit 2) and 3 months (visit 3), as well as at approximately 1, 2 and 3 years (visits 4-6) following the ischemic event. At visits 2 to 5, SWD and stroke outcome including subsequent cardio-cerebrovascular events and death of any cause were assessed using both validated questionnaires and clinical telephone interviews. At visit 6 only subsequent cardio-cerebrovascular events and death were assessed. Table 1 summarizes all study assessments per visit. The study was approved by the local ethics committees of Bern and Lugano (Switzerland).

Calculation of the sleep burden index

A sleep burden index was created using four variables:

1) *Respiratory event index (REI)* determined by respirography to quantify the severity of SDB. REI was assessed during acute hospitalization within hospital's clinical routine using either a NoxT3 device (Nox Medical, Inc., Reykjavik, Iceland, n=194) or an ApneaLink device (ResMed, Switzerland, n=200). The REI is considered an approximation of the apnea and hypopnea index (AHI) which is determined through polysomnography and the differentiation of sleep and wake states.
2) *Insomnia severity* using the Insomnia Severity Index (ISI) [23,24] that patients completed at 3 months post-stroke (if missing, the value at 1 month post-stroke was used). The sum score out of 7 items ranges between 0 and 28. According to a recent study by Morin and colleagues, a cut-off score of ≥ 10 revealed to be most specific and sensitive to define the presence of insomnia [24].
3) *RLS severity* using the International Restless Legs Syndrome Study Group rating scale (IRLS) [25] assessed at 3 months post-stroke (if missing, the value at 1 month post-stroke was used). This 10-item scale was used only in patients fulfilling the RLS diagnostic criteria evaluated by the study physician. The overall sum score ranges from 0 to 40. For patients without RLS this score was assumed to be 0.
4) *Absolute deviation from normal sleep duration.* Self-estimated sleep duration at 3 months post-stroke (if missing, the value at 1 month post-stroke was used). Either end of the duration spectrum of sleep was considered to represent a pathological sleep condition. Patients indicated their

average sleep duration during the last 4 weeks on week days/work days and on weekends/work-free days, respectively. The weighted mean between week/work days and weekend/work-free days per participant was calculated and then subtracted from the average sleep duration of 6.97 h obtained in an epidemiological study by Kerkhof [26]. Finally, absolute values were built. Kerkhof derived the average sleep duration from a sample of 2089 individuals aged between 18-70 years out of a database including 80'000 citizens of the Netherlands [26]. The mean sleep duration of the whole sample of Kerkhof's study was chosen as reference since it was close to that of the subsample of participants aged 55-70 years [26](the age group best representing the average age of our sample) and moreover because our sample also included approximately one quarter of younger participants.

These four facets of SWD were chosen since they 1) frequently affect ischemic stroke/TIA survivors; 2) can complicate stroke outcome and are associated with cardio-cerebrovascular morbidity; and 3) fragment sleep und thus interfere with its regenerative function.

REI values, the ISI and IRLS sum scores and the absolute deviations of sleep duration from reference were z-transformed based on the study sample (i.e., for each variable the mean was subtracted, and the results was divided by the standard deviation). The mean of all four z-values was then calculated as the final sleep burden index per participant.

This sleep burden index was then used as a predictor of subsequent cardio-cerebrovascular events including death occurring at least 3 months and up to 3.2±0.3 years (range: 2.8-4.7) after ischemic stroke or TIA.

All four components were weighed equally in the index since the current evidence did not allow to speculate about their relative contribution to cardio-cerebrovascular risk. Although there is evidence for a clear detrimental role of SDB and extreme sleep duration, insufficient data are available for insomnia and RLS [4].

Assessment of outcome – subsequent cardio-cerebrovascular events and death

The study's primary endpoint was a composite endpoint of death from any cause, stroke (ischemic and haemorrhagic), TIA, nonfatal myocardial infarction, unplanned hospitalization (or unplanned prolongation of

a planned hospitalization) for heart failure or unplanned hospitalization (or unplanned prolongation of a planned hospitalization) for unstable angina leading to urgent revascularization. Death was ascertained by patients' relatives, general practitioners or by an automatic query sent from the hospital's patient management system to the Central Compensation Office that registers all deaths of Swiss citizens or individuals working in Switzerland. Per protocol it was planned to only consider events occurring until the 2nd year post-stroke/TIA. However, already in the initial study protocol it was planned to assess death and the aforementioned cardio-cerebrovascular events also during a visit at 3 years to enhance the observation period and thus the potential number of detectable events to increase statistical power. All patients that could be reached, were contacted by the study physicians and/or a study nurse at each study visit. Whenever necessary their general practitioner, in addition to consulting their electronic medical reports, was contacted.

