

Supplement

Methods

The work was conducted under the auspices of the European Respiratory Society (ERS), the European Academy of Neurology (EAN), the European Stroke Organisation (ESO) and the European Sleep Research Society (ESRS). A working group of experts in neurology, respiratory medicine, sleep medicine and stroke care, together with a methodological support, was formed after consultation of the four societies. The document was drafted following the recommendations of the ERS and EAN for the Statement/Consensus Review documents.^{1,2,3} Roles and responsibilities of each party as they relate to the production of the document were regulated by a memorandum of understanding signed by the four societies involved. The first face-to-face meeting of the Task Force took place in Bologna, September 14th 2016. Two other face-to-face meetings (Marseille, April 5th 2017; Milan September 9th 2017) and several tele-conferences were held in order to complete the document.

The Task Force developed a document focusing on the following main topics:

- a) Sleep-wake disorders - such as sleep-related breathing disorders, insomnia, and restless legs syndrome/periodic limb movement disorder- as risk factors of stroke.
- b) Effect of treatment of sleep-wake disturbances on prevention of stroke.
- c) Frequency of sleep-wake disorders as a consequence of stroke.
- d) Outcome of sleep-related breathing and possible treatment effects of sleep-wake disturbances in patients with acute stroke.

The topics were organized in the following 13 questions (see PICO structure below):

Pre-stroke phase

1.1. Causation	Is SDB an independent risk factor of stroke?
1.2. Therapy	Does treatment of SDB prevent stroke?
2.1. Causation	Is insomnia an independent risk factor of stroke?
2.2. Therapy	Does treatment of insomnia prevent stroke?
2.3. Causation	Is RLS/PLMS an independent risk factor of stroke?
2.4. Therapy	Does treatment of RLS/PLMS prevent stroke?

Post-stroke phase

3.1. Prevalence	What is the frequency of SDB in stroke patients?
3.2. Prognosis	Does SDB affect mortality and outcome after stroke?
3.3. Therapy	Does treatment of SDB have any impact on mortality and outcome after stroke?
4.1. Prevalence	Is the frequency of insomnia increased in stroke patients?
4.2. Therapy	Does treatment of insomnia have any impact on mortality and outcome after stroke?
4.3. Prevalence	Is the frequency of RLS/ PLMS increased in stroke patients?
4.4. Therapy	Does treatment of RLS/PLMS have any impact on mortality and outcome after stroke?

1. Criteria for considering studies

Types of studies

- Causation questions
 - Primary studies: prospective and retrospective cohort studies, case-control studies
 - Systematic reviews of studies with eligible design
- Prevalence questions
 - Primary studies: prospective and retrospective cohort studies, concurrent cross-sectional studies
 - Systematic reviews of studies with eligible design
- Prognosis questions
 - Primary studies: prospective and retrospective cohort studies
 - Systematic reviews of studies with eligible design
- Therapeutic questions

¹ Brussels GG, Ganga M. ERS guidelines, statements and technical standards published in the ERJ in 2014: a year in review. Eur Respir J. 2015;45:863-6.

² Leone MA, Brainin M, Boon P, Pugliatti M, Keindl M, Bassetti CL. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2012. Eur J Neurol 2013; 20:410–419.

³ Leone MA, Keindl M, Schapira AH, Deuschl G, Federico A. Practical recommendations for the process of proposing, planning and writing a neurological management guideline by EAN task forces. Eur J Neurol 2015; 22:1505-10.

- Primary studies: randomized controlled trials, prospective and retrospective cohort studies
- Systematic reviews of studies with eligible design

Types of participants (target population)

- Causation questions: adult (18+ years) subjects of any sex from the general population or the high-risk population (either in terms of cerebrovascular risk or in terms of sleep disorder).
- Prevalence questions: adult (18+ years) subjects of any sex with ischemic and hemorrhagic strokes, primary intracerebral hemorrhage, and concurrent matched controls from the general population.
- Prognosis questions: adult (18+ years) subjects with the sleep disorder.
- Therapeutic questions in subjects at risk for stroke: adult (18+ years) subjects with the sleep disorder.
- Therapeutic questions in subjects with stroke: adult (18+ years) subjects with ischemic and hemorrhagic strokes, primary intracerebral hemorrhage.

Types of interventions /factors

- Causation questions: presence of the sleep disorder (SDB, insomnia, RLS/PLMD).
- Prevalence questions: not applicable.
- Prognosis questions: severity or type of the sleep disorder.
- Therapeutic questions: treatment of any kind.

Types of control

- Causation questions: absence of the sleep disorder.
- Prevalence questions: not applicable.
- Prognosis questions: absence of the the sleep disorder.
- Therapeutic questions: No treatment, placebo/sham treatment.

Types of outcomes

- Causation questions: incidence of ischemic or hemorrhagic strokes, primary intracerebral hemorrhage.
- Prevalence questions: prevalence of the sleep disorder (and subtypes).
- Prognosis questions with sleep disorder as risk factor for stroke: incidence of ischemic or hemorrhagic strokes, primary intracerebral hemorrhage.
- Prognosis questions with sleep disorder as risk factor in stroke patients: disability, recurrence, mortality.
- Therapeutic questions in subjects at risk for stroke: ischemic or hemorrhagic strokes, primary intracerebral hemorrhage.
- Therapeutic questions in subjects with stroke: disability, recurrence, mortality.

Review strategy and search methods for the identification of studies

Searches for each PICO was performed applying a step-wise hierarchical approach: at first, possible systematic reviews were searched starting from 1990. Then, a) in case of retrieval of systematic reviews, primary studies with proper design were searched setting the time limit at the end of the systematic review's search update; b) in case of absence of systematic reviews, primary studies were searched starting from 1990.

Published studies were identified from the National Library of Medicine's MEDLINE database, Elsevier's EMBASE database, and the Cochrane Central Register of Controlled Trials through the OVID platform. Specific search strategies used a combination of exploded terms and free text, using concepts regarding sleep disorders, stroke, and treatment for sleep disorders when needed. The strategies used for MEDLINE were translated to other databases. No language restriction was applied (see below for the detailed search strategies).

Study selection and data extraction

All abstracts or full papers were reviewed independently by two reviewers to identify potentially relevant studies and to assess studies for inclusion. Disagreement was resolved by discussion. For each study, data were extracted by the member of the TF on: topic domain, study design, participants; factors/interventions; outcomes; results.

Assessment of risk of bias of included studies

Each study was classified according to topic domain and type of publication (systematic reviews and primary studies). Quality of evidence was assessed according to different methods depending on the type of publication and topic. Systematic reviews were assessed for descriptive purposes using the criteria from the AMSTAR checklist⁴. According to the topic, primary studies were assessed with the Classification of Evidence Schemes of the Clinical Practice Guideline Process Manual of the American Academy

⁴Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, Porter AC, Tugwell P, Moher D, Bouter LM. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 2007 Feb 15;7:10.

of Neurology⁵. Briefly, each study is graded according to its risk of bias from class I (highest quality) to class IV (lowest quality). Risk of bias is judged by assessing specific quality elements (i.e., study design, patient spectrum, data collection, masking, etc.) for each clinical topic.

Data synthesis

Studies were grouped by review question. A descriptive summary of the included studies with details about study design, number and characteristics of enrolled patients, intervention(s) and comparator(s), outcomes, outcome measures and results were provided in tables.

Statements formulation

Statements for each PICO were developed by each group of experts, with final consensus by the whole TF. The statements aim to provide an overview of the literature and current practice. They do not make recommendations for clinical practice. The questions of the scenarios having no or few evidence were considered to identify research gaps and direct future research projects

⁵ American Academy of Neurology 2011. Clinical Practice Guideline Process Manual, 2011 Ed. St. Paul, MN: The American Academy of Neurology. Available at: <http://tools.aan.com/globals/axon/assets/9023.pdf>)

Questions as PICO format

Pre-stroke phase

Question 1.1 Is SDB an independent risk factor of stroke?

Topic domain	Causation
P (target population)	General population / High risk population
Intervention (factor)	Sleep disordered breathing
Comparator	Absence of sleep disordered breathing
Outcome	Ischaemic stroke and spontaneous intracerebral haemorrhage
Study design	cohort studies, case control studies, systematic reviews of these studies

Question 1.2: Does treatment of SDB prevent stroke?

Topic domain	Therapeutic
P (target population)	Subjects with sleep disordered breathing
Intervention	Treatment (any kind)
Comparator	No treatment, placebo, sham treatment
Outcome	Ischaemic stroke and spontaneous intracerebral haemorrhage
Study design	RCTs, cohort studies, systematic reviews of these studies

Question 2.1: Is insomnia an independent risk factor of stroke?

Topic domain	Causation
P (target population)	General population; high risk population
Intervention (factor)	Insomnia
Comparator	Absence of insomnia
Outcome	Ischaemic stroke and spontaneous intracerebral haemorrhage
Study design	cohort studies, case control studies, systematic reviews of these studies

Question 2.2: Does treatment of insomnia prevent stroke?

Topic domain	Therapeutic
P (target population)	Subjects with insomnia
Intervention	Treatment (any kind)
Comparator	No treatment, placebo
Outcome	Ischaemic stroke and spontaneous intracerebral haemorrhage
Study design	RCTs, cohort studies, systematic reviews of these studies

Question 2.3: Is RLS/PLMS an independent risk factor of stroke?

Topic domain	Causation
P (target population)	General population; high risk population
Intervention (factor)	RLS/PLMS
Comparator	Absence of RLS/PLMS
Outcome	Ischaemic stroke and spontaneous intracerebral haemorrhage
Study design	cohort studies, case control studies, systematic reviews of these studies

Question 2.4: Does treatment of RLS/PLMS prevent stroke?

Topic domain	Therapeutic
P (target population)	Subjects with RLS/PLMS
Intervention	Treatment (any kind)
Comparator	No treatment, placebo
Outcome	Ischaemic stroke and spontaneous intracerebral haemorrhage
Study design	RCTs, cohort studies, systematic reviews of these studies

Post-stroke phase

Question 3.1: What is the frequency of SDB in stroke patients?

Topic domain	Prevalence
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P (target population)	Ischemic stroke and spontaneous intracerebral haemorrhage (and matched controls from general population)
Intervention (factors)	n.a.
Comparator	n.a.
Outcome	Sleep disordered breathing
Study design	cross-sectional studies with concurrent matched controls, systematic reviews of these studies

Question 3.2: Does SDB affect mortality and outcome after stroke?

Topic domain	Prognosis
P (target population)	Ischaemic stroke and spontaneous intracerebral haemorrhage
Intervention (factors)	Sleep disordered breathing (differentiation of central and obstructive sleep apnoea), preexisting SDB and SDB secondary to incidents.
Comparator	Absence of sleep disordered breathing
Outcome	Mortality (all cause; stroke related; vascular) Disability (Rankin; Barthel; other) Recurrence
Time	After ≥6 months after incident
Study design	cohort studies, systematic reviews of these studies

Question 3.3: Does treatment of SDB have any impact on mortality and outcome after stroke?

Topic domain	Therapy
P (target population)	Ischaemic stroke and spontaneous intracerebral haemorrhage
Intervention	CPAP treatment, oxygen, other therapies
Comparator	No treatment (optimal conventional treatment of stroke), placebo, other treatment
Outcome	Mortality (all cause; stroke related; vascular) Disability (Rankin; Barthel, other) Recurrence
Time	After ≥6months treatment initiation
Study design	RCTs, cohort studies, systematic reviews of these studies

Question 4.1: Is the frequency of insomnia increased in stroke patients?

Topic domain	Prevalence
P (target population)	Ischemic stroke and spontaneous intracerebral haemorrhage (and matched controls from general population)
Intervention (factors)	n.a.
Comparator	n.a.
Outcome	Insomnia
Study design	cross-sectional studies with concurrent matched controls, systematic reviews of these studies

Question 4.2: Does treatment of insomnia have any impact on mortality and outcome after stroke?

Topic domain	Therapy
P (target population)	Ischemic stroke and spontaneous intracerebral haemorrhage
Intervention	Treatment of insomnia
Comparator	No treatment, placebo, other treatment
Outcome	Mortality Disability (Rankin plus any other outcome) Recurrence
Time	After 3 months/ 1year from enrolment
Study design	cohort studies, RCTs, systematic reviews of these studies of these studies

Question 4.3: Is the frequency of RLS/PLMS increased in stroke patients?

Topic domain	Prevalence
P (target population)	Ischemic stroke and spontaneous intracerebral haemorrhage (and matched controls from general population)
Intervention (factors)	n.a.

Comparator	n.a.
Outcome	RLS
Study design	cross-sectional studies with concurrent matched controls, systematic reviews of these studies

Question 4.4: Does treatment of RLS/PLMS have any impact on mortality and outcome after stroke?

Topic domain	Therapy
P (target population)	Ischemic stroke and spontaneous intracerebral haemorrhage
Intervention	Treatment of RLS
Comparator	No treatment, placebo, other treatment
Outcome	Mortality Disability (Rankin plus any other outcome) Recurrence
Time	After 3 months/ 1year from enrolment
Study design	cohort studies, RCTs, systematic reviews of these studies of these studies

Semantic concepts

Semantic concept	Strategy
Stroke - Ischaemic stroke (all in OR)	isch?emi* adj6 (stroke* or apoplex* or "cerebral vasc*" or cerebrovasc* or cva or attack*) (brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or "middle cerebr*" or mca* or "anterior circulation") adj5 (isch?emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi* or arterioscleros* or atheroscleros* or event* or accident*) exp Stroke/ or Cerebrovascular Disorders/ or Ischemic Attack, Transient/ or exp "Intracranial Embolism and Thrombosis"/ or Intracranial Arteriosclerosis/ stroke* or apoplex* or CVA or CVAs or TIA or "carotid artery thrombo*" or "sinus thrombo"
Stroke - Spontaneous intracerebral haemorrhage (all in OR)	(brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraventricular or infratentorial or supratentorial or "basal gangli*" or putaminal or putamen or "posterior fossa") adj10 (h?emorrhage* or h?ematoma* or bleed*) "Cerebral Hemorrhage"[Mesh] "Intracranial Hemorrhage, Hypertensive"[Mesh]
Sleep disorder breathing (all in OR)	sleep* adj3 disorder* adj3 breath* sleep* adj5 (apn?ea* or hypopn?ea* or apn?eahypopn?ea* or apn?eic) (((nighttime or sleep* or "night time") adj3 (((breath* or airway*) adj5 (obstruct* or restric*)) or (mouth adj3 breath*))) OSA or OSAS or OSAHS or SDB or SRBD or OSDB or SAHS or SAS exp Sleep Apnea Syndromes/ "Hypersomnia with Periodic Respiration" or "Pickwickian Syndrome" or Hypoventilation or "Ondine Syndrome" or "Cheyne-stokes respiration" or periodic breathing
SDB treatment - CPAP concept	(positive adj5 (airway or pressure)) or (sustained adj3 inflation) "positive pressur*" adj5 (ventilat* or respir* or breath* or airway*) ppv or cpap or ncpap or nm-cpap or np-cpap or peep a-pap or b-pap or c-pap pap or apap or bpap "positive end expiratory pressure" "continuous distend*" positiv* airway* pressur* Positive-Pressure Respiration [Mesh] Oxygen Inhalation Therapy [Mesh]
SDB treatment - Oral appliance concept	"oral appliance*" OR "intraoral appliance*" OR "dental appliance*" OR "mandibular advancement" OR "mandibular repositioning"
Other SDB treatment	exp Sleep Apnea Syndromes/dt, su, th [Drug Therapy, Surgery, Therapy]
Insomnia (all in OR)	Insomnia* or "sleep complaint*" or "sleep initiation" or "disorders of initiating and maintaining sleep" or "poor sleep quality" "Sleep Initiation and Maintenance Disorders"[Mesh] - excluding "Insomnia Fatal Familial" (submesh)
RLS/PLMS (all in OR)	"restless leg syndrome" "restless legs syndrome" (periodic OR movement) AND (leg OR legs) (periodic OR movement) AND (limb OR limbs) (periodic OR movement) AND extremities "nocturnal myoclonus syndrome" "periodic limb movement disorder*" RLS Ekbom "Restless Legs Syndrome"[Mesh] "Nocturnal Myoclonus Syndrome"[Mesh]

Study design filters

Cohort Studies & Case Control Studies Based on <http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html>

1. exp cohort studies/
2. cohort*.af
3. controlled clinical trial.pt.
4. epidemiologic methods/
5. limit 4 to yr=1966-1989
6. exp case-control studies/
7. (case* and control*).af
8. or/1-3,5-7

Cohort Studies Based on <http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html>

1. exp cohort studies/
2. cohort*.af
3. controlled clinical trial.pt.
4. epidemiologic methods/
5. limit 4 to yr=1971-1988
6. or/1-3,5

Randomized Control Trial Based on <http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html>

1. "randomized controlled trial".pt.
2. (random* OR placebo OR single-blind* OR double-blind* OR triple-blind*).ti,ab.
3. (retraction of publication OR "retracted publication").pt.
4. exp "RANDOMIZED CONTROLLED TRIALS AS TOPIC"/
5. or/1-4
6. (humans not animals).sh.
7. ((comment* or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.
8. ("random sampl*" or "random digit*" or "random effect*" or "random survey" or "random regression") not "randomized controlled trial". ti,ab
9. 5 and 6
10. 7 or 8
11. 9 not 10

Systematic Reviews Based on <http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html>

1. (review or review, tutorial or review, academic).pt.
2. (medline or medlars or embase or pubmed or cochrane).af.
3. (scisearch or psychinfo or psycinfo).af.
4. (psychlit or psyclit).af
5. cinahl.af.
6. ((hand adj2 search*) or (manual* adj2 search*)).*af
7. ("electronic database*" or "bibliographic database*" or "computeri?ed database*" or "online database*").*af
8. (pooling or pooled or "mantel haenszel").*af
9. (peto or dersimonian or der simonian or fixed effect).*af
10. (retraction of publication or "retracted publication").pt.
11. or/2-10
12. 1 and 11
13. meta-analysis.pt.
14. meta-analysis.sh.
15. (meta-analys* or meta analys* or metaanalys*).*af
16. (systematic* adj5 review*).*af
17. (systematic* adj5 overview*).*af
18. (quantitativ* adj5 review*).*af
19. (quantitativ* adj5 overview*).*af
20. (quantitativ* adj5 synthesis*).*af
21. (methodologic* adj5 review*).*af
22. (methodologic* adj5 overview*).*af
23. (integrative research review* or research integration).af.
24. or/13-23
25. 12 or 24

Search strategies by PICO

Question 1.1: Is SDB an independent risk factor of stroke

Concepts (see above search terms for each concept)
SDB
AND
Spontaneous intracerebral haemorrhage OR Ischaemic stroke
Limits / Filters: human; 1990-present; no language restriction

Question 1.2: Does treatment of SDB prevent stroke?

Concepts (see above search terms for each concept)
SDB
AND
Spontaneous intracerebral haemorrhage OR Ischaemic stroke
AND
CPAP OR Oral appliance OR Other SDB treatment
Limits / Filters: human; 1990-present; no language restriction

Question 2.1: Is insomnia an independent risk factor of stroke?

Concepts (see above search terms for each concept)
Insomnia
AND
Spontaneous intracerebral haemorrhage OR Ischaemic stroke
Limits / Filters: human; 1990-present; no language restriction

Question 2.2: Does treatment of insomnia prevent stroke?

Concepts (see above search terms for each concept)
Insomnia
AND
Spontaneous intracerebral haemorrhage OR Ischaemic stroke
Limits / Filters: human; 1990-present; no language restriction

Question 2.3: Is RLS/PLMS an independent risk factor of stroke?

Concepts (see above search terms for each concept)
RLS/PLMS
AND
Spontaneous intracerebral haemorrhage OR Ischaemic stroke
Limits / Filters: human; 1990-present; no language restriction

Question 2.4: Does treatment of RLS/PLMS prevent stroke?

Concepts (see above search terms for each concept)
RLS/PLMS
AND
Spontaneous intracerebral haemorrhage OR Ischaemic stroke
Limits / Filters: human; 1990-present; no language restriction

Question 3.1: What is the frequency of SDB in stroke patients?

Concepts (see above search terms for each concept)
Spontaneous intracerebral haemorrhage OR Ischaemic stroke
AND
SDB
Limits / Filters: human; 1990-present; no language restriction

Question 3.2: Does SDB affect mortality and outcome after stroke?

Concepts (see above search terms for each concept)
Spontaneous intracerebral haemorrhage OR Ischaemic stroke
AND
SDB
Limits / Filters: human; 1990-present; no language restriction

Question 3.3: Does treatment of SDB have any impact on mortality and outcome after stroke?

Concepts (see above search terms for each concept)
Spontaneous intracerebral haemorrhage OR Ischaemic stroke
AND
SDB
AND
CPAP OR Oral appliance OR Other SDB treatment
Limits / Filters: human; 1990-present; no language restriction

Question 4.1: Is the frequency of insomnia increased in stroke patients?

Concepts (see above search terms for each concept)
Spontaneous intracerebral haemorrhage OR Ischaemic stroke
AND
Insomnia
Limits / Filters: human; 1990-present; no language restriction

Question 4.2: Does treatment of insomnia have any impact on mortality and outcome after stroke?

Concepts (see above search terms for each concept)
Spontaneous intracerebral haemorrhage OR Ischaemic stroke
AND
Insomnia
Limits / Filters: human; 1990-present; no language restriction

Question 4.3: Is the frequency of RLS/PLMS increased in stroke patients?

Concepts (see above search terms for each concept)
Spontaneous intracerebral haemorrhage OR Ischaemic stroke
AND
RLS/PLMS
Limits / Filters: human; 1990-present; no language restriction

Question 4.4: Does treatment of RLS/PLMS have any impact on mortality and outcome after stroke?

Concepts (see above search terms for each concept)
Spontaneous intracerebral haemorrhage OR Ischaemic stroke
AND
RLS/PLMS
Limits / Filters: human; 1990-present; no language restriction

Results of systematic search and Tables of Evidence

Results of the systematic search

The literature search was performed between March and July 2017. A final update search was performed in January 18th 2019. Results of the search are reported in the **Table 1** and detailed in the pages below. A summary of the included evidence is reported in the **Table 2**.

Table e1. Results of the search reported by single question and by step.

<i>Question</i>	<i>Records assessed</i>	<i>Full text assessed</i>	<i>Studies included</i>
1.1 Is SDB an independent risk factor of stroke?	1602	56	23
1.2 Does treatment of SDB prevent stroke?	382	56	8
2.1 Is insomnia an independent risk factor of stroke?	696	26	4
2.2 Does treatment of insomnia prevent stroke?	969	26	3
2.3 Is RLS/PLMS an independent risk factor of stroke?	985	25	5
2.4 Does treatment of RLS/PLMS prevent stroke?	1111	8	0
3.1 What is the frequency of SDB in stroke patients?	1145	23	9
3.2 Does SDB affect mortality and outcome after stroke?	1412	21	7
3.3 Does treatment of SDB have any impact on mortality and outcome after stroke?	774	51	11
4.1 Is the frequency of insomnia increased in stroke patients?	822	58	8
4.2 Does treatment of insomnia have any impact on mortality and outcome after stroke?	886	41	1
4.3 Is the frequency of RLS/ PLMS increased in stroke patients?	986	39	9
4.4 Does treatment of RLS/PLMS have any impact on mortality and outcome after stroke?	1100	15	0
total	12870	445	88

Table e2. Synoptic view of literature search results and included papers by single question.

	<i>Question</i>	<i>Topic</i>	<i>Systematic Reviews (search update)</i>	<i>Primary studies published after systematic reviews</i>
PRE-STROKE	1.1 Is SDB an independent risk factor of stroke?	Causation	9 (2017)	14
	1.2 Does treatment of SDB prevent stroke?	Therapy	4 (2016)	4
	2.1 Is insomnia an independent risk factor of stroke?	Causation	2 (2016)	2
	2.2 Does treatment of insomnia prevent stroke?	Therapy	0	3
	2.3 Is RLS/PLMS an independent risk factor of stroke?	Causation	3 (2018)	2
	2.4 Does treatment of RLS/PLMS prevent stroke?	Therapy	0	0
POST-STROKE	3.1 What is the frequency of SDB in stroke patients?	Prevalence	3 (2017)	6
	3.2 Does SDB affect mortality and outcome after stroke?	Prognosis	2 (2014)	5
	3.3 Does treatment of SDB have any impact on mortality and outcome after stroke?	Therapy	2 (2016)	9
	4.1 Is the frequency of insomnia increased in stroke patients?	Prevalence	0	8
	4.2 Does treatment of insomnia have any impact on mortality and outcome after stroke?	Therapy	0	1
	4.3 Is the frequency of RLS/ PLMS increased in stroke patients?	Prevalence	1 (2018)	8
	4.4 Does treatment of RLS/PLMS have any impact on mortality and outcome after stroke?	Therapy	0	0

Question 1.1: Is SDB an independent risk factor of stroke?

Figure e1: 14-3-17 run with systematic reviews filter with temporal limit starting from 1990

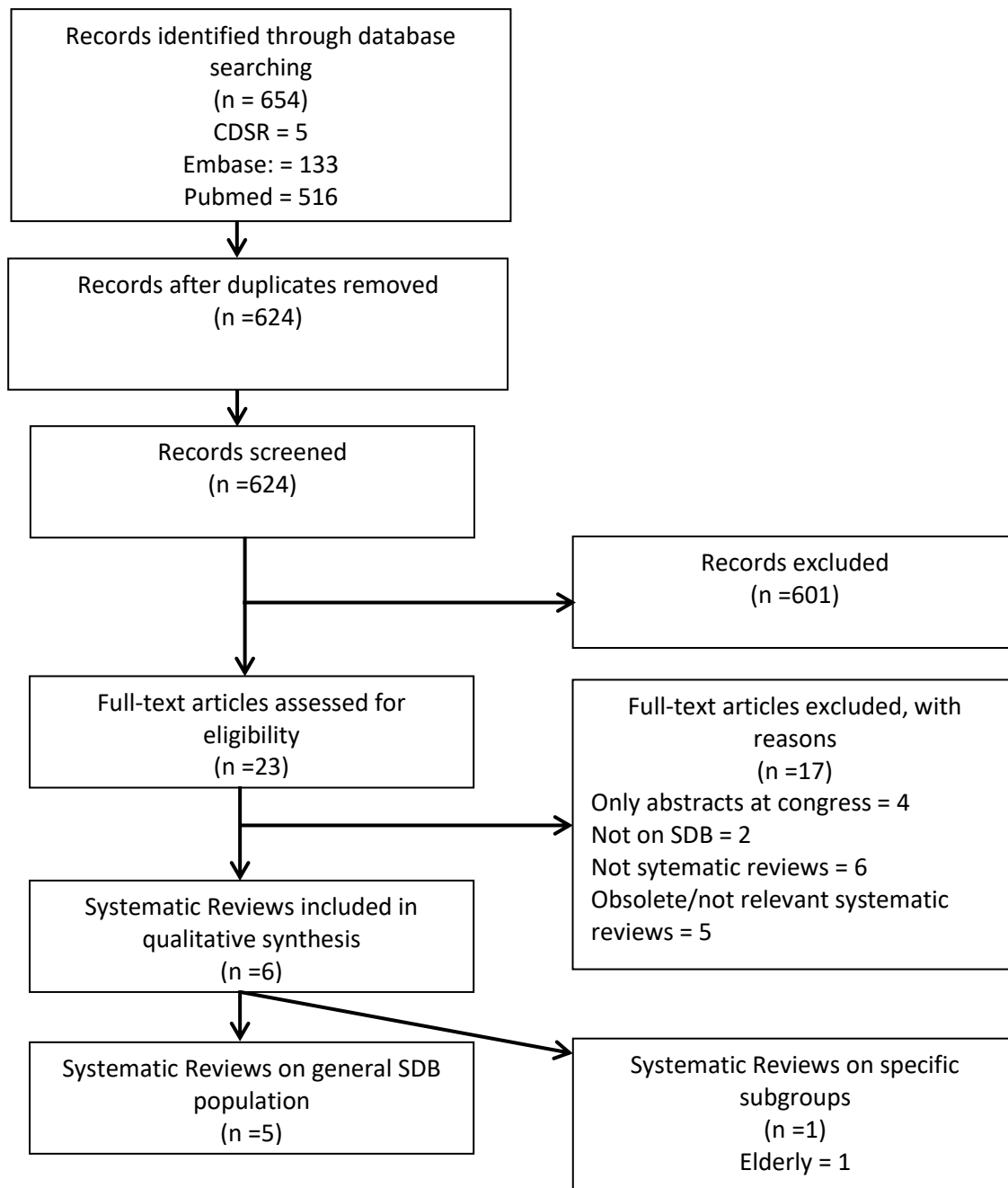


Figure e2: 3-5-17 run with Cohort Studies / Case Control Studies filters with temporal limit starting from the time limit of the most updated systematic review (2013 included)

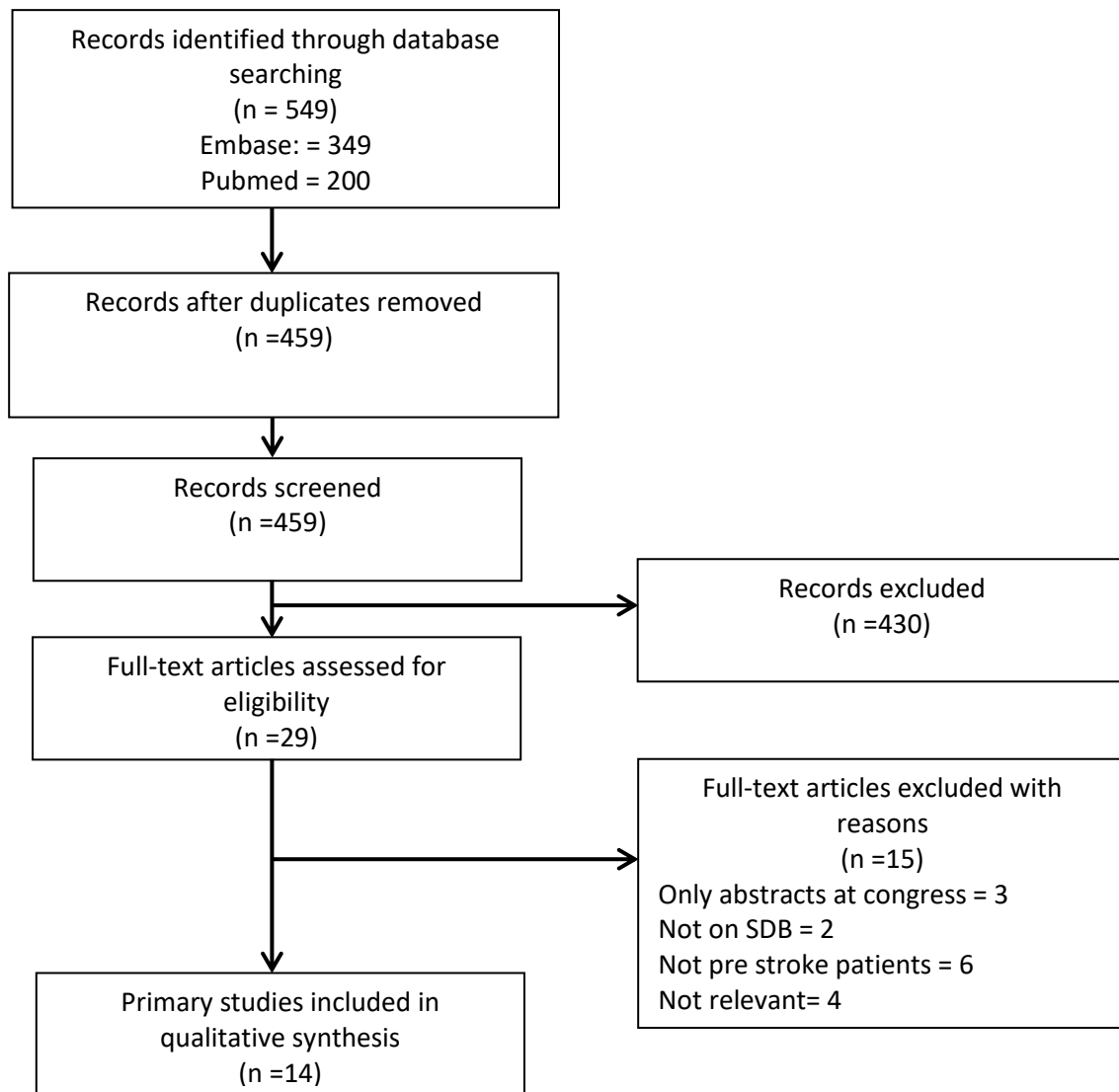


Figure e3: 18-1-19 run with temporal limit starting from 2017

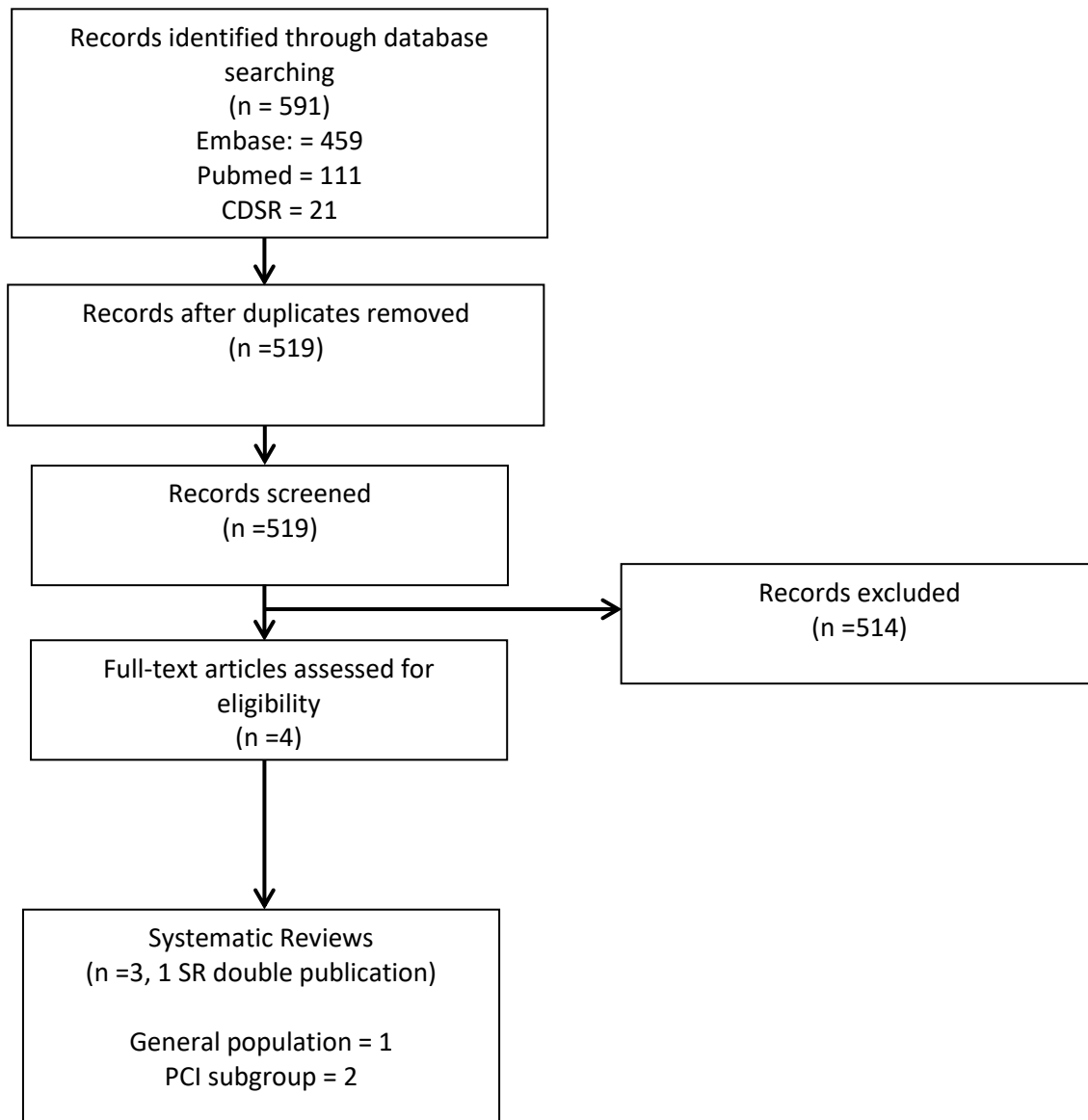


Table: Question 1.1 Is SDB an independent risk factor of stroke?

