ON-LINE APPENDIX

PICOS Framework

Objectives. Our strategy to address the primary and secondary questions above was informed by the PICOS framework recommended by the Cochrane Collaboration Handbook for Systematic Reviews.

Population. Our population of interest included individuals who are asymptomatic or symptomatic with nonstenotic carotid plaques (<50%), to assess both the natural history as well as the risk of recurrent events. Studies must explicitly report the degree of stenosis measured with either imaging technique (sonography/CT Angiography/MR Angiography/DSA). We did not limit our results to any age group.

Intervention. This study focusses both on the prevalence and prognosis of nonstenotic carotid plaques in an asymptomatic population as well as on the prognosis of known symptomatic nonstenotic plaques. Thus, we do not define any intervention. We also decided to include both randomized controlled trials and observational studies, given the potentially limited number of randomized trials conducted so far.

Comparator. We did not include a comparator group. The incidence of stroke in subjects with no stenosis (0%) and/or asymptomatic severe stenosis is well-described in the literature. Also, the recurrence risk of stroke in patients with no stenosis (eg, cardioembolic stroke or ESUS) is different from that in patients with SyNC, which may bias the estimate of effect size in our population of interest.

Outcome. Our outcomes of interest mainly included future risk of stroke in the asymptomatic group and risk of recurrence in symptomatic nonstenotic carotid plaques.

Study Design. We included both observational and interventional studies. Observational study types included the following: case-control, cohorts (prospective or retrospective), and cross-sectional. Clinical trials included both randomized and nonrandomized trials, with quality assessments applied to describe the degree of bias.

Search Strategy. Relevant literature was extracted from the following electronic databases: MEDLINE, EMBASE, and the Cochrane Collaboration Library up to December 6, 2019. After conducting abstract and full-text screening, 3 investigators (N.S., M.M., J.M.O.) scanned the reference sections of all included publications to identify any relevant literature not captured in the primary search. Experts in the field were contacted on an ongoing basis for information about other potential ongoing or unpublished studies. These experts were identified via the review process and personal communications as the study proceeded.

Subject headings and keywords for each data base were standardized and included 2 primary components: carotid stenosis and stroke. Keywords included "stroke" OR "transient ischemic attack") AND "carotid" AND ("plaque" OR "atherosclerosis" OR "disease." We did not include ESUS as a search component because our objective was to evaluate the prevalence of nonstenotic carotid plaques in a healthy as well as a symptomatic population. We systematically evaluated the reporting of nonstenotic carotid plaques via different imaging modalities in each identified study during the screening process, informed by NASCET and/or ECASS criteria.[1]

Each keyword and subject heading within each of these 2 components were combined using the OR operator and then combined with one another using the AND operator. We applied filters to remove any editorials, letters, and case reports and then removed any studies that comprised solely animal research. Therefore, the result contained human-focused primary research articles relevant to nonstenotic carotid plaques and stroke. An example of this methodology is shown in On-line Fig 1. Additional screening for study types, imaging modalities used to classify carotid stenosis, and satisfaction of inclusion/exclusion criteria noted in the following section was performed during abstract and full-text screening.

The search of on-line databases included full-text articles published in English. No publication date restrictions were imposed during the primary search to maximize the sensitivity of this search. We used the search strategy recommended by Egger for systematic reviews of observational studies.[2] We also declared a priori in our study protocol to follow the recommended Meta-Analysis Of Observational Studies in Epidemiology guidelines for meta-analyses and systematic reviews of observational studies.[3]

Study Selection. Independent agreement between 2 of the 3 authors was required for abstract screening and full-text review, with conflicts being resolved by consensus among all 3 authors.

Inclusion/Exclusion Criteria. Our criteria for inclusion and exclusion were as follows:

1. Only primary studies were included. Reviews, qualitative assessments, narrative/case studies, and other summary materials were excluded but were independently scanned for any relevant material not captured in the primary search.
2. Only clinicals trials and observational studies (cross-sectional, cohort, and case-control studies) were included because we did not want to limit the scope of this systematic review but wished to collate primary, quantitative data for meta-analysis.
3. Studies in which participants were found to have non-stenotic carotid plaques with no symptoms and studies that reported characteristics of participants with non-stenotic carotid plaques were included.
   a. Studies involving patients with only severe carotid stenosis and/or only cardioembolic strokes were excluded.
   b. Studies that included and/or reported perioperative strokes after carotid endarterectomy/carotid artery stenting or cardiac procedures (eg, carotid artery bypass grafting) were excluded because they would affect the outcome.
   c. Studies that reported only measures of effect size but no prevalence were excluded.
   d. We also included studies that reported outcomes by the number of carotid arteries rather than participants and divided by 2 to achieve the number of participants, considering the symptomatic side being reported in the outcomes.

e. Studies that included patients with all stenosis grades but that did not report outcomes of patients with <50% stenosis were excluded.
f. In studies that divided the degree of stenosis in to <30%, 30%–70%, and >70%, outcomes were considered only for the group with <30% stenosis; the remaining 2 groups were excluded.
g. Studies involving < 10 participants were excluded.

Title and Abstract Screening. All authors screened titles and abstracts and reviewed full text articles using the Covidence platform (https://www.covidence.org/home). Duplicate articles at the screening stage were identified and removed automatically by Covidence. Abstract and title screening used the basic functionality of the platform of "Yes/No/Maybe" to determine eligibility, with on-screen inclusion and exclusion criteria available to all authors. Title and abstract screening followed a basic decision tree outlined in On-line Fig 2.

Full-Text Screening. Full-text screening was carried over into the platform to systematically assess reasons for inclusion or exclusion. Articles were included or excluded in our systematic review as per the following sequence:

- Duplicate study
- Not a primary study
- Wrong study design (not a trial/observational study)
- Wrong patient population (peri-operative stroke)
- Wrong patient population (severe stenosis only)
- Wrong outcomes (results for non-stenotic carotid plaques not mentioned)

The flow diagram of study inclusion and exclusion at each state of the review is presented in On-Figs 3 and 4.

