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Sleep Patterns and the Risk of Acute Stroke: Results from the INTERSTROKE International Case-Control Study

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Abstract:

Background and Objectives:

Symptoms of sleep disturbance are common, and may represent important modifiable risk factors for stroke. We evaluated the association between a spectrum of sleep disturbance symptoms and risk of acute stroke in an international setting.

Methods:

INTERSTROKE is an international case-control study of patients presenting with first acute stroke and controls matched by age (+/- 5 years) and sex. Sleep symptoms in the previous month were assessed via a questionnaire. Conditional logistic regression estimated the association between sleep disturbance symptoms and acute stroke, expressed as odds ratios and 95% confidence intervals. The primary model adjusted for age, occupation, marital status and modified-Rankin Scale at baseline, with subsequent models adjusting for potential mediators (behavioural/disease risk factors).

Results:

Overall, 4,496 matched participants were included, with 1,799 of participants having experienced an ischemic stroke and 439 an intracerebral haemorrhage. Short sleep (<5hrs: 3.15, 2.09-4.76), long sleep (>9hr: 2.67, 1.89-3.78), impaired quality (1.52, 1.32-1.75), difficulty getting to sleep (1.32, 1.13-1.55) or maintaining sleep (1.33, 1.15-1.53), unplanned napping (1.59, 1.31-1.92), prolonged napping (>1hr: 1.88, 1.49-2.38), snoring (1.91, 1.62-2.24), snorting (2.64, 2.17-3.20) and breathing cessation (2.87, 2.28-2.60) were all significantly associated with increased odds of acute stroke in the primary model. A derived Obstructive Sleep Apnoea (OSA) score of 2-3 (2.67, 2.25-3.15) and cumulative sleep symptoms (>5: 5.06, 3.67-6.97) were also associated with a significantly increased odds of acute stroke, with the latter showing a graded association. Following extensive adjustment, significance was maintained for the majority of symptoms (not difficulty getting to/maintaining sleep and unplanned napping), with similar findings for stroke subtypes.

Discussion:
We found that sleep disturbance symptoms were common, and associated with a graded increased risk of stroke. These symptoms may be a marker of increased individual risk, or represent independent risk factors. Future clinical trials are warranted to determine the efficacy of sleep interventions in stroke prevention.

Introduction

Adequate sleep is essential to health.[1] Impairments in sleep represent a spectrum of disturbance, from mild deviations in duration, to impairments in different domains (quality, initiation, maintenance), associated symptoms (napping, snoring, snorting and breathing cessation) through to complex syndromes. While there is convincing evidence of an association between obstructive sleep apnoea (OSA) and stroke, the association of other sleep disorders or impairments in sleep, are less certain.[2] Given high global prevalence of symptoms, the latter association, in particular, may represent an important modifiable target for population-level interventions in stroke prevention.

Prior epidemiologic studies have evaluated the association of these sleep parameters and stroke, but the methodology and results are inconsistent.[3–12] Most studies have incompletely measured all relevant sleep domains, which precludes a thorough understanding of their independent contribution. Certain symptoms, such as nocturnal awakening and snorting, have also been interrogated infrequently, as potential independent risk factors.[12,13] A further limitation is that most studies have been confined to single countries, with underrepresentation of populations from many regions of the world.

In the INTERSTROKE study (a large international case-control study of risk factors for stroke) we evaluated the association of different symptoms of sleep impairment, individually and cumulatively, with risk of first acute stroke.

Methods and Materials

Population:

INTERSTROKE is a large international case-control study of patients presenting with first stroke and matched controls. The study design has been described in detail elsewhere.[14] In brief, cases were required to meet the World Health Organisation clinical definition for acute stroke, were within 72 hours of current symptom onset or 'last seen without deficit', and had a CT or MRI available or planned within 1 week of presentation. Stroke was further defined as either ischaemic stroke or intracranial haemorrhage (ICH), by hour of onset, and whether symptoms occurred on waking (*Supplemental Section 1*). Patients with severe stroke or aphasia (unable to communicate effectively) were included if a valid proxy

respondent was available. At least one control, without a previous stroke history, was recruited for each case, from either a community or hospital/outpatient setting. Controls were matched for sex and age (+/- 5 years), in addition to ethnicity in countries where there was a significant representation from multiple ethnic groups. A standardized questionnaire was administered by trained research staff, which collected information about known and potential risk factors. Non-fasting blood samples were collected from participants and clinical measurements (e.g. blood pressure, weight) were recorded at the time of interview and/or from the participants notes. A supplementary questionnaire addressing sleep practices in the previous month was introduced in July of 2012, with implementation in consecutive patients once adopted in centres. Matched cases/controls who undertook this questionnaire were the subjects of the primary analysis in this study.

Sleep Questionnaire:

Specific questions asked are detailed in the supplementary appendix (*Supplemental eTable 1*). In summary, participants were asked about sleep behaviours in the previous month (the month before stroke in cases). Areas addressed included: hours of nocturnal sleep duration (given in whole numbers, to the closest number of hours), sleep quality, sleep onset latency (SOL), nocturnal awakening, sleeping during the day (both duration and whether it was planned), snoring, snorting or gasping and breathing cessation or choking during sleep. Sleep duration categories were established for individual hour durations, truncated at <5 and >9. The reference level was set at 7 hours, based upon univariate exploration of data and findings from previous research.[15,16] The categorisation of other individual sleep symptoms are detailed in the supplementary appendix (*Supplemental eTable 1*). For symptoms of snoring, snorting and breathing cessation during sleep, we derived an OSA score (range 0-3) with lower scores signifying a lower probability of sleep apnoea (*Supplemental eTable 2*). Post-hoc, we also derived a summary count variable, based on cumulative presence of sleep impairment symptoms. Termed Sleep Disturbance Symptom Burden, it included all sleep variables that were individually associated with stroke risk on univariate analysis (*Supplemental eTable 2*). Sleep Disturbance Symptom Burden ranged from 0-9, with higher scores relating to greater numbers of sleep impairment symptoms.

