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Cognitive Impairment Associated with Atrial Fibrillation: A Meta-analysis

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Abstract

Background—Atrial fibrillation (AF) has been linked with an increased risk of cognitive impairment and dementia.

Purpose—To complete a meta-analysis of studies examining the association between AF and cognitive impairment.

Data Sources—Electronic search of 5 large databases and hand search of article references.

Study Selection—Prospective and non-prospective studies reporting adjusted risk estimates for the relationship between AF and cognitive impairment.

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Potential Conflicts of Interest:

SK: None

TAS: Royalties (modest) from Mosby/Elsevier and McGraw-Hill for editing textbooks; Honoraria (modest) from Reed-Elsevier for speaking on topics related to general hospital psychiatry; Salary as employee of the Academy of Psychosomatic Medicine (significant) for editing (*Psychosomatics*).

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Data Extraction—Two abstracters independently extracted data on study characteristics, risk estimates, methods of AF and outcome ascertainment, and methodological quality.

Data Synthesis—Twenty one studies were included in the meta-analysis. AF was significantly associated with a higher risk of cognitive impairment independent of stroke history (relative risk (RR) [95% confidence interval (CI)] =1.34 [1.13, 1.58]), in patients with first-ever or recurrent stroke (RR [95%] =2.7 [1.82, 4.00]) and in a broader population including patients with or without a history of stroke (RR [95% CI] =1.4 [1.19, 1.64]). However, there was significant heterogeneity among studies of the broader population (I^2 =69.4 %). Limiting the analysis to prospective studies yielded similar results (RR [95% CI] =1.36 [1.12, 1.65]). Restricting the analysis to studies of dementia eliminated the significant heterogeneity (*P* value =0.137) but did not alter the pooled estimate substantially (RR [95% CI] = 1.38 [1.22, 1.56]).

Limitations—There is an inherent bias due to confounding variables in observational studies. There was significant heterogeneity among included studies.

Conclusions—Evidence suggests that AF is associated with a higher risk of cognitive impairment and dementia, with or without a history of clinical stroke. Further studies are required to elucidate the relationship between AF and subtypes of dementia as well as the etiology of cognitive impairment.

Keywords

Atrial Fibrillation; Dementia; Cognitive Impairment; Meta-analysis

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the United States (US), affecting more than 2.7 million Americans in 2010. Of all US men and women ≥40 years of age, 25% will develop AF during their lifetime. In addition, the prevalence of AF is rising dramatically as the population ages (1).

Moreover, the prevalence of cognitive impairment and dementia is also rising in association with the increased longevity of the population and the accumulation of risk factors for cognitive impairment (2). Three putative risk factors for cognitive impairment are heart failure (3), diabetes (4, 5) and hypertension (6, 7), which are also known risk factors for AF (1). Several longitudinal studies and meta-analyses reported positive associations between these factors and cognitive decline (8). Notably, heart failure(3) and diabetes (5) were associated with a greater than 1.5 times increased risk of cognitive dysfunction and dementia, respectively. Mild cognitive impairment is characterized by an objective long-term memory impairment that does not adversely affect activities of daily living, while dementia is defined by a memory impairment and at least one other impairment in cognitive function that is severe enough to interfere with daily life. Of the many different types of dementia, Alzheimer's disease is the most prevalent, affecting 1 in 8 people over the age of 65 years; vascular dementia and Lewy body dementia are the next most common causes (9, 10). Given the significant burden that cognitive impairment and dementia have on patients, families, and the health care system (10), it is crucial to identify its major risk factors to facilitate implementation of appropriate preventive measures.

Recently, a growing body of evidence has linked AF with an increased risk of cognitive impairment and dementia (11-13). However, the association has not been consistent across studies (14-16). While AF increases the risk of stroke by a factor of 4 to 5 (17), it is not clear whether cognitive impairment in the context of AF is solely mediated through an increased risk of stroke or whether other factors are responsible. A recent review reported a significant association between AF and post-stroke dementia in patients with first-ever or recurrent stroke (18). However, the researchers did not attempt to estimate the association of dementia independent of a stroke history. Elucidating this association could be particularly helpful in understanding the underlying mechanisms that link AF with cognitive impairment. Therefore, we performed a comprehensive systematic review of the literature to explore and elucidate the association between AF and cognitive impairment (independent of stroke and in patients with first-ever or recurrent stroke).