Study dates ranged from 1978 to 2019 and 2008 to 2019, respectively.

The Cohen κ scores for interrater agreement were 83.31% at the abstract screening stage and 81.35% at the full-text review stage, which are both rated as good as per the Cochrane Handbook. In total, 13,428 participants had asymptomatic, nonstenotic carotid plaques, and 17 patients had recurrent strokes in the SyNC population.

Data Extraction and Quality Assessment. Demographic variables collected include age, sex, TOAST classification (if reported), atrial fibrillation, prior stroke, TIA or ischemic stroke, follow-up duration, progression of stenosis (if reported), imaging technique used for classification of carotid stenosis and degree of stenosis, treatment received (if reported). Additionally, we also collected information relevant to the SyNC population: age, sex, previous strokes, recurrence of cerebrovascular events, plaque features, and treatment received if available apart from the overall population.

Study quality was evaluated using Version 2 of the Cochrane Risk of Bias (ROBINS-I) tool for observational studies, as suggested by the Cochrane Handbook for Systematic Reviews of Interventions.[4] We also assessed the external validity of these studies using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group guidelines.[5]

Data Synthesis and Analysis. Analyses and visualizations were generated using STATA/IC, Version 15.0. Study descriptors and outcomes were tabulated and summarized on a per-study basis, with primary outcomes reported in terms of the number of participants who developed future strokes for the first primary question and number of patients with recurrent stroke/TIA for the latter question in 2 separate tables. The denominator in the former group was the total number of patients with nonstenotic carotid plaques, while the denominator in the latter group included the total number of patients with SyNC.

Meta-analysis was performed using the metaprop command in STATA, with prevalence and associated 95% confidence intervals reported. Meta-analysis was performed using a random-effects model of variance, in which we not only assume that the effects of individual studies deviate from the true intervention effect of all studies due to sampling error but that there is another source of variance introduced by the fact that the studies do not stem from 1 single population but are drawn from a "universe" of populations. Thus, we expected that there would be some level of heterogeneity inherent to the primary outcomes, confirmed via calculation of the Higgins I^2 statistic. Small P values (<.10) and Higgin I^2 statistics ≥50% were interpreted as suggestive of the presence of heterogeneity.

Due to heterogeneity, we evaluated primary outcomes through subgroup analyses using stratified random-effects meta-analysis. We could evaluate metabias using trim and fill or funnel plots because our study did not have any control groups. We obtained separate pooled estimates based on type of imaging technique used for classification of stenosis, treatment received, and study design because these were the most consistently reported variables across studies and provided a simplified basis on which to group.

Study Quality Assessment. For summary results of the judged risk of bias across the included studies for each domain, see On-line Figs 4 and 5.

Confounding. For the first group, we judged 5 studies as having a moderate risk of bias due to confounding.[6-10] We judged the remaining studies at low risk of allocation bias, and none were reported to have a high risk of bias. For the second group, we judged only 1 study to have a moderate risk of bias due to confounding,[11] while the remaining studies were judged to have low risk of bias due to confounding.

Selection. For the first group, we found 8 studies having moderate concerns in patient selection.[6-10,12-14] The remaining studies were judged to have a low risk of bias due to selection, and none were judged to have serious or critical risk of bias. For the second group, we found all except 2 studies having a moderate risk of bias for selection because they selected a specific subgroup of patients with specific plaque features for evaluation.

Intervention and Deviation from the Intended Intervention. All of our studies in either group were judged to have a low bias for intervention and deviation from the intended intervention because most of them did not have an active intervention arm.

Bias Due to Missing Data All of our studies in either group were judged to have a low bias for missing data.

Incomplete Outcome Data and Bias in Reporting Results. For the first group, future ischemic stroke is the primary outcome measure. Three studies were judged to have a moderate risk of bias for incomplete outcome data,[7,15] and 4 studies were judged to have a moderate risk of bias in selection of the reported result.[9,10,13,16] All the remaining studies were judged to have a low risk of bias in both domains.

For the second group, recurrent stroke is the primary outcome measure. Seven studies were judged to have a moderate risk of bias for incomplete outcome data because only the remaining 7 studies reported data on recurrent stroke.[7-23] None of the studies were judged to have a risk of bias in the selection of reported results.

Publication Bias Assessment for the ASyNC Population The initial Begg test suggests that our data did not report risk of bias: $Pr > |z| = 0.491$.

A funnel plot (On-line Fig 6) of the included studies to assess publication bias showed overall left-right symmetry. However, we can see that most of studies showing effect had a small sample size. This indicates that we need larger studies to assess outcome.

Publication Bias Assessment for the SyNC Population. The initial Begg test suggests that our data did not report risk of bias: $Pr > |z| = 0.652$.

A funnel plot (On-line Fig 7) of the included studies to assess publication bias showed, overall, some left-right asymmetry. We see that almost all the studies have a large sample, and studies showing effect are large and clustered against those not showing any effect.

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On-line Table 1: Summary of study characteristics for studies reporting rates of ischemic cerebrovascular events (stroke, TIA) in an asymptomatic patient population with nonstenotic carotid plaques