Covariates:

Further covariates of interest were determined a priori in the statistical analysis plan. Both potential confounders and potential partial mediators were selected, to be included in additive models. Occupation was categorised as “house wife”, “farmer”, ”labourer”, “business”, “professional” and “other”. Marital status was defined as either “currently

married or living with partner" or "separated/not currently married". Modified-Rankin Score (m-RS) at baseline was categorised as "0", "1" or ">1". Alcohol consumption was categorised as "never/former", "low/moderate" and "high intake/binge", whereby a weekly intake of 1-14 drinks for women and 1-21 drinks for men was determined low/moderate, and >14 drinks for women or >21 drinks for men was determined high intake/binge.[17] Leisure physical activity was categorised as "mainly active" and "mainly inactive", with mainly active defined as moderate or strenuous leisure activity for ≥ 4 hours per week." Diet quality was defined by the modified Alternative Healthy Eating Index (AHEI).[18] Waist-to-hip ratio (WHR) and body mass index (BMI) were obtained via anthropometric measurement. Depressive symptoms were determined based on the response to the question "During the last 12 months, was there ever a time when you felt sad, blue, or depressed for 2 weeks or more in a row?". Global stress was categorised as "none or some periods of stress" and "several periods or permanent stress". Hypertension was present if the participant had a past medical history of hypertension or adjusted blood pressure (BP) of >140/90mmHg at admission. Diabetes was defined as a history of diabetes or a HbA1c ≥ 6.5%, and history of both OSA diagnosis and atrial fibrillation/ flutter were obtained.

Statistical Analysis:

Demographic characteristics were described by means and standard deviations or proportions, as appropriate. Distributions were analysed via Kruskal-Wallis rank sum test, the Pearson's Chi-squared test and the Fischer's exact test, as appropriate.

We used univariate and multivariable conditional logistic regression to determine the association of individual sleep domains with odds of acute stroke. For each sleep domain, we selected reference categories based upon which category was associated with lowest odds of stroke on univariate analyses. Multivariable adjustment was conducted with additive models. Model 1 was univariate. Model 2 (Primary Model) adjusted for age, marital status, occupation and m-RS at baseline. This was selected as the primary model, as variables in subsequent models might include factors along the causal pathway. Model 3 further adjusted for behavioural risk factors that might mediate risk (alcohol consumption, smoking history, leisure physical activity, AHEI score, WTHR, BMI (kg/m2), depressive symptoms and global stress) and Model 4 further adjusted for disease risk factors that might mediate risk (hypertension, diabetes, history of atrial fibrillation/flutter and diagnosis of OSA). Missingness of individuals models was assessed, and missing data was not imputed. These models were also completed for the association of sleep duration, OSA score and Sleep Disturbance Symptom Burden, with ICH and ischaemic stroke. Excluding controls,

case-case analysis was also undertaken to determine whether these sleep domains had a stronger magnitude of association with ICH, compared to ischaemic stroke.

We used the Wald likelihood ratio test to test for interactions between sleep duration and other sleep parameters and sleep duration and other predefined demographic variables (age, sex, region, ethnicity). If a significant interaction was found, subgroup/stratified analyses were undertaken for large groups (≥1,000 available in unmatched cases/controls). Subgroup and case-case analysis were also undertaken for sleep domains (duration, OSA score and Sleep Disturbance Symptom Burden) and hour of onset/wake-up variables. This was to observe whether the effect of sleep disturbance was influenced by the stroke onset's proximity to sleep.

Sensitivity analysis included subgroup analysis by source of control (i.e. hospital or community) and the exclusion of cases with proxy respondents. Post hoc, additional adjustment for household income was also undertaken. Statistical significance was defined as a two tailed p value of ≤0.05. All statistical analyses were undertaken using R statistical software version 1.3.959.[19]

Standard Protocol Approvals, Registrations, and Patient Consents:
The INTERSTROKE study was approved by the ethics committees in all participating centres or countries, and participants (or proxy) provided written informed consent.

Data Availability Statement:
Information on the design and rationale of INTERSTROKE has been published previously.[14] Individual participant data, or other documents, will not be made available at this time.

Results

Demographic Characteristics:
Overall there were 4,496 matched participants, including 1,799 ischemic stroke cases and 439 ICH cases (16.7% of the INTERSTROKE population). The number that answered questions relating to sleep domains varied minimally (*Supplemental eTable 3*). Distribution of demographic, risk factor and sleep variables in matched cases and controls are described in *Table 1*.

Association of Sleep Duration with Acute Stroke:
In our primary multivariable model, short nocturnal sleep duration (<5 hours: OR: 3.15, 95%CI: 2.09-4.76) and long nocturnal sleep duration (>9 hours: OR: 2.67, 95%CI: 1.89-3.78) were associated with an increased odds of all stroke, compared to 7 hours (reference). A

significant U-shaped association persisted in all multivariable models, with similar associations found in relation to both ischaemic stroke (<5 hours: OR: 2.64, 95%CI: 1.69-4.12; >9 hours: OR: 2.68, 95%CI: 1.81-3.98) and ICH (<5 hours OR: 9.12, 95%CI: 2.57-32.34; >9 hours: OR: 2.60, 95%CI: 1.23- 5.52), (*Figure 1, Table 2*). Odds of ICH and ischemic stroke did not differ in case-case analysis (p>0.4; *Supplemental eTable 4*).

Napping:
Long duration (>1 hour) and unplanned napping were associated with significantly increased odds of all stroke in the primary model, while short duration (≤1 hour) and planned napping were not associated with an increased odds of all stroke. On further adjustment for potential mediators, napping of long duration remained significantly associated with stroke (*Supplemental eFigure 1, eFigure 2*). A combined analysis of nap duration and planning are reported in *Figure 2*, with highest OR associated with long (>1 hour) unplanned napping (OR: 2.46, 95%CI: 1.69-3.57), and lowest OR associated with short (≤1 hour) planned napping (OR: 0.91, 95%CI: 0.76-1.08), in the primary model.

Sleep Quality, Sleep Onset Latency and Nocturnal Awakening:
In our primary model, self-reported poor or fair sleep quality (OR: 1.52, 95%CI: 1.32-1.75), SOL (OR: 1.32, 95%CI: 1.13-1.55), and frequent waking (OR: 1.33, 95%CI: 1.13-1.53) were associated with an increased odds of acute stroke. On further adjustment for potential mediators, sleep quality alone remained significantly associated with increased odds of stroke (*Figure 2*).