Methods

Data Sources and Searches

We followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (19) to perform a meta-analysis of observational studies that reported an association between AF and cognitive impairment. Five large databases MEDLINE (Ovid interface), PsycINFO, Cochrane library (Ovid SP), CINAHL, and EMBASE were electronically searched from their inception to Sep 18, 2012. An electronic search was performed by one of the investigators (S.K.) with help from a qualified librarian, using text and explosion of Medical Subject Headings (Online Appendix 1). No language restriction was applied. To ensure a comprehensive search of the literature, we also manually searched the reference lists of the included studies and previously published systematic reviews and meta-analyses. We contacted the authors when required data were ambiguous or missing.

Study Selection

Prospective and non-prospective studies reporting the relationship between AF and cognitive impairment or total dementia were included in this systematic review. We excluded: 1) reviews, editorials, letters, case series, case reports, and conference proceedings; 2) studies evaluating cognitive decline after open heart surgery in patients with AF; 3) studies lacking a control group; 4) studies in which the presence or absence of dementia was only assessed by an informant review; 5) post-mortem studies; 6) studies in which the control group was selected from patients with other types of arrhythmia; 7) studies with inappropriate outcome measures (any outcomes other than cognitive impairment);and 8) studies that provided only unadjusted or crude analyses. The last exclusion criterion is particularly important because crude estimates of the association between atrial fibrillation and cognitive impairment are likely to be highly biased by confounding variables (such as age), and therefore misleading.

Outcome measures

The primary outcome of interest was cognitive impairment (from mild to severe dementia). The secondary outcomes were cognitive impairment and dementia, separately.

Data Extraction and Quality Assessment

The following data from eligible studies were extracted in duplicate by two independent abstracters: first author, year, design (case-control, cross-sectional, prospective cohort), comparison groups, inclusion and exclusion criteria, total sample size, number of subjects in the AF group and in the no AF group, and number of events within each group, population characteristics (e.g., age, number of females, history of stroke), outcome, methods of AF, outcome and stroke ascertainment, type of relative risk (RR) estimate (odds ratio, risk ratio, and hazard ratio), the RR estimate and its 95% confidence interval (CI), adjusted analysis (classified as minimal if adjusted for age and as multivariate if adjusted for at least two potential confounding variables in addition to age), along with a list of variables used in the adjusted analysis. Any disagreements or discrepancies were resolved by consensus.

The quality of included studies was assessed using an adaptation of two published checklists (20, 21) with the seven criteria most relevant to included studies, with only six criteria applicable to non-prospective studies: 1) was AF the main exposure of interest? (yes/no); 2) were the inclusion and exclusion criteria clearly stated? (yes/no); 3) potential for misclassification of AF based on AF ascertainment method: was an electrocardiogram used for AF diagnosis? (Yes/No/Unclear); 4) potential for misclassification of outcome based on outcome ascertainment method: for instance, using multiple neuropsychological tests for assessment of cognitive impairment was considered superior to using single MMSE test; and, using criteria from the Diagnostic and Statistical Manual of Mental Disorders third or fourth edition (22, 23) for assessment of dementia was judged superior to using codes from the International Classification of Diseases ninth or tenth revision (24, 25) from patient discharge files or data registries; 5) was temporality clear (i.e. was AF diagnosis made before the outcome?) (“yes” for prospective studies and “no” for non-prospective studies); 6) potential for attrition bias in prospective studies (≥10% versus <10% lost-to-follow-up); 7) Potential for confounding bias based on level of adjustment in multivariate models: minimal adjustment for age versus multivariate adjustment for age and at least two other potential confounding variables such as heart failure, hypertension and diabetes mellitus. Quality criteria were extracted in duplicates by two abstracters and discrepancies were resolved by a third reviewer (J.R. or T.S.). Superiority or acceptability of diagnostic methods for dementia and cognitive impairment was confirmed by one of the senior authors (T.S.).

When duplicates were identified, the most recent study was included unless the earlier version of the study reported the multivariable adjusted-risk estimate, in which case the earlier version was included. When both cross-sectional and prospective association of AF and cognitive impairment were reported, we only included the prospective assessment. When associations with cognitive impairment and dementia were both reported, for the main analysis, we used the broader definition of outcome that included the other outcome (e.g., dementia is a subset of cognitive impairment).