Author, Year	Study Design	Total Sample Size	SyNC (No.) (%)	Age (Mean/ Median) (yr)	Men (No.) (%)	Imaging Technique and Grading System	Median Follow-Up (yr)	Events (No.) (%)
AbuRahma et al,[17] 2003	Prospective, RCT	420	319 (75.9%)	NA	NA	US/–	NA	5 (1.5%)
Alexandrova et al,[39] 1996	Prospective, cohort	373	NA	70.0	223 (59.8%)	US/NASCET	NA	20 (NA)
Ballotta et al,[30] 2007	Prospective, cohort	599	294 (49.1%)	70.0	372 (62.1%)	US/NASCET	NA	1 (0.3%)
Bock et al,[10] 1993	Prospective, cohort	240	148 (61.7%)	68.1	191 (79.6%)	US/–	NA	15 (10.1%)
Cheng et al,[2] 2019	Retrospective, cohort	126	25 (18.8%)	72.2	69 (54.8%)	DSA/other	NA	15 (60.0%)
Goessens et al,[18] 2007	Retrospective, cohort	2684	2436(91.8%)	NA	NA	US/other	NA	43 (1.8%)
Hoegberg et al,[41] 2019	Prospective, cohort	3057	696 (22.8%)	65.0	3057 (100%)	US/NASCET	5.0	4 (0.6%)
Johnson et al,[42] 1995	Prospective, cohort	232	138 (59.5%)	62.5	78 (33.6%)	US/–	7.0	5 (3.6%)
Jungquist et al,[43] 1989	Retrospective, cohort	949	815 (85.9%)	69.0	815 (85.9%)	US/other	NA	17 (2.1%)
Kaul et al,[44] 2017	Prospective, cohort	1500	238 (15.9%)	58.1	1016 (67.7%)	US/–	8.0	14 (5.9%)
Lewis et al,[45] 1997	Prospective, RCT	713	293 (41.1%)	65.2	283 (39.7%)	US/other	1.6	28 (9.6%)
Mackey et al,[46] 1997	Prospective, cohort	715	358 (50.1%)	65.0	286 (40.0%)	US/other	3.6	35 (9.8%)
Masoomi et al,[47] 2017	Retrospective, cohort	712	446 (62.6%)	74.7	175 (49.2%)	US/other	5.1	30 (6.7%)
Moore et al,[48] 1978	Prospective, cohort	67	67 (100%)	63.0	NA	DSA/–	3.3	6 (9.0%)
Noh et al,[49] 2017	Retrospective, cohort	2006	1813 (90.3%)	64.5	1351 (67.3%)	US/NASCET	4.6	42 (2.3%)
Polak et al,[50] 1998	Prospective, cohort	5201	3332 (64.1%)	73.3	2246 (43.2%)	US/other	NA	238 (7.1%)
Prabhakaran et al,[51] 2006	Prospective, cohort	1939	159 (8.2%)	69.0	795 (41.0%)	US/–	6.2	45 (28.3%)
Roederer et al,[52] 1984	Prospective, cohort	203	141 (69.5%)	63.6	110 (54.9%)	US/other	3.0	4 (2.8%)
Singh et al,[9] 2015	Retrospective, cohort	214	110 (51.4%)	70.0	124 (57.9%)	DSA/NASCET	13.0	13 (11.8%)
Tong et al,[53] 1996	Retrospective, cohort	672	379 (56.4%)	64.9	149 (44.3%)	DSA/other	4.9	12 (3.2%)
Underhill et al,[55] 2009	Retrospective, cohort	67	67 (100%)	69.8	51 (76.1%)	MRI/other	1.5	0 (0%)
Wintermark et al,[31] 2008	Retrospective, cohort	272	142 (52.2%)	66.0	77 (56.6%)	CTA/NASCET	NA	25 (17.6%)
Yamada et al,[54] 2007	Prospective, cohort	392	152 (38.8%)	NA	NA	MRI/NASCET	1.0	0 (0%)
Zhang et al,[56] 2017	Prospective, cohort	1376	840 (61.1%)	69.5	618 (44.9%)	US/–	5.0	94 (11.2%)
Zierler et al,[57] 1990	Prospective, cohort	100	77 (77.0%)	NA	NA	DSA/other	2.8	15 (19.5%)

Note:—US indicates sonography; NA, not applicable; RCT, randomized controlled trial.

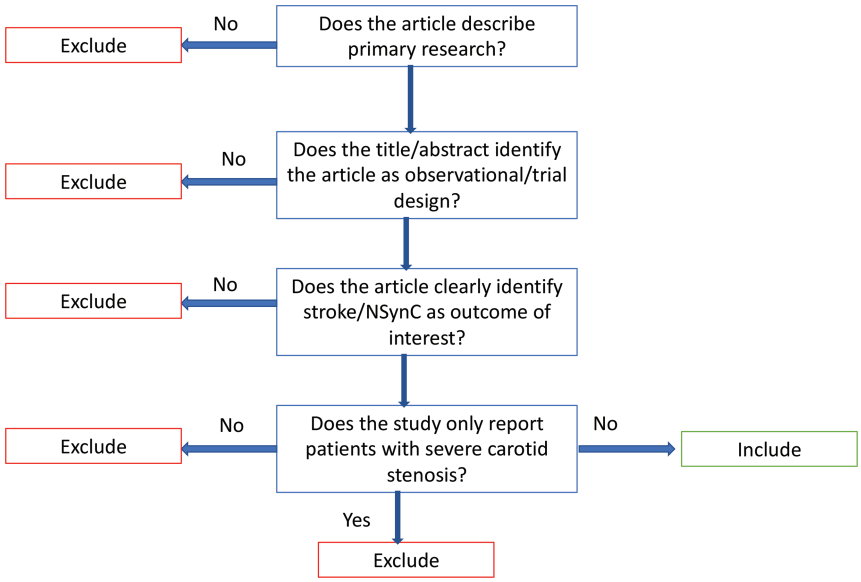
On-line Table 2: Summary of study characteristics for studies reporting rates of recurrent ischemic cerebrovascular events (stroke, TIA) in a symptomatic patient population with nonstenotic carotid plaques