Symptoms of OSA:
Self-reported snoring (OR: 1.91, 95%CI: 1.62-2.24), snorting (OR: 2.64, 95%CI: 2.17-3.20), and breathing cessation (OR: 2.87, 95%CI: 2.28-2.60) were associated with statistically significant increased odds of all stroke in the primary model, maintaining significance with all further adjustment. We observed a similar magnitude of association for responding 'don't know' as responding positively for these symptoms (*Figure 3*). An OSA score of 2-3 was associated with a significantly increased odds of all stroke (OR: 2.67, 95%CI: 2.25-3.15), ICH (OR: 4.07, 95%CI: 2.73-6.08) and Ischemic stroke (OR: 2.39, 95%CI: 1.98-2.89), in the primary model, maintaining significance with subsequent adjustment. Odds of ICH vs ischemic stroke did not differ significantly in case-case analysis (p=0.23).

Sleep Disturbance Symptom Burden:

In the analysis of Sleep Disturbance Symptom Burden, an increasing number of symptoms were associated with a graded increase in stroke risk (2-3: OR: 1.63, 95%CI: 1.36-1.96; 4-5: OR: 3.08, 95%CI: 2.49-3.80; >5: OR: 5.38, 95%CI: 4.03-7.18), with reference 0-1, in the primary model (*Figure 4, Supplemental eTable 5*). Findings were also consistent for ischemic stroke (>5: OR: 5.06, 95%CI: 3.67-6.97) and ICH (>5: OR: 8.36, 95%CI: 4.05-17.26), (*Supplemental eTable 5, eFigure3*). Odds of ICH and ischemic stroke did not differ in case-case analysis (p=0.73). Results for Sleep Disturbance Symptom Burden with OSA symptoms not included in score calculation are outlined in the supplementary appendix (*Supplemental eTable 6*).

Hour of Stroke Onset and Wake-up Stroke:

When cases/matched controls were divided into hour-of-onset categories and wake-up status categories (*Supplemental eFigure 4*), individual estimates were highest in the night-time subgroup and the wake-up subgroup for both short sleep duration and Sleep Disturbance Symptom Burden of >5 (*Supplemental eTables 7-10*). Differences were less pronounced for long sleep duration, and estimates in the OSA score of 2-3 were higher in the morning and wake-up subgroups (*Supplemental eTables 7-8, eTables 11-12)*. Confidence intervals crossed, however, and differences were not statistically significant in case-case analysis, other than for short sleep duration, which was associated with an increased odds of night time vs morning stroke (p=0.04; *Supplemental eTable 13).*

Interaction of Sleep Symptoms:

We observed a significant interaction between sleep duration and snoring (p=0.002), where estimates in the primary model were highest in snorers with short sleep duration (OR: 4.04, 95%CI: 3.12-5.25) and lowest in non-snorers with long sleep duration (OR: 1.39, 95%CI: 1.13-1.69), (*Supplemental eTable 14*). There was no significant interaction found between sleep duration and other individual sleep symptoms *(Supplemental eTable 15).*

Interaction in Demographic Variables:

An interaction was found between sleep duration and both ethnicity (p<0.001) and region (p<0.001). In the primary model, the association of short sleep duration with stroke was highest for South Asian ethnicity and South Asia, and non-significant for Chinese ethnicity and China (*Supplemental eTable 16-17, eFigure 5*). The association between long sleep duration and stroke remained significant in all ethnicity and region subgroups examined

(*Supplemental eTable 16-17, Figure 5*). There was no significant interaction between sleep duration and age or sex *(Supplemental eTable 15).*

Sensitivity Analysis:

The source of information for cases (i.e. patient or proxy) did not materially alter findings for the sleep domains (*Supplemental eTable 18*). Magnitude of ORs were generally higher for community vs hospital controls, but directions of estimates were consistent by source of control, in the primary model (*Supplemental e Table 19-20*). Additional adjustment for household income did not materially change results (*Supplemental eTable 21*).

Discussion:

In this large international case-control study, we found a significant association between sleep impairments and risk of acute stroke. The odds of acute stroke were increased with short and long sleep duration, poor sleep quality, symptoms of OSA (snoring, snorting and breathing cessation) and prolonged napping, following extensive adjustment. The magnitude of association was additive, with a graded increase in odds of acute stroke, for cumulative increase in sleep symptoms, with consistent findings for ischemic stroke and ICH. Impairments in sleep domains associated with increased risk of stroke were common, and may represent important, modifiable targets for stroke prevention interventions.

Associations between acute stroke and both short and long sleep duration have been reported in previous observational research.[20] In our study, there was a higher magnitude of association for short sleep duration, compared to long duration, on univariate analysis. However, following adjustment for co-existing risk factors, there was more marked attrition of the odds ratio for short sleep duration. This suggests that confounders and mediators of these associations differ, and that long sleep duration is more likely to have an independent association with acute stroke. In addition, the association for long sleep duration was found more consistently in different ethnicities and regions. This is complimentary to previous research, where associations have been more consistent for long sleep duration.[9–11] The mechanisms underlying this association could be influenced by blood pressure surges associated with sleep architecture changes, for example, or relate to lack of physiologic challenge.[21–23] The relationship, however, may also be subject to residual, universal confounding, as long sleep duration may represent an epiphenomenon of co-morbidity, older age, an otherwise sedentary lifestyle and sedative use.[24–30] A large proportion of participants in our study reported a nocturnal sleep duration within the range associated with stroke (<6 hours or >7 hours), making it an important potential risk factor for developing and evaluating public interventional studies.

Daytime sleeping (napping) has also been associated with increased cardiovascular disease risk, particularly when prolonged, a finding that has challenged whether the common practice of siesta is healthy, with some conflicting results.[12,24,27,30–33] The Prospective Urban Rural Epidemiology (PURE) study found that long duration napping was significantly associated with increased risk of major cardiovascular events, in those who slept longer than 6 hours at night.[34] While, in contrast, we found no significant interaction with sleep duration, our findings, in another international setting, also suggest that the association with daytime napping is contextual. Long duration and unplanned napping are potential risk factor for stroke, but short duration, planned napping (e.g. siesta) was not associated with an increased risk, with the point-estimate directionally suggestive of reduced odds. While our findings merit reproduction, they may help inform patient advice and management, where a prolonged nap may be harmful or representative of an underlying condition that requires further work up, and a brief, planned nap is less likely to increase the risk of stroke.