Data Synthesis and Analysis

Random effects models using the DerSimonian and Laird method (26) were incorporated to estimate the pooled RR of the association between AF and cognitive impairment or

dementia. The random effects model was used to account for both within- and between-studies variances. To evaluate the association independent of stroke history, we performed a meta-analysis of studies that either excluded patients with a history of stroke or adjusted for this co-morbidity in the multivariate adjusted model. To investigate the association between AF and cognitive impairment ascertained by the Mini Mental State Examination (MMSE), (the most widely used screening tool in practice), we performed a sensitivity analysis restricted to the studies that used the MMSE to define cognitive impairment (MMSE score of ≤ 24) or cognitive decline (MMSE decline ≥ 3 points during follow-up). Due to the methodological differences between prospective and non-prospective studies, we performed all the analyses within study designs and reported the pooled estimates only when separate analyses justified the combination. The main analysis combined dementia outcomes with cognitive impairment. To justify the combination and to report a separate pooled estimate for dementia, a subgroup analysis was performed separating studies of dementia from cognitive impairment. Heterogeneity was assessed using the *P* value from Q-statistics and was quantified by Higgins I-squared statistics where an I-squared value of 30% to 60% was considered to represent a moderate level of heterogeneity (27). Publication bias was evaluated by using Egger's regression test and illustrated using a funnel plot. A forest plot was used to graphically display the effect size in each study as well as in the pooled estimate. A *P* value<0.05 was considered significant. All the analyses were performed in Stata/IC 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). The funding sources played no role in the design, conduct, and analysis of the study or in the decision to submit the manuscript for publication.

Results

Of 3944 retrieved articles, 123 abstracts were chosen for full-text screening, including one Chinese and one Italian study that were translated to English. Among the 123 studies reviewed, 21 met the inclusion criteria. Three additional reports were eligible for full text screening when the reference lists of the included studies and previously published review papers were scanned, however, none met our inclusion criteria (Appendix Figure 1). Of the 21 included studies, 7 studies specifically examined the association of AF with post-stroke cognitive impairment or dementia and 14 reported the association between AF and cognitive impairment or dementia in a broader population (including patients with or without a history of stroke).

AF and Cognitive Impairment in Patients with or without History of Stroke

Fourteen studies (5 cross-sectional, and 9 prospective studies) investigated the association between AF and dementia or cognitive impairment. The characteristics of these studies are tabulated in Appendix Table 1. Results, description of the multivariate models, methods of AF, stroke and outcome ascertainments are described in Appendix Table 2. In a combined analysis of all 14 studies (Figure 1), AF was significantly associated with the risk of developing cognitive impairment (RR [95% CI] =1.40 [1.19, 1.64]). The adjusted prospective estimate was virtually the same as the adjusted cross-sectional estimate, justifying their combination. However, as anticipated, there was significant heterogeneity among studies. The overall heterogeneity resulted mainly from variability among

prospective studies. Such heterogeneity might have originated from variances in characteristics of the participants (e.g., age and co-morbidities), methods of AF ascertainment, and outcome measures (Appendix Table 2). Among the 14 included studies, the most common method of AF ascertainment was the electrocardiogram followed by the International Classification of Diseases codes. The remaining studies either did not report the AF ascertainment method or used physical examination and medical history. Cognitive impairment was most commonly assessed by the use of the MMSE, and dementia diagnosis was most commonly confirmed by the Diagnostic and Statistical Manual of Mental Disorders criteria. The International Classification of Diseases codes and neuropsychological batteries were used in the remainder of the studies for the diagnosis of dementia. Stroke diagnosis was mainly self-reported or determined by medical records and rarely confirmed by imaging evaluations.