Statistics

This exploratory analysis included all recruited subjects who fulfilled all selection criteria for the study. We used multiple logistic and Cox regression to predict cardio-cerebrovascular events and/or death based on the sleep burden index, and, unless otherwise specified, adjustments for NIHSS at admission, age and sex. For the prediction analysis we only considered events occurring at least 3 months after stroke (since the SWD used to build the sleep burden index were assessed within the first three months after stroke/TIA) and patients that did not withdraw from the study prior to month 3 (N = 394). Hence, we differentiated between a so called exposure period to assess the different SWD (up to 3 months after the acute ischemic event) and an observational period assessing our composite outcome of subsequent cardio-cerebrovascular events and death of any cause (from 3 months up to on average 3.2 years). The Wilcoxon rank-sum test was used to compare means between two independent patient groups. Unless otherwise specified, tests of statistical hypotheses were conducted against two-sided alternatives and with a 5% significance level. No adjustment was made for multiple comparisons.

In case of missing data in any of the variables used to calculate the sleep burden index (REI, ISI, sleep duration, IRLS) we replaced the missing value with the sample mean. In case of premature discontinuation and loss to follow-up, we assumed that no event occurred after discontinuation. For survival analyses, we censored the observation at the last contact.

The planned sample size for this study was about 520 patients, which was justified in relation to the assessment of the prognostic value of individual SWD with respect to cardio-cerebrovascular events. The final number of patients enrolled in the pre-determined recruitment period end evaluable for this analysis (437 patients, 394 contributing to the key regression analysis) is still considered adequate, also in consideration of the number of primary events [27].

All analysis were performed in R version 4.0.4 R Core [28].

RESULTS

Descriptive data – patients' characteristics, frequency of sleep-wake disturbances in the first 3 months and outcomes

Out of 447 initially recruited patients, 10 patients had to be excluded from the dataset because of non-fulfillment of an inclusion criterion or uncertain diagnosis of ischemic stroke or TIA. Thus, our study sample consists of 437 patients with confirmed ischemic stroke (87%, age M±SD: 64.6±13.2, range: 20.8-85.8 years, 64.3% male) or TIA (13%, age M±SD: 68.6±11.0, range: 30.8-85.4 years, 60.7% male). Most of them (90%) were recruited at the University Hospital in Bern. For follow-up visits 363 (83%) could be contacted at month 1 (visit 2), 367 (84%) at month 3 (visit 3), 349 (80%) at year 1 (visit 4), 326 (75%) at year 2 (visit 5) and 287 (66%) at year 3 (visit 6) following stroke.

On average, patients presented with an ischemic stroke/TIA of mild to moderate severity with a mean NIHSS at admission of 3.5±4.5 (0-40) located mainly supratentorially (71.2%). Baseline demographic and stroke/TIA characteristics are summarized in table 2.

Twenty-six percent of the examined patients showed severe SDB (i.e. more than 20 events per hour). Slightly more than one fourth of the patients had clinically relevant insomnia symptoms within the first 3 month of stroke (as assessed with an ISI $\geq$ 10). RLS was present in 9% of the patients during the more acute (month 1) and in 6 % during the more chronic phase (month 3) of stroke or TIA. More stroke patients reported longer compared to shorter sleep durations (see table 3 for a summary on the frequency of SWD in the first 3 months of stroke/TIA). (See [22] for more descriptive results).

We observed 70 primary endpoint events representing the first event in a patient that occurred at least 3 months after the initial ischemic event. The longest time interval to a first event was 3.5 years. The most frequently observed first subsequent events 3 months after stroke/TIA were recurrent TIA (20 events) and stroke (18 events), as well as death of any cause (17 events). In addition, 10 subsequent events of heart failure leading to unplanned or prolonging planned hospitalization, 3 myocardial infarctions and 2 events of unstable angina requiring urgent revascularization were recorded.