Obstructive sleep apnoea is an established risk factor for acute ischaemic stroke.[35] Our findings suggest that individual symptoms, which may represent OSA, are independently associated with stroke. This is complimentary to previous research, where snoring has been studied more frequently than snorting and breathing cessation.[4,8,12,36] Patients with these self-reported symptoms of OSA may be at risk of stroke, independent of OSA severity and treatment, as has been suggested by a recent post-hoc analysis of the SAVE trial.[36] Symptoms were common prior to stroke, in our study, where 59% of cases reported snoring, with 25% and 19% reporting snorting and breathing cessation, respectively. In addition, participants who were unsure about OSA related symptoms had a similar increased odds of stroke as participants who endorsed these symptoms, suggesting a potential lack of awareness of OSA symptoms, rather than absence. This has important implications for questionnaire based OSA screening in clinical practice, and for conducting and interpreting clinical research in this context. While randomised controlled trials looking at positive airway pressure (PAP) in OSA have not reproduced evidence of lower cardiovascular events found in observational studies, there does appear to be a potential risk reduction when adherence is high, and when PAP is used >4 hours per night.[37–39] Given the frequency of symptoms in our study, and their relationship with stroke, exploring interventions that improve PAP adherence may be of benefit in primary stroke prevention. Identifying subgroups that are more likely to benefit, in addition to exploring alternative management strategies in patients with self-reported symptoms, are also important areas for future research.

Sleep quality, a self-reported subjective measure, was fair or poor in 46% of patients with acute stroke, in the preceding month. Further individual symptoms of frequent nocturnal awakening and SOL were also common, self-reported in 42% and 32% of cases, respectively. In our primary model, each of these sleep impairments were associated with increased odds of acute stroke. However, after full adjustment, the latter two exposures were no longer significantly associated, similar to previous research. These results imply that the association was confounded or mediated by cerebrovascular risk factors. The challenge in interpretation is to determine which of these adjustment variables are confounders, and which reside along a potential causal pathway. For example, increased alcohol intake may cause disruptions in sleep quality, but impairments in sleep quality may result in increased use of alcohol, as a sedative.[42] Our primary model, which did not include cerebrovascular risk factors, is expected to overestimate the independent association of sleep impairment and stroke risk, while the fully adjusted model likely underestimates the association, given that mediator variables are included. While numerous observational studies have reported bi-directional associations between sleep impairment and cerebrovascular risk factors, interventional clinical trials are required to determine whether improvement in sleep quality results in prospective changes in these factors and subsequent disease risk.[43] Few trials have been conducted to determine the effect of behavioural sleep interventions on cerebrovascular risk factors to date, with overall results being inconclusive.[44] The SLEPT trial, a Phase IIb trial reported modest improvements in sleep quality with digital cognitive behavioural therapy (dCBT-I), but did not effect change in blood pressure.[45] The results of the recent DISCO trial, however, where dCBT-I was associated with improvement in cognitive complaints, shows potential promise for this type of intervention in the cerebrovascular domain.[46]

The graded association between the accumulation of these outlined sleep disturbance symptoms and stroke also has important implications from a public health and interventional trial perspective, particularly given the magnitude of estimates. To our knowledge, this is the most extensive study of sleep disturbance in this context, confirming previous findings in a limited amount of previous studies.[4,5,41] Even if the relationship is not causal, those with multiple sleep disturbance symptoms should be thought of as at high risk of stroke, and important targets for primary prevention studies involving both traditional risk factor management and interventions for sleep disturbance.

Limitations:

Our study has a few potential limitations. Firstly, sleep symptoms were ascertained via subjective reporting, and validated tools/scores were not used to examine sleep

quality/OSA symptoms and their association with stroke. Our assessments of sleep practices were similar to previous research in this area, however, and undertaking a prolonged sleep questionnaire would not have been possible in the context of this multifaceted study.[24] Secondly, as incident stroke may result in sleep disturbance, there is a risk of misclassification and recall bias.[47] Uncertainty surrounding OSA symptoms may be subject to similar biases, with stroke patients potentially more likely to answer "don't know". Efforts taken to reduce the risk of these biases included recruiting cases within 72 hours of hospital admission, and asking about sleep over a short time frame. Prospective cohort studies in this area have generally asked about sleep practices over a longer time frame. As sleep can change over time, our shorter time frame may have resulted in more accurate sleep symptom reporting.[24,48] In addition, our results may be partially due to trigger effects of sleep disturbance on stroke, given the shorter time frame. Findings in relation to risk of night time and wake-up stroke may also be suggestive of this. Thirdly, there may be a risk of healthy volunteer bias among community controls. In an effort to combat this, however, some hospital/outpatient controls were recruited. Given the findings of our sensitivity analysis, this inclusion likely biased our findings towards the null, underestimating the odds of stroke associated with sleep symptoms in a healthy community setting, with results more likely reflective of the true global population risk. Fourthly, subgroup analyses were limited by participant numbers, and associations between sleep duration and stroke in different regions/ethnicities, for example, could not be fully assessed. Finally, despite extensive adjustment, residual cofounding cannot be excluded. We were also unable to adjust for shift work or sedative use, and levels of diagnosed OSA were low.

Conclusions:

In conclusion, our results suggest that individual and cumulative symptoms of sleep disturbance may be important modifiable risk factors for stroke, and/or their presence identifies individuals at increased risk of stroke. Our findings also suggest a complex relationship of sleep impairment, intermediate cerebrovascular risk factors and stroke risk. Given that individual sleep disturbance symptoms were common, and associated with increased odds of stroke, interventional studies in patients with high sleep disturbance burden, and in those with individual sleep symptoms, should be considered a priority research target, in the global effort to reduce stroke incidence.