Author, Year	Study Design	Total Sample Size	Age (Mean/ Median) (yr)	Men (%)	Imaging Technique and Grading System	Treatment	Median Follow-Up (yr)	Recurrent Events (No.) (%)
Altaf et al,[27] 2008	Prospective	22	72.7	NA	MRI/NASCET	Medical	2.0	4 (18.2%)
Coutinho et al,[6] 2016	Retrospective	85	70.0	41 (48.2%)	US/NASCET	Medical	NA	NA
de Haro et al,[20] 2018	Retrospective	21	73.3	16 (76.2%)	US/–	Medical, stent placement	2.2	0 (0%)
Freilinger et al,[21] 2012	Prospective	33	71.7	22 (66.7%)	MRI/other	Medical	NA	NA
Gupta et al,[22] 2015	Prospective	27	71.0	14 (51.9%)	MRI/NASCET	NA	NA	NA
Hyafil et al,[23] 2016	Prospective	18	70.0	7 (38.9%)	MRI/other	Medical	NA	NA
Ishikawa et al,[58] 2017	Retrospective	249	68.5	192 (77.1%)	US/NASCET	NA	NA	NA
Kashiwazaki et al,[13] 2019	Prospective	16	72.8	16 (100%)	MRI/NASCET	Surgical	3.2	0 (0%)
Komatsu et al,[24] 2018	Prospective	53	65.0	39 (73.6%)	US/ECST	NA	NA	NA
Singh et al,[25] 2018	Prospective	35	74.3	16 (45.7%)	MR imaging/–	NA	NA	NA
Takai et al,[14] 2018	Retrospective	18	68.3	18 (100%)	US/NASCET	Stent placement, surgical	3.2	0 (0%)
Xu et al,[26] 2016	Retrospective	58	58.0	34 (58.6%)	MRI/NASCET	Medical	NA	NA
Yoshida et al,[28] 2012	Prospective	25	74.4	23 (92.0%)	MRI/NASCET	Medical, surgical	2.6	2 (8.0%)
Yoshida et al,[8] 2019	Prospective	17	72.9	16 (94.1%)	CT/NASCET	Medical, surgical	5.9	11 (64.0%)

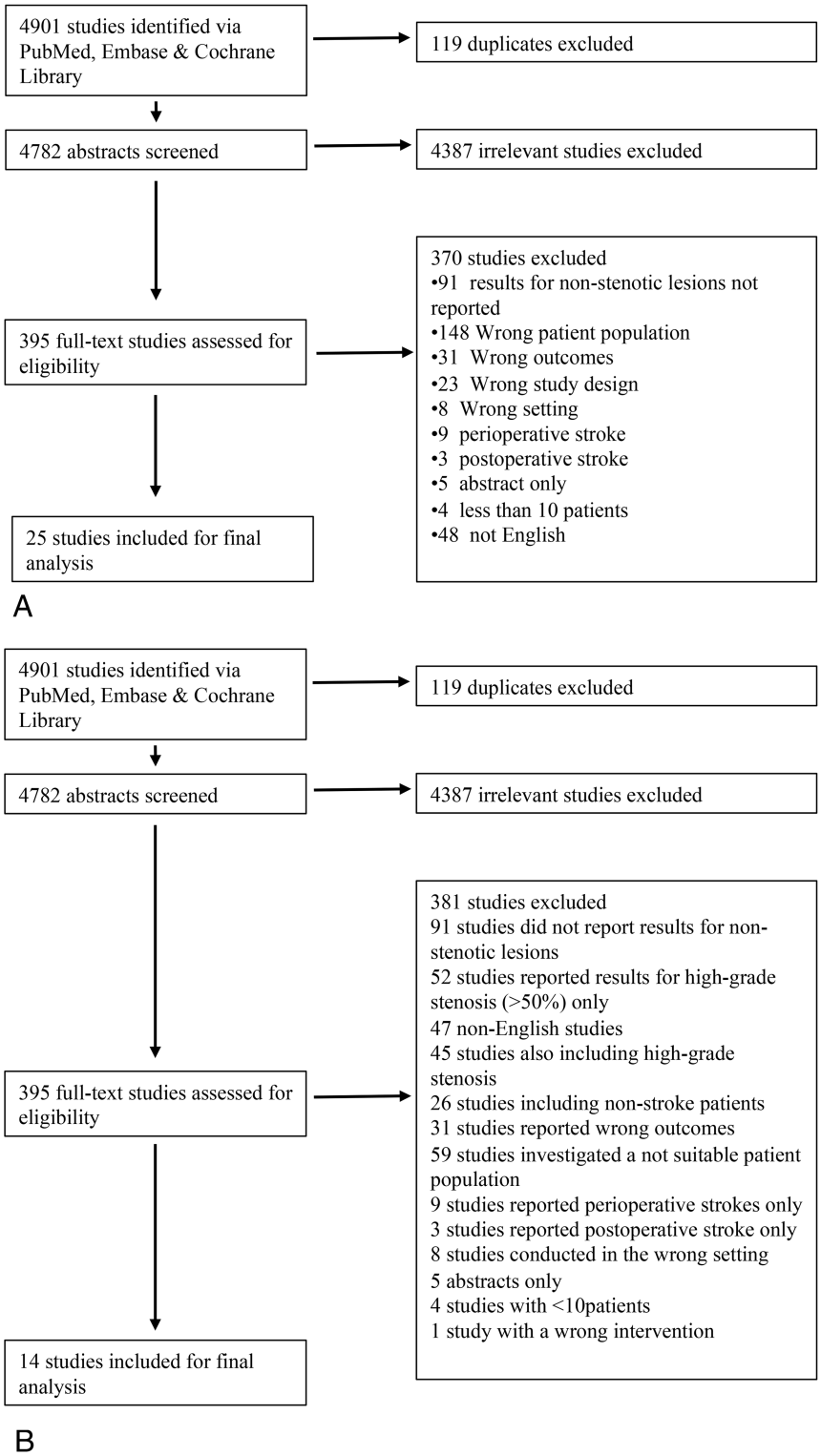
Note:—US indicates sonography; NA, not applicable.