Sleep burden index as a predictor of death and subsequent cardio-cerebrovascular events

The sleep burden index combining baseline REI, severity of insomnia (ISI) and RLS symptoms (IRLS), as well as the deviation of sleep duration from a population reference [26] ranged from -0.93 to 3.26

(M±SD: 0.0±0.58) with higher values indicating higher severity of combined SWD. Figure 1 shows that the mean sleep burden index was significantly higher for stroke/TIA patients with a subsequent event (n = 70, 0.21±0.63) compared to stroke/TIA patients without a subsequent event occurring at least 3 months following stroke/TIA (n = 324, -0.04±0.56) (Wilcoxon rank-sum test: $p = 0.0003$).

Logistic regression showed that the sleep burden index was associated with a higher risk for subsequent cardio-cerebrovascular events and death even when adjusting for age, sex, and NIHSS at admission (Odds Ratio = 1.80 per index unit, 95% CI: 1.19-2.72, p=0.0056). This association remained significant when excluding TIAs (representing events of minor severity) from the composite primary endpoint (Odds Ratio = 2.09 per index unit, 95% CI: 1.30-3.37, p=0.0024). A survival analysis of the time to the first event using a Cox regression model adjusted for the same parameters supported this finding (hazard ratio per unit of the sleep burden index 1.66, 95% CI: 1.19-2.30, p=0.0026). The Kaplan-Meyer plot showing the probability for no event with increasing days following the acute ischemic stroke or TIA is displayed in figure 2.

As a single component, only sleep duration (deviation from reference) (Odds Ratio = 1.36 per index unit, 95% CI: 1.06-1.74, p=0.0147) was a significant predictor for subsequent cardio-cerebrovascular events or death. REI, RLS or insomnia severity alone showed a positive, non-significant association with the reoccurrence of a cardio-cerebrovascular events or death of any cause (Odds $\text{Ratio}_{\text{REI}}$ = 1.01 per index unit, 95% CI: 0.99-1.03, p=0.1754; Odds $\text{Ratio}_{\text{IRLS}}$ = 1.02 per index unit, 95% CI: 0.97-1.08, p=0.4291; Odds $\text{Ratio}_{\text{ISI}}$ = 1.04 per index unit, 95% CI: 0.99-1.10, p=0.0882). Since according to the literature, SDB is considered a relevant predictor for recurrent and subsequent cardio-cerebrovascular events and worse stroke outcome in our investigated population [4], we excluded the REI from the sleep burden index to investigate if this reduced 3-variable index remains a significant predictor of subsequent cardio-cerebrovascular events. The sleep burden index without REI remained a significant predictor of subsequent cardio-cerebrovascular events (Odds Ratio = 1.64 per index unit, 95% CI: 1.14-2.37, p=0.0078). We repeated this analysis analogously with excluding the sleep duration component - as the only independently significant predictor for subsequent events. This reduced 3-variable sleep burden index also remained a significant predictor of subsequent cardio-cerebrovascular events and death (Odds Ratio = 1.50 per index unit, 95% CI: 1.04-2.15, p=0.0302). This indicates that the predictive power of the sleep burden index is not driven by REI or extreme sleep duration alone.

DISCUSSION

In this study, the presence of multiple SWD predicted subsequent cardio-cerebrovascular events and death in stroke and TIA patients occurring 3 months to 3.2±0.3 years post-stroke and TIA. The combined sleep burden index was a better predictor for subsequent events and death than single SWD (sleep disordered breathing, insomnia, RLS severity, sleep duration) taken in isolation.

Our finding is in line with a series of recently published epidemiological studies using data from the UK Biobank to provide evidence that combined multiple sleep problems, i.e., insomnia symptoms, extreme sleep durations, snoring, late chronotype and daytime sleepiness together, are associated with an increased risk for cardiovascular diseases, including stroke and coronary heart disease separately [20]; for all-cause, cardiovascular and cancer-specific mortality [3]; as well as for incident heart failure [21]. Similarly, Wallace and colleagues [29] found that combining sleep characteristics – especially continuous sleep and circadian rhythmicity – improves predictive power of mortality in elderly men (age > 72 years).

So far, studies have focused only on individual SWD and their impact on stroke recovery [12, 30-34].

The best studied SWD is SDB. Whereas two systematic reviews (one also including a meta-analysis) published in 2014 suggested that the AHI in stroke patients increases the risk for recurrent stroke and subsequent cardio-cerebrovascular events and all-cause mortality [12, 31], studies published thereafter challenged this conclusion [4, 35-37]. The current study also does not support REI alone (considered an approximation of AHI) as predictor for subsequent cardio-cerebrovascular events including deaths of any cause. Recent studies suggest that the nocturnal hypoxic burden, might be a better predictor of an increased cardio-cerebrovascular risk than the AHI/REI in patients with SDB [38, 39].