Topic domain	Causation
P (target population)	General population / High risk population
Intervention (factors)	Sleep disordered breathing
Comparator	Absence of sleep disordered breathing
Outcome	Ischaemic stroke and spontaneous intracerebral haemorrhage

Table e1: Systematic reviews including general population (6)

- Dong, J. Y., L. Q. Qin, and Y. H. Zhang. 2013. 'Obstructive sleep apnea and cardiovascular risk: Meta-analysis of prospective cohort studies', *Atherosclerosis*, 229: 485-95.
- Kendzerska, Tetyana, Tatyana Mollayeva, Andrea S. Gershon, Richard S. Leung, Gillian Hawker, and George Tomlinson. 2014. 'Untreated obstructive sleep apnea and the risk for serious long-term adverse outcomes: a systematic review', *Sleep medicine reviews*, 18: 49-59.
- Li, M., W. S. Hou, X. W. Zhang, and Z. Y. Tang. 2014. 'Obstructive sleep apnea and risk of stroke: A meta-analysis of prospective studies', *International journal of cardiology*, 172: 466-69.
- Loke, Yoon K., J. William L. Brown, Chun Shing Kwok, Alagaratnam Niruban, and Phyo K. Myint. 2012. 'Association of obstructive sleep apnea with risk of serious cardiovascular events: a systematic review and meta-analysis', *Circulation. Cardiovascular quality and outcomes*, 5: 720-28.
- Wang, X., Y. Ouyang, L. Liu, Z. Wang, G. Zhao, and Y. Bi. 2013. 'Obstructive sleep apnea and risk of cardiovascular disease and all-cause mortality: A meta-analysis of prospective cohort studies', *International journal of cardiology*, 169: 207-14.
- Xie, C., R. Zhu, Y. Tian and K. Wang (2017). "Association of obstructive sleep apnoea with the risk of vascular outcomes and all-cause mortality: a meta-analysis." *BMJ open* 7(12): e013983.

Author, Year (last search update)	Quality of the systematic review (Amstar tool)	Included studies	Participants	Length of follow-up	Results	Quality of the studies included (according to the review Authors)	Notes
Dong 2013 (2012)	10/11	9 cohort studies	18,271 (community samples or clinic based)	3.4 – 10 years	RR 2.02 (95% CI 1.40-2.90) for stroke in patients with SDB	Median score of included studies = 7 (range 5-9), according to the Newcastle-Ottawa Quality Assessment Scale*	Cardiovascular risk with separate data for stroke
Kendzerska 2014 (2011)	8/11	5 studies (all included in Dong's paper)	-	-	-	-	No metanalysis. Adds nothing to Dong report
Li 2014 (2013)	7/11	10 cohort studies (9 included in Dong's paper)	18,679 (community samples or clinic based)	3.4 – 10 years	RR 2.1 (95% CI 1.50-2.93) for stroke in patients with SDB	Median score of included studies = 7 (range 5-9), according to the Newcastle-Ottawa Quality Assessment Scale*	Strength is that this paper focused exclusively on stroke risk
Loke 2012 (2011)	8/11	5 cohort studies (all included in Dong's and Li's papers)	8,435	2.8-10.1 years	RR 2.24 (95% CI 1.57-3.19) for stroke in patients with SDB	Qualitative assessment of biases. Confounding as possible source of bias	-
Wang 2013 (2012)	7/11	4 studies (all included in Li's paper)	8,053	-	RR 2.15 (CI 95% 1.42-3.24) for stroke in patients with SDB	Median score of included studies = 3 (range 3-4), according to a modified scoring system§	Adds nothing to Dong report
Xie 2017 (2016)	9/11	4 cohort studies (all included in Dong's and Li's papers)	8,053	4.0 – 8.7 years	RR 2.15 (95% CI 1.42 to 3.24) for stroke in patients with SDB	Median score of included studies = 7 (range 7-8), according to the Newcastle-Ottawa Quality Assessment Scale*	Cardiovascular risk with separate data for stroke. Adds nothing to Dong report

*Newcastle-Ottawa Quality Assessment Scale: possible range 1 (lowest) to 9 (highest)

§Modified scoring system: possible range 0 (lowest) to 6 (highest).

Table e2: Systematic reviews (3) including elderly patients (1), patients with percutaneous coronary intervention (2)

- Qu, H., M. Guo, Y. Zhang and D.-z. Shi (2018). "Obstructive sleep apnea increases the risk of cardiac events after percutaneous coronary intervention: a meta-analysis of prospective cohort studies." *Sleep and Breathing* 22(1): 33-40.
- Wang, X., J.-Y. Fan, Y. Zhang, S.-P. Nie and Y.-X. Wei (2018). "Association of obstructive sleep apnea with cardiovascular outcomes after percutaneous coronary intervention: A systematic review and meta-analysis." *Medicine* 97(17): e0621.
- Xu, P. 2016. 'Association of Obstructive Sleep Apnea with Incidence of Serious Cardiovascular Events in the Elderly: A Meta-analysis', *International Journal of Gerontology*.

Author, Year (last search update)	Quality of the systematic review (Amstar tool)	Included studies	Participants	Length of follow-up	Results	Quality of the studies included (according to the review Authors)
Qu 2018 (2016)	8/11	4 cohort studies	1,764 patients with percutaneous coronary intervention	1-4.8 years	RR 1.68 (95% CI 0.91-3.11) for stroke in patients with SDB	Median score of included studies = 8 (range 6-8), according to the Newcastle-Ottawa Quality
Wang 2018 (2017)	9/11	5 cohort studies	1,850 patients with percutaneous coronary intervention	1-5.6 years	RR 1.55 (95% CI 0.90-2.67) for stroke in patients with SDB	Median score of included studies = 9 (range 6-9), according to the Newcastle-Ottawa Quality
Xu 2016 (2014)	8/11	6 cohort studies (5 included in Dong's and Li's papers)	13,857 elderly patients (mean age in studies > 60 years)	5-8.7 years	RR 2.29 (95% CI 1.49-3.51) for stroke in patients with SDB	Median score of included studies = 7 (range 5-9), according to the Newcastle-Ottawa Quality Assessment Scale*

*Newcastle-Ottawa Quality Assessment Scale: possible range 1 (lowest) to 9 (highest)

Table e3: Primary studies (14)

- Campos-Rodriguez F, Martinez-Garcia MA, Reyes-Nuñez N, Caballero-Martinez I, Catalan-Serra P, Almeida-Gonzalez CV. Role of sleep apnea and continuous positive airway pressure therapy in the incidence of stroke or coronary heart disease in women. *American journal of respiratory and critical care medicine*. 2014;189(12):1544-50.
- Chang C-C, Chuang H-C, Lin C-L, Sung F-C, Chang Y-J, Hsu CY, et al. High incidence of stroke in young women with sleep apnea syndrome. *Sleep medicine*. 2014;15(4):410-4.
- Holmqvist F, Guan N, Zhu Z, Kowey PR, Allen LA, Fonarow GC, et al. Impact of obstructive sleep apnea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation-Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *American heart journal*. 2015;169(5):647.
- Kendzerska T, Gershon AS, Hawker G, Leung RS, Tomlinson G. Obstructive sleep apnea and risk of cardiovascular events and all-cause mortality: a decade-long historical cohort study. *PLoS medicine*. 2014;11(2):e1001599.
- Lamberts M, Nielsen OW, Lip GYH, Ruwald MH, Christiansen CB, Kristensen SL, et al. Cardiovascular risk in patients with sleep apnoea with or without continuous positive airway pressure therapy: follow-up of 4.5 million Danish adults. *Journal of internal medicine*. 2014;276(6):659-66.
- Lee J-E, Lee CH, Lee SJ, Ryu Y, Lee W-H, Yoon IY, et al. Mortality of patients with obstructive sleep apnea in Korea. *Journal of clinical sleep medicine: JCSM : official publication of the American Academy of Sleep Medicine*. 2013;9(10):997-1002.
- Loo, G., A. Y. Tan, C.-Y. Koo, B.-C. Tai, M. Richards and C.-H. Lee (2014). "Prognostic implication of obstructive sleep apnea diagnosed by post-discharge sleep study in patients presenting with acute coronary syndrome." *Sleep medicine* 15(6): 631-636.
- Lee C-H, Sethi R, Li R, Ho H-H, Hein T, Jim M-H, et al. Obstructive Sleep Apnea and Cardiovascular Events After Percutaneous Coronary Intervention. *Circulation*. 2016;133(21):2008-17.
- Lipford MC, Flemming KD, Calvin AD, Mandrekar J, Brown RD, Somers VK, et al. Associations between Cardioembolic Stroke and Obstructive Sleep Apnea. *Sleep*. 2015;38(11):1699-705.
- Marshall NS, Wong KKH, Cullen SRJ, Knuiman MW, Grunstein RR. Sleep apnea and 20-year follow-up for all-cause mortality, stroke, and cancer incidence and mortality in the Busselton Health Study cohort. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*. 2014;10(4):355-62.
- Molnar MZ, Mucsi I, Novak M, Szabo Z, Freire AX, Huch KM, et al. Association of incident obstructive sleep apnoea with outcomes in a large cohort of US veterans. *Thorax*. 2015;70(9):888-95.
- Stone KL, Blackwell TL, Ancoli-Israel S, Barrett-Connor E, Bauer DC, Cauley JA, et al. Sleep Disordered Breathing and Risk of Stroke in Older Community-Dwelling Men. *Sleep*. 2016;39(3):531-40.
- Tuohy CV, Montez-Rath ME, Turakhia M, Chang TI, Winkelman JW, Winkelmayer WC. Sleep disordered breathing and cardiovascular risk in older patients initiating dialysis in the United States: a retrospective observational study using medicare data. *BMC nephrology*. 2016;17:16.
- Yaranov DM, Smyrlis A, Usatii N, Butler A, Petrini JR, Mendez J, et al. Effect of obstructive sleep apnea on frequency of stroke in patients with atrial fibrillation. *The American journal of cardiology*. 2015;115(4):461-5.

Author, Year, Country	Quality of the study AAN scheme	Study design	Participants	Length of follow-up	Results	Notes
Campos-Rodriguez 2014 Spain	Class I	Prospective cohort	967 women with suspected OSA. Three groups: AHI<10 (median age 52; BMI 32, ESS 9); AHI≥10 untreated (median age 59; BMI 35, ESS 11); AHI≥10 treated with CPAP (median age 58; BMI 37.6, ESS 12). CPAP treatment defined as compliance >4h/night. Confounders: smoking>30 pack/yr; arterial HT, type 2 diabetes, hyperlipidemia, AF	Median 82 mos, IQR 63-99	Composite outcome CHD + stroke untreated OSA: adjusted HR 2.76 (CI 1.35-5,62); stroke only: adjusted HR 6.44 (CI 1.46-28.34), CHD only: not significant. Higher risk in women <65 yrs. Same trend for nonfatal stroke. CPAP normalized risk	Clinic based

Chang 2014 Taiwan	Class II	Retrospective cohorts	29,961 OSA patients diagnosed between 1997 and 2010; 119,844 non-OSA subjects matched for age, sex and index date. Comorbidities: obesity, diabetes, HT, CHF hyperlipidemia, CAD, AF.	From index date to end of 2010, or incident stroke	Stroke incidence (cases for 10,000 individuals-year): OSA M: 52.4, F: 61.7; no OSA M: 40.7, F: 37.3. Adjusted HR for stroke risk M: 1.21 (CI 95% 1.01-1.24); HR F: 1.44 (CI 95% 1.20-1.72). Significant stroke risk by age: M aged 36-50 (1.33, CI 95% 1.10-1.62); F aged 20-35 (4.90, CI 95% 1.93-12.4), decreasing until age 65. OSA+comorbidities not associated with stroke	Administrative database with retrospective analysis of ICD-9 codes in two matched cohorts. Detailed personal information, including BMI and smoking status, not recorded in database
Holmqvist 2015 US	Class II	Retrospective cohort	10,132 patients with AF (entire cohort), 1841 patients with previous OSA diagnosis (18%), 58% on CPAP. Mean age of entire cohort: 75 yrs (range 67-82); M 58%, BMI 29; OSA pts younger (age 69, range 62-77), more obese (BMI 34) M 69%, and with higher prevalence of comorbidities	2 years	OSA patients with no difference vs non-OSA patients in a composite index (CV death, MI, stroke/TIA) or progression of AF. CPAP-treated patients showed lower AF progression risk than untreated OSA (adjusted OR 0.66, CI 95% 0.46-0.94).	Cohort from AF registry. No data on CPAP compliance
Kendzerska 2015 Canada	Class II	Restrospective cohort	Patients undergoing PSG for suspected OSA (n=10,149) followed until all-cause death, or hospitalization for MI, stroke or exacerbation of CHF, or PCI/CABG, or end of follow-up. At baseline 2,109 no OSA (AHI<5) patients. Analysis corrected for confounders	Median 68 months	Composite outcome incidence 11.5%. Stroke (100 events) significantly associated with gender, age, HT, previous stroke, number of awakening and total sleep time, but not with nocturnal hypoxemia.	1994-2010 hospital database + administrative database until 2011. This study found association of composite outcome with PSG indexes other than AHI.
Lamberts 2014 Denmark	Class II	Retrospective cohort	4.5 million Danish subjects; 33,274 (0.7%) with first-time diagnosis of OSA (mean age 53, M 79%), 14,468 (43.5%) received CPAP	11 years	OSA: adjusted incidence rate ratio of ischemic stroke 1.23 (CI 95% 1.11-1.36); in patients aged <50 yrs: 1.80 (1.36-2.39); CPAP: no protective effect	Data from administrative registries. No info on clinical variables, however adjustment for many CV risk factors.
Lee 2013 Korea	Class I	Prospective cohort	2240 adult South Korean subjects with suspected OSA: 1669 M, 571 F; mean age 55 years (range 40-87); HT 1669 (74.5%), diabetes 569 (25.4%); history of CVD or stroke 155 (6.9%). Non OSA patients (AHI<5) as reference group	61.4 months (range 34-106)	After adjustments for age, sex, BMI, HT, diabetes, CVD, previous stroke, severe OSA was associated with increased all-cause (HR 2.47; 95% CI, 1.09-5.57) and cardiovascular (HR 4.66; 95% CI 1.03-21.08) mortality. No significance for both all cause and CV mortality after including CPAP treatment	CVD/stroke deaths pooled.
Lee 2016 Singapore, China, Hong Kong,	Class I	Prospective cohort (registry)	1311 patients undergoing a sleep study by 7 days after PCI (age 58.2±10.3; M 85.2%, BMI 25.7±3.7,	1.9 years (IQR 0.8 yr)	141 events, primary endpoint: MACCE. Nonfatal stroke: 20 pts. Adjusted HR for MACCE in OSA: 1.57; (95% CI 1.10-2.24)	No data on stroke only. Mostly Asian patients.

Brazil, Myanmar, India			overweight 42%, obese 13%, ESS 5.8±4.3, ESS>10: 18.8%). OSA (AHI≥15) present in 45.3%			
Lipford 2015 US	Class II	Case-control study	Consecutive pts (n=53) undergoing PSG and having a stroke in the following year. Mean age 64.9±11.7 yrs, 66% M, mean BMI 33.3±6.7; diabetes 32%, HT 81%, hyperlipidemia 62%, CAD 30%. CCS and TOAST criteria to determine stroke etiology. Patients with AHI 10/h or less served as controls.	1 year after PSG	OSA in 32, no OSA in 21. AHI>30 in 40% of the OSA group. AF more common in OSA than non-OSA (19 vs 5, p=0.01). Cardioembolic stroke more common in OSA, small vessel stroke more common in non-OSA. Similar T90% in OSA and no-OSA groups. OR for CE stroke in OSA around 4, even after correcting for AF.	Small sample, borderline significance. Paroxysmal AF or other pathogenetic factors may be involved in increased risk for CE stroke in OSA.
Loo 2014 Singapore	Class II	Prospective cohort	68 patients with acute coronary syndrome (M 87%, age 54±9, BMI 25.5±3.8) studied by PG in the first month after discharge; OSA (AHI≥15/h) in 35.3%, none accepted treatment	20 mos (range 4- 30)	Risk for MACCE in OSA compared to non-OSA: adjusted HR 6.95 (1.17-41.4)	Only 2 strokes; higher % of males in non-OSA than in OSA group; small study.
Marshall 2014 Australia	Class II	Prospective cohort	397 subjects (103 F), age at study entry 40- 65 yrs. No OSA: 74.8%; mild OSA: 20.6%; AHI>15: 4.6%. Statistical analysis adjusted for age, gender, obesity, smoking status, BP, total and HDL cholesterol, cancer history and diabetes.	20 years	77 deaths, 103 CVD events, 31 strokes, 59 CHD events, 125 cancer events. In moderate- severe OSA, all cause mortality HR 4.2 (95% CI 1.9-9.2); incident stroke HR 3.7 (95% CI 1.2-11.8).	Info on events derived from hospital charts/registries. Small sample, all untreated subjects. Analysis possibly underpowered, especially to detect gender-related differences. Mild OSA was associated with decreased all- cause mortality risk.
Molnar 2015 US	Class II	Retrospective cohort (Administrative database analysis of ICD- 9 codes)	3,079,514 veterans (93% M); mean age 60.5±14.4 yrs, 93% M, diabetes 22%, all GFR >60., incident OSA in 21,764 without CPAP treatment; incident OSA treated with CPAP in 1478.	Median follow-up 7.74 yrs (IQR 5.99- 8.37 yrs)	OSA-negative group incident stroke in 1.8% (event rate 3.07/1000 patient-yrs); untreated OSA group, incident stroke in 8.1% (event rate 13.3/1000 patient-yrs); treated OSA incident stroke in 9.2%, event rate 14.6/1000 patient- yrs. Fully adjusted models, risk for incident stroke in untreated OSA: HR 3.48 (CI 3.28-3.64); treated OSA: HR 3.50 (CI 2.92- 4.19). Risk for post-stroke mortality in untreated OSA: HR 1.21 (CI 1.10-1.33), but similar to non-OSA in treated patients.	Analysis limited to incident OSA and related risk, previous OSA diagnosis cases not considered. Very high risk independent of treatment for stroke in OSA, but OSA severity and type of treatment not reported
Stone 2016 US	Class II	Restrospective cohort	2872 community dwelling elderly men (mean age 76) studied by home PSG at 6 clinical sites.	7.3±1.9 years	Incidence of stroke 5.4% (156 events, 31 fatal). In minimally adjusted models, significant risk for SpO2<90% for ≥10% of time: HR 1.83, CI 1.12-2.98,	Info on events derived from hospital charts. No data reported on CPAP-treated group,

			Large database on comorbidities, drugs, inflammatory markers and AF at baseline.		attenuated after full adjustment. Effect of nocturnal hypoxemia stronger in fatal stroke group (fully adjusted HR 2.76, CI 0.91-8.37). No difference according to SDB types. Similar results after adjustment for COPD.	but analysis after exclusion of treated pts gave similar results
Tuohy 2016 US	Class II	Retrospective cohort	184,217 Patients with end-stage renal disease); previous OSA diagnosis in 8.2%. OSA+ patients: median age 74 vs 77 non-OSA, M 62.3 vs 52.4 non-OSA, higher comorbidity burden and BMI (median 31.4 vs 25.7 non-OSA).	1.6 yrs (range 0-6)	In fully adjusted models, SDB+ group had lower mortality (HR 0.93, CI 0.91-0.96), and lower incidence of ischemic stroke (4.7% vs 5.6%) and MI.	Data derived from ICD diagnosis codes (US Renal Data System registry). Protective role of SDB in elderly with ESRD. Possible survival bias.
Yaranov 2015 US	Class II	Retrospective cohort	332 patients undergoing PSG for OSA screening with AF. OSA (AHI>5) in 283 patients (85.2%). Exclusion criteria: age<18; previous TIA or stroke, split-night studies. Male gender and CAD prevalence higher in OSA than non-OSA.	4.4 years	Occurrence of stroke in 22.9% (25.4% OSA, 8.2% non-OSA, p=0.006). OR after full adjustments 3.65 (1.25-10.62). Dose effect relationship between AHI and incidence of stroke. High risk for stroke in OSA also after CPAP in 252 pts (89%). Adjusted OR 1.75 (1.16-2.60). Highest risk in low CHADS2 (0-1) or CHAD2DS2-VASc groups (no anticoagulation)	Info on events derived from hospital charts. First study assessing OSA as a risk factor for stroke in AF. Compliance to CPAP poorly analyzed.

AF = atrial fibrillation; AHI = apnea–hypopnea index; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHD = coronary heart disease; CHF = chronic heart failure; CPAP = continuous positive airway pressure; ESRD = end-stage renal disease; ESS = Epworth Sleepiness Scale; GFR = glomerular filtration rate; HAT = hypertension; MACCE = major adverse cardiac and cerebrovascular event; PCI = percutaneous coronary intervention

Question 1.2: Does treatment of SDB prevent stroke?

Figure e4: 14-3-17 run with systematic reviews filter with temporal limit starting from 1990

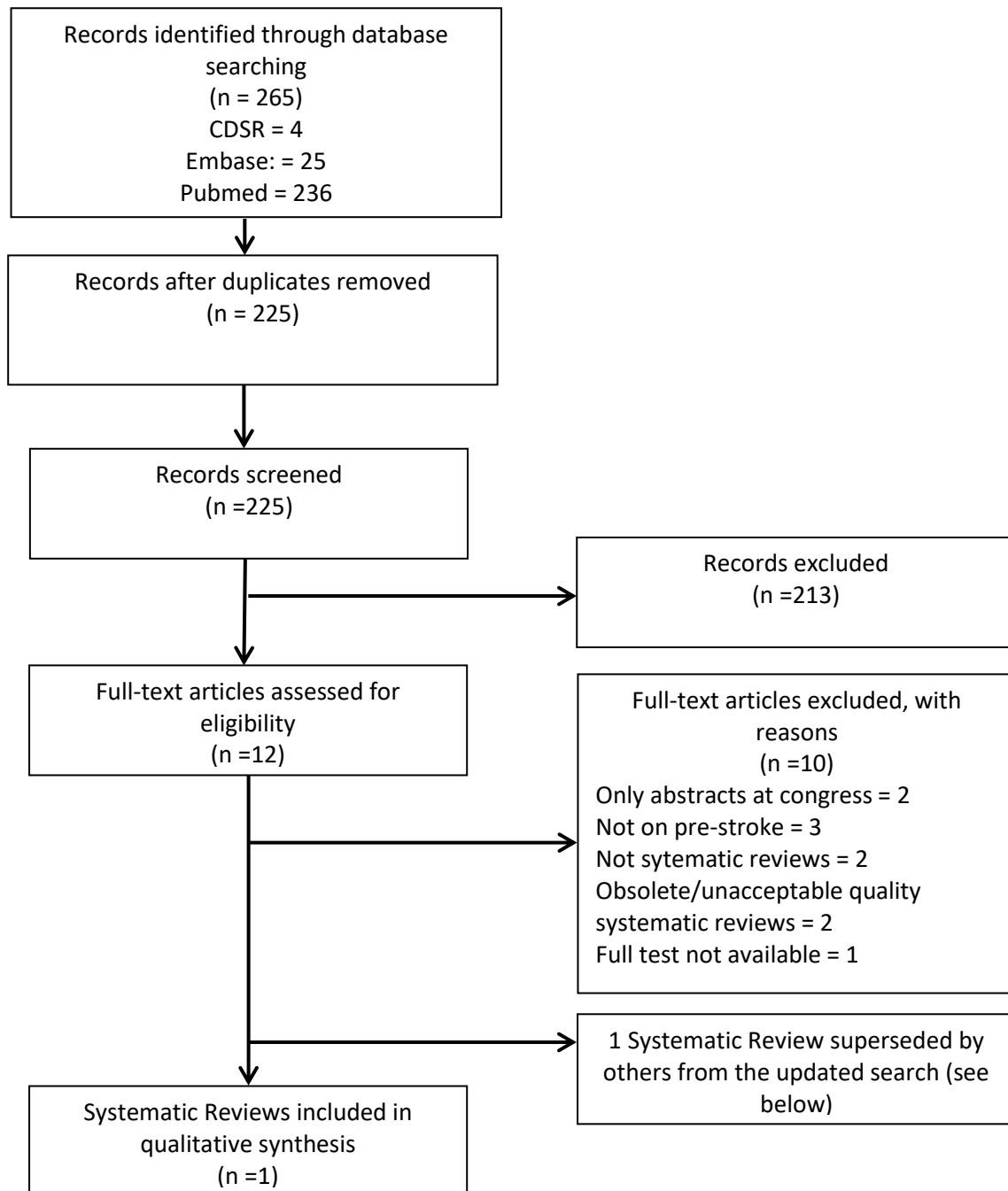


Figure e5: 3-5-17 run with Cohort Studies / RCTs studies filters with temporal limit starting from the time limit of the most updated systematic review (2015 included)

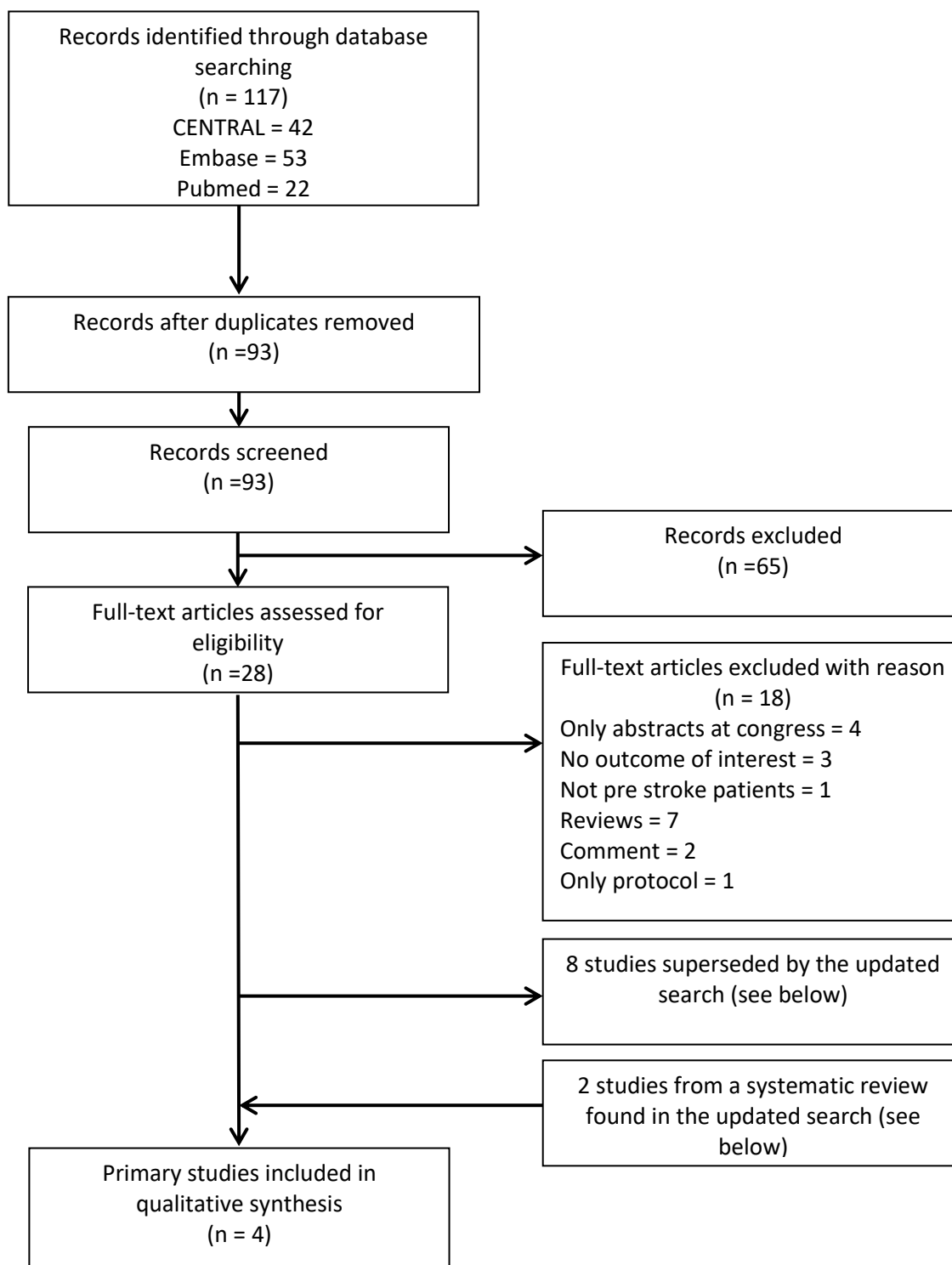
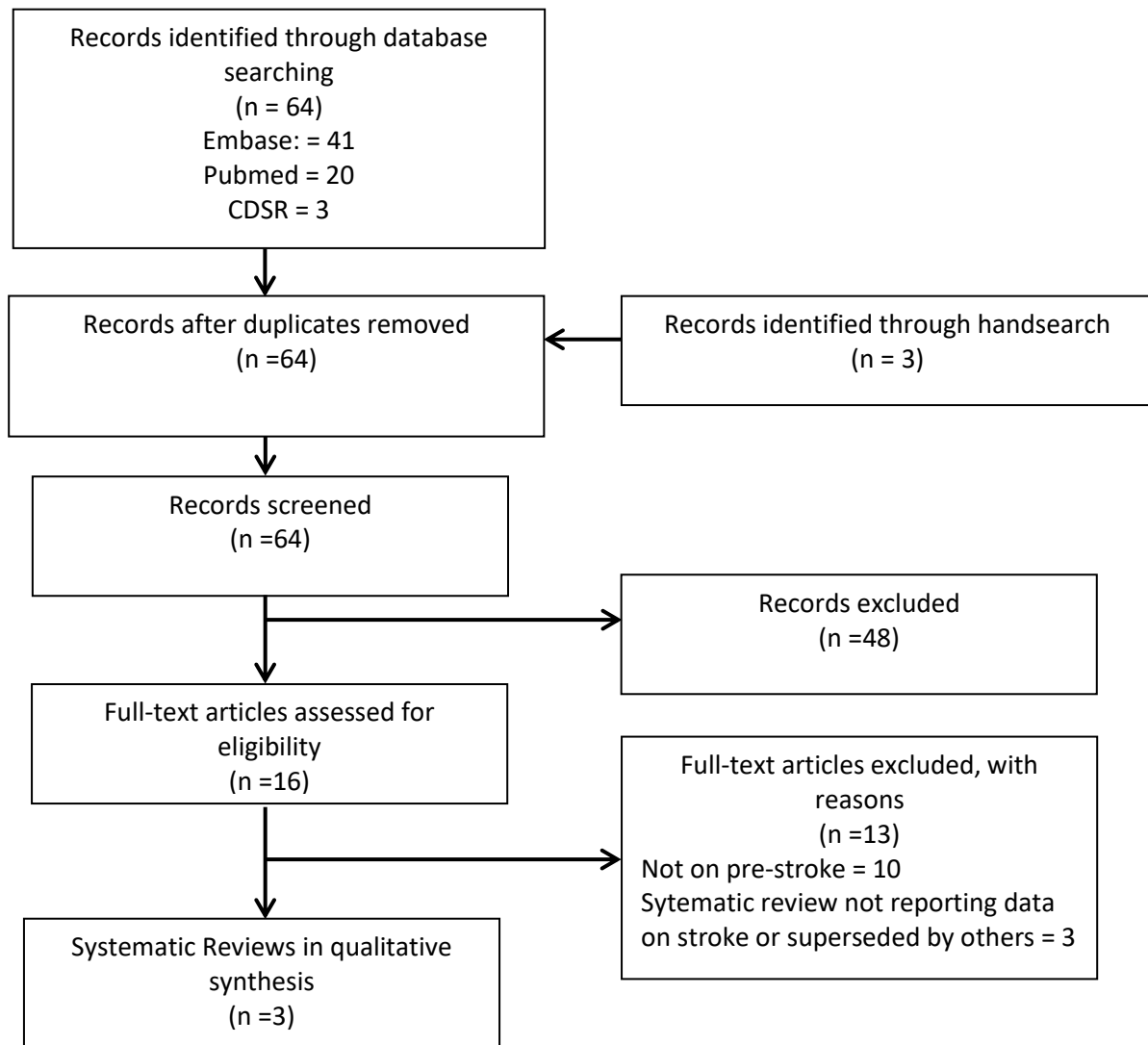


Figure e6: 18-1-19 run with temporal limit starting from 2017



Question 1.2: Does treatment of SDB prevent stroke?