# ▲	Searches
1	carotid.ti,kf.
2	stroke.tw,kf. or exp Stroke/
3	cerebrovascular accident*.tw,kf.
4	((brain or vascular or lacunar or cerebral or isch?emic) adj2 (accident$ or infarct$ or event$ or attack$)).tw,kf.
5	2 or 3 or 4
6	cryptogenic.ti,kf.
7	unknown.ti,kf.
8	undetermined.ti,kf.
9	6 or 7 or 8
10	1 and 5 and 9
11	(carotid adj3 (athero$ or stenos$ or ulcer$ or plaque$ or narrow$ or constrict$)).tw,kf.
12	(carotid adj3 (high risk or low grade or low-grade)).tw,kf.
13	11 or 12
14	5 and 13
15	limit 14 to animals
16	limit 14 to humans
17	15 not 16
18	14 not 17

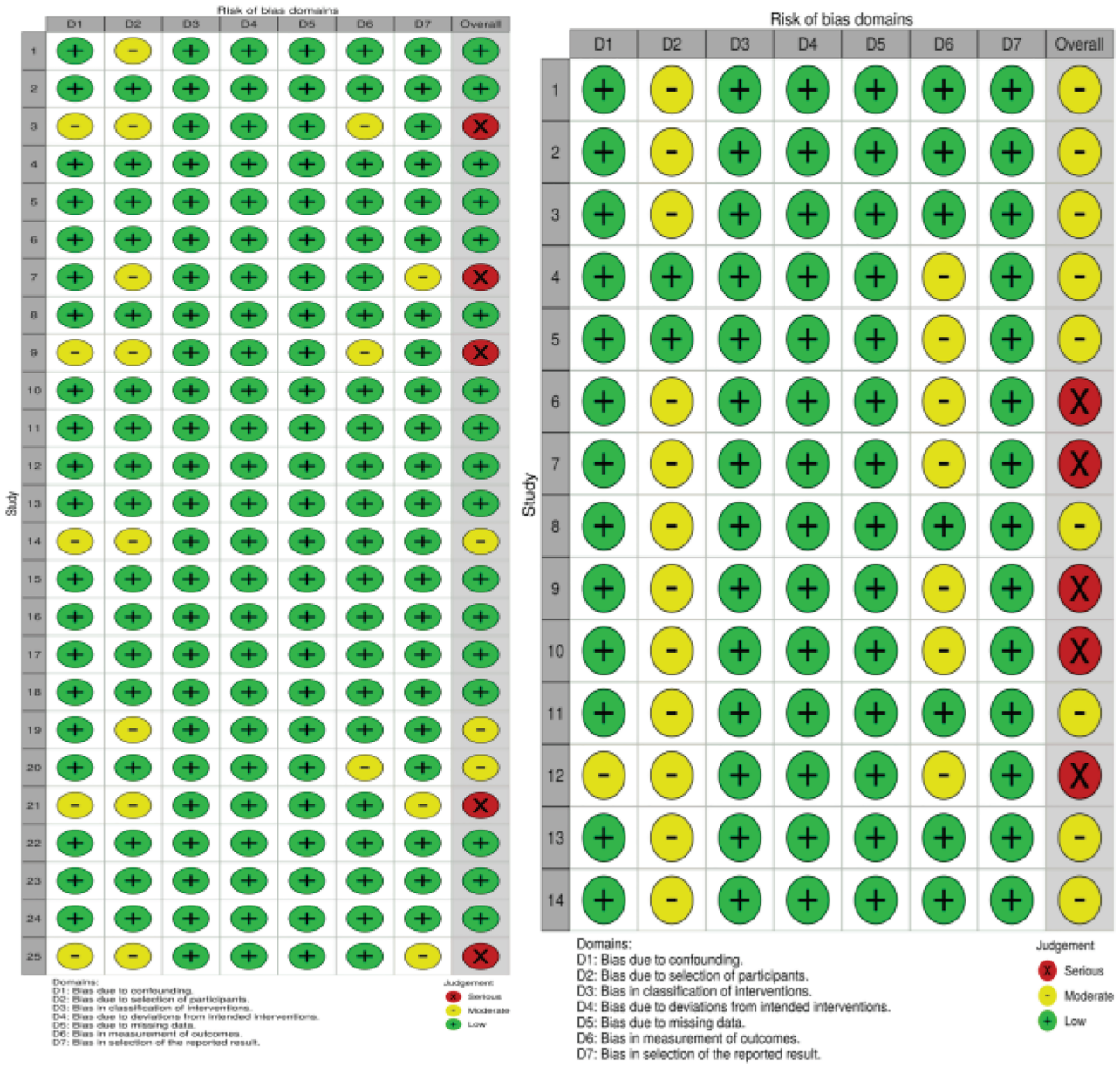
ON-LINE FIG 1. Example of strategy used for search.



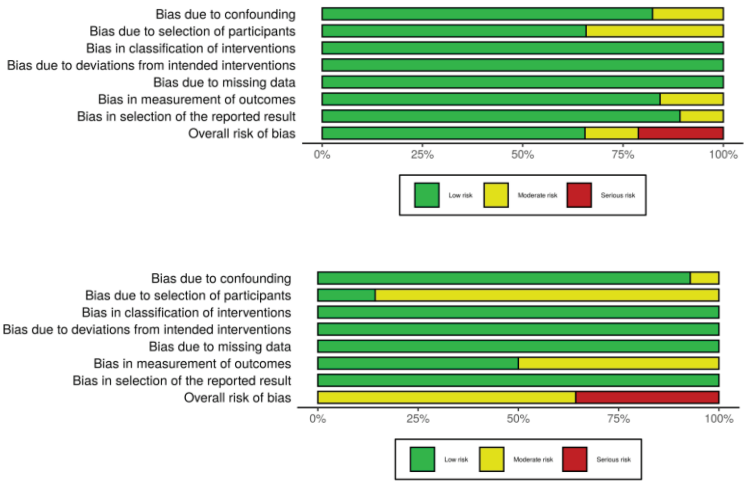
ON-LINE FIG 2. Decision flowchart for title and abstract screening.