Studies assessing the prognostic impact of insomnia and RLS in stroke survivors are scarce [4]. In one prospective study including 1062 first-time stroke patients, insomnia was associated with increased mortality within a follow-up of 6 years after the event [15]. In three other cohort studies, insomnia was associated with worse functional, mental and socio-economic outcomes [30, 33, 40]. For post-stroke RLS, Medeiros and colleagues observed a worse functional outcome for ischemic stroke survivors with RLS versus no RLS at the 1 year follow-up, although occurrence of new non-fatal cardiovascular diseases did not differ between groups [41]. This later finding is in line with our data, suggesting that RLS on its own is not a significant predictor for subsequent cardio-cerebrovascular events including death. Hence RLS and insomnia – as single SWD in stroke survivors - may predominantly affect functional stroke outcome and life quality.

All investigated SWD assessed individually (in models adjusted for age, sex and stroke severity) were positively associated with post-stroke cardio-cerebrovascular events and death, but the effect was significant only for extreme sleep duration (representing very short and long sleep duration). This latter association of extreme sleep duration with cardio-cerebrovascular risk is consistently reported in meta-analyses [16-18, 42, 43]. Although, extreme sleep duration has a significant negative impact on subsequent cardio-cerebrovascular events including death, the reduced 3-variable sleep burden index (including SDB, insomnia and RLS only) also remained a significant predictor of subsequent events in our study. Taken together, our results suggest that SDB, insomnia, RLS and extreme sleep durations in combination are best predictive for subsequent events and death in stroke and TIA survivors. Concerning the choice of the reference sleep duration for our index, we considered Kerkhof's study from the Netherlands [26] a suitable non-stroke reference due to the demographic and socio-economic similarity to our Swiss population. It is also in line with recent data from a very larger cohort (mean sleep duration 7.1 ± 1.0 h for adults aged above 18 years and 7.0 ± 1.2 h for adults aged above 41 years, respectively[44]). Importantly, by the construction of the score and the models, our findings are robust to a different choice of the reference sleep duration.

The current study does not provide any insights into the mechanisms that may link sleep fragmentation/loss secondary to multiple SWD with an increased cardio-cerebrovascular risk. However, animal and human data suggest several potential mechanisms. First, sleep loss/fragmentation in humans leads to sympathetic overactivation and detrimental (neuro)metabolic changes [45, 46]. Second, in rodent models of stroke, sleep loss/fragmentation enhances inflammatory processes and oxidative stress, reduces neuroplasticity processes and eventually impairs functional recovery [47, 48].

Whereas there is good evidence that SDB treatment in patients improves neurofunctional outcome and in some cases even long-term cardiovascular survival [49, 50], treatment studies on insomnia and RLS are sparse or non-existent. Pharmacotherapy of insomnia, especially with GABAergic agents, may even increase cardio-cerebrovascular morbidity and re-induce neurological deficits in stroke patients [51, 52]. The potential benefit of cognitive behavioural therapy for insomnia (CBT-I, the treatment of choice) in stroke patients has not been systematically studied. Only two studies with small samples of stroke patients provide evidence for the feasibility and also effectiveness of CBT-I in terms of sleep quality and daytime functioning, at least in short-term [53, 54]. The impact of RLS-treatment on mortality and subsequent events in stroke survivors has, to

our knowledge, not been studied. Hence, more interventional randomized clinical trials investigating a causal relationship between SWD and stroke recovery are necessary.

This study has two main limitations: 1) Missing data and the loss of patients with increasing time to follow-up made data imputation necessary and 2) The study population consists of mainly mild to moderately affected stroke patients since the study protocol required good cooperation and communication.. Data from the Swiss Stroke Registry of the Swiss Stroke Society show that patients with ischemic stroke and TIA present most often with rather mild symptoms. Fifty-eight percent out of 2102 patients hospitalized between February 2015 and December 2019 at the stroke unit of the Bern University Hospital presented with a NIHSS score ≤ 4 (no to mild symptoms) and 89% with a NIHSS score ≤ 15 (no to moderate symptoms) (missing NIHSS values in 9 patients). Median NIHSS score in our study cohort was 2.0. Regarding age and sex, our cohort was comparable to the Bernese ischemic stroke/TIA cohort recorded in this registry (N: 2102, age M±SD: 67 ± 14, 61% male patients, unpublished data). In this sense, our sample is rather well representative of a typical stroke population, with the exception of the most severe cases.