Topic domain	Therapeutic
P (target population)	Subjects with sleep disordered breathing
Intervention	Treatment (any kind)
Comparator	No treatment, placebo, sham treatment
Outcome	Ischaemic stroke and spontaneous intracerebral haemorrhage
Study design	RCTs, cohort studies, systematic reviews of these studies

Table e4: Systematic Reviews (4)

- Abuzaid AS, Al Ashry HS, Elbadawi A, Ld H, Saad M, Elgendy IY, Elgendy A, Mahmoud AN, Mentias A, Barakat A, Lal C. Meta-Analysis of Cardiovascular Outcomes With Continuous Positive Airway Pressure Therapy in Patients With Obstructive Sleep Apnea. *Am J Cardiol*. 2017 Aug 15;120(4):693-699. Update: 2016
- Halle, T. R., M. S. Oh, N. A. Collop, A. A. Quyyumi, D. L. Bliwise and R. C. Dedhia (2017). "Surgical Treatment of OSA on Cardiovascular Outcomes: A Systematic Review." *Chest* 152(6): 1214-1229. Update 2016
- Kim, Yeshin, Yong Seo Koo, Hee Young Lee, and Seo-Young Lee. 2016. 'Can Continuous Positive Airway Pressure Reduce the Risk of Stroke in Obstructive Sleep Apnea Patients? A Systematic Review and Meta-Analysis', *PLoS ONE*, 11: e0146317. Update: 2015
- Khan, S. U., C. A. Duran, H. Rahman, M. Lekkala, M. A. Saleem and E. Kaluski (2018). "A meta-analysis of continuous positive airway pressure therapy in prevention of cardiovascular events in patients with obstructive sleep apnoea." *European Heart Journal* **39**(24): 2291-2297. Update 2016

Author, Year (last search update)	Quality of the systematic review (Amstar)	Study types	Participants	Intervention and comparison	Length of follow-up	Results according to the predefined outcome measures	Quality of the studies included (according to the review Authors)	Notes
Abuzaid 2017 (2016)	9/11	4 RCTs included (only 3 included in the forest plot for stroke)	3,780 participants; mean age 61 yrs; 74% men. Weighted mean AHI 34. Mean BMI (28 and 31) and mean ESS (5.5-8.5)	CPAP vs standard therapy alone (control group).	mean FU from 23 months to 4 yrs	CPAP not associated with reduction in: stroke (RR 1.01, 95% CI 0.73-1.38, p = 0.86), or transient ischemic attack (RR 1.36, 95% CI 0.69-2.68, p = 0.24) Subgroup analysis without data from the SAVE trial; CPAP use more than 4 hours/night associated with a significant risk reduction for incident MACE (RR 0.70, 95% CI 0.52-0.94, p = 0.02,)	All RCTs low risk of bias (Cochrane collaboration tool).	The forest plot on stroke outcome does not include the numbers of Peker's trial in the <i>Am J Respir Crit Care Med</i> 2016.
Halle 2017 (2016)	7/11	17 case series, 7 controlled before-and-after studies, 4 retrospective cohort studies,	Only 2 RCTs with different treatments report stroke outcomes. Please review	Only 2 RCTs with different treatments report stroke outcomes. Please review	Only 2 RCTs with different treatments report stroke	Only 2 RCTs with different treatments report stroke outcomes. Please review	Only 2 RCTs with different treatments report stroke outcomes. Please review	Only 2 RCTs with different treatments report stroke outcomes. Please review

		4 prospective cohort studies, 1 RCT therapy withdrawal study	the table with the Primary Studies.	the table with the Primary Studies.	outcomes. Please review the table with the Primary Studies.	the table with the Primary Studies.	the table with the Primary Studies.	the table with the Primary Studies.
Kim 2016 (2015)	8/11	6 studies 1 RCT, 5 prospective cohort studies, 2 administrative health data studies	60,186 participants (range: 168 – 33,274). 18,293 treated vs 41,893 untreated patients. Sex: One study only women, otherwise male dominance (67-96%) Variable mean age (52-72)	CPAP (1 study CPAP or BiPAP or intraoral appliance)	Stroke studies 72-89 months FU in RCT: 48 months. FU for cohort studies 72-89 months. FU for administrative databases 72-132 months.	1 RCT: Adjusted IDR compared with untreated: 0.81(0.61–1.06) in overall treated; 0.69 (0.50–0.94) in adherent group (CPAP for 4hours per night or longer) 1 women cohort study: untreated OSA associated with stroke (adjusted HR 6.44, 95% CI 1.46-28.34). Risk normalized in those treated with CPAP for stroke (adjusted HR 1.31 95% CI 0.26-6.59), compared with the controls without OSA. CPAP not effect on the incidence of stroke in two studies using administrative data. Meta-analysis from 3 cohort studies decrease in risk with CPAP with an RR 0.27 (95% CI 0.14-0.53) for stroke.	RCT: Low risk of bias. Cohort studies selection bias. (OSA at baseline more severe in the treated group in four studies as well as the degree of EDS in the female cohort)	Incidence data of CV events adequately controlled for treatment adherence only in one analysis (RCT study) Reported adherence defined as mean CPAP use \geq 4h/night varied between 64% and 100%, not reported in 3 studies
Khan 2018 (2016)	7/11	7 RCTs	4,268 participants; mean age 6 yrs; 79.5% men; 59% hypertension; 52% CAD, 33% DM.	CPAP vs no active intervention with the exemption of 1 study (CPAP vs nocturnal supplemental oxygen)	mean FU 37 months	CPAP use not associated with reduction in stroke incidence (RR 0.95, 95% CI 0.72-1.24, p = 0.69).	Risk of bias assessment (modified Cochrane risk assessment bias tool): low risk identified in 3 RCTs. Unclear	PREDICT, RICCADSA and SAVE had mean adherence to CPAP time of <4 hours/day. Exclusion of SAVE RCT only

						Sensitivity analysis excluding low CPAP adherence trials did not change the effect of CPAP on stroke incidence	blinding in 4 RCTs, unclear allocation concealment in 1 RCT.	associated with a strong trend of reduced stroke incidence (RR 0.54, 95% CI 0.29 to 1.01, $p = 0.05$, $I^2 = 0\%$). Sensitivity analysis using SAVE's pre-specified estimates (CPAP treatment at an average of ≥ 4 h/night and 1:1 matching of CPAP adherers to patients from the usual care arm who never used CPAP) revealed a significant risk reduction in stroke incidence (RR 0.56, 95% CI 0.37 to 0.84, $p = 0.01$).
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RCTs: Randomised Controlled Trials, yrs: years, DM: Diabetes Mellitus, CPAP: Continuous positive airway pressure, CV: CardioVascular, FU: Follow Up, EDS: Excessive Daytime Sleepiness

Table e5: Primary studies (4)

- Catalan-Serra, P., F. Campos-Rodriguez, N. Reyes-Nuñez, M. J. Selma-Ferrer, C. Navarro-Soriano, M. Ballester-Canelles, J.-J. Soler-Cataluña, P. Roman-Sanchez, C. V. Almeida-Gonzalez and M. A. Martinez-Garcia (2018). "Increased Incidence of Stroke, but Not Coronary Heart Disease, in Elderly Patients With Sleep Apnea." *Stroke*: STROKEAHA118023353.
- Chen S-Y, Cherng Y-G, Lee F-P, Yeh C-C, Huang S-Y, Hu C-J, et al. Risk of Cerebrovascular Diseases After Uvulopalatopharyngoplasty in Patients With Obstructive Sleep Apnea: A Nationwide Cohort Study. *Medicine*. 2015;94(41):e1791.
- Partinen M, Guilleminault C. Daytime Sleepiness and Vascular Morbidity at Seven-Year Follow-up in Obstructive Sleep Apnea Patients. *Chat* 1990; 97:27-32.
- Wu X, Lv S, Yu X, Yao L, Mokhlesi B, Wei Y. Treatment of OSA reduces the risk of repeat revascularization after percutaneous coronary intervention. *Chest*. 2015;147(3):708-18.

Author, Year	Quality of the study AAN scheme	Study design	Participants	Intervention and comparison	Length of follow-up	Results	Notes
Catalan-Serra 2018 Spain	Class III	Prospective Cohort	Age ≥65 yrs New diagnosis of OSA. 859 participants; reference group: 141 with AHI <15 events/h; untreated mild-moderate OSA: 99 with AHI of 15-29 events/h and CPAP not prescribed or compliance <4 hours/day; untreated severe OSA: 149 with AHI ≥30 events/h and CPAP not prescribed or compliance <4 hours/day; CPAP-treated OSA: 470 with AHI ≥15 events/h and CPAP compliance ≥4 hours/day.	Intervention: CPAP with compliance >4 hours / day Comparator: No CPAP or CPAP with compliance <4 hours/ day.	Median 72 months (IQR: 50–88.5).	Compared with the reference group: higher cumulative incidence of stroke in the severe untreated OSA group (log-rank test, 11.87; P=0.001). HR (95%CI) for the incidence of stroke in the untreated severe OSA group (fully adjusted Cox analysis): severe untreated OSA (HR, 3.42; 95% CI, 1.37–8.52), AF (HR, 1.97; 95% CI, 1.14–3.4), and age (HR, 1.12; 95%CI, 1.06–1.18) independently associated with an increased risk of incident stroke.	Post-hoc analysis. Data from Sleep Units in Spain between 1998 and 2007. Statistical significant differences in baseline characteristics (p<0.05) amongst the 4 study groups: age, BMI, ESS, AHI, smoking habit, sleep clinic and type of sleep study
Chen 2015 Taiwan (from Halle 2017 systematic review)	Class III	Prospective Cohort	Age >18yrs Primary new diagnosis of OSA (2005-2007). OSA and UPPP(5635) vs OSA without UPPP (4704)	Intervention: UPPP Comparator: Not UPPP	12 months	OSA and UPPP vs OSA without UPPP: Hemorrhagic stroke 0.07% vs 0.47%; P<0.0001 Ischemic stroke 0.30% vs 1.76%; P<0.0001 Other stroke 0.35% vs 1.45%; P<0.0001 TIA 0.25% vs 0.68%; P<0.0001 Risk of Cerebrovascular Disease, OSA and UPPP vs OSA without UPPP RR (95%CI): unadjusted 0.21 (0.16-0.27) full adjusted (sex, age, income, medical conditions,	Taiwan's National Health Insurance Program

						medication) 0.45 (0.33-0.61) Risk of Ischemic Stroke and Other Stroke OSA and UPPP vs OSA without UPPP RR (95%CI): 0.41 (95% CI 0.27–0.62) and 0.53 (95% CI 0.38–0.73)	
Partinen and Guilleminault 1990 USA (from Halle 2017 systematic review)	Class IV	Retrospective Cohort	Age ≥16 yrs; 127 patients with conservative management versus 71 with tracheostomy. MI prevalence higher in the surgically treated group. Surgical group was younger, with higher BMI, higher AHI.	Intervention: Tracheostomy vs medical approach encouraging weight loss and better sleep hygiene	7 yrs	tracheostomy group: higher prevalence of ischemic stroke at baseline (5% vs 9.8% respectively). At follow up, the ischemic stroke incidence in the tracheostomy group was 11% vs 10.2% in the medical approach group.	Tracheostomy vs medical management: statistically significant difference (p = 0.046) in vascular morbidity at follow-up.
Wu 2015, China	Class III	Retrospective cohort	Patients with PCI for CAD and either moderate-severe OSA (AHI≥15 events/h) or mild OSA (AHI of 5-14.9 events/h). 390 participants; 128 with treated moderate-severe OSA (CPAP & AHI≥15), 167 with untreated moderate-severe OSA (NO CPAP but AHI≥15), and 95 with untreated mild OSA (NO CPAP & AHI 5-14.9).	CPAP plus usual care vs usual care only	Median 4.8yrs (IQR:3.0-7.1).	Stroke: 8.6% in the CPAP & AHI≥15, 8.4% in the NO CPAP but AHI≥15 and 8.4% in the NO CPAP & AHI 5-14.9 group No differences in mortality (4.7% vs 7.2% vs 5.3%, P=0.64), MACE MACCE or strokes. In the fully adjusted models, untreated moderate-severe OSA not associated with an increased HR for MACCE (HR, 1.16; 95% CI, 0.70-1.92; P=0.57).	Baseline characteristics for OSA & CPAP & AHI≥15 vs OSA without CPAP & AHI≥15 vs mild OSA without CPAP & AHI 5-14.9: BMI and AHI statistically significant, difference

AF = Atrial Fibrillation; AHI = Apnea–Hypopnea Index; BMI = Body Mass Index; CABG = Coronary Artery Bypass Grafting; CAD = Coronary Artery Disease; CAS = Coronary Artery Stenting; CHF = Congestive Heart Failure; COPD = Chronic Obstructive Pulmonary Disease; CPAP = Continuous Positive Airway Pressure; DM: Diabetes Mellitus; ESS = Epworth Sleepiness Scale; HTN = hypertension; IHD = Ischemic Heart Disease; ITT = Intention To Treat; LVEF = Left Ventricle Ejection Fraction; MACCE: Major Adverse Cardiac or Cerebrovascular events; MACE: Major Adverse Cardiac Events; MI = Myocardial Infarction; OSA = obstructive Sleep Apnea; PCI: Percutaneous Coronary Intervention; PG = Polysomnography; TIA = Transient Ischaemic Attack; UPPP = uvulopalatopharyngoplasty

Question 2.1: Is insomnia an independent risk factor of stroke?

Figure e7: 5-4-17 run with systematic reviews filter with temporal limit starting from 1990

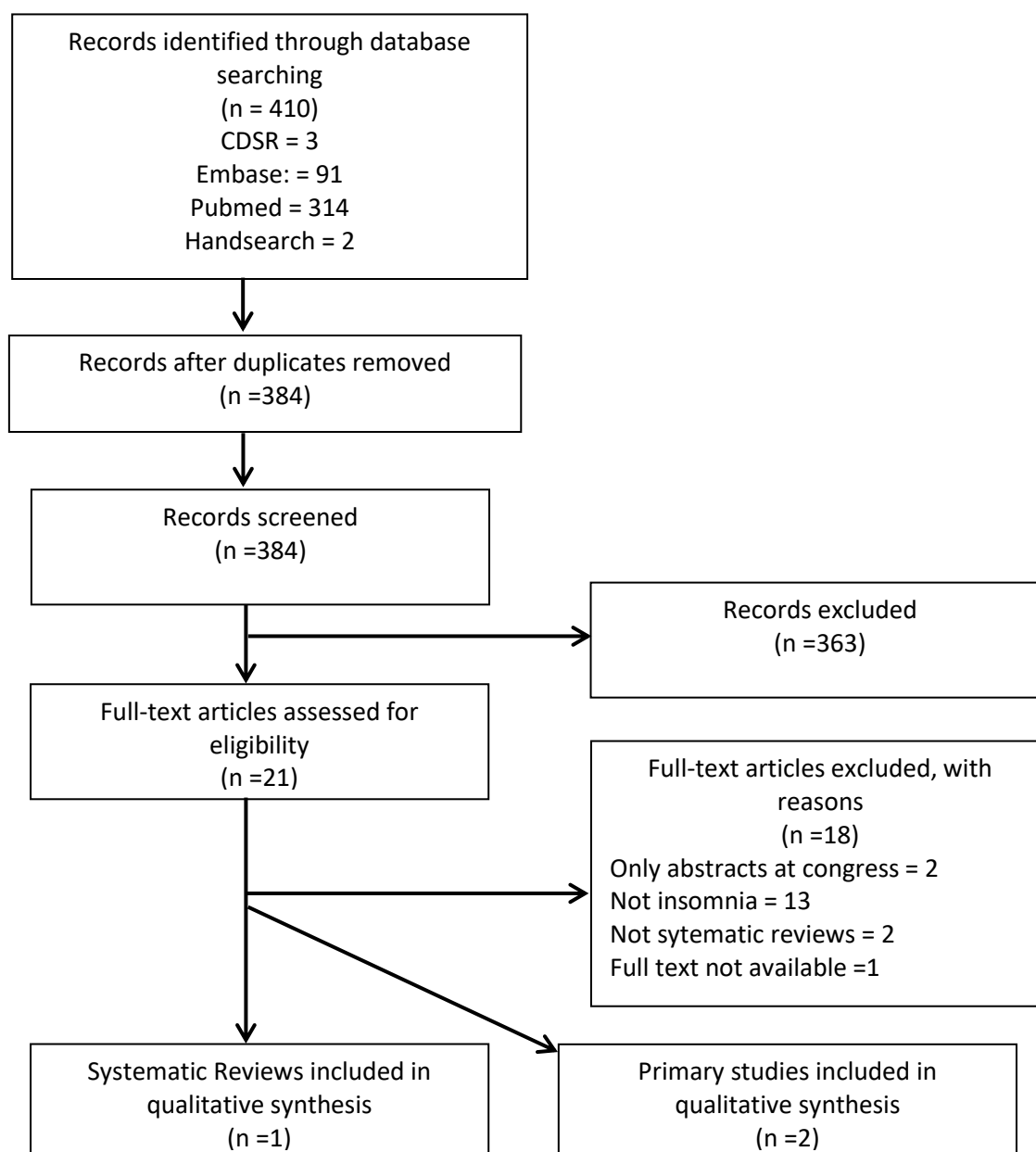


Figure e8: 3-5-17 run with Cohort Studies / Case Control studies filters with temporal limit starting from the time limit of the most updated systematic review (2016 included)

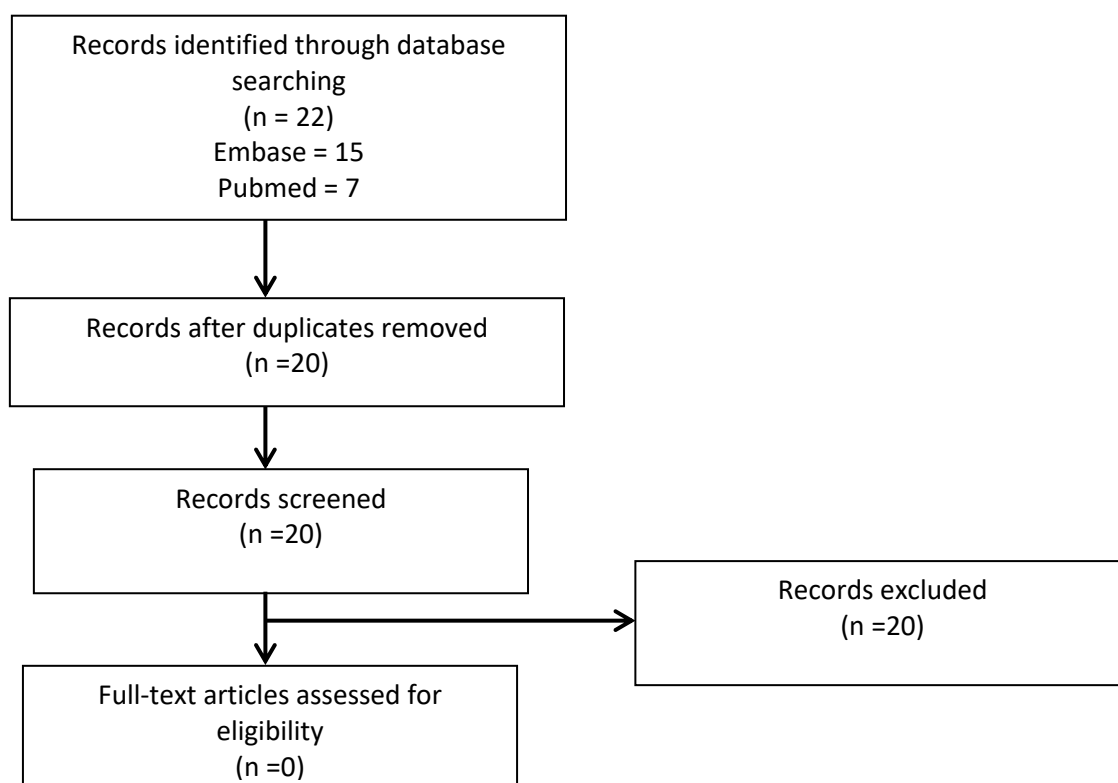
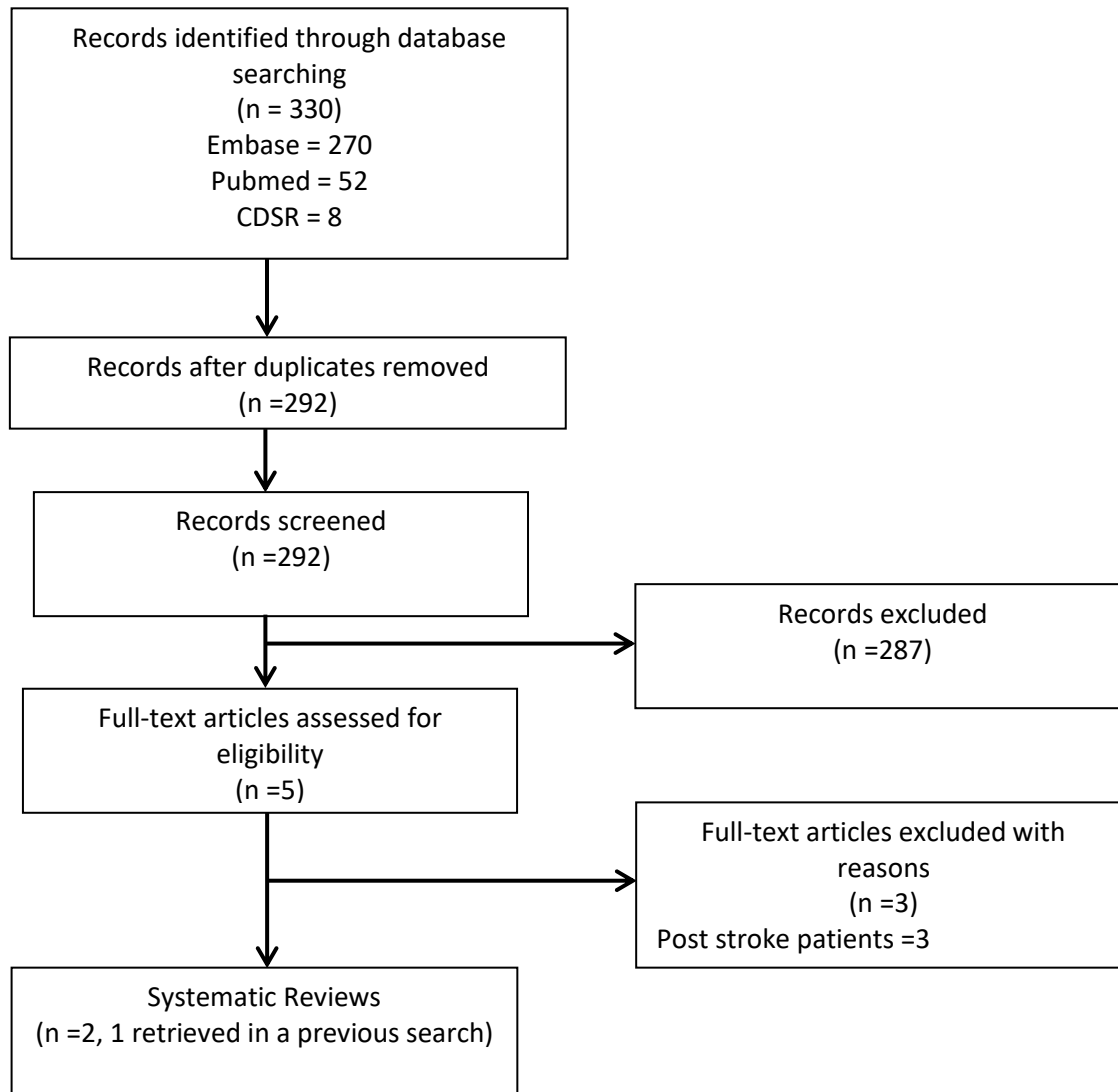


Figure e9: 18-1-19 run with temporal limit starting from 2017



Question 2.1: Is insomnia an independent risk factor of stroke?

Topic domain	Causation
P (target population)	General population; high risk population
Intervention (factors)	Insomnia
Comparator	Absence of insomnia
Outcome	Ischaemic stroke and spontaneous intracerebral haemorrhage
Study design	cohort studies, case control studies, systematic reviews of these studies

Table e6: Systematic Reviews (2)

- He Q, Zhang P, Li G, Dai H, Shi J. The association between insomnia symptoms and risk of cardio-cerebral vascular events: A meta-analysis of prospective cohort studies. *Eur J Prev Cardiol* 2017; 24:1071-1082.
- Kwok, C. S., E. Kontopantelis, G. Kuligowski, M. Gray, A. Muhyaldeen, C. P. Gale, G. M. Peat, J. Cleator, C. Chew-Graham, Y. K. Loke and M. A. Mamas. Self-Reported Sleep Duration and Quality and Cardiovascular Disease and Mortality: A Dose-Response Meta-Analysis. *J Am Heart Assoc* 2018; 7(15): e008552.

Author, Year (last search update)	Quality of the systematic review (Amstar score)	Design of included studies	Participants	Length of follow-up	Results	Quality of the studies included (according to the review Authors)
He 2017 (2016)	8/11	14 prospective cohort studies 1 study with only stroke as outcome; 1 study with both stroke and Cardiovascular events (separate data for stroke) 4 studies with both stroke and cardiovascular events (separate data for stroke not available) 9 studies with only cardiovascular events as outcome	160,867 (M 118,386) The study with stroke outcome: 15,476 patients The study with both stroke and cardiovascular events and separate data for stroke: 41,192 patients	3-29.6 years	Risk of cardio-cerebral vascular events DIS vs non DIS RR 1.27 (95% CI 1.15–1.40), DMS vs non DMS RR 1.11 (95% CI 1.04–1.19) NRS vs non-NRS 1.18 (95% CI 1.05–1.33) Manuscript with only stroke as outcome (Heilbig 2015): significant associations between trouble falling asleep and difficulty staying asleep occurred in the crude models but they were not related to after adjustment for covariates. Crude HR for fatal strokes in men with trouble falling asleep and difficulty staying asleep: 1.95 (95% CI: 1.15 –3.31) and 1.84 (95% CI: 1.18 –2.86); for women they were 1.90 (95% CI: 1.18–3.07) and 1.56 (95% CI: 0.98–2.49) (crude analysis). Models adjusted for age and survey: no significant associations. Similar results are obtained in the study where separate data for stroke are available (Westerlund 2013).	7.1 (range from 5 to 9) according to Newcastle-Ottawa Quality Assessment Scale* The 2 studies with stroke outcome scored 9
Kwok 2018 (2015)	7/11	11 studies	525,620 participants with 14,946 stroke events	Not reported	“Poor sleep quality was associated with a significant and moderate increase in coronary heart disease (risk ratio, 1.44 95% confidence interval, 1.09–1.90) but not for any other outcomes.”	Only qualitative analysis

DIS = difficulties initiating sleep; DMS difficulties maintaining sleep; NRS: non restorative sleep

*Newcastle-Ottawa Quality Assessment Scale: possible range 1 (lowest) to 9 (highest)

Table e7: Primary studies (2)

- Wu MP, Lin HJ, Weng SF, Ho CH, Wang JJ, Hsu YW. Insomnia subtypes and the subsequent risks of stroke: report from a nationally representative cohort. *Stroke* 2014; 45:1349-54.

- Hsu CY, Chen YT, Chen MH, Huang CC, Chiang CH, Huang PH, Chen JW, Chen TJ, Lin SJ, Leu HB, Chan WL. The Association Between Insomnia and Increased Future Cardiovascular Events: A Nationwide Population-Based Study. *Psychosom Med* 2015; 77:743-51.