WNL-2023-000134_sup ---http://links.lww.com/WNL/C721
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Tables:

Table 1: Demographic characteristics in matched cases and controls*

Characteristic	Case N = 2243 (50%)[1]	Control N = 2253 (50%)[1]	p-value[2]
Age, yrs	63 (14)	62 (14)	<0.001
Sex			>0.99
Female	931 (42%)	935 (42%)	
Male	1,312 (58%)	1,318 (58%)	
Region			>0.99
Western Europe/North America/Australasia	566 (25%)	567 (25%)	
Eastern/Central Europe/Middle East	370 (16%)	370 (16%)	
Africa	177 (7.9%)	183 (8.1%)	
South Asia	511 (23%)	514 (23%)	
China	408 (18%)	408 (18%)	
South East Asia	81 (3.6%)	81 (3.6%)	
South America	130 (5.8%)	130 (5.8%)	
Ethnicity			>0.99
European	828 (37%)	832 (37%)	
Chinese	407 (18%)	409 (18%)	
South Asian	583 (26%)	584 (26%)	
Other Asian	65 (2.9%)	67 (3.0%)	
Arab	74 (3.3%)	73 (3.2%)	
Latin American	125 (5.6%)	126 (5.6%)	
Black African	124 (5.5%)	123 (5.5%)	
Other African	1 (<0.1%)	0 (0%)	
Other	36 (1.6%)	39 (1.7%)	
m-RS at baseline			<0.001
0	1,747 (78%)	1,565 (70%)	
1	360 (16%)	495 (22%)	
>1	135 (6.0%)	190 (8.4%)	
Occupation			0.007
Housewife	374 (17%)	361 (16%)	
Farmer	225 (10%)	247 (11%)	
Business	136 (6.1%)	171 (7.6%)	
Professional	474 (21%)	531 (24%)	
Labourer	793 (35%)	753 (33%)	
Other	240 (11%)	187 (8.3%)	
Marital Status			<0.001
Currently Married or Living with Partner	1,636 (73%)	1,810 (80%)	
Separated/Not Currently Married	607 (27%)	441 (20%)	
Alcohol History and Frequency			<0.001
Never/former	1,551 (69%)	1,606 (71%)	

Characteristic	Case N = 2243 (50%)[1]	Control N = 2253 (50%)[1]	p-value[2]
Low/moderate	579 (26%)	593 (26%)	
High intake/binge	110 (4.9%)	52 (2.3%)	
Smoking History			<0.001
Never or Former Smoker	1,601 (71%)	1,759 (78%)	
Current Smoker	640 (29%)	494 (22%)	
Leisure Physical Activity			<0.001
Mainly Inactive	1,850 (83%)	1,641 (73%)	
Mainly Active	392 (17%)	611 (27%)	
Total AHEI Score	22.5 (6.6)	23.4 (7.2)	<0.001
Waist-to-Hip Ratio	0.94 (0.09)	0.91 (0.08)	<0.001
Body Mass Index (kg/m2)	26.4 (5.0)	25.8 (4.8)	<0.001
Depression			<0.001
Not Sad in Last 2 Weeks	1,671 (75%)	1,820 (81%)	
Sad in Last 2 Weeks	567 (25%)	430 (19%)	
Global Stress			<0.001
None or Some Periods	1,637 (73%)	1,899 (84%)	
Several Periods or Permanent	603 (27%)	351 (16%)	
History of Hypertension or Adjusted BP>140/90 at admission	1,706 (76%)	1,159 (51%)	<0.001
History of Diabetes or HbA1c>=6.5%	624 (28%)	405 (18%)	<0.001
History of Atrial Fibrillation/Flutter	318 (14%)	68 (3.0%)	<0.001
Diagnosis of Obstructive Sleep Apnoea	54 (2.4%)	47 (2.1%)	0.48
Subjective Sleep Duration in Hours			<0.001
<5	162 (7.2%)	43 (1.9%)	
5	220 (9.8%)	98 (4.3%)	
6	358 (16%)	526 (23%)	
7	486 (22%)	683 (30%)	
8	674 (30%)	674 (30%)	
9	188 (8.4%)	145 (6.4%)	
>9	151 (6.7%)	84 (3.7%)	
Self-Rated Overall Sleep Quality			<0.001
Very Good	232 (10%)	292 (13%)	
Good	966 (43%)	1,194 (53%)	
Fair	713 (32%)	623 (28%)	
Bad	238 (11%)	114 (5.1%)	
Very Bad	88 (3.9%)	26 (1.2%)	
Frequency of Nocturnal Awakening			<0.001
Waking once or less	1,289 (58%)	1,534 (68%)	
Waking more than once	948 (42%)	717 (32%)	

Characteristic	Case N = 2243 (50%)[1]	Control N = 2253 (50%)[1]	p-value[2]
Difficulty Falling Asleep	707 (32%)	535 (24%)	<0.001
Napping (duration)			<0.001
No nap	1,151 (51%)	1,230 (55%)	
1 hour nap	700 (31%)	791 (35%)	
>1 hour nap	389 (17%)	229 (10%)	
Napping, planned or unplanned			<0.001
No Nap	1,152 (51%)	1,226 (54%)	
Unplanned Nap	405 (18%)	296 (13%)	
Planned Nap	686 (31%)	731 (32%)	
Snoring			<0.001
Never	726 (32%)	1,013 (45%)	
Don't know	182 (8.1%)	115 (5.1%)	
Does	1,331 (59%)	1,125 (50%)	
Snorting or gasping			<0.001
Never	1,397 (62%)	1,839 (82%)	
Don't know	276 (12%)	139 (6.2%)	
Does	566 (25%)	275 (12%)	
Breathing Cessation or choking			<0.001
Never	1,531 (68%)	1,918 (85%)	
Don't know	286 (13%)	132 (5.9%)	
Does	422 (19%)	203 (9.0%)	

* Case-id matched participants answering the supplementary questionnaire

[1]Mean (SD); n (%)

[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 2: The association of sleep duration with all stroke, ischaemic stroke and ICH