CONCLUSION

The presence of multiple SWD, which in this study was assessed by a newly created sleep burden index, combining the severity of SDB, insomnia, RLS as well as the extreme ends of the duration spectrum of sleep, was predictive for subsequent cardio-cerebrovascular events including death in ischemic stroke and TIA patients. The current study supports human and experimental data suggesting a detrimental effect of multiple SWD on stroke outcome and subsequent cardio-cerebrovascular events and death. Future studies should test the clinical utility of the sleep burden index as a predictor of stroke outcome.

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Disclosures

The authors declare no conflict of interest.

Data availability statement

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

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Tables

Table 1. Summary of assessments at each study visit used to calculate the Sleep Burden Index and analyse its predictive value for subsequent cardio-cerebrovascular events and death of any cause.

	INCLUSION	**PREDICTORS**		**OBSERVATIONAL PERIOD**		
Study Periods:	PATIENTS & STROKE CHARACTER-ISTICS	ASSESSMENTS OF PREDICTORS & SHORT-TERM OUTCOME		ASSESSMENT OF LONG-TERM OUTCOME & CCVE		FOLLOW-UP: CCVE
Visit	*1*	*2* ☎	*3* ☎	*4* ☎	*5* ☎	*6* ☎
Time	*Days 1-7*	*1 month*	*3 months*	*1 year*	*2 years*	*3 years*
Eligibility screening & collection of informed consent	**x**					
Collection of demographics & medical history	**x**					
Current medication/treatment	**x**	**x**	**x**	**x**	**x**	
Stroke data (including NIHSS at hospital admission and discharge)	**x**		**x** (**no** NIHSS)			
Sleep Apnea Screening	**x**					
Sleep related questionnaires and clinical interview - Sleep duration - Insomnia severity: ISI [23] - RLS criteria according to ICSD-3, if fulfilled: - IRLS [25]	**x** (pre stroke situation)	**x**	**x**	**x**	**x**	
Death, new cardio-/ cerebrovascular events	**x** (pre stroke events)	**x**	**x**	**x**	**x**	**x**

Abbreviations: CCVE: cardio-cerebrovascular events, ISI: Insomnia Severity Index, ICSD-3: International Classification System of Sleep Disorders 3rd edition, IRLS: International Restless Legs Scale, NIHSS: National Institute of Health stroke scale, RLS: Restless Legs Syndrome.

Table 2. Demographics and stroke characteristics.

	Stroke n = 381 (87%)	TIA n = 56 (13%)
Demographics		
Sex [% male]	64.3	60.7
Age [years, M±SD, range]	64.6±13.2 (20.8-85.8)	68.6±11.0 (30.8-85.4)
Stroke severity and wake-up symptoms		
NIHSS at admission –[M±SD, range]	3.9±4.7 (0-40)	0.9±1.1 (0-5)
Wake-up-symptoms/stroke % yes	20.7	16.4
Stroke localisation		
supratentorial %	76.9	32.1
infratentorial %	19.2	5.4
both %	3.1	1.8
not known %	0.8	60.7
Previous stroke/TIA:		
% yes / no / not known	20.2/ 79.5 / 0.3	35.7 / 62.5 / 1.8

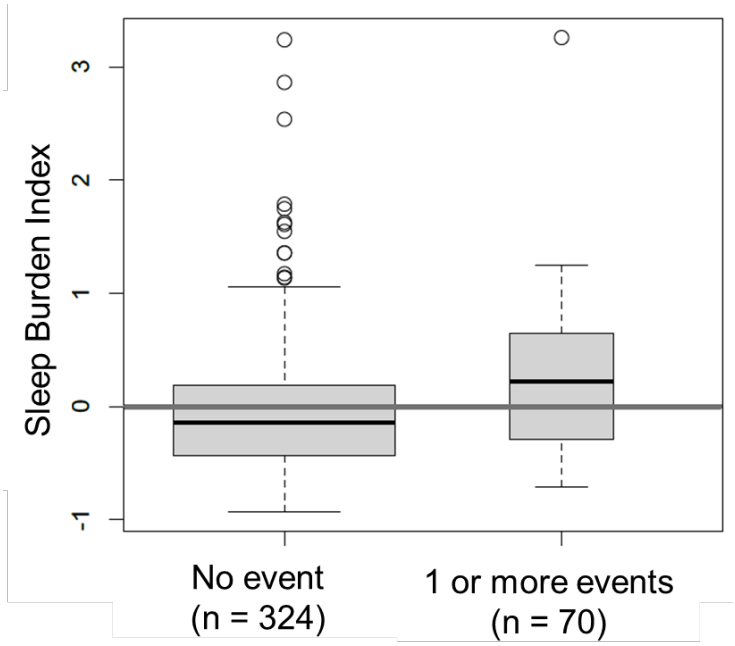
Table 3. Sleep-Wake-Disturbances up to 3 months post stroke.