Author, Year, Country	Quality of the study AAN scheme	Study design	Participants	Length of follow-up	Results	Notes
Wu 2014 Taiwan	Class III	Case-control nested in a cohort (Administrative database analysis of ICD-9 codes)	21 438 (mean age, 52±16 years) insomniacs and 64 314 matched noninsomniacs (mean age, 51±16 years)	4 years	<p>The incidence rate of stroke (crude analysis): IRR, 1.85; 95% CI, 1.67–2.05) in insomniacs than in noninsomniacs. Adjusted HR 1.54 95% CI 1.38–1.72.</p> <p>Stroke subtypes: ischemia IRR 1.79 95% CI 1.56–2.06, transient ischemic attack IRR 2.84 95% CI 2.23–3.61, hemorrhage IRR 1.32 95% CI 1.03–1.68, unspecified stroke IRR 2.07 95% CI 1.41–3.03. Across all age groups and sex groups, individuals with insomnias higher incidence rate of stroke than noninsomniacs. Insomniacs-to-noninsomniacs IRR for stroke decreased as age advanced; the largest IRR for stroke was observed in those aged 18 to 34 years (IRR 8.06) and it continually decreased thereafter.</p> <p>Insomnia subtypes, persistent insomniacs compared with the noninsomniacs, crude HR 2.04 95% CI 1.78–2.34), those with a relapse of insomnia crude HR 1.76 95% CI 1.53–2.02, remission of insomnia crude HR 1.55 95% CI 1.20–2.01. HRs were attenuated and became similar among the 3 insomnia subtypes after adjusting for other relevant covariates.</p>	Accuracy of insomnia diagnoses in the database, as coding errors may have occurred in various local clinics and hospitals of different levels. Covariates for the multivariate analysis included age, sex, comorbidities, socioeconomic status, and geographic region.
Hsu 2015 Taiwan	Class III	Case-control nested in a cohort (Administrative database analysis of ICD-9 codes)	22,040 participants with insomnia during the study period (exposure group) and an age-, sex-, and comorbidity-matched group of 22,040 participants without insomnia (nonexposure group). Mean 47.7 years (SD 15.7); 42.9% men.	10 years	<p>Individuals with insomnia higher incidence of stroke (8.01 versus 3.69 per 1000 person-years); crude HR 2.16 (95% CI 1.89–2.47); adjusted HR 1.85 (1.62–2.12).</p>	Accuracy of insomnia diagnoses in the database, as coding errors may have occurred in various local clinics and hospitals of different levels. Covariates for the multivariate analysis included age, sex, history of hypertension, diabetes mellitus, coronary artery disease, hyperlipidemia, chronic kidney disease, congestive heart failure, peripheral artery disease, and chronic pulmonary disease. Other potentially important confounders not taken into account in

the analysis (race, socioeconomic status, physical activity, smoking, body mass index, alcohol and caffeine consumption, dietary factors, and family history).

Question 2.2: Does treatment of insomnia prevent stroke?

Figure e10: 14-3-17 run with systematic reviews filter with temporal limit starting from 1990

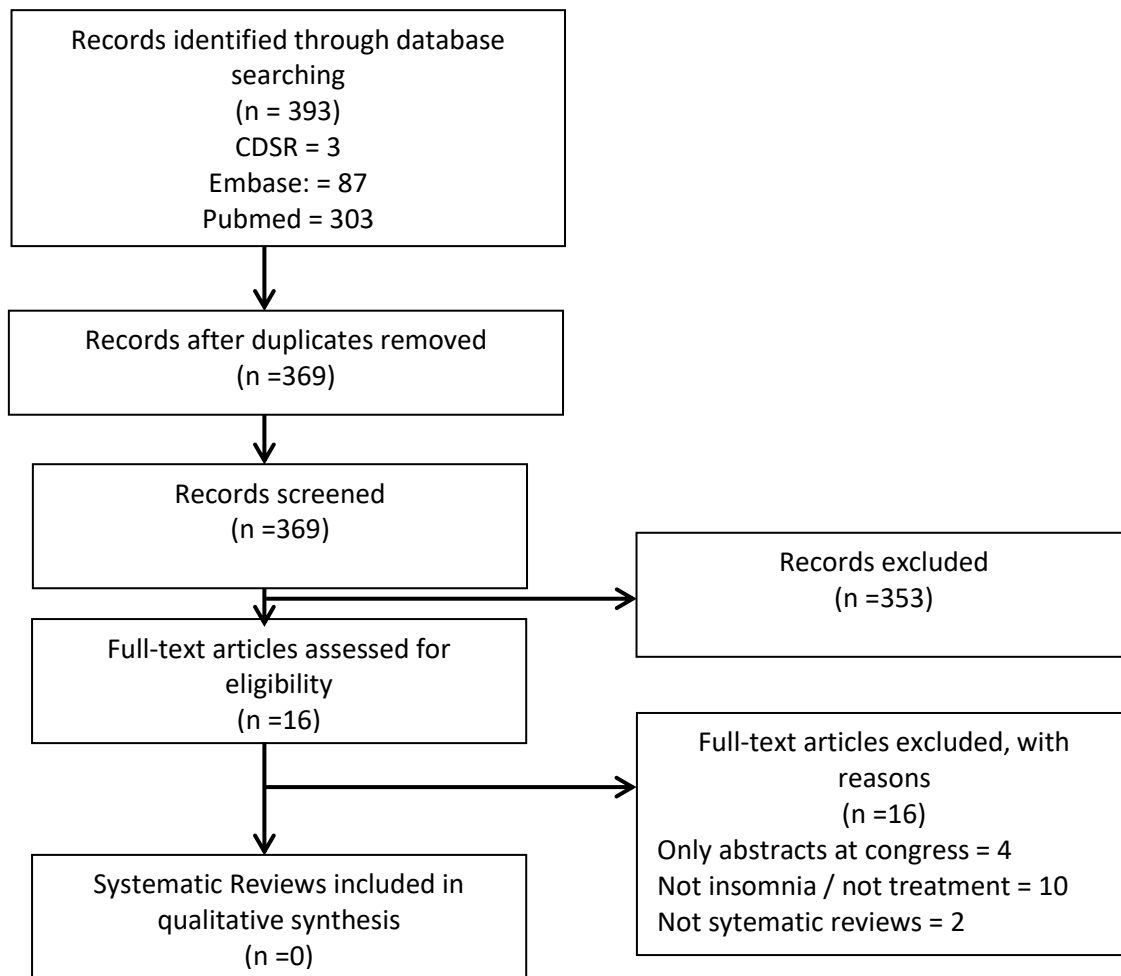


Figure e11: 3-5-17 run with RCTs and cohort studies filters with temporal limit starting from 1990

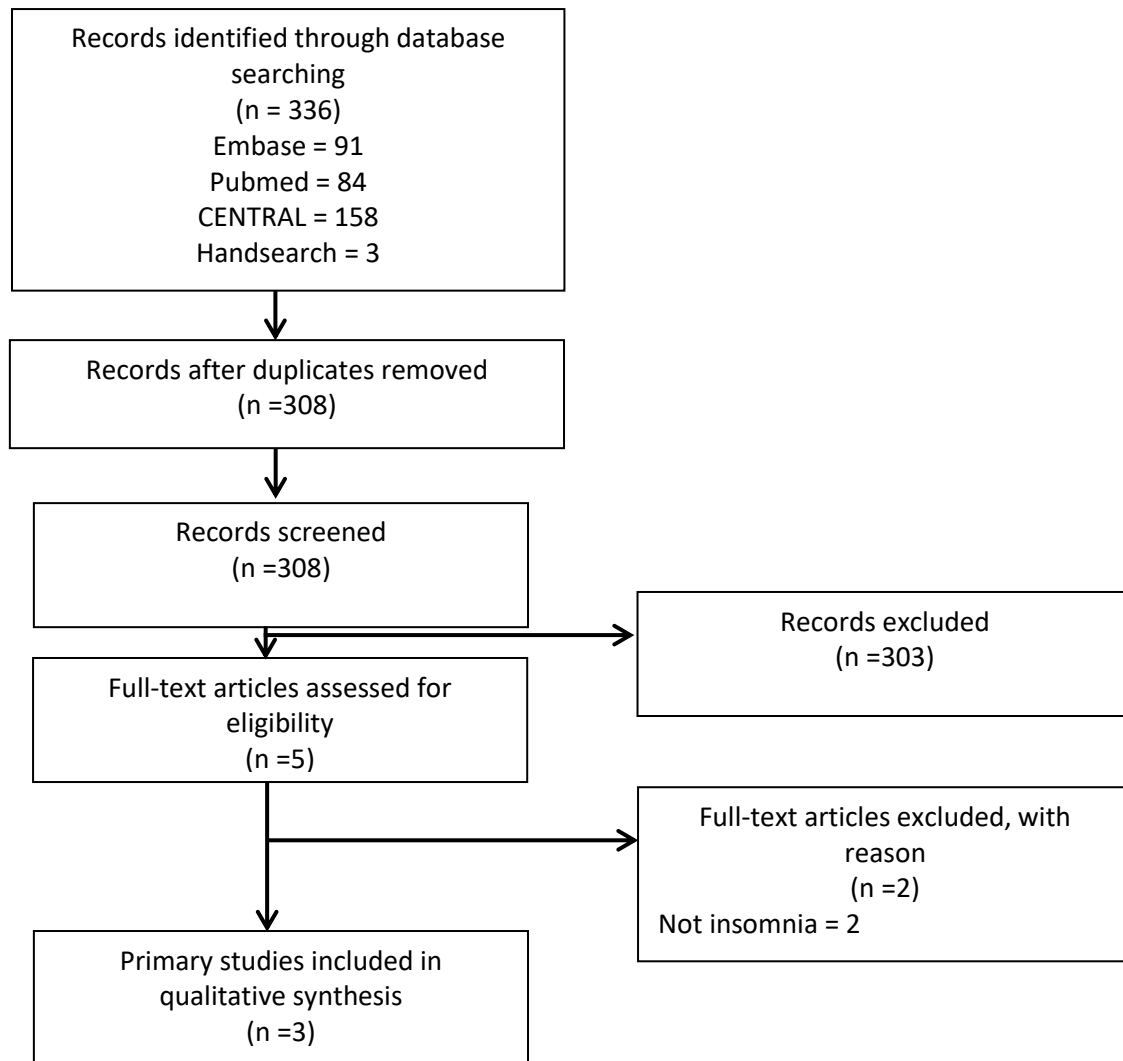
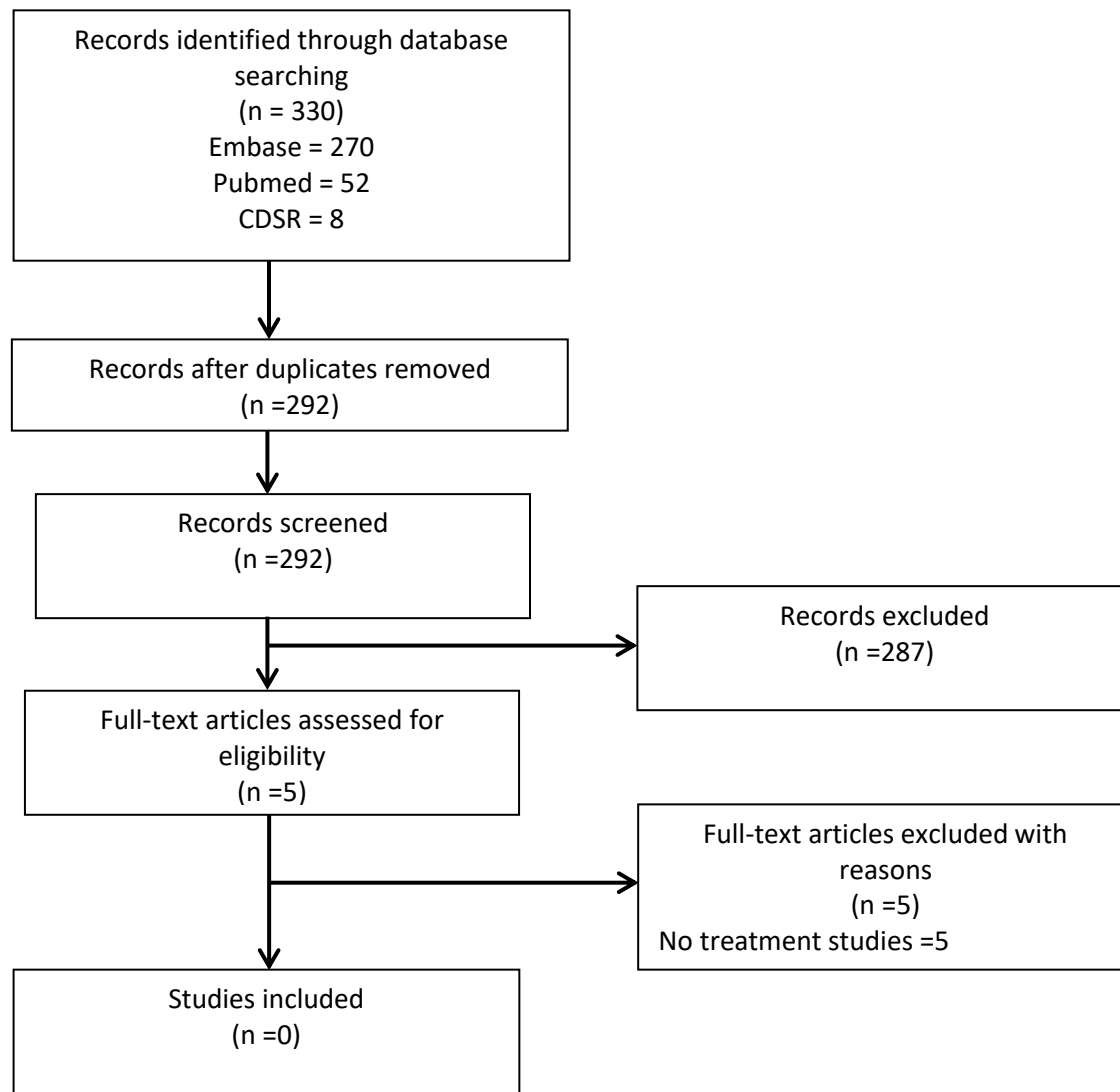


Figure e12: 18-1-19 run with temporal limit starting from 2017



Question 2.2: Does treatment of insomnia prevent stroke?

Topic domain	Therapeutic
P (target population)	Subjects with insomnia
Intervention	Treatment (any kind)
Comparator	No treatment, placebo
Outcome	Ischaemic stroke and spontaneous intracerebral haemorrhage
Study design	RCTs, cohort studies, systematic reviews of these studies

Table e8: Primary studies (3)

- Huang WS, Muo CH, Chang SN, et al. Benzodiazepine use and risk of stroke: a retrospective population-based cohort study. *Psychiatry Clin Neurosci.* 2014;68(4):255-62.
- Taipale H, Koponen M, Tanskanen A, et al. Use of benzodiazepines and related drugs is associated with a risk of stroke among persons with Alzheimer's disease. *Int Clin Psychopharmacol.* 2017;32(3):135-41.
- Zhu J, Jiang J, Zhang Y, et al. Non-benzodiazepine hypnotic drug is correlated with decreased risk of ischemic stroke. *Int J Clin Exp Med* 2016;9(12):23777-80.

Author, Year	Quality of the study AAN scheme	Study design	Participants	Intervention and comparison	Length of follow-up	Results	Notes
Huang 2014 Taiwan	Class II	Two matched cohorts	38,671 patients with new BZD use and 38,663 people without BZD use	BZD users vs non-users	6-9 years	HR of hemorrhagic stroke significantly lower in the BZD group when compared with the non-BZD group. For patients aged 20–39 years, HR of ischemic stroke significantly higher in the BZD group. Compared to the nonBZD group, patients with a lower annual dosage (<1 g) or duration (<30 days) of BZD use had a lower risk of stroke in the elder group (P<0.0001) Patients with a higher annual dosage (≥ 4 g) or duration (≥95 days) of BZD use had a higher risk of stroke in all age groups (P<0.0001)	
Zhu 2016 China	Class III	Case-control study	752 ischemic stroke patients and 760 controls.	BZD versus controls Non-BZD use versus controls	>10 years	A significant decrease in ischemic stroke risk was observed for using non-BDZ (adjusted odds ratio, OR = 0.48; 95% confidence interval, CI = 0.32-0.72). BDZs use was not associated with	

						<p>ischemic stroke (adjusted OR = 1.25; 95% CI = 0.91-1.72). Adjusted ORs were 0.75 (95% CI = 0.39-1.46) for using non-BDZs 0 to 5 years, 0.44 (95% CI = 0.25-0.77) for 5 to 10 years, and 0.38 (95% CI = 0.16-0.90) for >10 years.</p>	
Taipale 2017 Finland	Class II	Cohort study	45,050 community-dwelling individuals with Alzheimer's disease	benzodiazepine and related drug users (BZDR; 9,879 pts) vs non-users		<p>BZDR use: increased risk of any stroke [adjusted hazard ratio (aHR): 1.21; 95% confidence interval (CI): 1.04–1.40] and ischemic stroke (aHR: 1.21; 95% CI: 1.02–1.44). Association between BZDR use and hemorrhagic stroke did not reach significance (aHR: 1.26; 95% CI: 0.91–1.74). Z-drug use associated with a similar risk as benzodiazepine use.</p>	

Question 2.3: Is RLS/PLMS an independent risk factor of stroke?

Figure e13: 14-3-17 run with systematic reviews filter with temporal limit starting from 1990

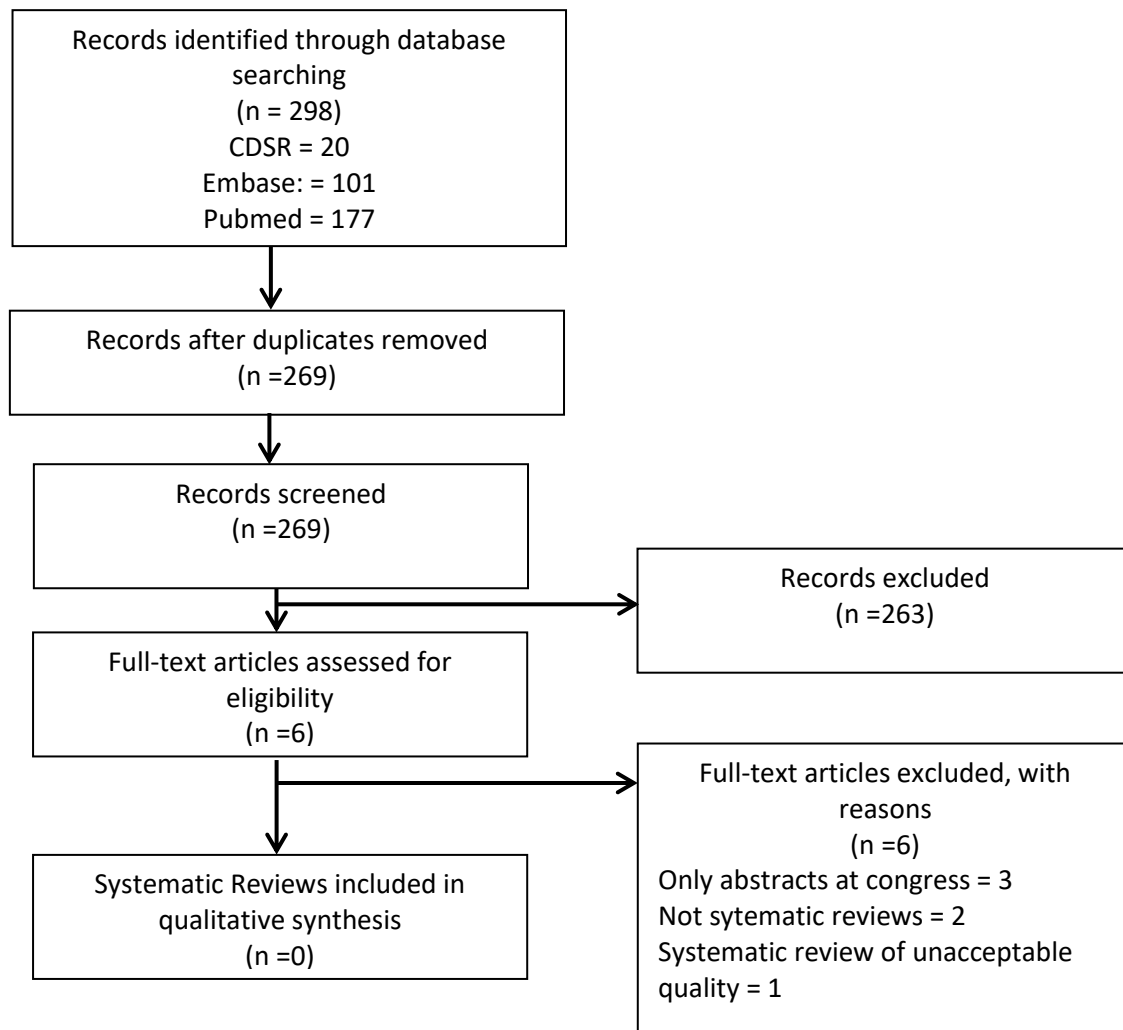


Figure e14: 21-7-17 run with Cohort Studies / RCTs studies filters with temporal limit starting from 1990

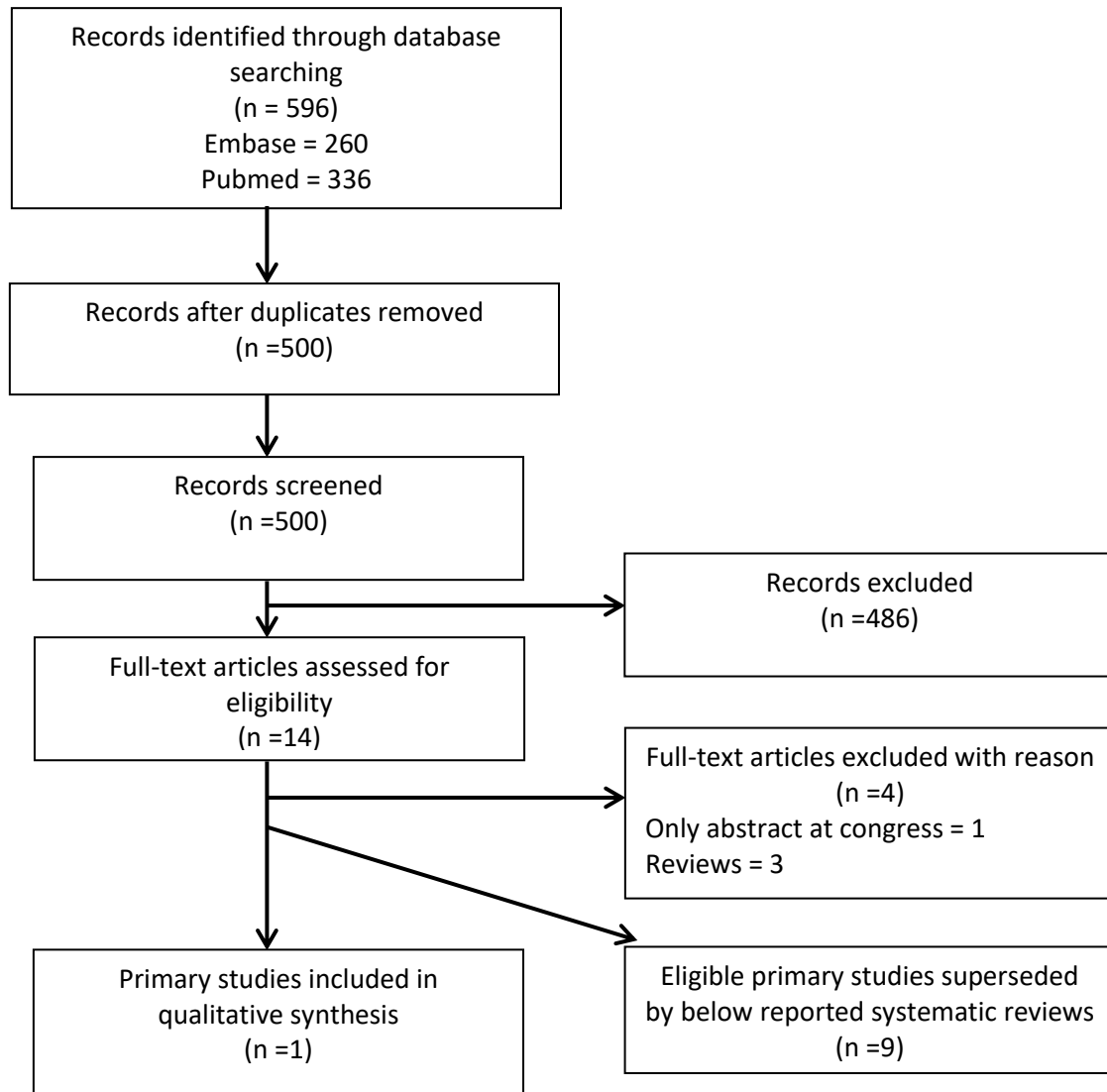
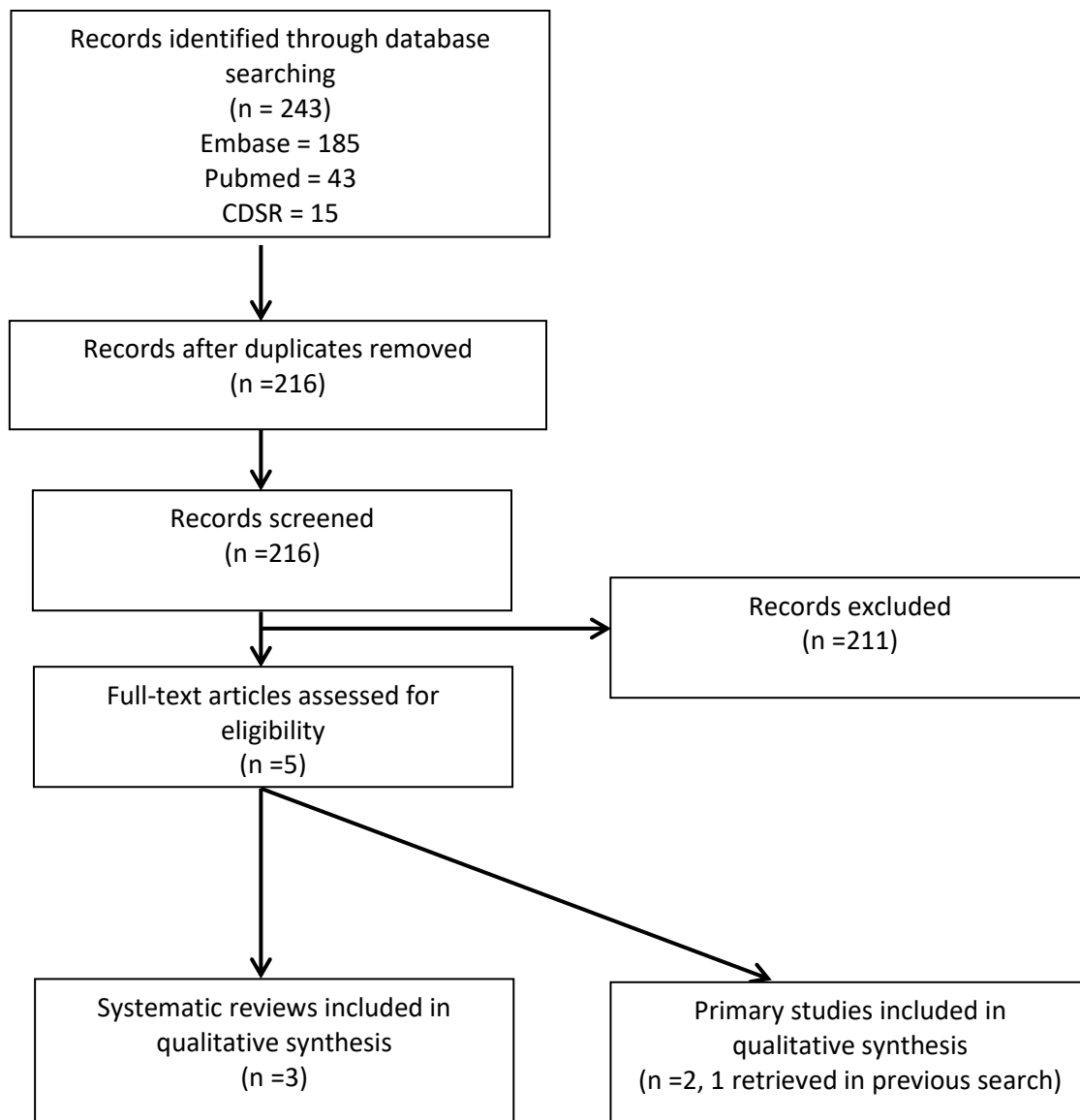


Figure e15: 18-1-19 run with temporal limit starting from 2017



Question 2.3: Is RLS/PLMS an independent risk factor of stroke?

Topic domain	Causation
P (target population)	General population; high risk population
Intervention (factors)	RLS/PLMS
Comparator	Absence of RLS/PLMS
Outcome	Ischaemic stroke and spontaneous intracerebral haemorrhage
Study design	cohort studies, case control studies, systematic reviews of these studies

Table e9: Systematic Reviews (3)

- Katsanos, A. H., M. Kosmidou, S. Konitsiotis, G. Tsigoulis, A. Fiolaki, A. P. Kyritsis and S. Giannopoulos (2018). "Restless legs syndrome and cerebrovascular/cardiovascular events: Systematic review and meta-analysis." *Acta Neurologica Scandinavica* 137(1): 142-148.
- Kendzerska, T., B. J. Murray, M. I. Boulos and M. Kamra (2017). "Incident cardiovascular events and death in individuals with restless legs syndrome or periodic limb movements in sleep: A systematic review." *Sleep* 40(3).
- Lin, T. C., B. Y. Zeng, Y. W. Chen, M. N. Wu, T. Y. Chen, P. Y. Lin, C. K. Wu, P. T. Tseng and C. Y. Hsu (2018). "Cerebrovascular Accident Risk in a Population with Periodic Limb Movements of Sleep: A Preliminary Meta-Analysis." *Cerebrovascular Diseases*: 1-9.

Another systematic review (Trenkwalder C, Allen R, Högl B, Paulus W, Winkelmann J. Restless legs syndrome associated with major diseases: A systematic review and new concept. *Neurology* 2016; 86:1336-43) was excluded since it did not perform a meta-analysis and scored as unacceptable quality (AMSTAR tool).

Author, Year (last search update)	Quality of the systematic review (Amstar score)	Design of included studies	Participants	Length of follow-up	Results	Quality of the studies included (according to the review Authors)	Notes
Katsanos 2018 (2017)	7/11	8 cohort studies 4 cohorts (3 studies) considered stroke as outcome	644506 patients (all studies on all outcomes). Not reported the number for stroke studies	Not reported	Stroke risk in RLS pts: unadjusted RR 1.68 (95% CI 1.12, 2.52); Adjusted HR 1.74 (0.81, 3.73)	Not reported	
Kendzerska 2017 (2016)	9/11	18 cohort studies (from 13 studies). 6 cohorts (4 studies) considered stroke as outcome	63824 patients included in the cohorts with stroke as outcome	2.1-10 years	Two of six cohort studies found an association between RLS and stroke (Elwood 2006; Molnar 2016)	According to the Quality in Prognosis Studies (QUIPS) Tool, 17 studies were assessed as having "Partly" or "No" on all bias criteria; 8 were of high quality	Qualitative analysis of results
Lin 2018 (2018)	9/11	5 case-control studies	9,823 patients with PLMS and 9,416 controls from 5 studies	<8 years	Significantly higher comorbidity rates of cerebrovascular accidents in the patients with PLMS than in the controls without PLMS (OR 1.267, p = 0.019)	7.25 according to Newcastle-Ottawa Quality Assessment Scale*	

*Newcastle-Ottawa Quality Assessment Scale: possible range 1 (lowest) to 9 (highest)

Table e10: Primary Studies (2)

- Cholley-Roulleau M, Chenini S, Béziat S, Guiraud L, Jausse I, Dauvilliers Y. Restless legs syndrome and cardiovascular diseases: A case-control study. *PLoS One* 2017 Apr 26;12(4):e0176552.
- Winkelman, J. W., T. Blackwell, K. Stone, S. Ancoli-Israel and S. Redline (2017). "Associations of Incident Cardiovascular Events With Restless Legs Syndrome and Periodic Leg Movements of Sleep in Older Men, for the Outcomes of Sleep Disorders in Older Men Study (MrOS Sleep Study)." *Sleep* 40(4).