Sensitivity and Subgroup Analyses and Assessment of Heterogeneity

In view of the significant heterogeneity observed in this meta-analysis, we incorporated a random effects model and performed several sensitivity analyses to assess the robustness of the results. The pooled estimates were virtually the same for prospective and cross-sectional studies (Figure 1). However, significant heterogeneity was observed among prospective studies. This heterogeneity may be due in part to variances in outcome measures. Restricting the analysis to studies of dementia (Figure 2 A), which is more reliably diagnosed than cognitive impairment, eliminated the significant heterogeneity without changing the pooled estimate substantially (RR [95% CI] =1.38 [1.22, 1.56]). Limiting the analysis to the 8 studies that ascertained cognitive impairment or decline by MMSE score $\leq$24 or MMSE decline $\geq$3 points, did not appreciably change the results (RR [95% CI] = 1.38 [1.11, 1.71]) (Appendix Figure 2). We assessed the effect of any single study on the pooled estimate by removing one study at a time. Removing no single study changed the significance of the pooled estimate or heterogeneity. Investigating subtypes of dementia failed to demonstrate a significant association between AF and Alzheimer's disease (RR [95% CI] =1.22 [0.96, 1.56]); however, the association was significant for vascular dementia (RR [95% CI] =1.72 [1.27, 2.32]).

AF and Cognitive Impairment Independent of Stroke History

Limiting the analysis to participants without a history of a stroke and to studies that adjusted for this co-morbidity in multivariate analyses did not appreciably affect the primary results (RR [95% CI] =1.34 [1.13, 1.58]) (Figure 3). Furthermore, restricting the analysis to studies that specifically excluded patients with a history of stroke did not alter the results (RR [95% CI] =1.37 [1.08, 1.73]).

AF and Post-Stroke Cognitive Impairment

The association between AF and post-stroke cognitive impairment or dementia was reported in 7 studies. The characteristics of these studies are tabulated in Appendix Table 3. Overall, AF was associated with a more than two-fold increase in the risk of developing post-stroke cognitive impairment or dementia (RR [95%] =2.7 [1.82, 4.00]) (Figure 4). Although prospective and cross-sectional studies showed overlapping risk estimates, the association was stronger within prospective studies (RR [95%] =3.01 [1.96, 4.61]). Additionally,

prospective studies were more homogeneous than non-prospective ones. Appendix table 4 describes the results of individual studies, multivariate models, and methods of AF, outcome and stroke ascertainment. Almost all studies of post-stroke cognitive impairment or dementia confirmed the diagnosis of stroke by detailed imaging studies.

Quality of Included Studies

The quality of the prospective and cross-sectional studies was assessed by 7 and 6 objective criteria, respectively. Studies which meet a higher number of quality criteria have a more favorable methodological quality and less risk of bias. Appendix Table 5 describes the quality criteria of studies that evaluated patients with or without history of stroke. Seven prospective studies (11-14, 16, 34, 36) had favorable methodological quality with adequate adjustment for confounding factors but variable methods of AF and outcome ascertainment. There was no single criterion that would stand out as the main problem in these prospective studies. The quality of one prospective study (33) was poor due to the potential for misclassification of AF and outcome, and risk of attrition and confounding bias. Among the non-prospective studies, 3 (29-31) had an overall higher risk of bias mostly due to the potential for misclassification of AF and outcome. Two (28, 32) had better overall methodological quality with adequate adjustment for confounding variables and accurate diagnosis of AF. Eliminating studies which met 3 or fewer quality criteria had little effect on the pooled estimate (RR [95% CI] = 1.32 [1.12, 1.57]).

Appendix Table 6 describes the quality criteria of post-stroke studies. Among the prospective studies, none evaluated AF as their main exposure of interest and all except one (39) were at risk of attrition bias. Overall, non-prospective studies (42, 43) were of poor quality mainly due to potential for misclassification of AF and outcome. Restricting the analysis to studies which met 3 or fewer quality criteria did not substantially change the results (RR [95% CI] = 3.01 [1.96, 4.61]).

Publication bias

The funnel plot resembles a symmetrical funnel for the 14 studies of patients with or without a history of stroke, which rules out publication bias (Appendix Figure 3). We used Egger's regression test to objectively assess the symmetry of the plot. The estimated bias coefficient was 0.64 (*P* value =0.40) which excludes publication bias. The Egger's regression test was also performed for the 7 studies of post-stroke cognitive impairment. The estimated bias coefficient was 2.46 (*P* value=0.009) which suggests the presence of publication bias. Excluding the smallest study with the most unbalanced result (41) did not significantly change the association between AF and post-stroke cognitive impairment or dementia (RR [95% CI] = 2.57 [1.75, 3.79]).