	Day 1-7	Month 1	Month 3
Respiratory-Event-Index [events/h]	n = 394		
M±SD (range)	14.4±15.9 (0-119.2)		
REI <5	33.8 %		
REI ≥5-20	40.6 %		
REI >20	25.6 %		
Insomnia Severity Index (ISI)		n = 322	n = 324
M±SD (range)		6.6±5.6 (0-25)	6.1±5.2 (0-27)
≥10		28.3 %	26.2 %
Restless Legs Syndrome		n = 311	n = 345
RLS diagnostic criteria fulfilled [%]		9.3 %	6.4%
Average restless legs severity, IRLS		15.3±10.5 (1-34)	15.1±9.1 (5-36)
[M±SD, range]		(n = 22)	(n = 19)
Sleep Duration (Ref. M±SD = 6:58±1:08*)		n = 335	n = 350
[M±SD, range]		7:54±1:27 (03:30-12:30)	7:41±1:25 (02:00-12:00)
≤4:41		1.8%	2.3%
4:42-5:49		5.7%	5.4%
5:50-08:06		53.4%	57.2%
8:07-9:14		25.1%	23.7%
>=9:15		14.0%	11.4%
Sleep Burden Index		n = 394	
[M±SD, range]		0.01±0.58 (-0.93-3.26)	

*Kerkhof et al. (2017), Sleep Medicine, Reference [26]

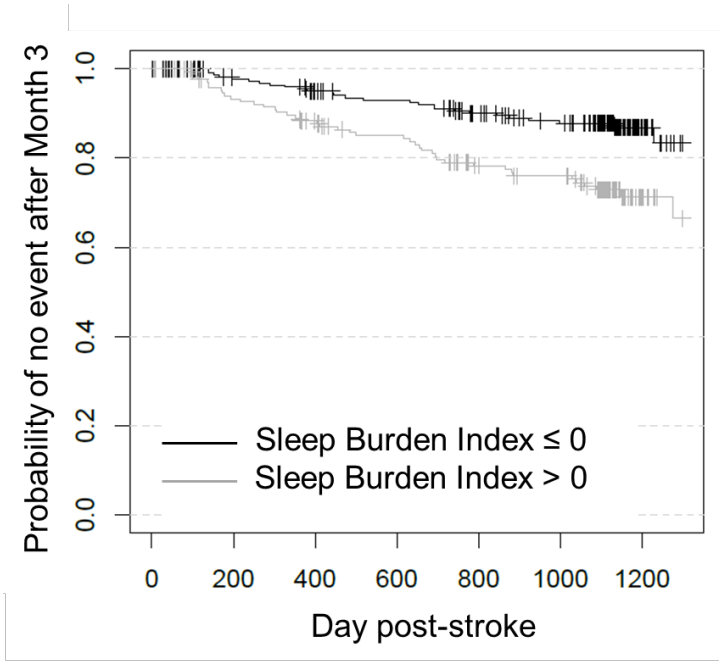
Figures

Figure 1. Distribution of sleep burden index for stroke/TIA patients without and with at least one subsequent cardio-cerebrovascular event or death.



Caption: The mean of the sleep burden index in the entire sample is 0 by construction. In this subsample of patients not prematurely withdrawn during the first 3 months (n = 394), the mean is 0.01 (median: -0.12). The width of each boxplot is proportional to the square root of the number of observations in the group.

Figure 2. Kaplan-Meyer plot for the probability of no event depending on a high or low sleep burden index in patients with acute ischemic stroke or TIA



Caption: 228 and 166 patients have a Sleep Burden Index ≤ 0 and > 0, respectively. Events occurring before day 91 post-stroke/TIA are not considered for this analysis.