The Association of Nocturnal Sleep Duration (in hours) and All Stroke; Odds Ratio (95% CI)							
Model	<5	5	6	7	8	9	>9
Model 1[1]	5.03 (3.47-7.30)	2.86 (2.19-3.75)	0.98 (0.81-1.18)	1.00	1.37 (1.15-1.62)	1.82 (1.40-2.37)	2.73 (1.99-3.76)
Model 2[2]	3.15 (2.09-4.76)	2.35 (1.74-3.17)	1.03 (0.84-1.27)	1.00	1.35 (1.12-1.64)	1.59 (1.20-2.11)	2.67 (1.89-3.78)
Model 3[3]	2.22 (1.37-3.59)	1.96 (1.39-2.75)	1.00 (0.79-1.27)	1.00	1.25 (1.02-1.54)	1.52 (1.12-2.06)	2.27 (1.58-3.27)
Model 4[4]	1.99 (1.17-3.38)	2.06 (1.42-2.99)	0.93 (0.72-1.20)	1.00	1.24 (0.99-1.55)	1.41 (1.01-1.98)	2.14 (1.46-3.15)
The Association of Nocturnal Sleep Duration (in hours) and Ischemic Stroke; Odds Ratio (95% CI)							
Model	<5	5	6	7	8	9	>9
Model 1[1]	4.40 (2.96-6.54)	2.65 (1.97-3.57)	0.95 (0.77-1.17)	1.00	1.38 (1.14-1.67)	1.73 (1.29-2.33)	2.57 (1.80-3.68)
Model 2[2]	2.64 (1.69-4.12)	2.21 (1.58-3.08)	0.95 (0.75-1.20)	1.00	1.37 (1.11-1.69)	1.44 (1.04-1.99)	2.68 (1.81-3.98)
Model 3[3]	2.05 (1.23-3.41)	1.99 (1.36-2.91)	0.92 (0.71-1.20)	1.00	1.30 (1.03-1.64)	1.37 (0.97-1.94)	2.17 (1.43-3.30)
Model 4[4]	1.72 (0.97-3.02)	1.91 (1.27-2.89)	0.82 (0.61-1.09)	1.00	1.27 (0.98-1.64)	1.26 (0.85-1.86)	2.04 (1.30-3.18)
The Association of Nocturnal Sleep Duration (in hours) and ICH; Odds Ratio (95% CI)							
Model	<5	5	6	7	8	9	>9
Model 1[1]	11.61 (3.50-38.55)	3.65 (1.92- 6.92)	1.07 (0.71- 1.62)	1.00	1.25 (0.84- 1.85)	2.16 (1.22- 3.82)	3.15 (1.56- 6.39)
Model 2[2]	9.12 (2.57-32.34)	2.84 (1.41- 5.74)	1.35 (0.85- 2.15)	1.00	1.17 (0.77- 1.79)	2.13 (1.17- 3.88)	2.60 (1.23- 5.52)
Model 3[3]	5.01 (0.86-29.34)	1.48 (0.63- 3.49)	1.60 (0.89- 2.87)	1.00	0.98 (0.60- 1.61)	2.15 (1.10- 4.21)	2.79 (1.23- 6.33)
Model 4[4]	8.23 (0.95-71.63)	2.22 (0.83- 5.94)	1.76 (0.91- 3.39)	1.00	0.95 (0.55- 1.65)	1.99 (0.94- 4.21)	2.71 (1.10- 6.65)

[1]Univariate (conditional); [2]Adjusted for occupation, age, marital status and pre-admission m-RS (conditional); [3]Adjusted for occupation, age, marital status, pre-admission m-RS, alcohol consumption, smoking history , leisure physical activity, total AHEI score, waist-to-hip ratio, body mass index (kg/m2), depressive symptoms and global stress (conditional); [4]Adjusted for occupation, age, marital status, m-RS, alcohol consumption, smoking history, leisure physical activity, total AHEI score, waist-to-hip ratio, body mass index (kg/m2), depressive symptoms, global stress, history of hypertension or adjusted bp>140/90 at admission, history of di abetes or hba1c>=6.5%, history of atrial fibrillation/flutter and diagnosis of OSA (conditional)

Figure Headings and Captions:

Figure 1: Odds of all stroke, ICH and ischaemic stroke*

*Conditional logistic regression adjusted for age, occupation, marital status and m-RS at baseline (primary model); OR = Odds ratio; OR presented on a log scale

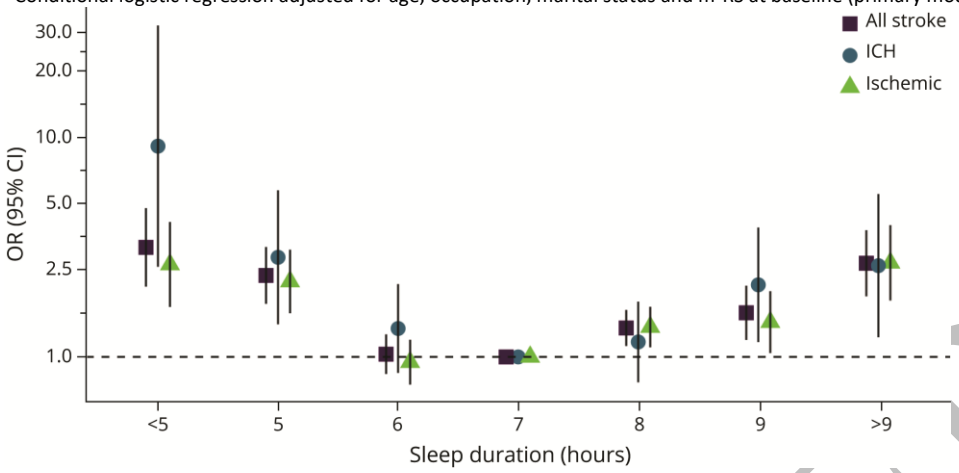


Figure 2: Odds of all stroke for poor or fair sleep quality, sleep onset latency, waking more than once, and napping

Figure 2: Odds of all stroke for poor or fair sleep quality, sleep onset latency, waking more than once, napping status. Adjustment models are as follows: Model 1: Univariate (conditional); Model 2: Adjusted for occupation, age, marital status and m-RS at baseline (conditional); Model 3: Adjusted for occupation, age, marital status, m-RS at baseline, alcohol consumption, smoking history, leisure physical activity, total AHEI score, waist-to-hip ratio, body mass index (kg/m2), depressive symptoms and global stress (conditional); Model 4:Adjusted for occupation, age, marital status, m-RS at baseline, alcohol consumption, smoking history, leisure physical activity, total AHEI score, waist-to-hip ratio, body mass index (kg/m2), depressive symptoms, global stress, history of hypertension or adjusted bp>140/90 at admission, history of diabetes or hba1c>=6.5%, history of atrial fibrillation/flutter and diagnosis of OSA (conditional)

*For all panels (a-d) the reference level for each individual sleep parameter is displayed in brackets.