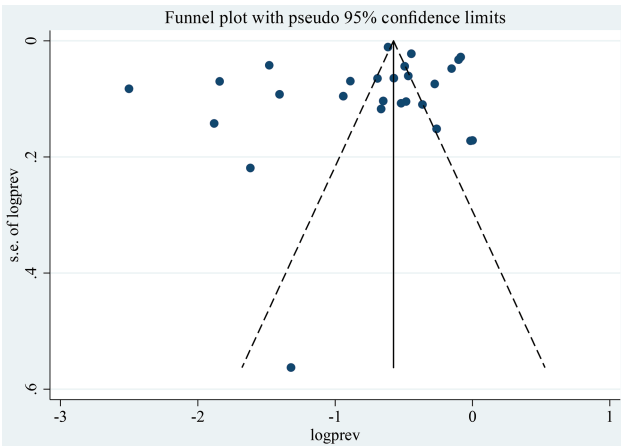
ON-LINE FIG 3. *A*, PRISMA flow diagram of the screening process for included studies (question 1). *B*) Question 2.



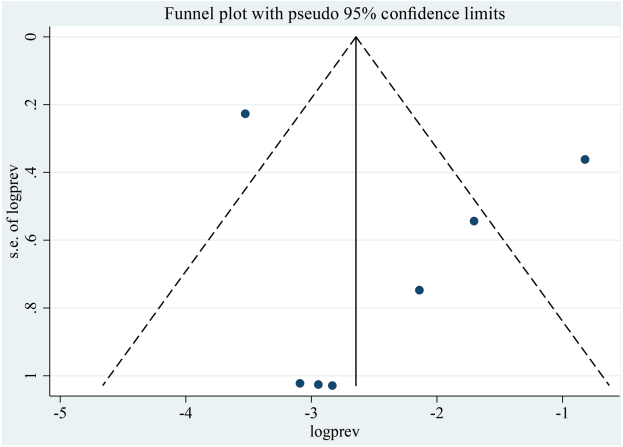
ON-LINE FIG 4. Risk of bias assessment with a traffic light plot for $n = 25$ and $n = 14$ studies using the Cochrane ROBINS-I tool for observational studies.



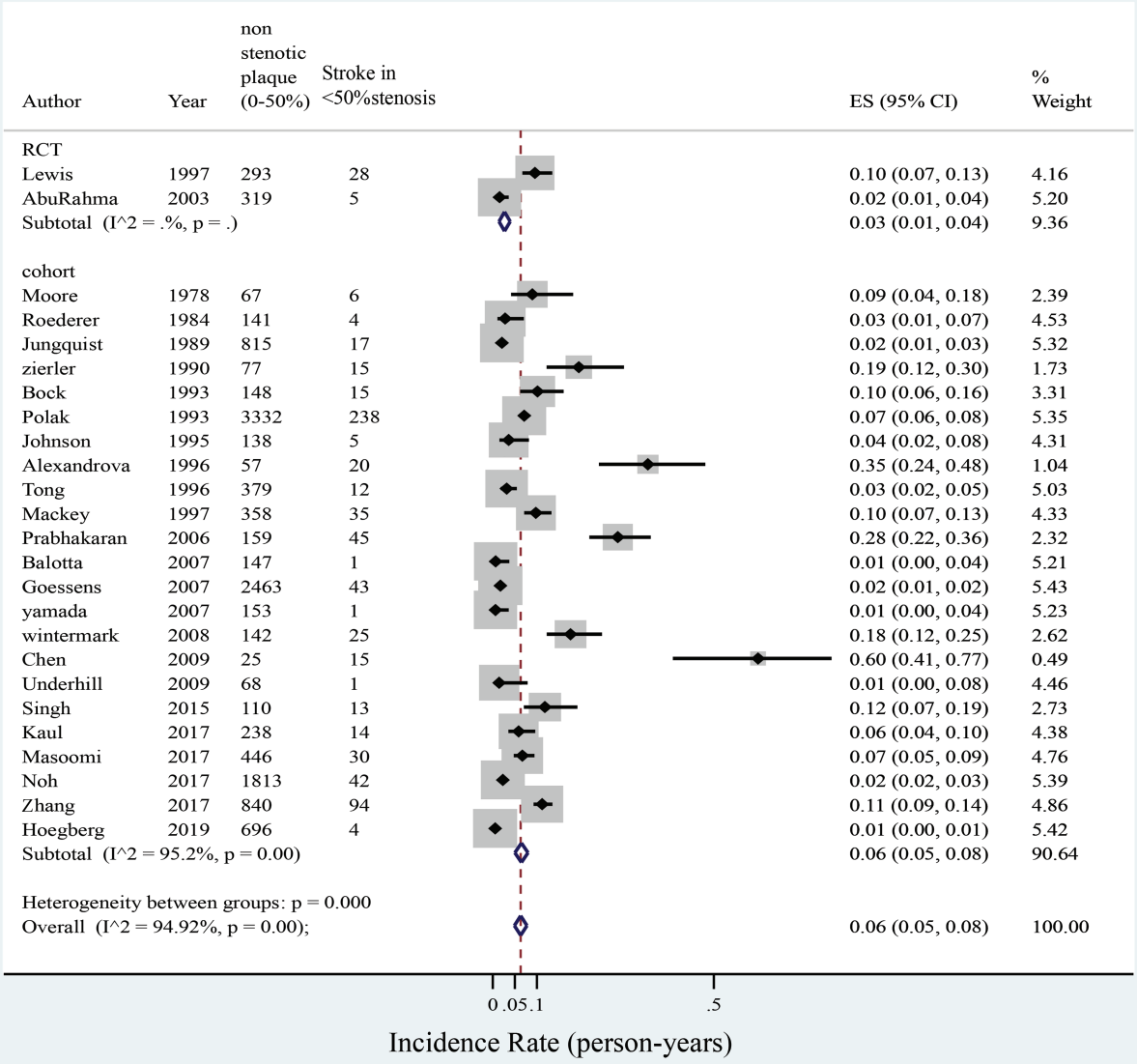
ON-LINE FIG 5. Risk of bias assessment with a weighted summary plot for $n = 25$ and $n = 14$ studies using the Cochrane ROBINS-I tool for observational studies.