Author, Year	Quality of the study	Study type (design)	Participants	Length of follow-up	Results	Notes
Cholley-Roulleau 2017 France	Class III	Case-control study	487 primary RLS (median age= 71 years; 67.4% women) according to the International RLS Study Group (IRLSSG) criteria. 91.7% under treatment 354 controls from patients entourage (e.g., spouse/partner, friends or	n.a.	Stroke: 4.72 % of RLS patients, 2.84% of controls. Unadjusted risk for stroke OR 1.69 (95% CI 0.80-3.61),	Pts from RLS patient association. They may not well represent RLS patients of the

			colleagues) (median age= 68years; 47.7% women).		Adjusted OR 1.51 (95% CI 0.68-3.37) for age, sex, BMI; OR 1.40 (95%CI 0.39-5.04) adjusted for age, sex, BMI, alcohol, antidepressant intake, sleep apnea, depression, Insomnia Severity Index and Epworth Sleepiness Scale Score	general population Almost RLS patients were treated. Possible recall bias
Winkelman 2017, USA	Class II	Cohort study	5994 community-dwelling men 65 years or older; 2823 with PSG data (mean age = 76.3 years)	8.7 ± 2.6 years	Multivariate adjusted association of RLS with stroke not significant (HR = 1.81, 95% CI, 0.83–3.94). Multivariate adjusted association of periodic limb movement with stroke not significant (HR = 0.97, 95% CI, 0.83–1.13).	MrOS Sleep Study RLS was identified from responses to two questions asked as part of MrOS sleep study. A periodic limb movement of sleep index (PLMI) was derived from unattended in-home polysomnography.

Question 2.4: Does treatment of RLS/PLMS prevent stroke?

Figure e16: 14-3-17 with systematic reviews filter with temporal limit starting from 1990

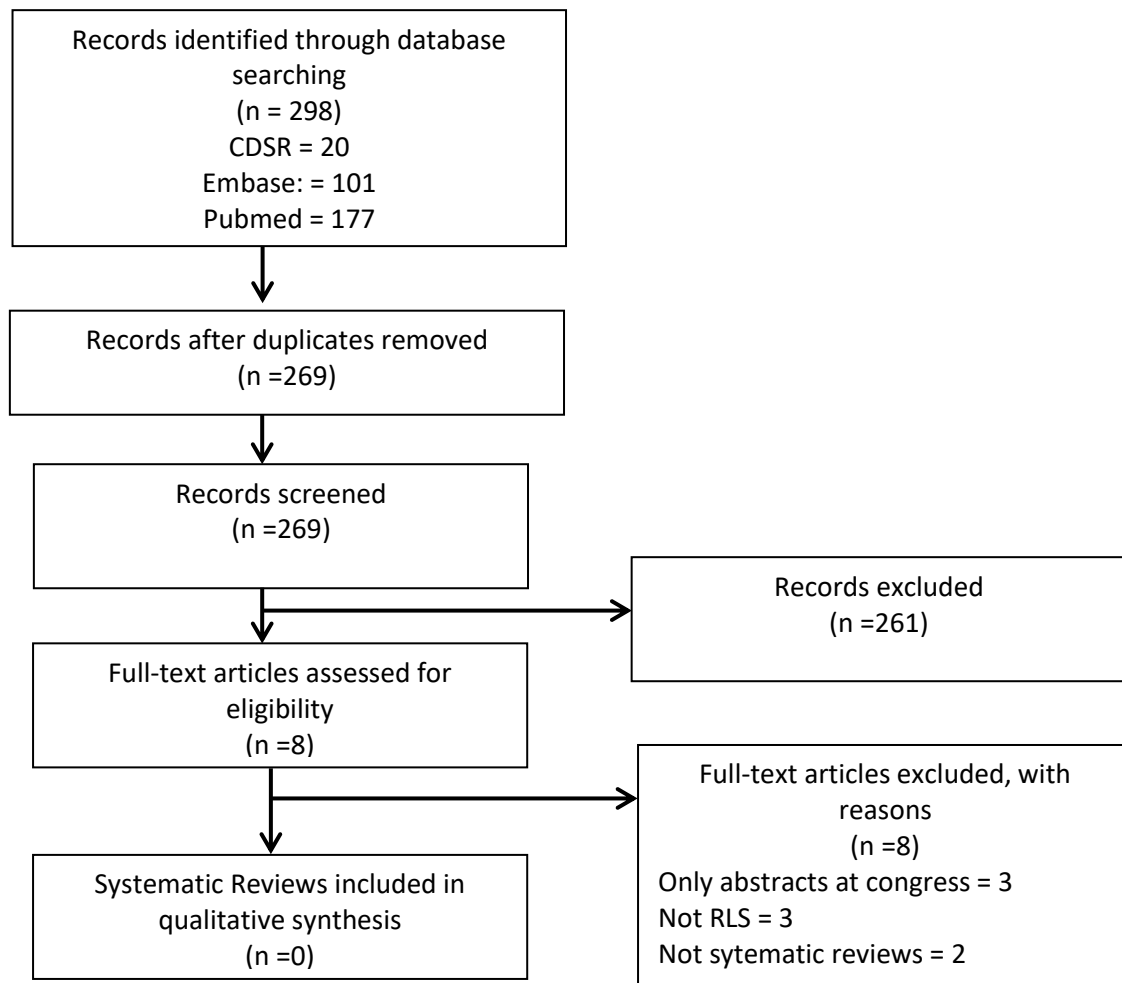


Figure e17: 3-5-17 run with RCTs and cohort studies filters with temporal limit starting from 1990

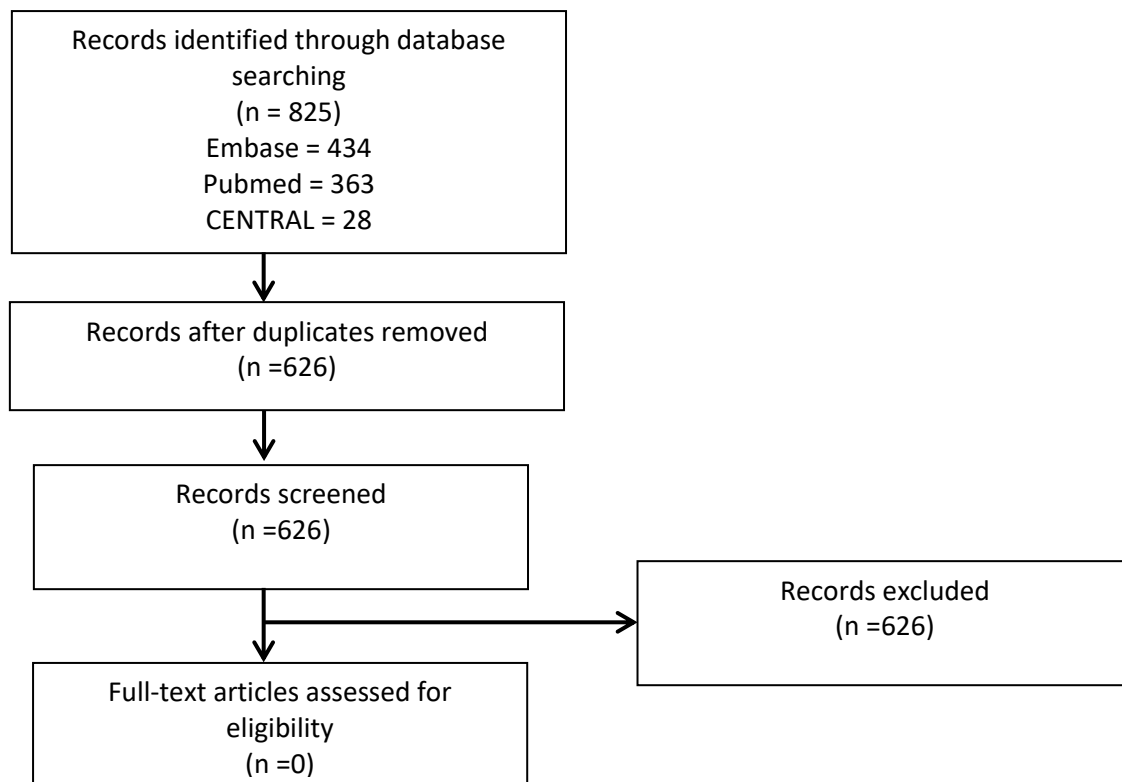
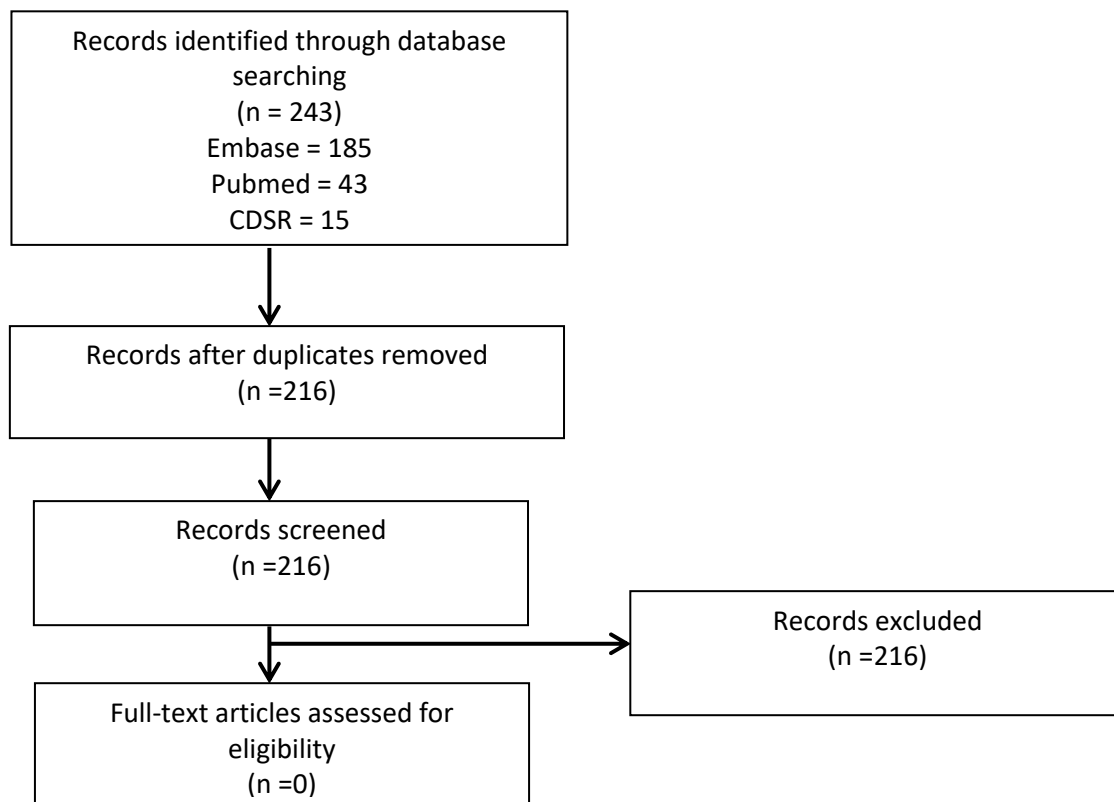


Figure e18: 18-1-19 run with temporal limit starting from 2017



Question 2.4: Does treatment of RLS/PLMS prevent stroke?

Topic domain	Therapeutic
P (target population)	Subjects with RLS/PLMS
Intervention	Treatment (any kind)
Comparator	No treatment, placebo
Outcome	Ischaemic stroke and spontaneous intracerebral haemorrhage
Study design	RCTs, cohort studies, systematic reviews of these studies

No studies retrieved

Question 3.1: What is the frequency of SDB in stroke patients?

Figure e19: 14-3-17 run with systematic reviews filter with temporal limit starting from 1990

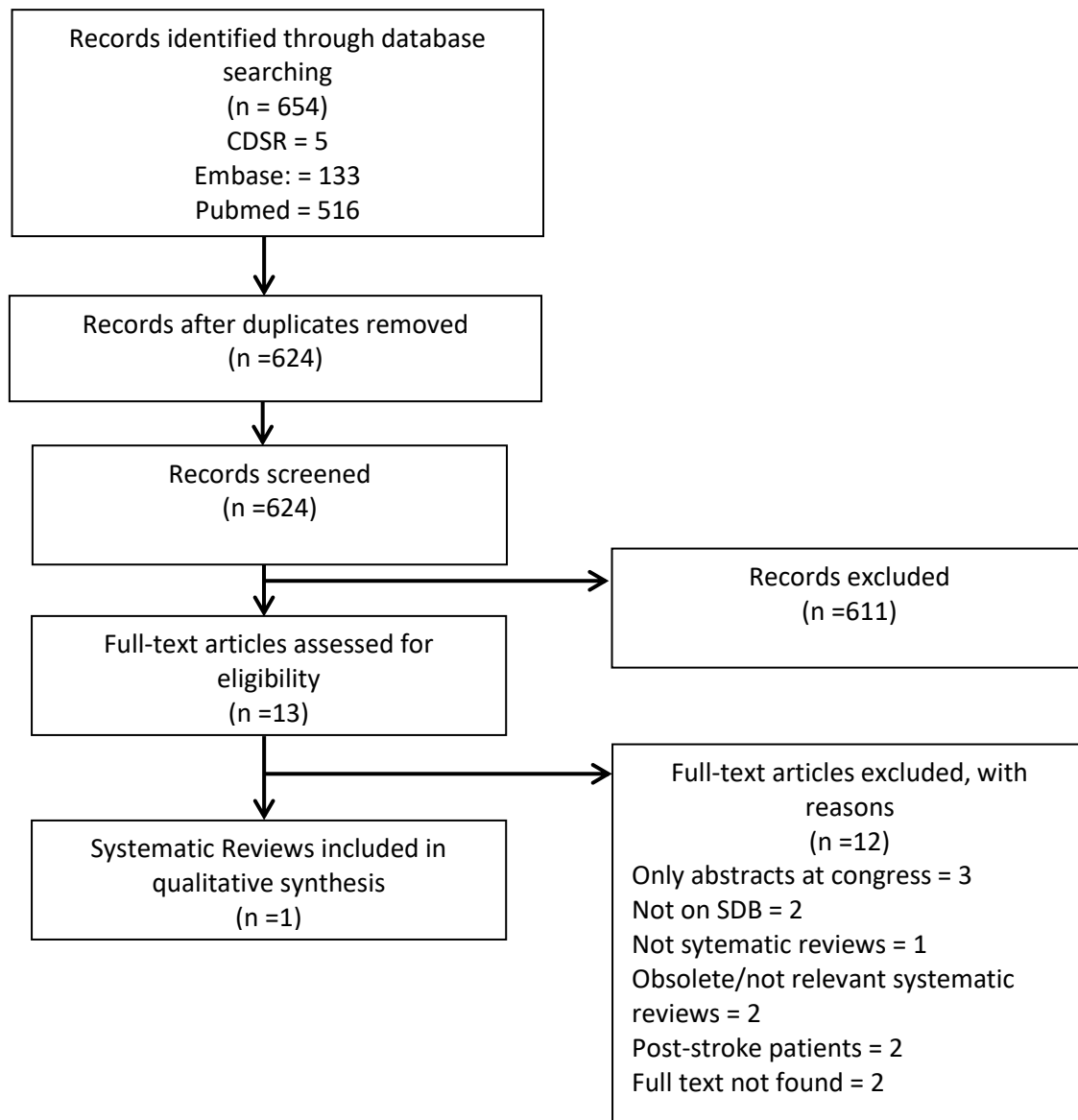
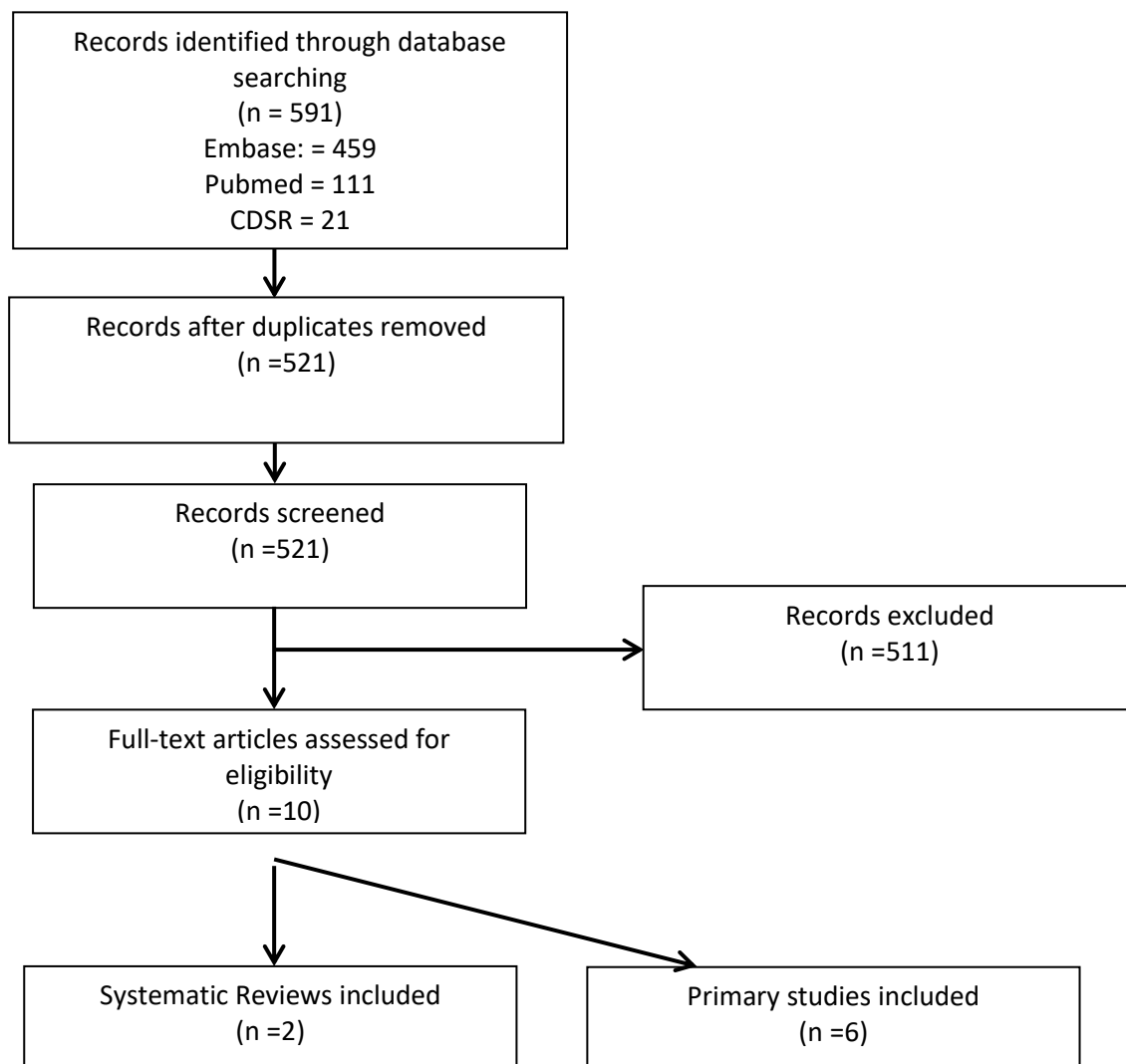


Figure e20: 18-1-19 run with temporal limit starting from 2017



Question 3.1: What is the frequency of SDB in stroke patients?

Topic domain	Prevalence
P (target population)	Ischemic stroke and spontaneous intracerebral haemorrhage (and matched controls from general population)
Intervention (factors)	n.a.
Comparator	n.a.
Outcome	Sleep disordered breathing
Study design	cross-sectional studies with concurrent matched controls, systematic reviews of these studies

Table e11: Systematic reviews (3)

- Dong, R., Z. Dong, H. Liu, F. Shi and J. Du (2018). "Prevalence, Risk Factors, Outcomes, and Treatment of Obstructive Sleep Apnea in Patients with Cerebrovascular Disease: A Systematic Review." *Journal of Stroke and Cerebrovascular Diseases* 27(6): 1471-1480.
- Johnson KG, Johnson DC. Frequency of sleep apnea in stroke and TIA patients: a meta-analysis. *J Clin Sleep Med* 2010;6:131-137.
- Seiler, A., M. Camilo, L. Korostovtseva, A. G. Haynes, A.-K. Brill, T. Horvath, M. Egger and C. L. Bassetti (2019). "Prevalence of sleep-disordered breathing after stroke and TIA." *Neurology*: 10.1212/WNL.0000000000006904.

Author, Year (last search update)	Quality of the systematic review (Amstar tool)	Included studies	Participants	Length of follow-up	Results	Quality of the studies included (according to the review Authors)	Notes
Dong 2018 (2017)	5/11	37	3,242	Time interval of sleep study after CV disease onset: within 7 days in 18 studies, 10 studies in 7- 28 days; 3 studies over 28 days	SDB with AHI > 5 was 70% (95% CI 62-79), with AHI > 30 was 30%.(23-37)	Not assessed	
Johnson and Johnson 2010 (2008)	6/11	29	2,343	1 week 16 studies, 7-28 days 8 studies), over 28 days in 5 studies	SDB with AHI > 5 was 72% (95% CI 60-81), with AHI > 30 was 29%.(21-37)	Not assessed	A funnel plot did not suggest publication bias.
Seiler 2019 (2017)	8/11	89	7,096	1 night -5.6 years	SDB with AHI > 5/h in 71% of participants (CI 66.6%–74.8%), AHI > 30/h in 30% (95% CI 24.4–35.5), high heterogeneity between studies -Mean AHI 26/h (CI 21.7-31.2) -sleep apnea testing is feasible with portable devices - no difference in SDB prevalence between assessment timepoints in cross-sectional analysis, but improvement in longitudinal studies	-very heterogeneous studies	- funnel plot asymmetries for the prevalence of AHI >5, >20, and>30. publication bias for the overall mean AHI (p < 0.001) and prevalence of SDB with AHI >5 (p < 0.001)

Table e12: Primary Studies (6)

- Boulos, M. I., S. Elias, A. Wan, J. Im, F. Frankul, M. Atalla, S. E. Black, V. S. Basile, A. Sundaram, J. J. Hopyan, K. Boyle, D. J. Gladstone, R. H. Swartz and B. J. Murray (2017). "Unattended Hospital and Home Sleep Apnea Testing Following Cerebrovascular Events." *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association* 26(1): 143-149.
- Festic, N., D. Alejos, V. Bansal, L. Mooney, P. A. Fredrickson, P. R. Castillo and E. Festic (2018). "Sleep apnea in patients hospitalized with acute ischemic stroke: Underrecognition and associated clinical outcomes." *Journal of Clinical Sleep Medicine* 14(1): 75-80.
- Huhtakangas, J. K., J. Huhtakangas, R. Bloigu and T. Saaresranta (2017). "Prevalence of sleep apnea at the acute phase of ischemic stroke with or without thrombolysis." *Sleep medicine* 40: 40-46.
- Kumar, R., J. C. Suri and R. Manocha (2017). "Study of association of severity of sleep disordered breathing and functional outcome in

stroke patients." Sleep medicine 34: 50-56.

- Menon, D., S. Sukumaran, R. Varma and A. Radhakrishnan (2017). "Impact of obstructive sleep apnea on neurological recovery after ischemic stroke: A prospective study." Acta neurologica Scandinavica 136(5): 419-426.
- Scherbakov, N., A. Sandek, N. Ebner, M. Valentova, A. H. Nave, E. A. Jankowska, J. C. Schefold, S. von Haehling, S. D. Anker, I. Fietze, J. B. Fiebach, K. G. Haeusler and W. Doeblner (2017). "Sleep-Disordered Breathing in Acute Ischemic Stroke: A Mechanistic Link to Peripheral Endothelial Dysfunction." Journal of the American Heart Association 6(9).

Author, Year	Quality of the study	Study type (design)	Participants	Length of follow-up	Results	Notes
Boulos 2017 Canada	Class III	Cross-sectional study	102 inpatients or outpatients who had stroke or TIA	1.7 days	OSA (AHI ≥ 15 or AHI ≥ 5 with a documented lowest nocturnal oxygen desaturation $\leq 88\%$) prevalence: 63.4%	
Festic 2018 US	Class III	Retrospective cohort	989 patients hospitalized with acute ischemic stroke	Not reported	190 (19%) were considered to have sleep apnea	Probable underrecognition of sleep apnea
Huhtakangas 2017 Finland	Class II	Prospective cohort	204 consecutive ischemic stroke patients either receiving (110) or not receiving thrombolysis (94)	2 days	AHI $> 5/h$: 91.2% of patients; higher in the thrombolysis (96.4%) compared to the nonthrombolysis (85.1%) group ($p = 0.007$). Mean baseline AHI 33.7/h in the thrombolysis group compared to 26.8/h in the nonthrombolysis group ($p = 0.017$).	
Kumar 2017 India	Class III	Prospective cohort	50 patients: 30 with ischemic stroke and 20 with hemorrhagic stroke	Not reported	AHI > 5 78% patients AHI > 15 46% patients AHI > 30 18% patients	
Menon 2017 India	Class III	Prospective cohort	99 ischemic stroke patients	Not reported	OSA 59.6% AHI 5-15 27.3% AHI 15-30 17.2% AHI > 30 15.2%	
Scherbakov 2017 Germany	Class II	Prospective cohort	101 ischemic stroke patients	4(+/-2 days)	SDB (AHI ≥ 5) 57%	

Question 3.2: Does SDB affect mortality and outcome after stroke?

Figure e21: 14-3-17 run with systematic reviews filter with temporal limit starting from 1990

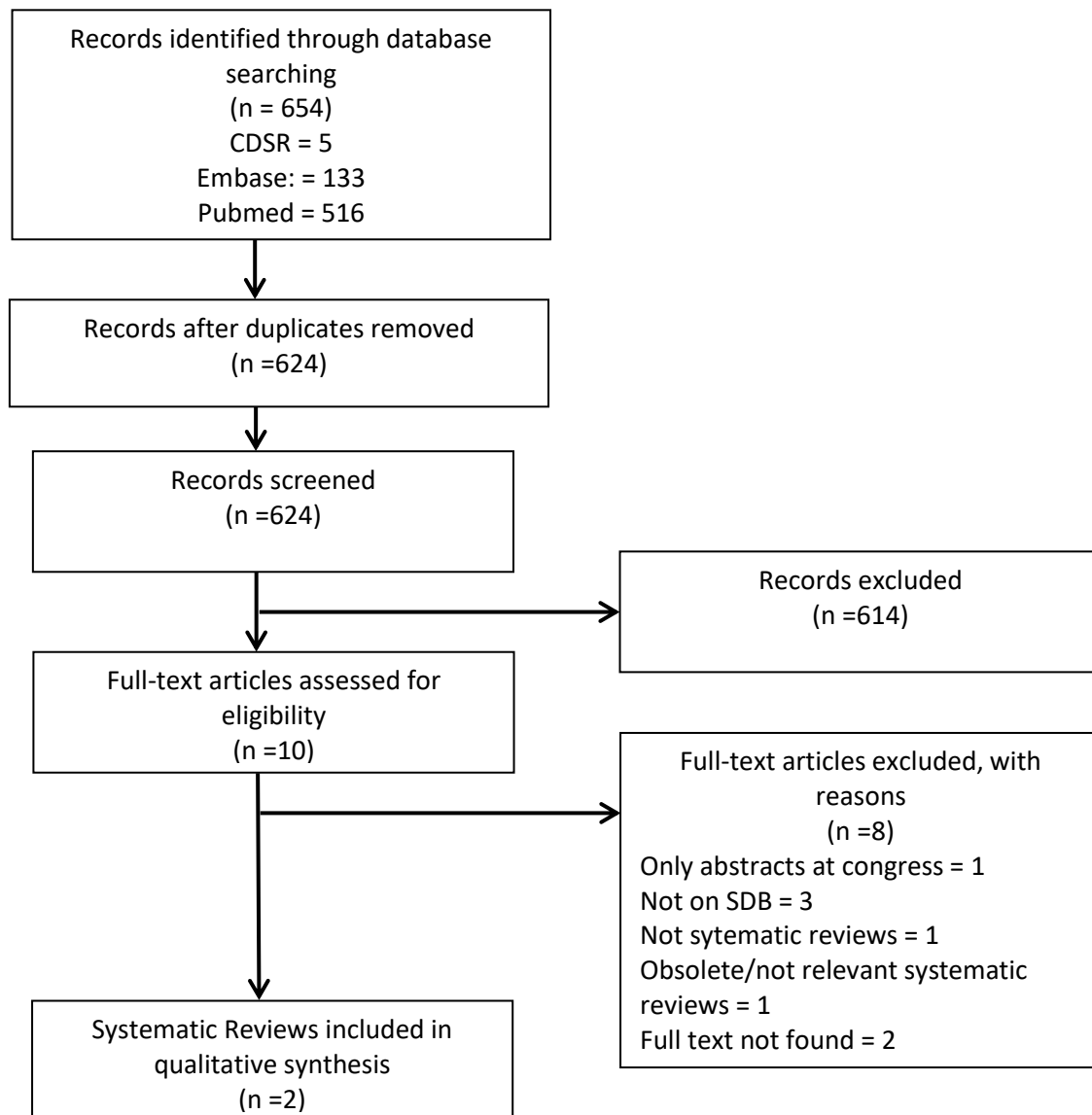


Figure e22: 3-5-17 run with Cohort Studies / Case Control Studies filters with temporal limit starting from the time limit of the most updated systematic review (2014 included)

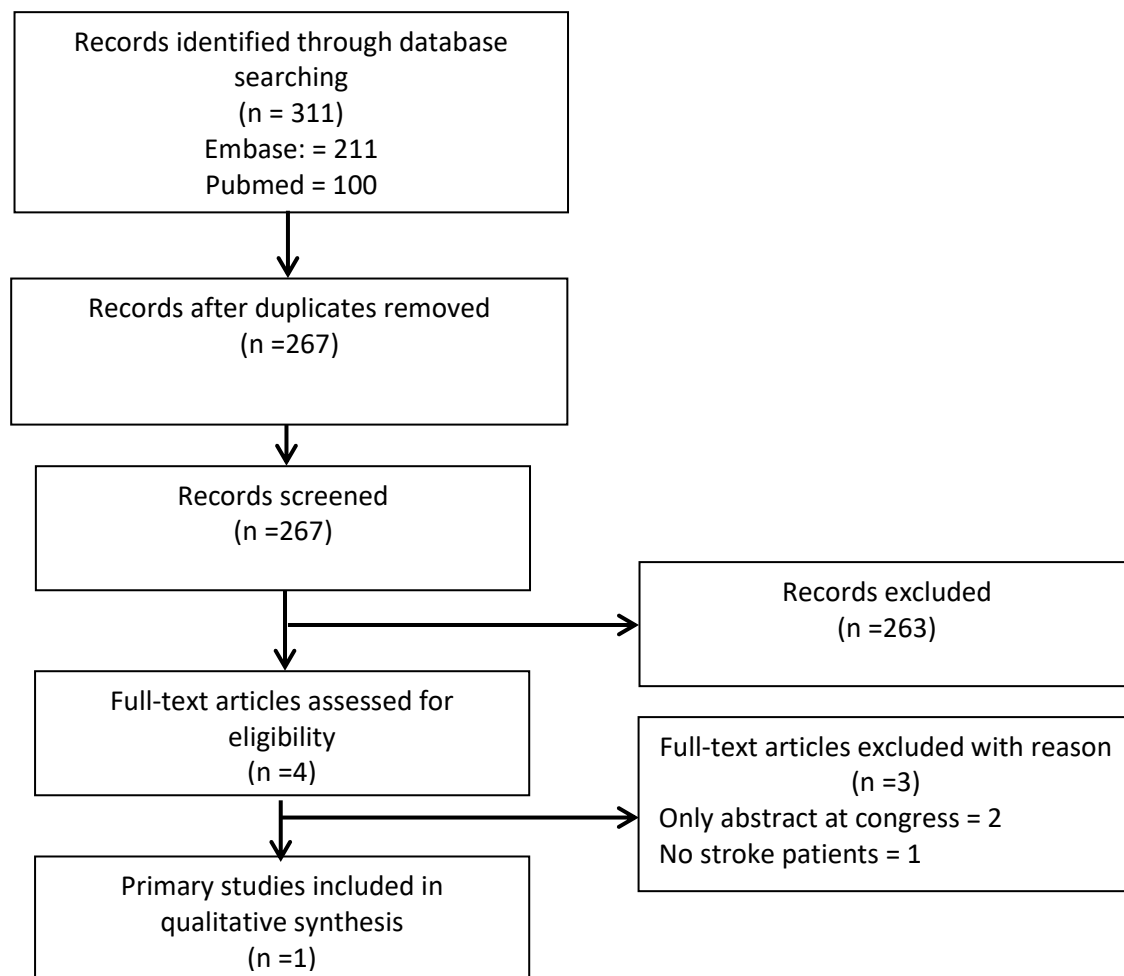
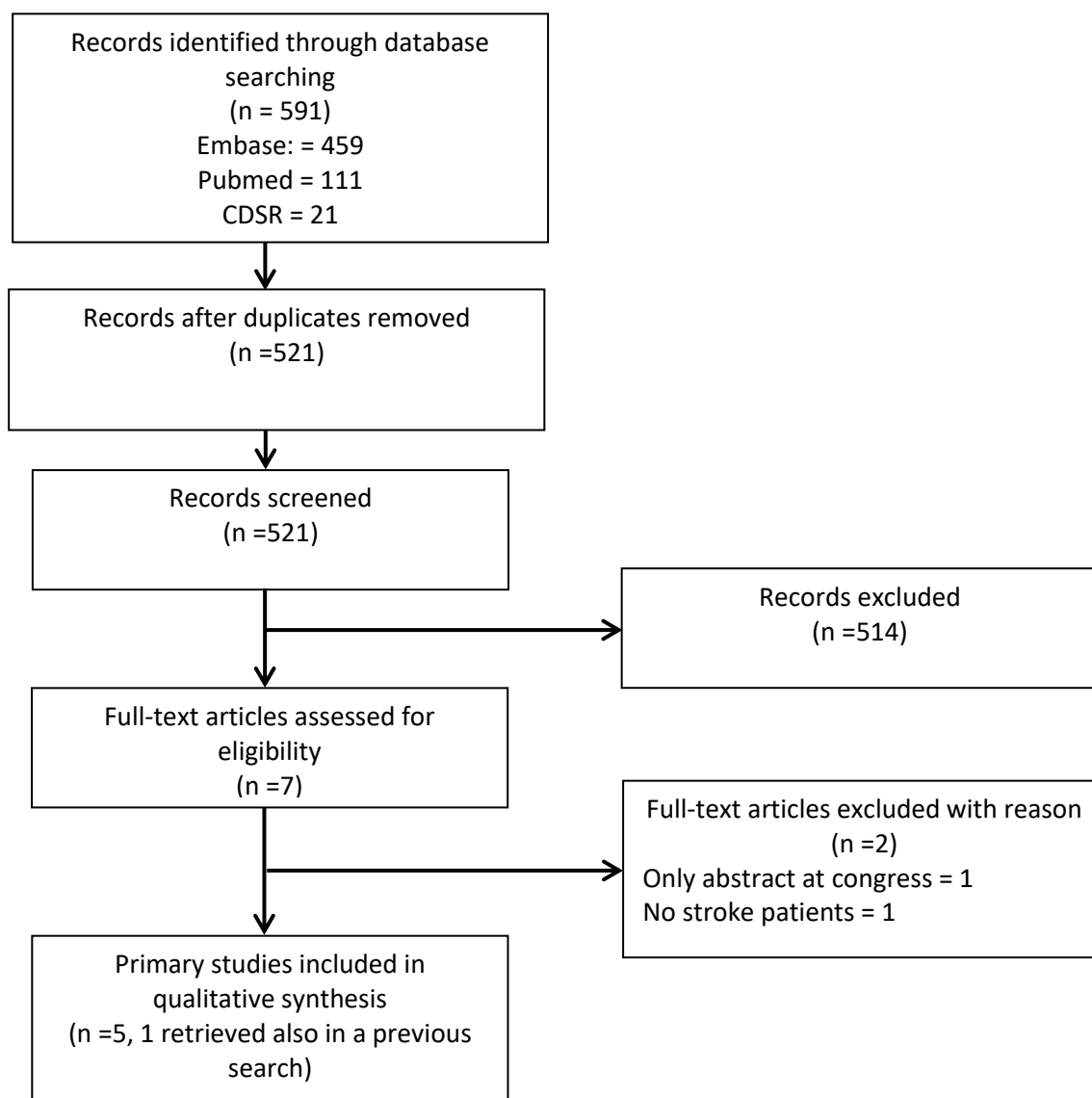


Figure e23: 18-1-19 run with temporal limit starting from 2017



Question 3.2: Does SDB affect mortality and outcome after stroke?