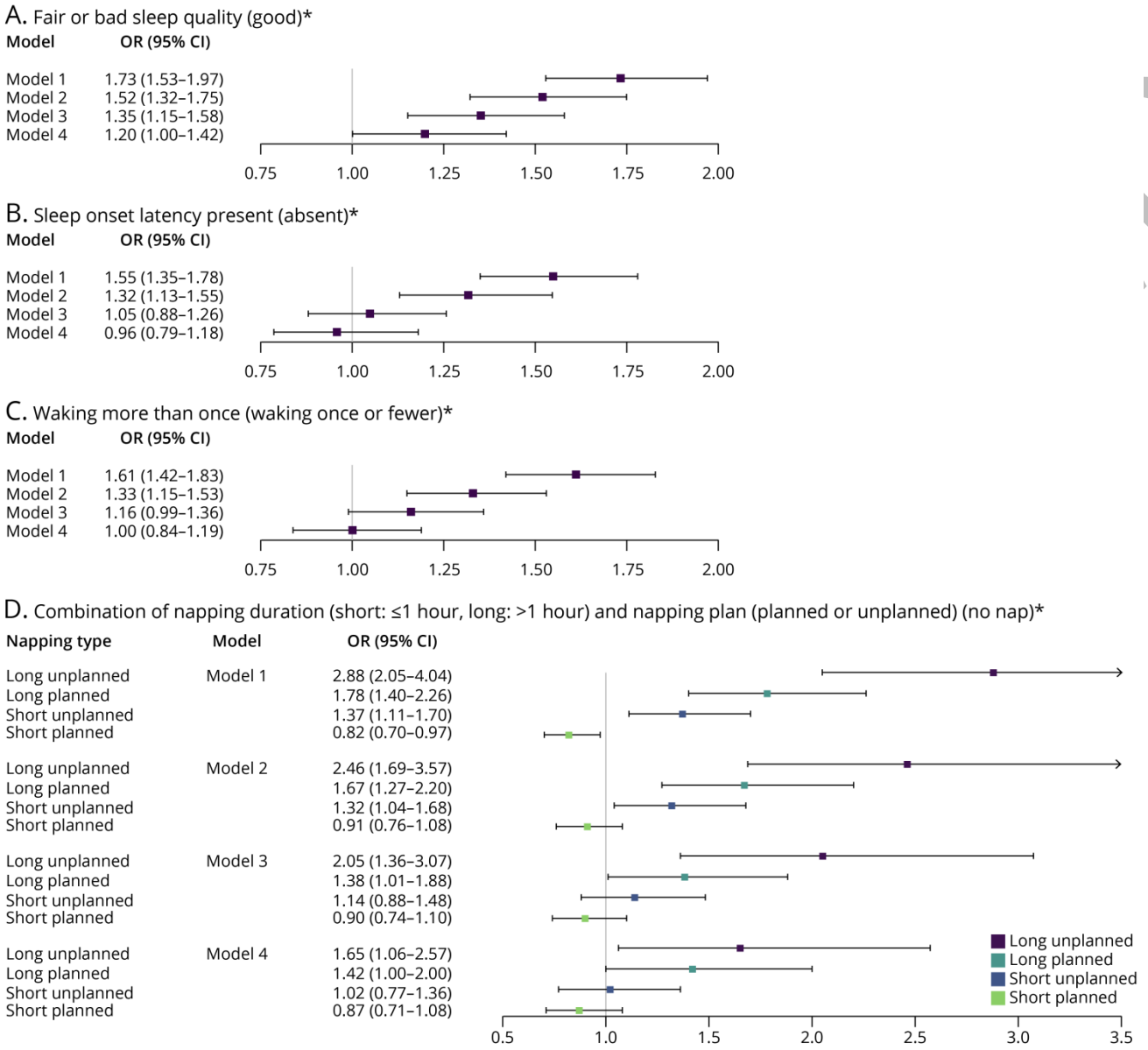


Figure 3: Odds of all stroke for snoring, snorting, breathing cessation and OSA score

Figure 3: Panels a-c demonstrate odds of all stroke for symptoms of, or uncertainty surrounding, snoring, snorting or gasping and breathing cessation respectively. Panel d demonstrates the odds of all stroke, ischaemic stroke and ICH with a Potential OSA Score of 2-3. Adjustment models are as follows: Model 1: Univariate (conditional); Model 2: Adjusted for occupation, age, marital status and m-RS at baseline (conditional); Model 3: Adjusted for occupation, age, marital status, m-RS at baseline, alcohol consumption, smoking history, leisure physical activity, total AHEI score, waist-to-hip ratio, body mass index (kg/m2), depressive symptoms and global stress (conditional); Model 4:Adjusted for occupation, age, marital status, m-RS at baseline, alcohol consumption, smoking history, leisure physical activity, total AHEI score, waist-to-hip ratio, body mass index (kg/m2), depressive symptoms, global stress, history of hypertension or adjusted bp>140/90 at admission, history of diabetes or hba1c>=6.5%, history of atrial fibrillation/flutter and diagnosis of OSA (conditional)

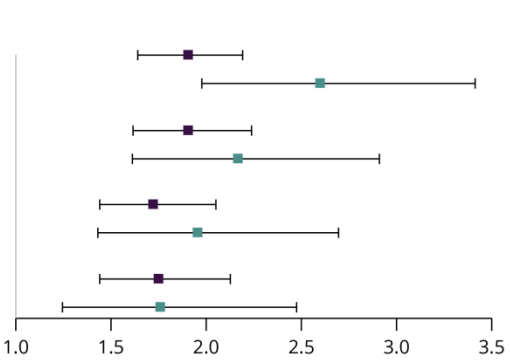
*For all panels (a-d) the reference level for each individual sleep parameter is displayed in brackets