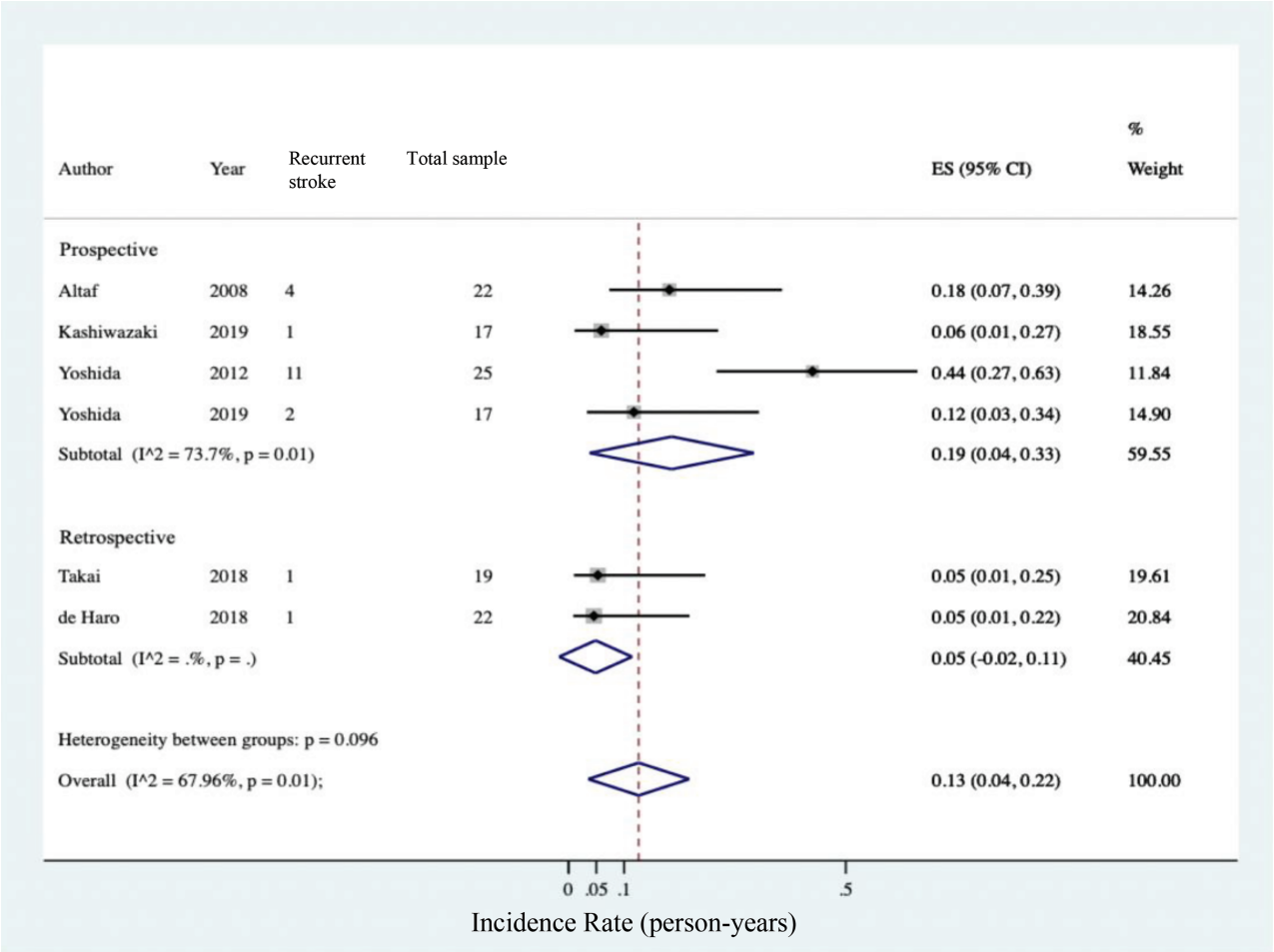
ON-LINE FIG 6. Funnel plot of the 25 studies reporting the risk of stroke with asymptomatic nonstenotic (<50%) carotid plaques in patients with stroke. *Blue circles* represent individual studies. The log of the pooled risk of strokes for asymptomatic nonstenotic carotid plaques (x-axis) is plotted against the standard error of the log of the pooled risk (y-axis). *Dashed diagonal lines* indicate the expected distribution of studies.



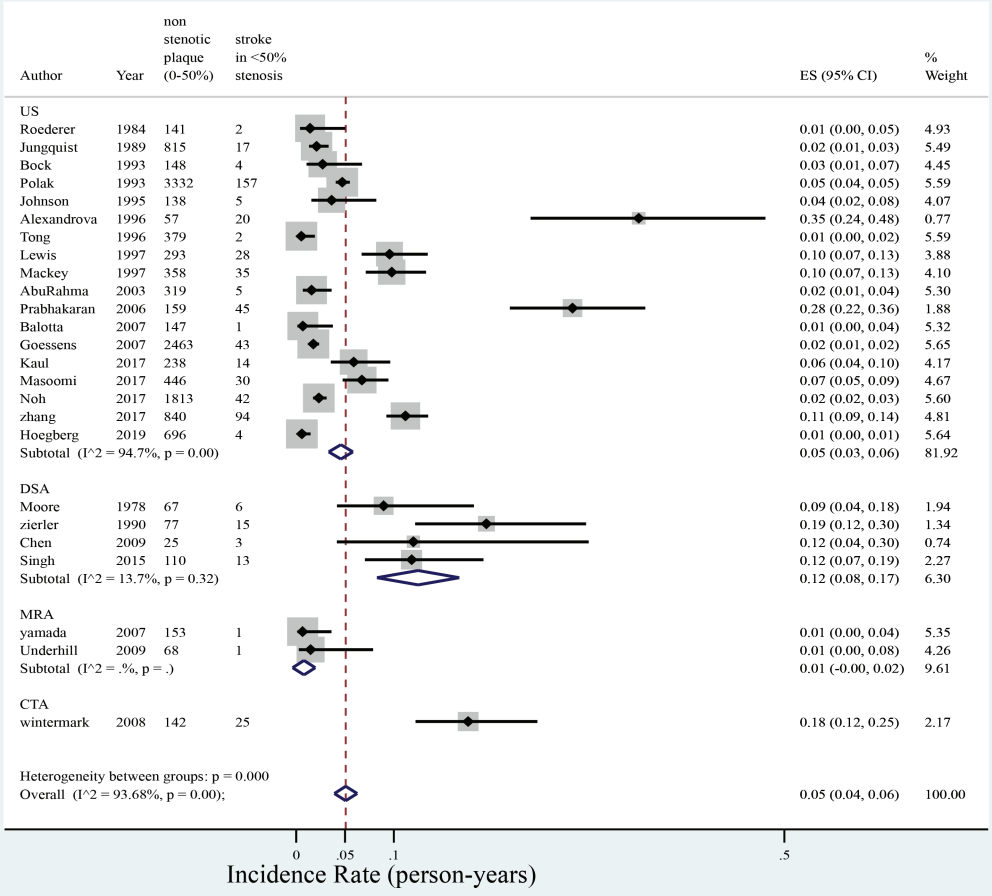
ON-LINE FIG 7. Funnel plot of the 7 studies reporting recurrence of stroke with nonstenotic (<50%) carotid plaques in patients with stroke. *Blue circles* represent individual studies. The log of the pooled risk of recurrent strokes for nonstenotic carotid plaques (x-axis) is plotted against the standard error of the log of the pooled risk (y-axis). *Dashed diagonal lines* indicate the expected distribution of studies.