Topic domain	Prognosis
P (target population)	Ischaemic stroke and spontaneous intracerebral haemorrhage
Intervention (factors)	Sleep disordered breathing (differentiation of central and obstructive sleep apnoea), preexisting SDB and SDB secondary to incidents.
Comparator	Absence of sleep disordered breathing
Outcome	Mortality (all cause; stroke related; vascular) Disability (Rankin; Barthel; other) Recurrence
Time	After ≥6 months after incident
Study design	cohort studies, systematic reviews of these studies

Table e13: Systematic reviews (2)

- Birkbak, Johannes, Alice J. Clark, and Naja Hulvej Rod. 2014. 'The effect of sleep disordered breathing on the outcome of stroke and transient ischemic attack: a systematic review', Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine, 10: 103-08.
- Xie, Wuxiang, Fanfan Zheng, and Xiaoyu Song. 2014. 'Obstructive sleep apnea and serious adverse outcomes in patients with cardiovascular or cerebrovascular disease: a PRISMA-compliant systematic review and meta-analysis', Medicine, 93: e336.

Author, Year (last search update)	Quality of the systematic review (Amstar tool)	Included studies	Participants	Prognostic factor	Length of follow-up	Results	Quality of the studies included (according to the review Authors)	Notes
Birkbak 2014 (2012)	7/11	7 cohort studies, 1 cross-sectional study	1203 patients (range 47-174) stroke and TIA patients Male: 41-87% Age (mean/SD): 65/14-79/11	AHI	6 months-10 years 1 study cross-sectional	Higher risk of recurrent strokes or TIA's (2 cohorts, 1 cross-s.) Higher risk of recurrent non-fatal cardiovascular events (1 cohort). Relationship between OSA severity and stroke recurrence (cross-s.) All-cause mortality/fatal cardiovascular events (6 cohorts) Premature death among stroke pts. (1 cohort)	Qualitative risk of bias assessment	Different levels of severity as measured by the AHI. Adjustments for confounders heterogeneous between the studies. No PSG. Huge variety of time intervals between stroke and OSA diagnosis
Xie 2014 (2014)	8/11	13 hospital-based cohort studies. 5 on stroke, 11 on all cause death or cardiovascular death	860 on stroke 1930 on mortality Age range 56-73 yrs. Males 40.9-86.8%.	AHI	0.5-7 yrs.	OSA significantly associated with risk of stroke, and all-cause mortality after stroke. Pooled relative risks were 1.94 (95% CI, 1.29–2.92) for stroke, and 1.59 (95% CI, 1.33–1.89) for all-cause mortality.	Modified scoring system*: 6 studies scored ≥5 (high quality), 3 studies scored equal to 4, 4 studies scored equal to 3 (low quality).	Advantages: Prospective cohort studies; no evidence of significant between-study heterogeneity; no change in sensitivity analyses for the outcomes of stroke and all-cause mortality. Limitations: no adjustments for cv confounders in primary studies; inconsistent range of AHI; only hospital-based studies.

*Modified scoring system on the basis of the PRISMA statement: total score of 0 to 6 points (6 refers to the highest quality)

Table e13: Primary Studies (5)

- Festic, N., D. Alejos, V. Bansal, L. Mooney, P. A. Fredrickson, P. R. Castillo and E. Festic (2018). "Sleep apnea in patients hospitalized with acute ischemic stroke: Underrecognition and associated clinical outcomes." *Journal of Clinical Sleep Medicine* 14(1): 75-80.
- Kim, T. J., S. B. Ko, H. G. Jeong, K. Nam, H. Mo, S. J. An, B. W. Yoon, C. K. Kim, Y. Kim and H. A. Choi (2017). "Nocturnal desaturation is associated with neurological deterioration following ischemic stroke: A retrospective observational study." *Journal of Clinical Sleep Medicine* 13(11): 1273-1279.
- Kumar, R., J. C. Suri and R. Manocha (2017). "Study of association of severity of sleep disordered breathing and functional outcome in stroke patients." *Sleep medicine* 34: 50-56.
- Menon, D., S. Sukumaran, R. Varma and A. Radhakrishnan (2017). "Impact of obstructive sleep apnea on neurological recovery after ischemic stroke: A prospective study." *Acta neurologica Scandinavica* 136(5): 419-426.
- Ponsaing, L. B., H. K. Iversen and P. Jennum (2017). "Polysomnographic indicators of mortality in stroke patients." *Sleep & breathing* 21(2): 235-242.

Author, Year	Quality of the study	Study type (design)	Participants	Prognostic factor (confounders)	Length of follow-up	Results	Notes
Festic 2018 US	Class III	Retrospective cohort	989 patients hospitalized with acute ischemic stroke	Sleep Apnea (congestive heart failure, NIHSS scale, GCS)	Not reported	OSA was not a significant predictor in the multivariate model in addition to NIHSS and GCS (respectively independent significant predictors of hospital mortality: OR 1.06, 95% CI 1.01–1.11, and OR 0.61, 95% CI 0.51–0.69, $P < .001$).	Sleep Apnea diagnosed by PSG without specification
Kim 2017 Korea	Class III	Retrospective cohort	276 patients with ischemic stroke admitted to the stroke unit	nocturnal oxygen desaturation (NOD) with ODI ≥ 5 events/h (confounders: stroke mechanism, nocturnal mean blood pressure, mean NOD, total cholesterol)	7 days for the primary outcome Early neurological deterioration	NOD in the END group: 45.2% versus 12.8%, $p < .001$. After adjusting for confounders, NOD was independently associated with END (odds ratio 7.57; 95% confidence interval 3.14–18.27).	(Early neurological deterioration [END] defined as an increase in NIHSS score ≥ 2 points from the baseline NIHSS score during the 7 days after symptom onset)
Kumar 2017 India	Class III	Prospective cohort	50 patients: 30 with ischemic stroke and 20 with hemorrhagic stroke	AHI4%	6 weeks after the PSG	AHI4% predictive (OR 1.20; 95% CI 1.01-1.43) of the functional dependence (Barthel Index) AHI4% (OR 1.14; 95% CI 1.03-1.25) and body mass index (OR 0.75; 95% CI 0.59-0.96) predictive of poor outcome (modified Rankin Scale)	
Menon 2017	Class III	Prospective cohort	99 ischemic stroke patients admitted to the Comprehensive Centre for Stroke Care with onset within 2 weeks 40.4% without OSA, 59.6% with OSA (AHI > 5) Men 68.7% Mean age 60.1 \pm 14 years Mean NIHSS on admission: OSA group: 11.03, non-OSA group:	SDB (age, stroke etiology)	3 months and later follow-up at variable time points (mean 22.4 months, range 3-39 months)	SDB effect on mortality: a multivariate analysis found no association of OSA and mortality. SDB effect on clinical outcome: - No sign. interaction between OSA status and change in mRS from admission to 3 months. - OSA was associated with poor functional outcome (mRS >3) in a multivariate analysis	- the study does not justify the conclusion that SDB is associated with poor outcome as no comparison of groups at a defined follow-up adjusted for relevant confounders (particularly baseline NIHSS)

			9.17, P=0.073 Mean mRS on admission: OSA group: 3.76, non-OSA group: 3.32, P=0.013			using cox regression.	is provided. - details of outcome assessment not reported.
Ponsaing 2017 Denmark	Class III	Retrospective cohort	57 stroke and 6 TIA patients in a stroke unit	AHI 2–24/h vs >24/h	19–37-month	Highest mortality risk (HR 9.71; 95 % CI 1.20–78.29; p = 0.0328) for AHI>24 AHI > 24 do not affect survival, when adjusted for age (p = 0.0897), disability measured with the mBI (p = 0.0975), atrial flutter/fibrillation (p = 0.0610).	Everybody with an AHI <15 survived the follow-up period. For these reason survival analysis was tested on two equally sized groups (based on the median value for the given parameter).

Question 3.3: Does treatment of SDB have any impact on mortality and outcome after stroke?

Figure e24: 14-3-17 run with systematic reviews filter with temporal limit starting from 1990

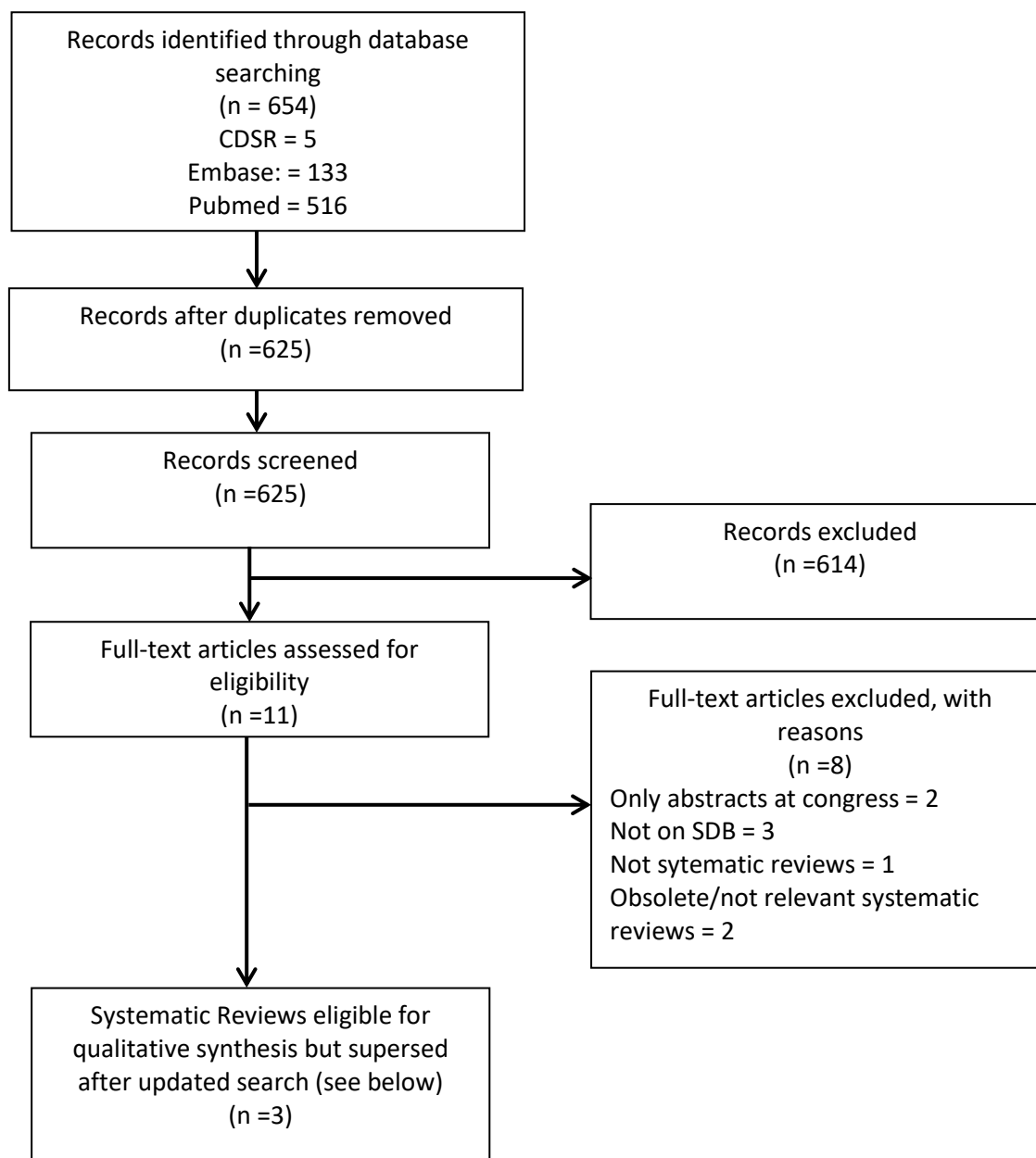


Figure e25: 13-7-17 run with Cohort Studies / RCTs studies filters with temporal limit starting from the time limit of the most updated systematic review (2015 included)

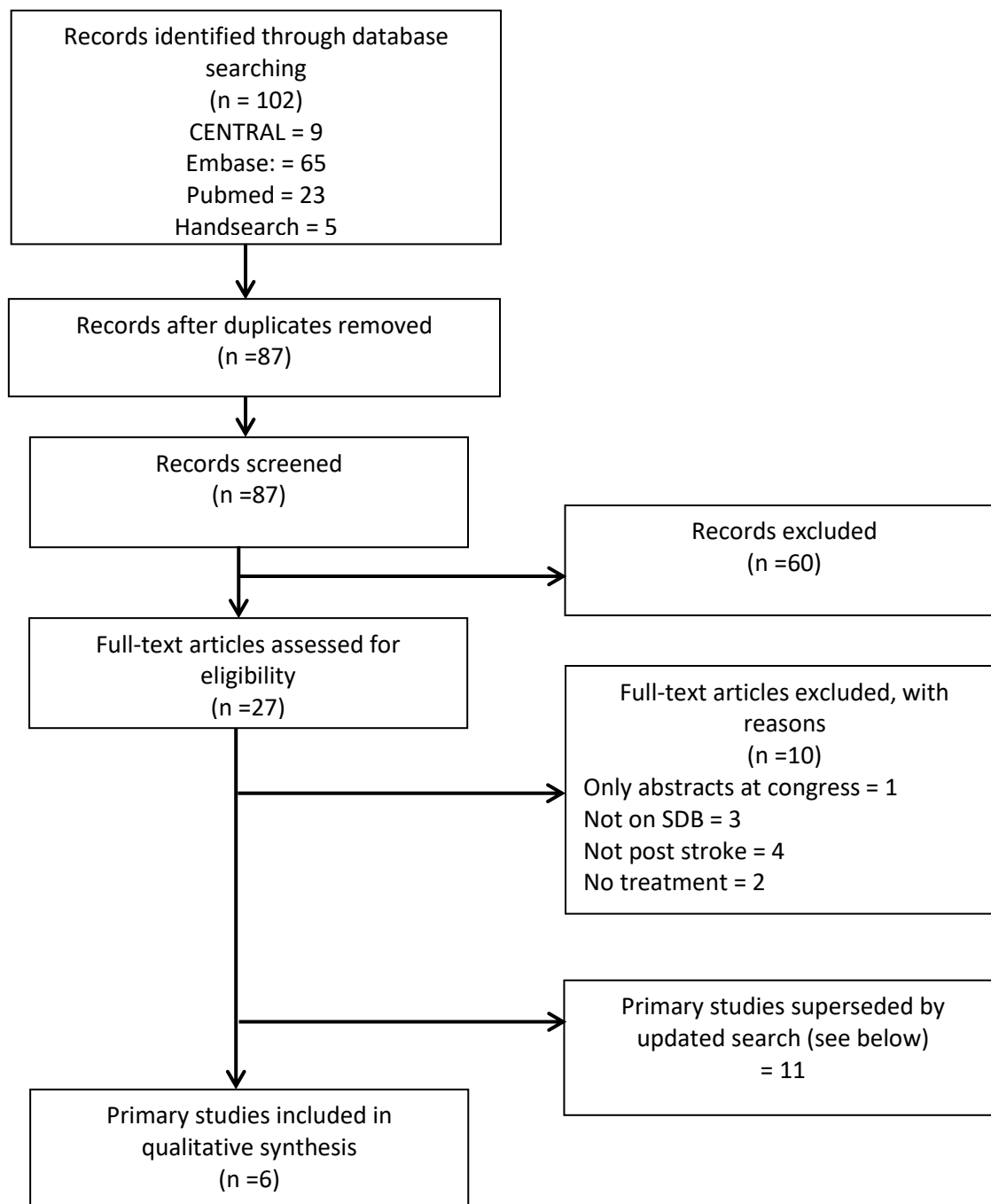
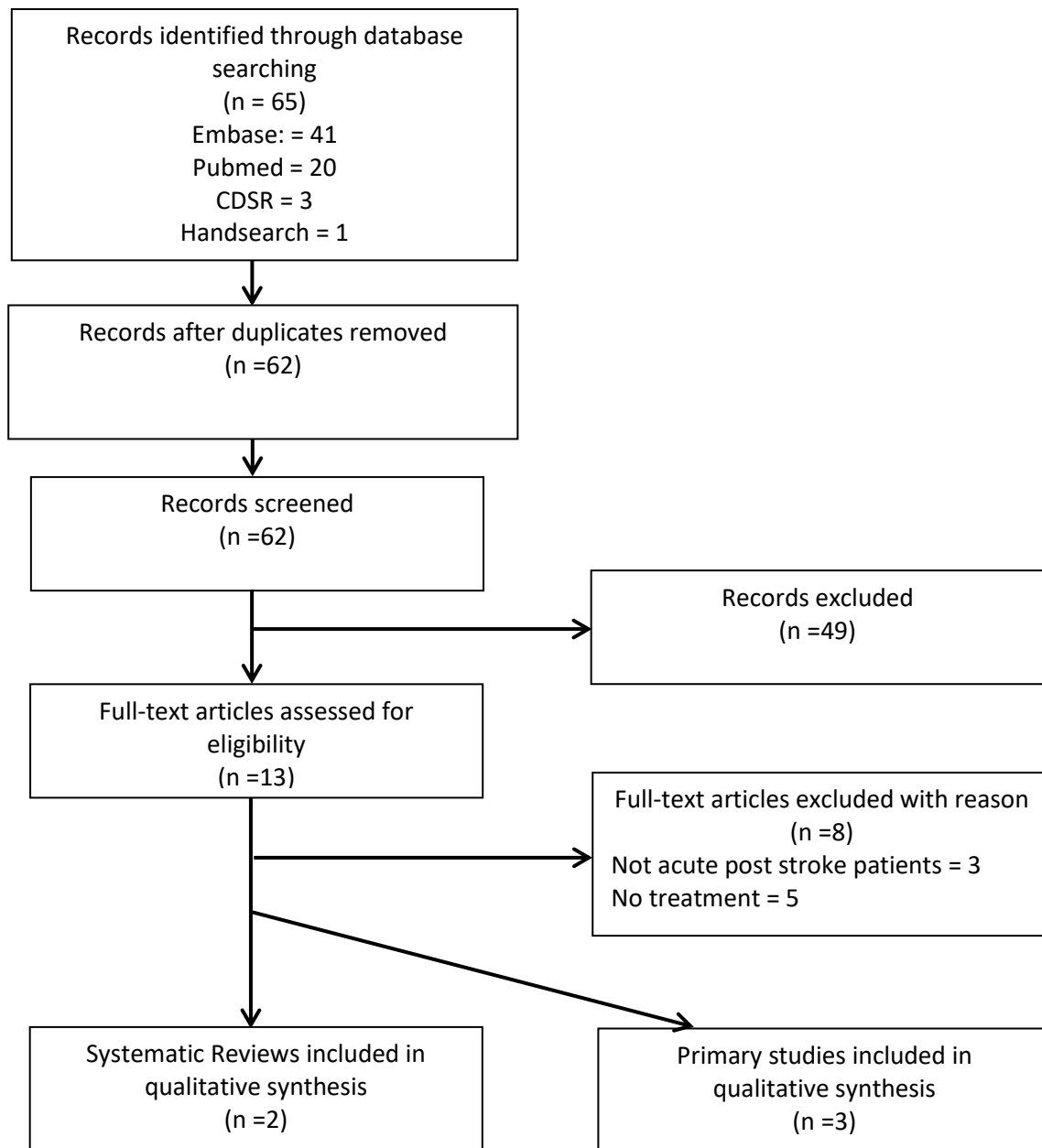


Figure e26: 18-1-19 run with temporal limit starting from 2017



Question 3.3: Does treatment of SDB have any impact on mortality and outcome after stroke?

Topic domain	Therapy
P (target population)	Ischaemic stroke and spontaneous intracerebral haemorrhage
Intervention	CPAP treatment, oxygen, other therapies
Comparator	No treatment (optimal conventional treatment of stroke), placebo, other treatment
Outcome	Mortality (all cause; stroke related; vascular) Disability (Rankin; Barthel, other) Recurrence
Time	After ≥6months treatment initiation
Study design	RCTs, cohort studies, systematic reviews of these studies (meta-analysis currently performed)

Table e15: Systematic reviews (2) on CPAP or non-invasive ventilation as treatment for SDB

- Brill, A.-K., T. Horvath, A. Seiler, M. Camilo, A. G. Haynes, S. R. Ott, M. Egger and C. L. Bassetti (2018). "CPAP as treatment of sleep apnea after stroke." *Neurology* 90(14): e1222.
- Tsigoulis, G., A. V. Alexandrov, A. H. Katsanos, K. Barlinn, R. Mikulik, V. Lambadiari, A. Bonakis and A. W. Alexandrov (2017). "Noninvasive Ventilatory Correction in Patients With Acute Ischemic Stroke: A Systematic Review and Meta-Analysis." *Stroke* 48(8): 2285-2288.

Author, Year (last search update)	Quality of the systematic review (Amstar tool)	Included studies	Participants	Length of follow-up	Results	Quality of the studies included (according to the review Authors)
Brill 2018 (2016)	9/11	10 RCTs with additional individual patient data of n=5 studies	564	8 days - 5.6 years	Mean CPAP usage 4.53h/night Greater neurofunctional improvement (NIHSS/CSS) with CPAP (SMD 0.5406, 95% CI 0.0263-1.0548, p= 0.00394; I2 78.9%), best results in studies with early initiated treatment Long-term cardiovascular survival improved with CPAP in 1 trial, no difference in overall event-free survival, the other RCTs not powered or designed for the assessment of cardiovascular events	Mixed risk of bias, less risk of bias in the newer studies (Cochrane risk of bias tool)
Tsigoulis 2017 (2016)	9/11	5 RCTs, 1 prospective matched cohort study	389	7 days -5.6 years	Greater Neurofunctional improvement during the first days after stroke with early NIVC (= non-invasive ventilator correction) (SMD 0.38, CI 0.11-0.66, p=0.007; I2=0%; P=0.89) No difference on risk of vascular events (RR 0.53, CI 0.25-1.14, p=0.11; I2=0) and mortality (RR 0.71, CI 0.37-1.3, p=0.3	Mixed risk of bias (Cochrane risk of bias tool)

Table e16: Primary Studies (2) on CPAP or non-invasive ventilation as treatment for SDB

- Bravata, D. M., E. J. Miech, M. S. Matthias, L. S. Williams, C. Austin, J. Ferguson, R. L. Roudebush, C. S. Ivan, J. D. Fleck, J. Sico, C. A. Vaz Fragoso, J. Concato, R. Lampert, L. Tobias, R. Radulescu, L. Iannone, C. Won, H. Klar Yaggi, S. Ofner, S. Taylor and L. Qin (2018). "Diagnosing and treating sleep apnea in patients with acute cerebrovascular disease." *Journal of the American Heart Association* 7(16).
- Gupta, A., G. Shukla, M. Afsar, S. Poornima, V. Goyal, C. Srivastava, D. Vibha, M. Behari and R. M. Pandey (2018). "Role of positive airway pressure therapy for Obstructive sleep apnea in patients with stroke: A randomized controlled trial." *Journal of Clinical Sleep Medicine* 14(4): 511-521.

Author, Year	Quality of the study AAN scheme	Study design	Participants	Intervention and comparison	Length of follow-up	Results	Notes
Bravata 2018 USA	Class II	RCT	252 TIA or ischemic stroke patients within 1 week of neurological symptom onset (84, control; 86,	2 strategies (standard [protocol focused on technical issues related to the CPAP equipment] or enhanced	1 year	Intention-to-treat analyses, changes: National Institutes of Health Stroke Scale and modified Rankin Scale scores similar across groups. In as-treated analyses	Open. Analysis of the secondary objective

			standard; 82, enhanced) OSA prevalence (AHI ≥ 5): control, 69%; standard, 74%; and enhanced, 80%	[focused on delivering the patient-tailored behavioral adherence program]] for the diagnosis and treatment (auto-titrating CPAP) of OSA versus usual care		among patients with OSA, increasing continuous positive airway pressure use associated with improved National Institutes of Health Stroke Scale score ($p=0.0064$) and improved modified Rankin Scale score ($p=0.0237$).	
Gupta 2018 India	Class II	RCT	70 ischemic stroke (6 months prior to enrollment) with AHI > 15	CPAP treatment vs non-CPAP (best medical treatment) groups	12 months	Primary outcome: 1 vascular event (3.33%) in the CPAP group vs 6 events (15%) in the non-CPAP group ($P = 0.23$). Secondary outcome: Modified Rankin scale score improvement by ≥ 1 CPAP group 53% vs non-CPAP group 27% ($p=0.03$).	Open trial. Attrition bias.

Table e17: Primary Studies (7) using other interventions

- Brill AK, Rosti R, Hefti JP, Bassetti C, Gugger M, Ott SR. Adaptive servo-ventilation as treatment of persistent central sleep apnea in post-acute ischemic stroke patients. *Sleep Med.* 2014; 15:1309-1313.
- Brunner H. Success and failure of mirtazapine as alternative treatment in elderly stroke patients with sleep apnea-a preliminary open trial. *Sleep Breath.* 2008; 12:281-285.
- Frohnhofen H, Olthmann B, Orth G, Hagen O, Rang P, Meier U. Nocturnal oxygen therapy and cognitive function in conscious elderly patients with ischemic stroke and obstructive sleep apnea (osa) - a controlled study. *Somnologie* (1998) 2, 172-183. 1998.
- Haba-Rubio J, Andries D, Rey V, Michel P, Tafti M, Heinzer R. Effect of transnasal insufflation on sleep disordered breathing in acute stroke: A preliminary study. *Sleep Breath.* 2012;16:759-764.
- Svatikova A, Chervin RD, Wing JJ, Sanchez BN, Migda EM, Brown DL. Positional therapy in ischemic stroke patients with obstructive sleep apnea. *Sleep Med.* 2011;12:262-266.
- Wheeler NC, Wing JJ, O'Brien LM, Hughes R, Jacobs T, Claflin E, et al. Expiratory positive airway pressure for sleep apnea after stroke: A randomized, crossover trial. *J Clin Sleep Med.* 2016; 12:1233-1238.
- Ye D, Chen C, Song D, et al. Oropharyngeal Muscle Exercise Therapy Improves Signs and Symptoms of Post-stroke Moderate Obstructive Sleep Apnea Syndrome. *Front Neurol.* 2018;9:912.

Author, Year	Quality of the study AAN scheme	Study design	Participants	Intervention and comparison	Length of follow-up	Results	Notes
Brill 2014 Switzerland	Class IV	Case-series (before-after analysis)	15 stroke patients (median 11 months before) with AHI>5	Adaptive servoventilation	6 months	AHI improved from 46.7 ± 24.3 to $8.5 \pm 12/h$, $p = 0.001$ ESS reduced from 8.7 ± 5.7 to 5.6 ± 2.5 , $p = 0.08$)	Feasibility study
Brunner 2008 Germany	Class IV	Open label (before-after analysis)	10 stroke patients (mean 51.9 ± 9.4 days before), with Barthel Index 21.5 ± 7.7	Mirtazapine	51.9 ± 9.4 days	A moderate increase in respiratory disturbance index ($137.4 \pm 15.3\%$ of baseline) during initial mirtazapine administration (intake duration 15.8 ± 5.5 days). After 51.9 ± 8.4 days, the respiratory disturbance index was either reduced (51.9% in "responders") or increased (154.4% in "non-responders").	Feasibility study
Frohnhofen 1998 Germany	Class III	RCT	29 stroke patients (mean 27 ± 17 days before; Scandinavian stroke scale 33 ± 6) with AHI ≥ 10	Nocturnal oxygen 3 l/min (therapy group, n=15) or nocturnal oxygen 0,5 l/min (control group, n=14)	1 week	About 50% of the patients of the therapy group showed a significant improvement in cognitive function tests after one week of oxygen therapy compared with the control	

						group. The improvements were related to the visual cognitive function, word fluency and spatial recognition.	
Haba-Rubio 2012 Switzerland	Class IV	Open label (before-after analysis)	10 stroke patients (1-15 days before; NIH stroke scale 4±4.3) with AHI>15	Transnasal insufflation (18 L/min)	1 night	TNI decreased the AHI from 40.4 ± 25.7 to 30.8 ± 25.7/h (p = 0.001) and the oxygen desaturation index >3% from 40.7 ± 28.4 to 31 ± 22.5/h (p = 0.02).	Feasibility study
Svatikova 2011 USA	Class III	Cross over RCT	18 stroke patients (<14 days before; NIH stroke scale 3) with AHI≥5	Positional therapy (a therapeutic pillow on either the first or second night) vs hospital pillow and were positioned ad lib	1 night	The AHI was reduced by 19.5% (95% CI: 4.9-31.9%, p=0.011), when using positional therapy compared to sleeping ad lib	Feasibility study
Wheeler 2016 USA	Class III	Cross over RCT	19 stroke patients (<14 days before) with AHI>15	Nasal expiratory positive airway pressure vs CPAP	1 night	Nasal expiratory positive airway pressure treatment was associated with a nonsignificant absolute difference in AHI of -5.73 events/h in the primary analysis (p = 0.183, 95% confidence interval -14.4, 2.97)	
Ye 2018 China	Class II	Open RCT	50 post-stroke patients with moderate OSAS	oropharyngeal muscle exercises (25 pts) vs sham therapy of deep breathing (25 pts)	6-week	The apnea–hypopnea index, snore index, arousal index, and minimum oxygen saturation improved after exercise (P < 0.05). Oropharyngeal muscle exercises improved subjective measurements of sleep quality (P = 0.017), daily sleepiness (P = 0.005), and performance (both P < 0.05) except for neurocognition (P = 0.741).	