ICH=Intracerebral Haemorrhage

OSA=Obstructive sleep apnoea

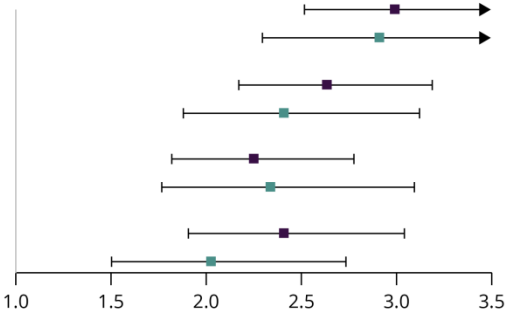
A. Snoring — yes/don't know (no)*

Symptom	Model	OR (95% CI)
Yes	Model 1	1.90 (1.64–2.19)
Don't know		2.60 (1.98–3.41)
Yes	Model 2	1.91 (1.62–2.24)
Don't know		2.17 (1.61–2.91)
Yes	Model 3	1.72 (1.44–2.05)
Don't know		1.96 (1.43–2.69)
Yes	Model 4	1.75 (1.44–2.12)
Don't know		1.76 (1.25–2.47)



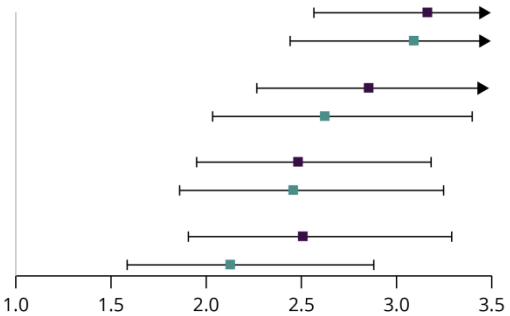
B. Snoring or gasping — yes/don't know (no)*

Symptom	Model	OR (95% CI)
Yes	Model 1	3.00 (2.52–3.58)
Don't know		2.91 (2.30–3.68)
Yes	Model 2	2.64 (2.17–3.20)
Don't know		2.42 (1.88–3.13)
Yes	Model 3	2.25 (1.82–2.78)
Don't know		2.34 (1.77–3.10)
Yes	Model 4	2.41 (1.91–3.05)
Don't know		2.03 (1.50–2.74)



C. Breathing cessation or choking — yes/don't know (no)*

Symptom	Model	OR (95% CI)
Yes	Model 1	3.18 (2.58–3.92)
Don't know		3.11 (2.45–3.95)
Yes	Model 2	2.87 (2.28–3.60)
Don't know		2.64 (2.04–3.42)
Yes	Model 3	2.50 (1.96–3.20)
Don't know		2.47 (1.87–3.27)
Yes	Model 4	2.52 (1.92–3.31)
Don't know		2.14 (1.59–2.90)



D. OSA score 2-3 (0–1)* for odds of all stroke, ischemic stroke, and ICH

Model	OR (95% CI)

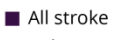
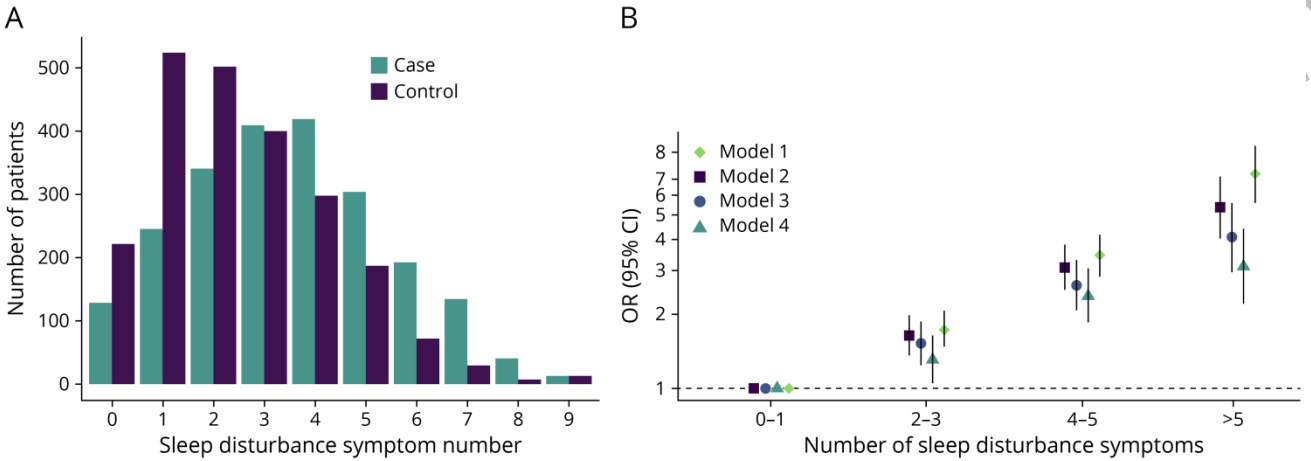


Figure 4: Sleep disturbance symptom burden

a) Cumulative number of sleep disturbance symptoms in cases and controls, where sleep disturbance symptoms include: sleeping for < 6 or > 7 hours at night, SOL, waking more than once, napping for > 1 hour, unplanned napping and presence or uncertainty surrounding snorting, snorting or gasping and breathing cessation or choking.
SOL = sleep onset latency

b) Odds of all stroke in sleep disturbance symptom number categories. OR= Odds Ratio; OR presented on a log scale.
Model 1 is univariate (conditional); Model 2 adjusts for occupation, age, marital status and m-RS at baseline (conditional); Model 3 adjusts for occupation, age, marital status, m-RS at baseline, alcohol consumption, smoking history, leisure physical activity, total AHEI score, waist-to-hip ratio, body mass index (kg/m2), depressive symptoms and global stress (conditional); Model 4 adjusts for occupation, age, marital status, m-RS at baseline, alcohol consumption, smoking history, leisure physical activity, total AHEI score, waist-to-hip ratio, body mass index (kg/m2), depressive symptoms, global stress, history of hypertension or adjusted bp>140/90 at admission, history of diabetes or hba1c>=6.5%, history of atrial fibrillation/flutter and diagnosis of OSA (conditional).



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