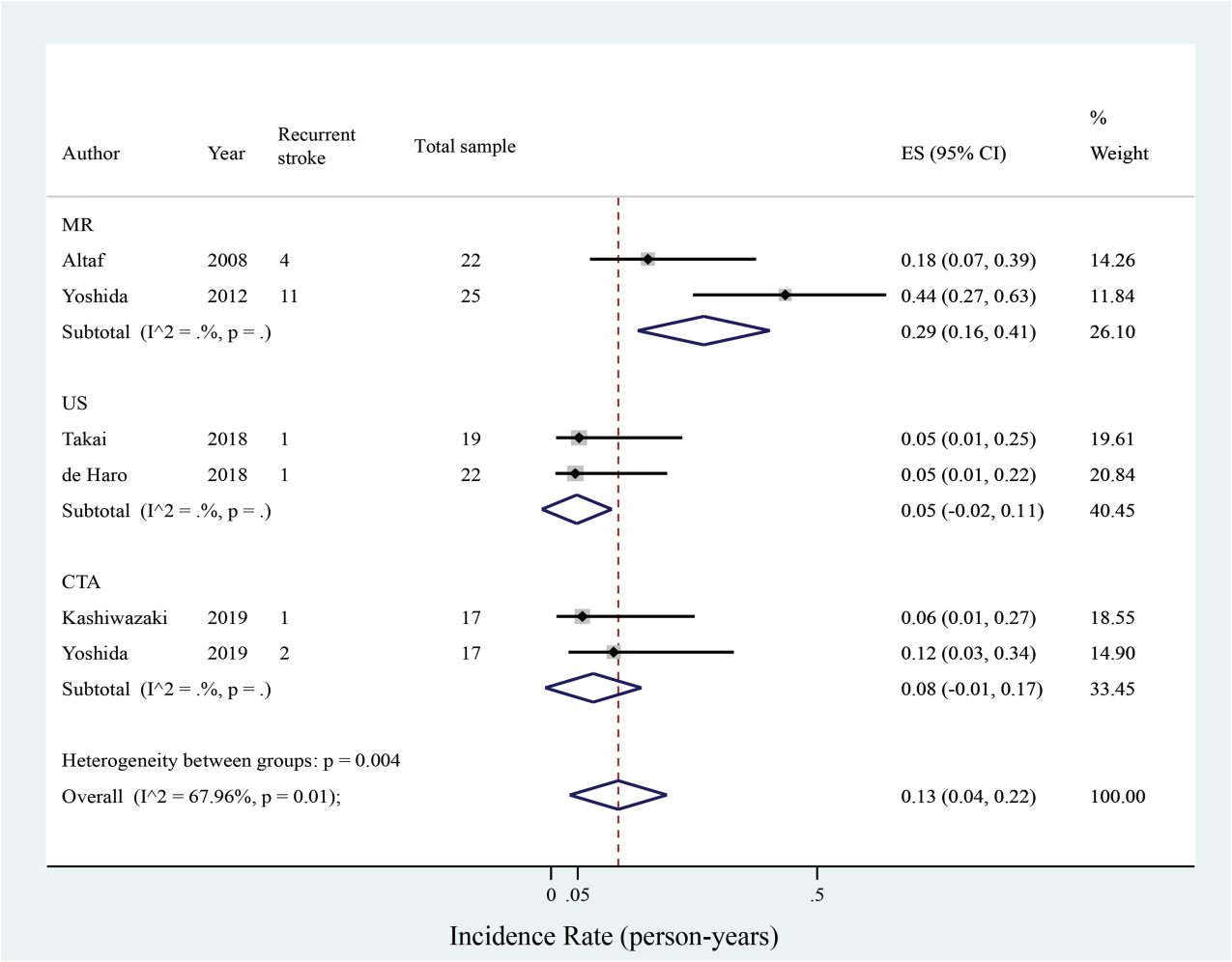
ON-LINE FIG 8. Pooled risk of stroke in patients with ASyNC, stratified by study design. ES indicates effect size.



ON-LINE FIG 9. Pooled risk of recurrent stroke in patients with SyNC, stratified by study design. ES indicates effect size.



ON-LINE FIG 10. Pooled risk of patients with stroke and ASyNC stratified by imaging technique. ES indicates effect size.



ON-LINE FIG 11. Pooled risk of recurrent stroke in patients with SyNC, stratified by imaging technique. ES indicates effect size.