Question 4.1: Is the frequency of insomnia increased in stroke patients?

Figure e27: 5-4-17 run with systematic reviews filter with temporal limit starting from 1990

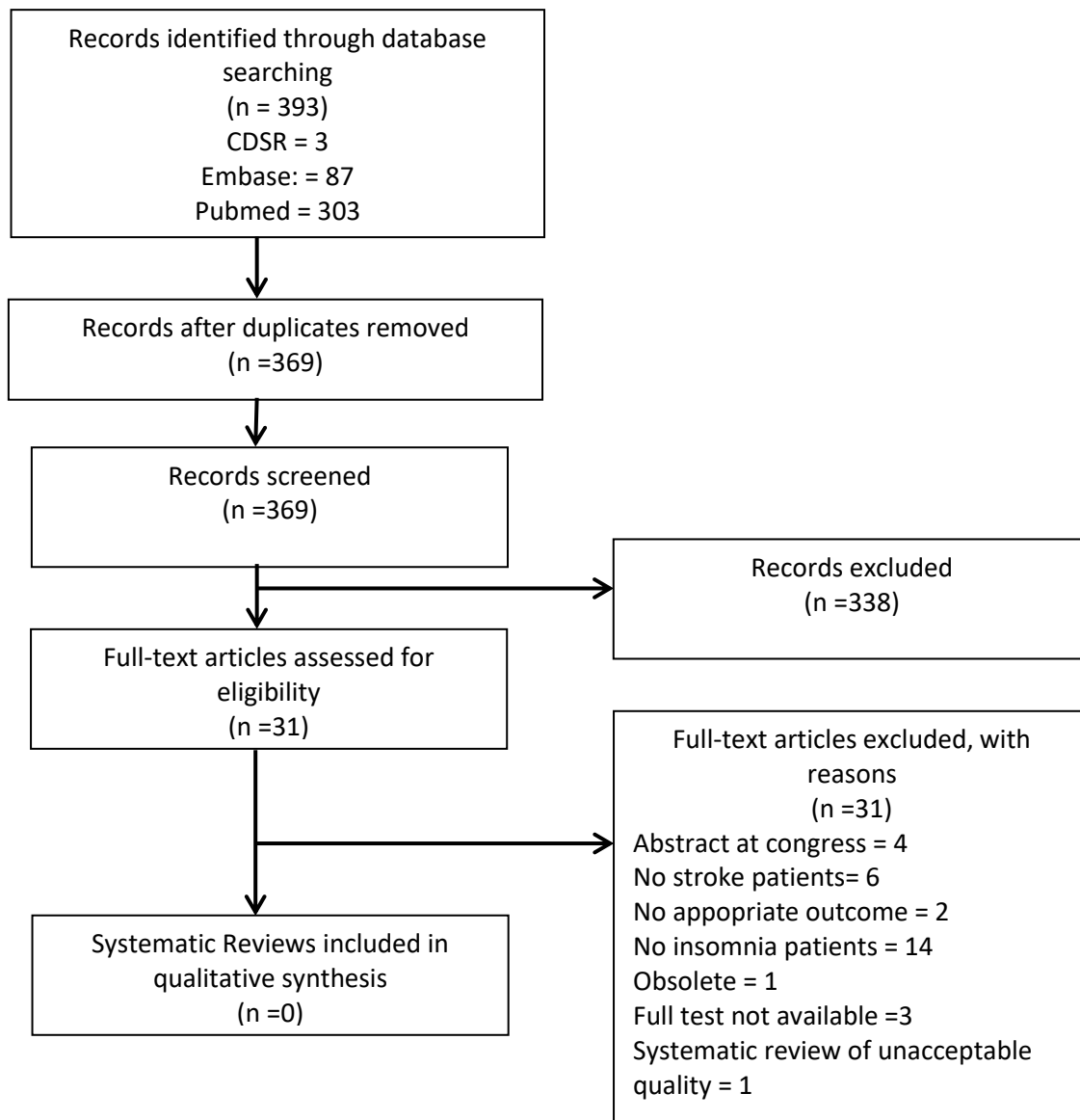


Figure 28: 3-5-17 run with Cohort Studies / Case Control Studies filters with temporal limit starting from 1990

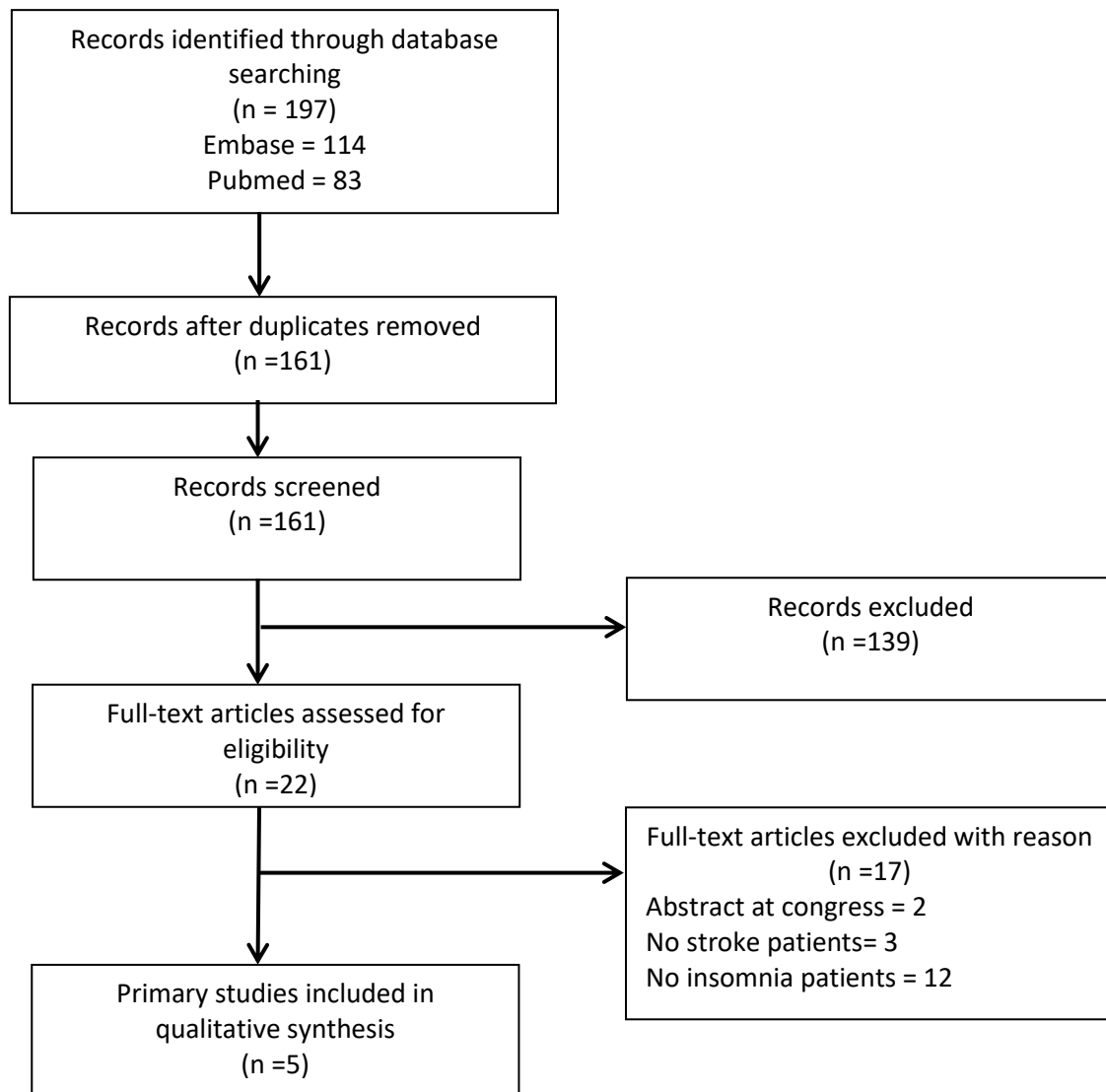
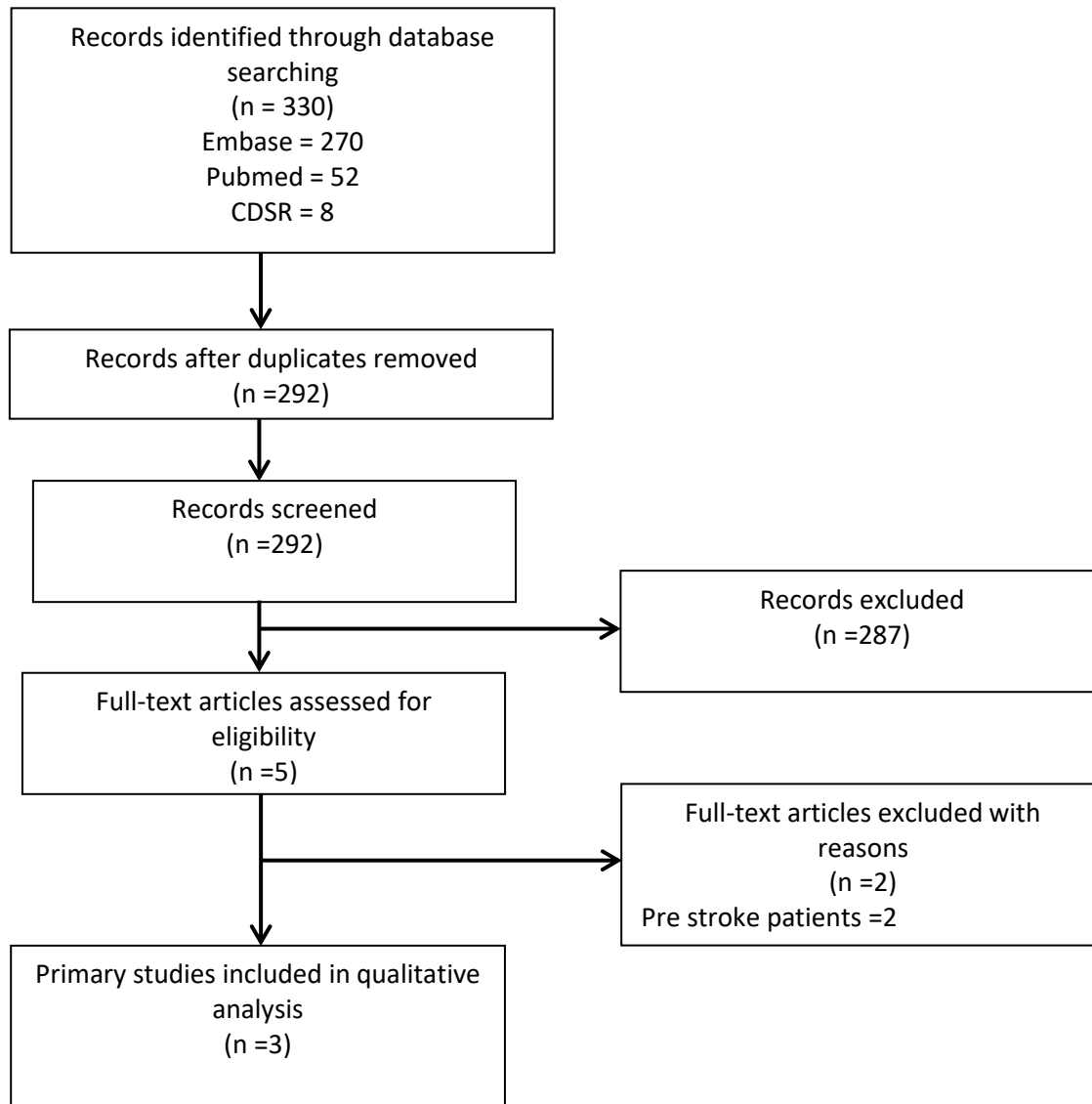


Figure 29: 18-1-19 run with temporal limit starting from 2017



Question 4.1: Is the frequency of insomnia increased in stroke patients?

Topic domain	Prevalence
P (target population)	Ischemic stroke and spontaneous intracerebral haemorrhage (and matched controls from general population)
Intervention (factors)	n.a.
Comparator	n.a.
Outcome	Insomnia
Study design	cross-sectional studies with concurrent matched controls, systematic reviews of these studies

Systematic reviews

One systematic review (Mayer, Geert, Poul Jennum, Dieter Riemann, and Yves Dauvilliers. 2011. 'Insomnia in central neurologic diseases--occurrence and management', Sleep medicine reviews, 15: 369-78) was excluded since it scored as unacceptable quality (AMSTAR tool).

Table e18: Primary Studies (8)

- Da Rocha, P. C., M. T. M. Barroso, A. A. T. S. G. Dantas, L. P. Melo and T. F. Campos (2013). "Predictive factors of subjective sleep quality and insomnia complaint in patients with stroke: implications for clinical practice." *Anais da Academia Brasileira de Ciencias* 85(3): 1197-1206.
- Glozier, N., T. J. Moullaali, B. Sivertsen, D. Kim, G. Mead, S. Jan, Q. Li and M. L. Hackett (2017). "The Course and Impact of Poststroke Insomnia in Stroke Survivors Aged 18 to 65 Years: Results from the Psychosocial Outcomes In Stroke (POISE) Study " *Cerebrovascular diseases extra* 7(1): 9-20.
- Joa, K.-L., W.-H. Kim, H.-Y. Choi, C.-H. Park, E.-S. Kim, S.-J. Lee, S.-Y. Kim, S.-H. Ko and H.-Y. Jung (2017). "The Effect of Sleep Disturbances on the Functional Recovery of Rehabilitation Inpatients Following Mild and Moderate Stroke." *American Journal of Physical Medicine & Rehabilitation* 96(10): 734-740.
- Kim, K. T., H. J. Moon, J. G. Yang, S. I. I. Sohn, J. H. Hong and Y. W. Cho (2017). "The prevalence and clinical significance of sleep disorders in acute ischemic stroke patients-a questionnaire study." *Sleep and Breathing* 21(3): 759-765
- Leppävuori, A., T. Pohjasvaara, R. Vataja, M. Kaste and T. Erkinjuntti (2002). "Insomnia in ischemic stroke patients." *Cerebrovascular diseases (Basel, Switzerland)* 14(2): 90-97.
- Li, L. J., Y. Yang, B. Y. Guan, Q. Chen, N. Zhang, C. X. Wang, A. X. Wang and Y. J. Wang (2018). "Insomnia is associated with increased mortality in patients with first-ever stroke: A 6-year follow-up in a Chinese cohort study." *Stroke and Vascular Neurology* 3(4): 197-202.
- Palomäki, H., A. Berg, E. Merinnee, M. Kaste, R. Lönnqvist, M. Lehtihalmes and J. Lönnqvist (2003). "Complaints of poststroke insomnia and its treatment with mianserin." *Cerebrovascular diseases (Basel, Switzerland)* 15(1-2): 56-62.
- Tang, W.-K., C. Grace Lau, V. Mok, G. S. Ungvari and K.-S. Wong (2015). "Insomnia and health-related quality of life in stroke AU." *Topics in Stroke Rehabilitation* 22(3): 201-207.

Author, Year	Quality of the study	Study type (design)	Participants	Sleep disorder	Length of follow-up	Results
Da Rocha 2013 Brasil	Class III	Case-control	70 subjects, 40 stroke patients (57 ± 7 years) and 30 healthy controls (52 ± 6 years)	Isomnia determined by the Sleep Habits Questionnaire	Lesion time between 1 and 36 months (11 ± 9 months)	Insomnia complaint was the most prevalent (patients: 37.5%; controls: 6.7%; p= 0.007). Female sex (OR= 11.098; 95%CI= 1.167-105.559; p= 0.036) and fragmented sleep (OR= 32.040; 95%CI= 3.236-317.261; p= 0.003) were the risk factors for insomnia complaint.
Glozier 2017 UK	Class II	Prospective cohort (cross sectional analysis)	441 young (<65 years) consecutive stroke survivors from 20 public hospitals in the New South Wales Stroke Service network.	Insomnia ascertained using 3 items from the Karolinska Sleep Questionnaire.	Self-report and interview at 28 days, 6 months, 12 months after stroke	The point prevalence of insomnia at each time point in the year after stroke was stable at 30–37% and more common in females. Fifty-eight (16%) of all participants reported "chronic" insomnia, with symptoms at both baseline and 6 months

						later. At 12 months, this group was more likely to be depressed (OR 6.75, 95% CI 2.78–16.4), anxious (OR 3.31, 95% CI 1.54–7.09), disabled (OR 3.60, 95% CI 2.07–6.25),
Joa 2017 Republic of Korea	Class II	Prospective cohort (cross sectional analysis)	208 patients with first-time stroke from three hospitals	insomnia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), using a questionnaire, which addressed types of sleep disturbances and daytime consequences.	1-month poststroke	Prevalence of the symptoms of insomnia: difficulty in initiating sleep 43.3%; difficulty in maintaining sleep 47.6%; early morning awakening 33.7%; and nonrestorative sleep, 40.4%. The prevalence of DSM-IV insomnia 26.9%
Kim 2017 South Korea	Class II	Prospective cohort	241 acute ischemic stroke or TIA (36) patients Mean age 64.2 ± 11.9 M60.6% NIHSS 3.26 ± 3.64 modified Rankin Scale-3 0.21 ± 0.82	Insomnia Severity Index (ISI) assessed by a questionnaire; clinical insomnia if ISI ≥15.5	5.4 ± 3.1 days after the onset of stroke symptoms.	Prevalence Insomnia 12.0% Stroke prognosis: modified Rankin Scale- 3 associated with Insomnia (standardized β = 0.219, p = 0.001) and the Sleep Obstructive apnea score optimized for Stroke (standardized β = 0.171, p = 0.011).
Leppävuori 2002 Finland	Class II	Prospective cohort (cross sectional analysis)	277 patients from a consecutive series of 486 ischemic stroke patients aged 55–85 years	Insomnia complaint: (1) delayed sleep (at least 1 h), (2) nighttime insomnia (at least 1 h), or (3) early waking (at least 1 h), (4) poor quality of sleep, and/or (5) use of sleep- promoting drugs during the week prior to the interview. Insomnia was defined if present insomnia complaints lasted at least for 1 month and had an impact on the patient's daily life (DSM-IV criteria A–C for insomnia). The onset of insomnia complaint/insomnia designated as 'prestroke' if present already before the index stroke. 'Poststrokeonset' insomnia complaint/insomnia if insomnia complaint/insomnia appeared after stroke.	Comprehensive psychiatric evaluation 3–4 months after stroke	56.7% reported any insomnia complaint and 37.5% fulfilled the DSM-IV criteria of insomnia. In 38.6%, insomnia complaint/insomnia present prior to the stroke and in 18.1% consequence of the stroke.
Li 2018 China	Class II	Prospective cohort	1062 patients with acute stroke recruited from 56 hospitals	Insomnia ascertained using three items from the Hamilton Rating Scale for Depression 17 items (core symptoms of insomnia in DSM-IV) and defined as difficulty falling asleep, difficulty staying asleep, waking up early, for at least two consecutive visits	Baseline and Four follow-up visits occurred within the first year after stroke, and a last follow-up call 6 years later.	Insomnia was reported by 38.4% of patients at baseline. During the 6 years of follow-up, after adjusting for all confounders, insomnia associated with increased mortality

						(HR=1.66, 95% CI 1.10 to 2.48).
Palomäki 2003 Finland	Class III	cross sectional analysis of patients included in a RCT	100 consecutively hospitalized Isckemic stroke patients randomized to receive 60 mg/day of mianserin (n = 51) or placebo for 1 year in a double-blind trial with a 6-month follow-up after the therapy.	Complaints of insomnia determined as one or more positive ratings in any of the three sleep items in Hamilton Depression Scale (early, middle, and late insomnia corresponding to disturbances in initiating sleep, or maintaining sleep, or to waking up too early in the morning).	From admission till 18 months	Complaints of insomnia occurred in 68% of patients on admission, and in 49% at 18 months. They were as frequent in all subgroups of patients. From 2 months, symptoms of insomnia were associated independently with depression. Living alone before stroke (at 0 and 2 months) and age (at 12 months) were independent predictors of insomnia.
Tang 2015 Hong Kong	Class III	Prospective cohort	336 acute stroke patients	7-item insomnia questionnaire designed in Hong Kong. Participants who considered themselves as having experienced 1 or more days of insomnia per week in the current month were identified as patients with self-reported insomnia	3 months after their index stroke	insomnia (in 44% of patient The insomnia group significantly lower overall Stroke Specific Quality of Life, energy and thinking scores after adjusting for sex, BI, and GDS scores

Question 4.2: Does treatment of insomnia have any impact on mortality and outcome after stroke?

Figure e30: 5-4-17 run with systematic reviews filter with temporal limit starting from 1990

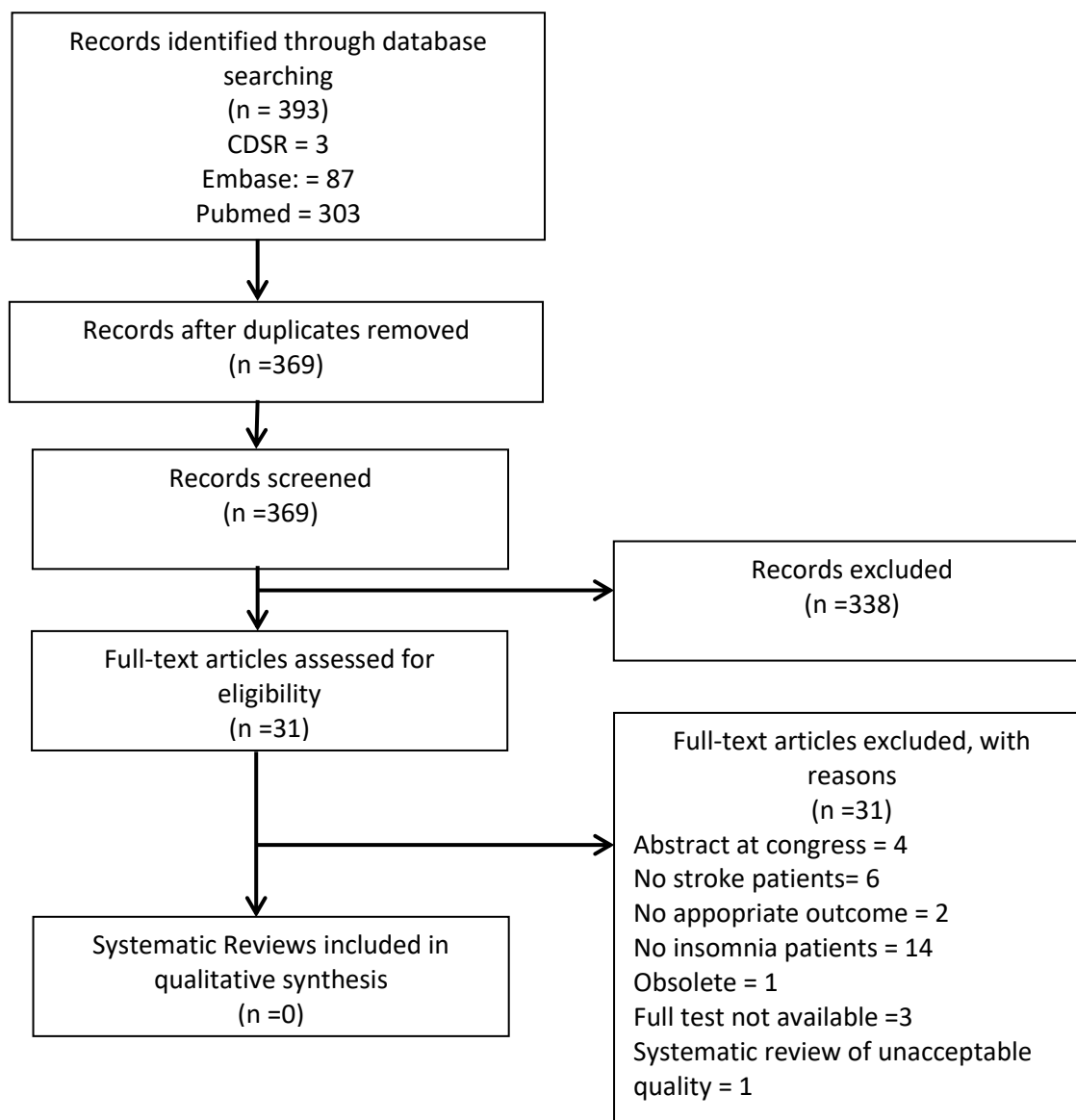


Figure e31: 3-5-17 run with RCTs and cohort studies filters with temporal limit starting from 1990

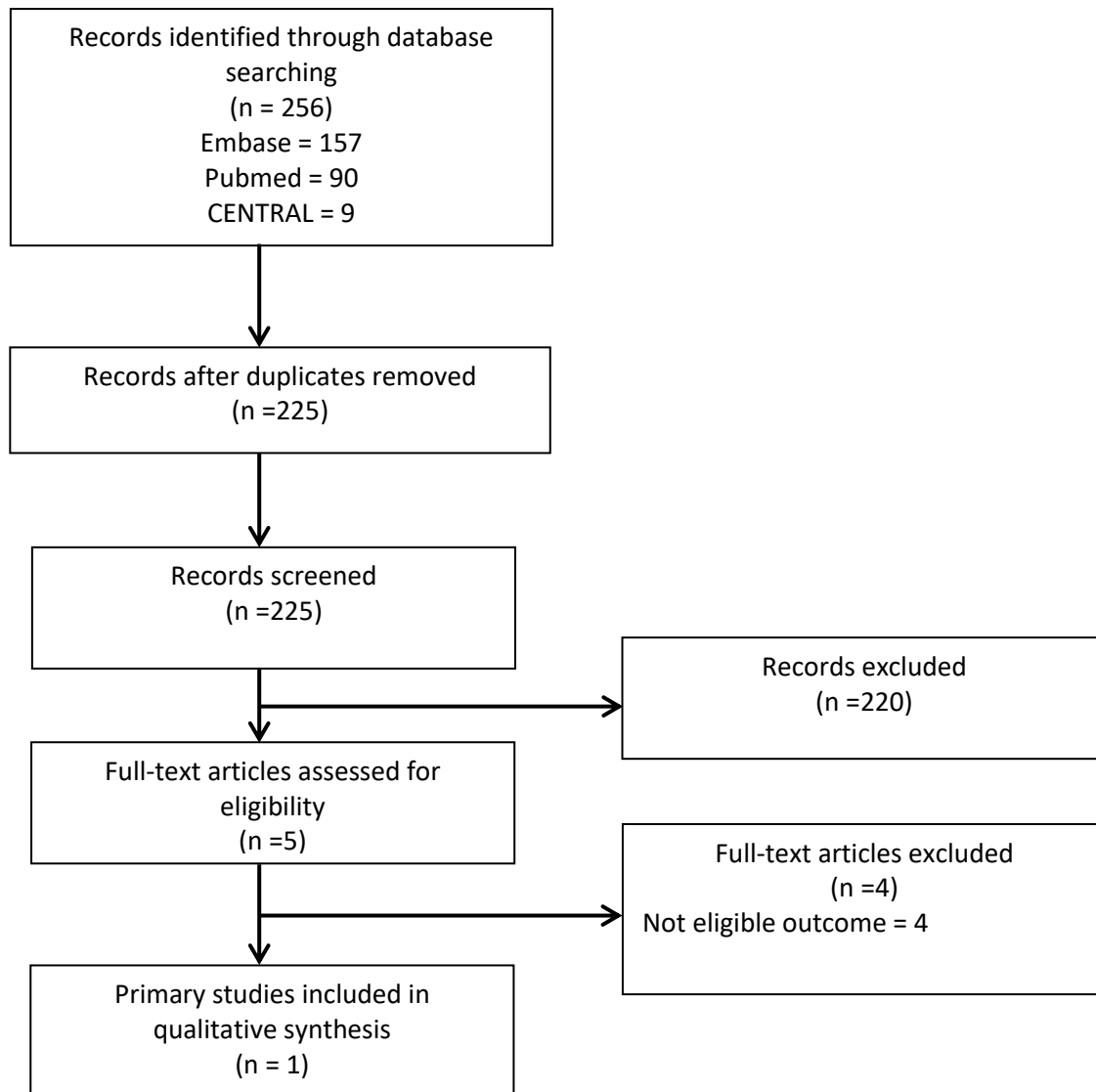
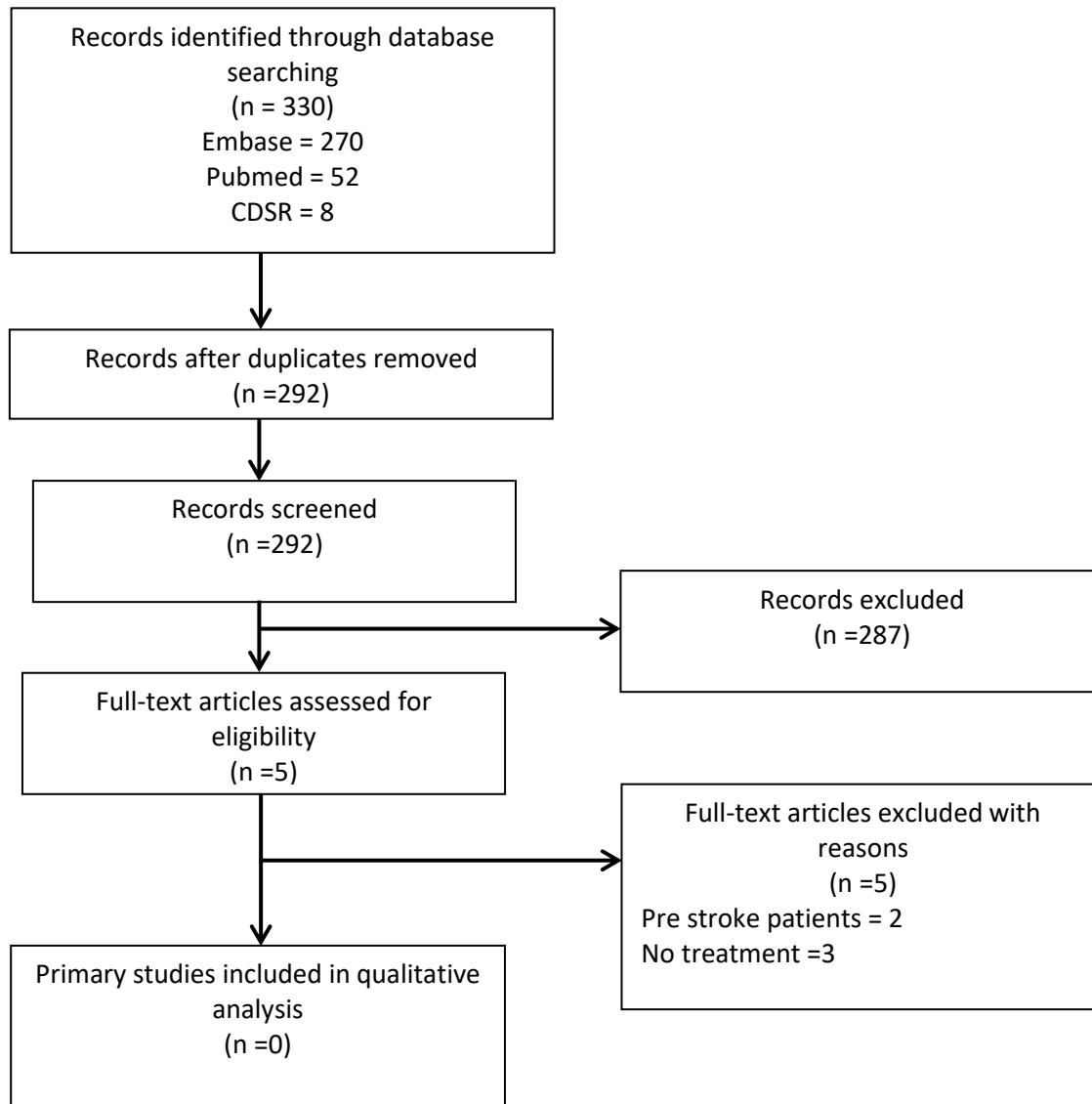


Figure e32: 18-1-19 run with temporal limit starting from 2017



Question 4.2: Does treatment of insomnia have any impact on mortality and outcome after stroke?

Topic domain	Therapy
P (target population)	Ischemic stroke and spontaneous intracerebral haemorrhage
Intervention	Treatment of insomnia
Comparator	No treatment, placebo, other treatment
Outcome	Mortality Disability (Rankin plus any other outcome) Recurrence
Time	After 3 months/ 1year from enrolment
Study design	cohort studies, RCTs, systematic reviews of these studies of these studies

Systematic reviews: none retrieved

Table e19: Primary Studies (1)

- Kim, C. R., M. H. Chun and E. Y. Han (2010). "Effects of hypnotics on sleep patterns and functional recovery of patients with subacute stroke." American journal of physical medicine & rehabilitation 89(4): 315-322.

Author, Year	Quality of the study AAN scheme	Study design	Participants	Intervention and comparison	Length of follow-up	Results	Notes
Kim 2010 Korea	Class IV	Before-after study with concurrent control	15 patients with insomnia in a rehabilitation center < 1 month after stroke (+ 15 patients with stroke < 1 month and no insomnia, considered as controls)	The 15 subjects in the case group received 10 mg zolpidem for 1 wk, then 0.125 mg triazolam, or 25 mg of trazodone if zolpidem had no effect	15.8 days	Poor sleep quality, decreased total sleep time, and increased frequency of nocturnal awakening observed in patients with insomnia improved under hypnotics, to levels comparable with those of the (noninsomnia) control group. No significant difference in functional (Barthel Index), cognitive, or depressive status between the insomnia and noninsomnia groups at baseline. At follow-up, functional and cognitive status had improved in both groups, and there was no significant difference between the two groups	Heterogeneity of study population. Small sample size. No power calculation.

Question 4.3: Is the frequency of RLS/PLMS increased in stroke patients?

Figure e33: 14-3-17 with systematic reviews filter with temporal limit starting from 1990

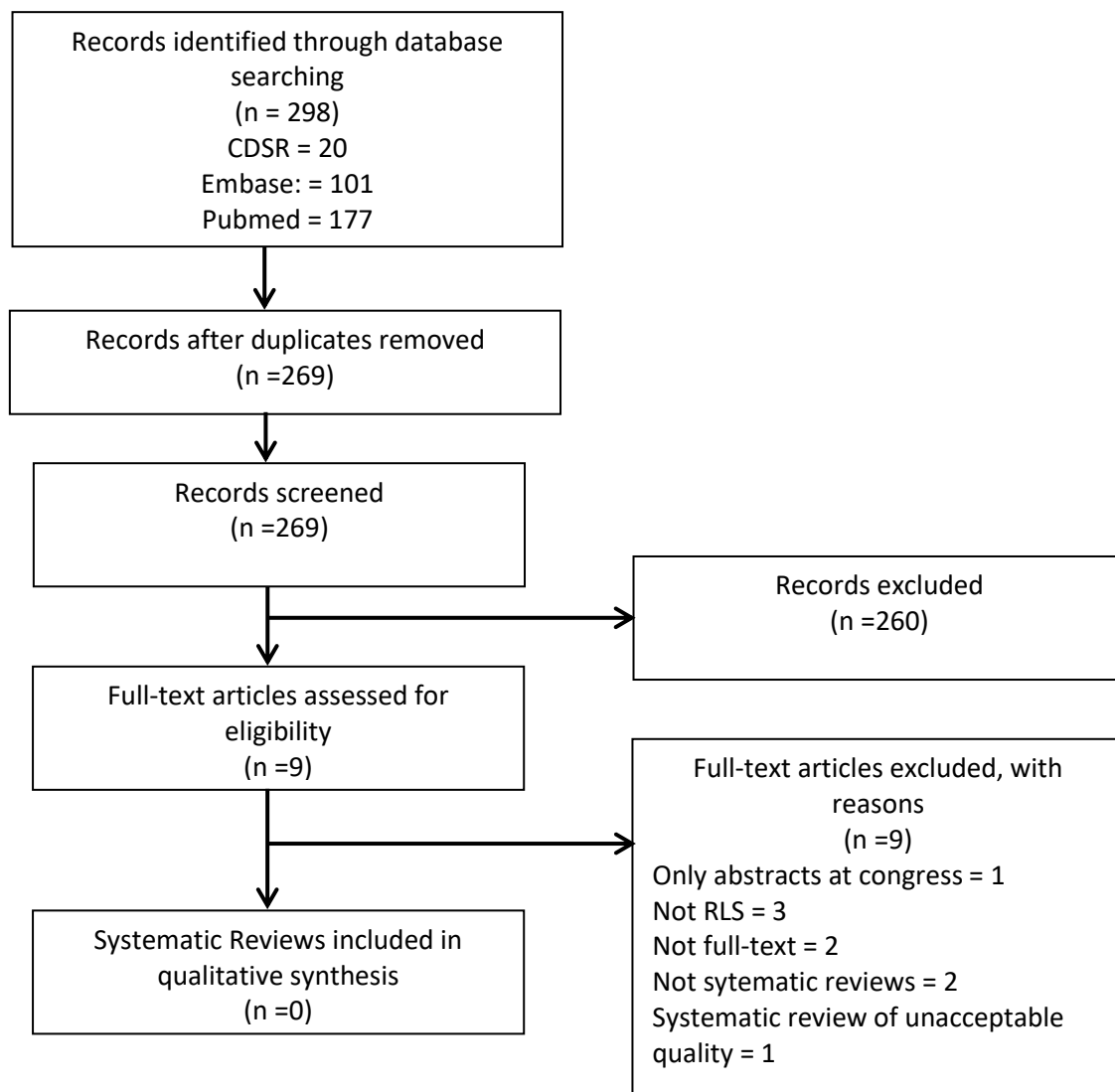


Figure e34: 21-7-17 run with Cohort Studies / RCTs studies filters with temporal limit starting from 1990

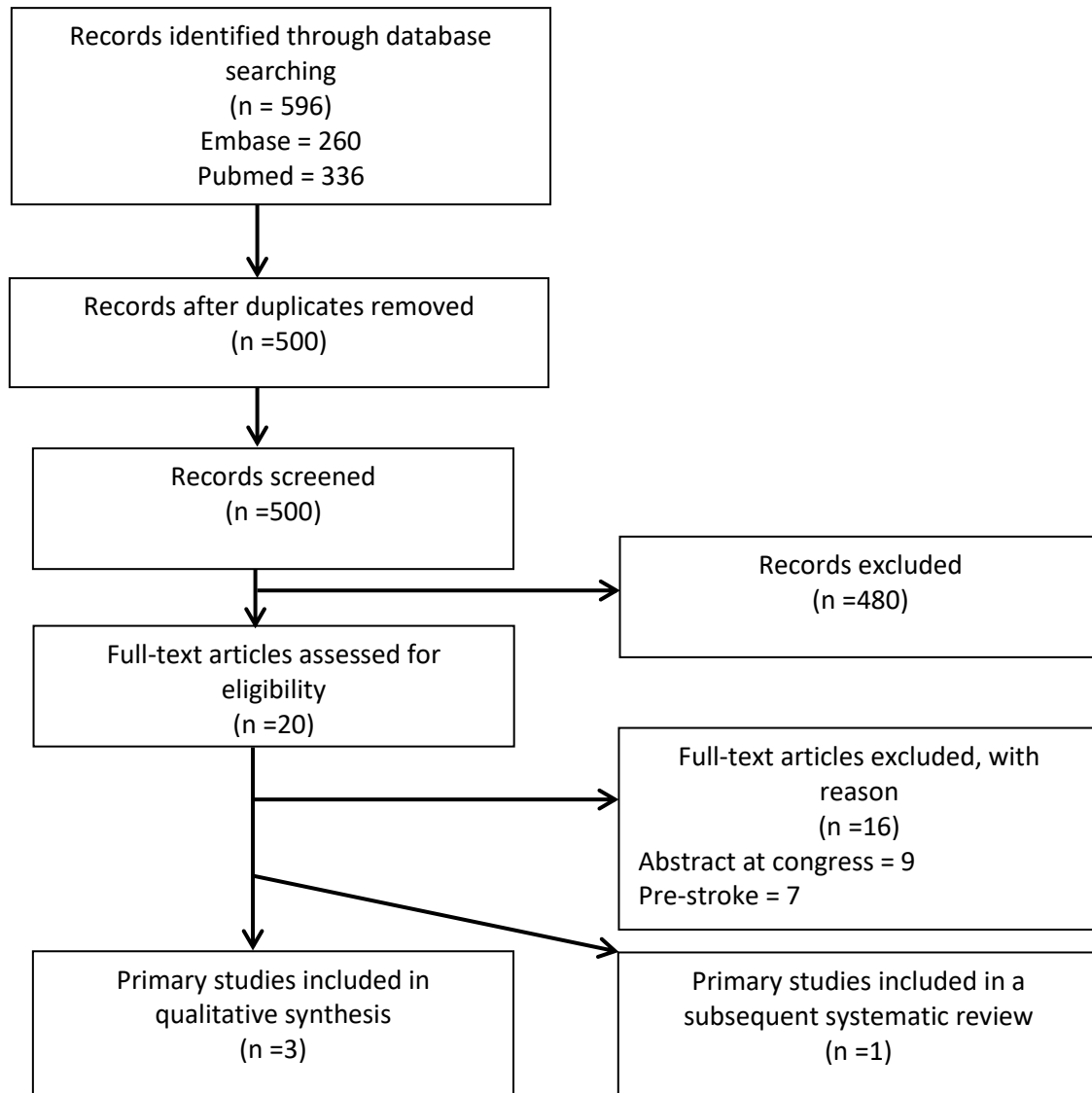
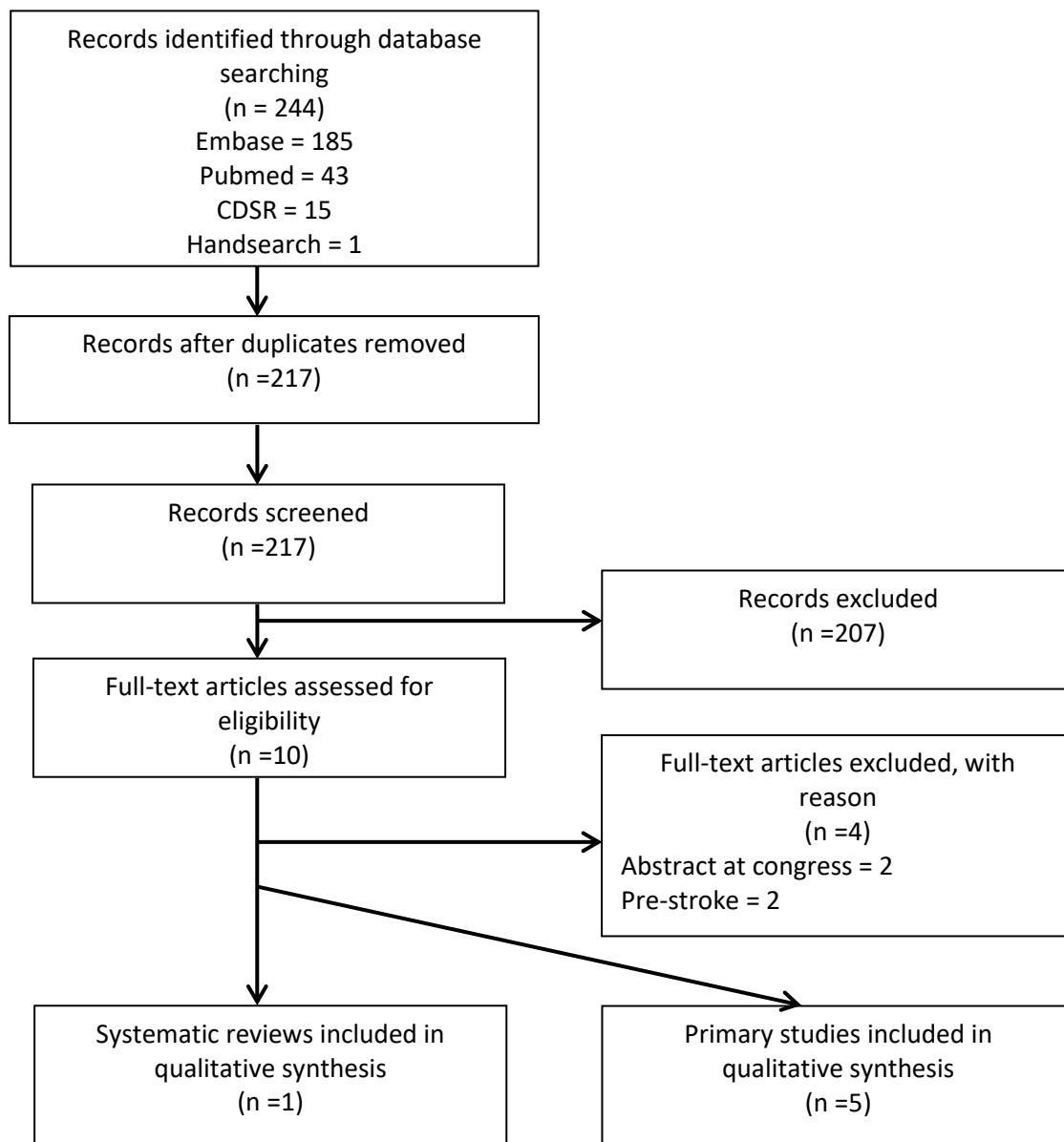


Figure e35: 18-1-19 run with temporal limit starting from 2017



Question 4.3: Is the frequency of RLS/PLMS increased in stroke patients?

Topic domain	Prevalence
P (target population)	Ischemic stroke and spontaneous intracerebral haemorrhage (and matched controls from general population)
Intervention (factors)	n.a.
Comparator	n.a.
Outcome	RLS
Study design	cross-sectional studies with concurrent matched controls, systematic reviews of these studies

Table e20: Systematic Reviews (1)

- Lin, T. C., B. Y. Zeng, Y. W. Chen, M. N. Wu, T. Y. Chen, P. Y. Lin, C. K. Wu, P. T. Tseng and C. Y. Hsu (2018). "Cerebrovascular Accident Risk in a Population with Periodic Limb Movements of Sleep: A Preliminary Meta-Analysis." *Cerebrovascular Diseases*: 1-9.

Author, Year (last search update)	Quality of the systematic review (Amstar score)	Design of included studies	Participants	Length of follow-up	Results	Quality of the studies included (according to the review Authors)
Lin 2018 (2018)	9/11	3 case control studies	158 patients with PLMS with cerebrovascular accident (CVA) and 88 PLMS controls without CVA	<8 years	Significantly higher PLM index in patients with CVA than in the controls (Hedges' $g = 0.860$, 95% CI 0.359–1.361, $p = 0.001$; difference in means: 4.435, 95% CI 0.836–8.034, $p = 0.016$)	7-8 according to Newcastle-Ottawa Quality Assessment Scale*

*Newcastle-Ottawa Quality Assessment Scale: possible range 1 (lowest) to 9 (highest)

Table e21: Primary Studies (8)

- Boulos, M. I., A. Wan, S. E. Black, A. S. Lim, R. H. Swartz and B. J. Murray (2017). "Restless legs syndrome after high-risk TIA and minor stroke: association with reduced quality of life." *Sleep Med* 37: 135-140.
- Boulos, M. I., B. J. Murray, R. T. Muir, F. Gao, G. M. Szilagyi, M. Huroy, S. E. Black, A. S. Lim, R. H. Swartz, A. Kiss and A. S. Walters (2017). "Periodic limb movements and white matter hyperintensities in first-ever minor stroke or high-risk transient ischemic attack." *Sleep* 40(3).
- Gupta, A., G. Shukla, A. Mohammed, V. Goyal and M. Behari (2017). "Restless legs syndrome, a predictor of subcortical stroke: a prospective study in 346 stroke patients." *Sleep medicine* 29: 61-67.
- Lee, S.-J., J.-S. Kim, I.-U. Song, J.-Y. An, Y.-I. Kim and K.-S. Lee (2009). "Poststroke restless legs syndrome and lesion location: anatomical considerations." *Movement disorders : official journal of the Movement Disorder Society* 24(1): 77-84.
- Manconi, M., F. Fanfulla, R. Ferri, S. Miano, J. Haba-Rubio, R. Heinzer, T. Horvath, P. Proserpio, P. Young, G. Moschovitis, A. Seiler, C. Cereda, L. Nobili, R. Wiest, S. R. Ott and C. L. Bassetti (2018). "Periodic limb movements during sleep in stroke/TIA: Prevalence, course, and cardiovascular burden." *Neurology* 90(19): e1663.
- Medeiros, C. A. M., P. F. C. de Bruin, T. R. Paiva, W. M. Coutinho, R. P. Ponte and V. M. S. de Bruin (2011). "Clinical outcome after acute ischaemic stroke: the influence of restless legs syndrome." *European journal of neurology* 18(1): 144-149.
- Schlesinger, I., I. Eriq, M. Nassar and E. Sprecher (2015). "Restless legs syndrome in stroke patients." *Sleep Medicine* 16(8): 1006-1010.
- Shiina, T., K. Suzuki, M. Okamura, T. Matsubara and K. Hirata (2018). "Restless legs syndrome and its variants in acute ischemic stroke." *Acta Neurologica Scandinavica*.

Author, Year	Quality of the study	Study type (design)	Participants	Sleep disorder	Length of follow-up	Results
Boulos 2017 Sleep Medicine Canada	Class III	Consecutive patients with cross-sectional analysis	94 patients within 14 days of symptoms with either a neuroimaging-confirmed minor ischemic stroke (NIH Stroke Scale score $15 \leq 3$; 53%) or high-risk TIA (47%)	RLS Diagnostic Questionnaire (IRLSSG 2003)	2-6 months after stroke	RLS 24.4% (=23 pts; 11 new diagnosis; 12 RLS preceding stroke/TIA)
Boulos 2017	Class III	Consecutive	30 patients within 14	in-hospital	51 days	PLM 50%

Sleep Canada		patients with cross sectional analysis	days of symptoms with either a neuroimaging-confirmed minor ischemic stroke (NIH Stroke Scale score ≤ 3 ; 53%) or high-risk TIA (47%)	polysomnography PLM index ≥ 5	(median; IQR 18–109) after the cerebrovascular events.	
Gupta 2017 India	Class III	Consecutive patients with cross sectional analysis	346 consecutive stroke patients in a single unit (80% males).	IRLSSG Rating Scale (IRLSSG diagnostic criteria)	Not reported	43 patients with RLS: 35 pre-stroke (10%), 8 post-stroke RLS (2%) 29 of 35 patients with pre-stroke RLS (82.8%) imaging evidence of subcortical stroke. Difference between patients with subcortical stroke and those with cortical stroke: pre-stroke RLS (22.8% vs 2.74%, $p < 0.001$)
Lee 2009 Korea	Class III	Consecutive patients with cross sectional analysis	137 with ischemic stroke (mean age= 63.9 years, 54% M).	International RLS Study Group (IRLSSG) criteria	1 month after stroke	17 patients (12.4%) with RLS after the stroke. One patient in the cortical group had stroke-related RLS, whereas 16 in the subcortical group had stroke-related RLS.
Manconi 2018 Switzerland	Class II	Consecutive patients with cross sectional analysis and controls	169 35-75-year-old patients with TIA or ischemic stroke, admitted to the stroke unit within 2 days from the onset 162 sex- and age matched healthy controls randomly selected from the HypnoLaus cohort	PLMS at Polysomnography according to the official World Association of Sleep Medicine standards	< 9 days after stroke	PLMI > 10: 32.3% acute stroke patients and 44.4% healthy controls (NS) PLMI > 15: 25.1% acute stroke patients and 36.4% healthy controls (NS) PLMI > 30: 13.8% acute stroke patients and 22.0% healthy controls (NS)
Medeiros 2011 Brazil	Class III	Consecutive patients with cross sectional analysis	96 acute ischemic stroke patients (mean age= 64 y, 61.4% M).	International RLS Study Group (IRLSSG) criteria	<15 days after stroke	RLS 12.5 %, all before stroke. Stroke outcome was significantly worse at 3 and 12 months (ANCOVA, $p < 0.005$) in RLS patients, remaining after adjustment for diabetes and body mass index ($p < 0.05$)
Schlesinger 2015 Israel	Class II	Consecutive patients with cross sectional analysis and controls	149 stroke/TIA 298 sex- and age matched controls from a preventive medicine centre	questionnaire based on the questions developed by the International RLS Study Group and diagnosis confirmed by a senior neurologist	Not reported	Twenty-two of 149 patients (15%) and 10 of 298 controls (3%) suffered from RLS ($p < 0.0001$). In 22 patients with RLS, RLS preceded the stroke/TIA
Shiina 2018 Japan	Class III	Consecutive patients with cross sectional analysis	104 consecutive patients with acute ischemic stroke,	International RLS Study Group criteria,	<7 days after stroke	RLS: 8 patients (7.7%); 3 (3.3%) had poststroke RLS

Question 4.4: Does treatment of RLS/PLMS have any impact on mortality and outcome after stroke?

Figure e36: 14-3-17 run with systematic reviews filter with temporal limit starting from 1990

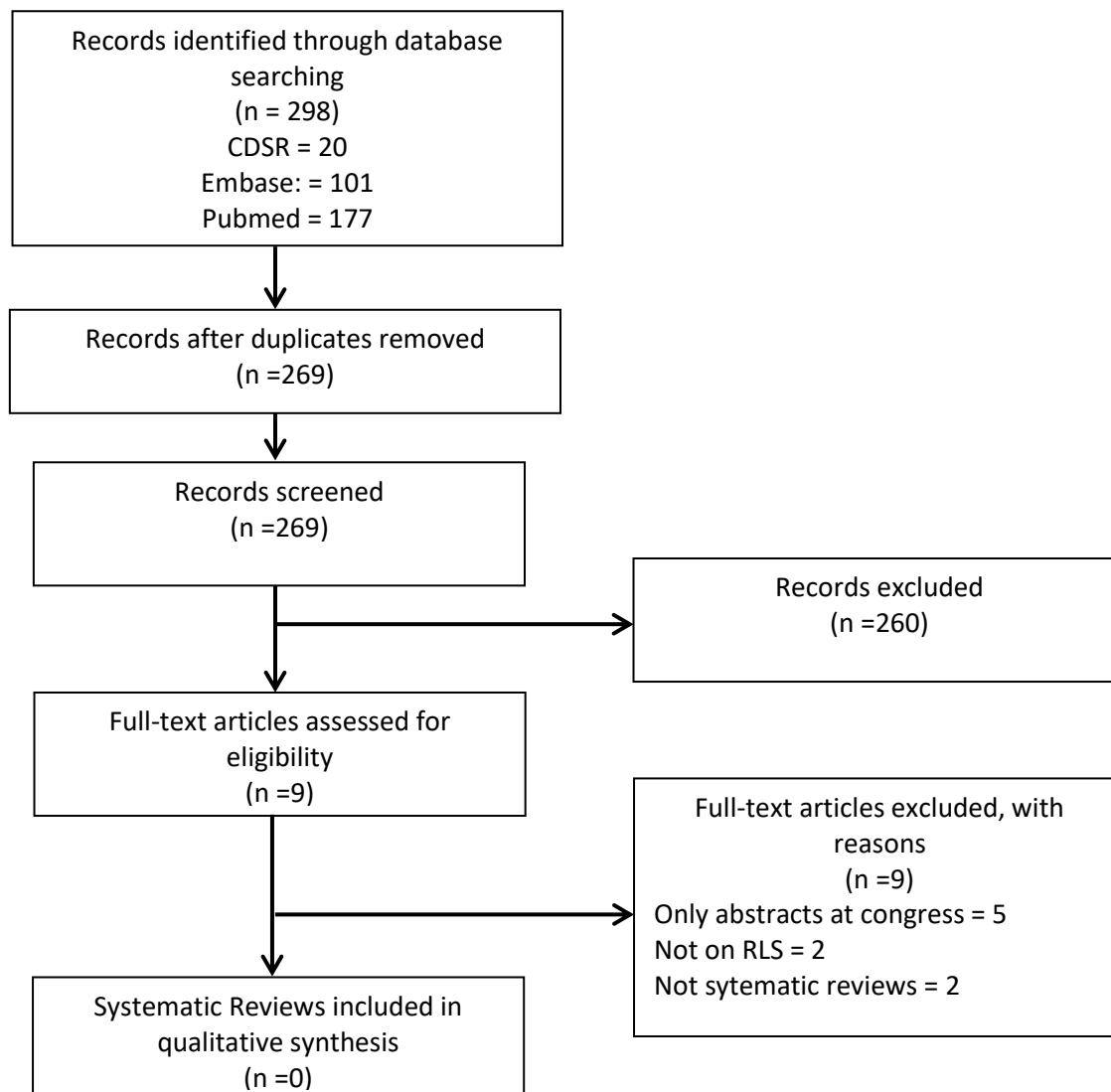


Figure e37: 3-5-17 run with RCTs and cohort studies filters with temporal limit starting from 1990

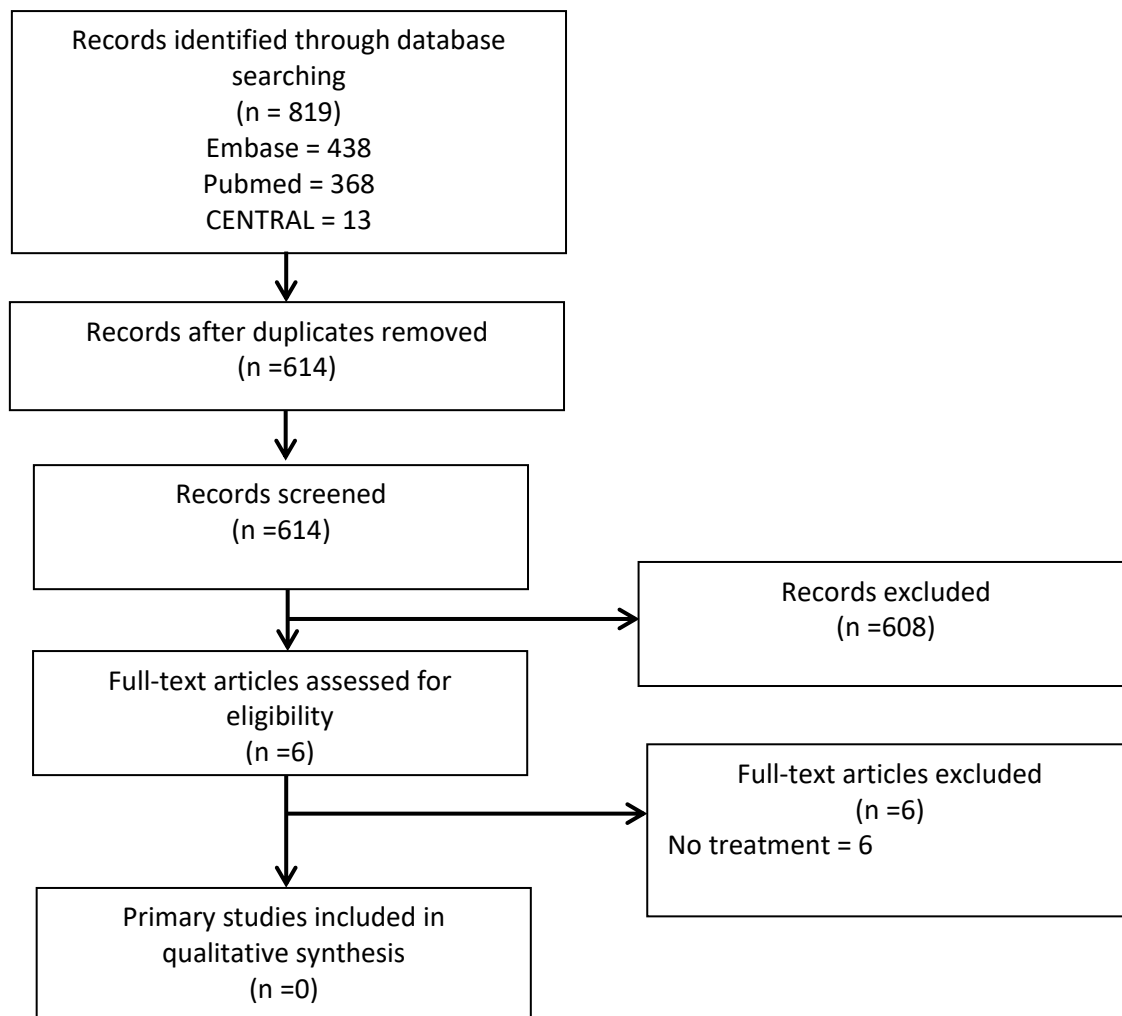
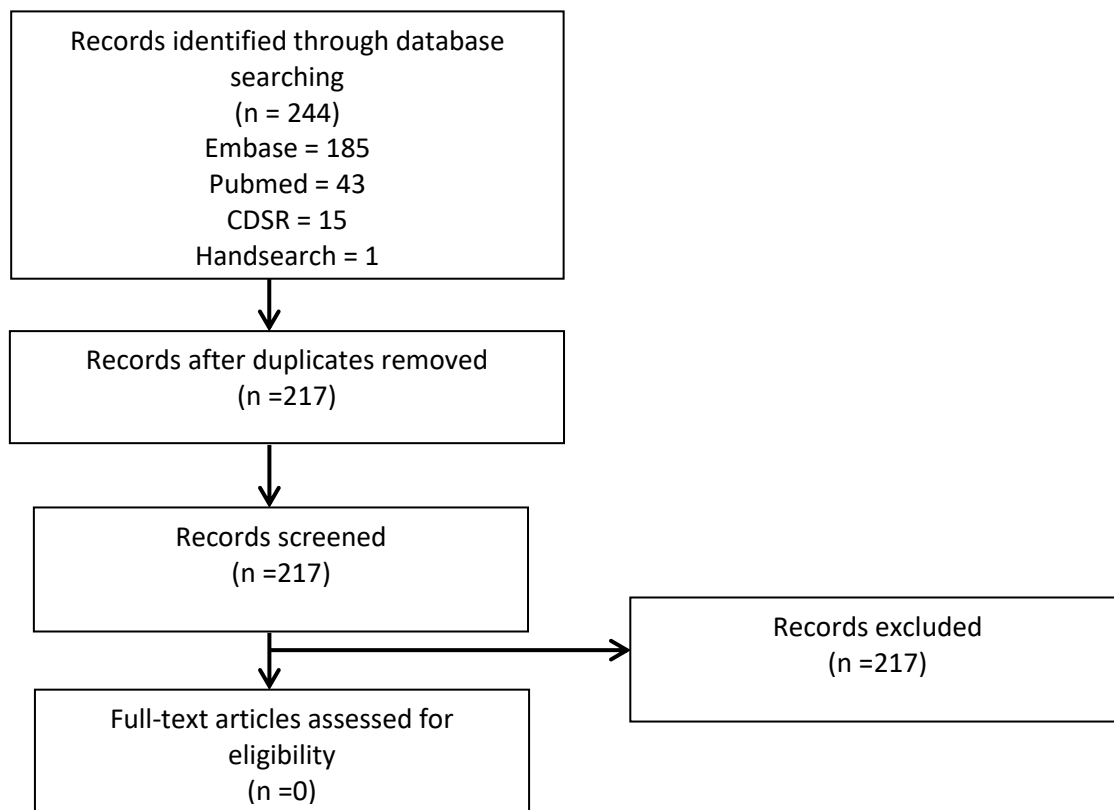


Figure e38: 18-1-19 run with temporal limit starting from 2017



Question 4.4: Does treatment of RLS/PLMS have any impact on mortality and outcome after stroke?

Topic domain	Therapy
P (target population)	Ischemic stroke and spontaneous intracerebral haemorrhage
Intervention	Treatment of RLS
Comparator	No treatment, placebo, other treatment
Outcome	Mortality Disability (Rankin plus any other outcome) Recurrence
Time	After 3 months/ 1year from enrolment
Study design	cohort studies, RCTs, systematic reviews of these studies of these studies

No studies retrieved