Discussion

Our findings suggest a significant association between AF and cognitive impairment or dementia independent of stroke, in patients with first-ever or recurrent stroke, and in a broader population including patients with or without a history of stroke. Restricting the analysis to dementia outcomes, which are more accurately diagnosed than cognitive

impairment, eliminated the heterogeneity but did not change the significance of the association.

Several mechanisms have been proposed for the association between AF and cognitive impairment. One explanation is the presence of shared risk factors (e.g., hypertension, congestive heart failure, diabetes) between AF and cognitive impairment (8). Further, these risk factors tend to accumulate as the population ages. However, this observation fails to explain the association between AF and cognitive impairment in longitudinal studies that controlled for such co-morbidities (13, 36). Another potential mechanism is a hypercoagulable state (44) in patients with AF, as well as stasis of blood in the left atrium that may lead to formation of thrombi in the left atrial appendage and ultimately to clinical and sub-clinical strokes (45, 46). The results of this meta-analysis cannot rule out the possibility of silent stroke as a potential mechanism of the association. However, one study that excluded patients with a history of stroke by detailed imaging also showed an association between AF and cognitive impairment (47). This observation is particularly important as it highlights the need for further studies to elucidate new mechanisms for this association. Other potential but unproven mechanisms include: brain hypoperfusion due to beat-to-beat variability in the length of the cardiac cycle and reduced cardiac output (48); the pro-inflammatory state in AF (49, 50); and periventricular white matter lesions (51).

Our study has several strengths. We performed a comprehensive search of literature without language restriction, contacted authors for clarifications in case of ambiguity, and requested additional data when necessary. Second, data extraction was performed by two independent investigators. Third, we performed several sensitivity analyses to assess the robustness of our results. There was a consistent significant association between AF and cognitive impairment. Fourth, to our knowledge, this is the first study that collected and presented separate data for dementia and cognitive impairment outcomes. Fifth, the studies included in this report were from geographically diverse regions (Asia, North and South America, Europe, and Australia), thus increasing generalizability. Sixth, this meta-analysis has substantial statistical power to detect a clinically meaningful association because of the large number of events observed. Finally, we used multiple objective criteria to assess the quality of individual studies. This allowed us to identify studies with a higher risk of bias from those with lower risk of bias.

This review has several limitations. A significant heterogeneity was observed in the prospective studies of patients with or without history of stroke. However, we attempted to account for both within- and between-studies variability by using a random effects model. Also, to investigate different endpoints as a source of heterogeneity, we separated dementia outcomes from cognitive impairment in a sensitivity analysis and found no significant heterogeneity in studies of dementia. Some degree of subjectivity is inevitable in assessing the quality of studies of cognitive impairment and dementia due to the wide range of diagnostic tools available. Six of the 21 studies included in this report met 3 or fewer quality criteria, mainly because of a higher potential for misclassification of AF or outcome, inadequate adjustment for potential confounders, and the presence of attrition bias. However, exclusion of these studies in sensitivity analyses had little effect on the reported results. We have reported a significant association between atrial fibrillation and cognitive

impairment independent of stroke history. However, it is important to note that a history of stroke was mainly self-reported or derived from medical records and rarely confirmed by imaging evaluations. Therefore, the reported association is only independent of clinically overt stroke and the possibility of silent stroke cannot be ruled out. The results of the Egger's tests suggested an absence of publication bias in the 14 studies of patients with or without a history of stroke, and a presence of publication bias in the 7 studies of patients with stroke. The Egger's test has limited power in detecting publication bias especially when the number of studies included in the meta-analysis is small. Conversely, in some instances *P* values from the Egger's test are erroneously very small (suggesting publication bias) due to a correlation between the standard error of the log RR and the size of the RR. This is more likely to happen when the effect size is large or when there is significant between-study heterogeneity or when the number of events per study is small(52). Therefore, over-interpretation of Egger's test should be avoided. Finally, the results of the subgroup analysis separating Alzheimer's disease from vascular dementia should be interpreted with caution because accurate distinction between Alzheimer's disease and vascular dementia can only be made through autopsy data and epidemiologic studies have limited ability to reliably separate dementia subtypes. In addition, patients often present with features of both types of dementia and, finally, subgroup analyses are usually underpowered to detect significant associations owing to the limited number of studies included.

Although this meta-analysis must be interpreted in the context of the limitations of the studies included, the current study provides the most comprehensive evidence to date on the potential effects of AF on cognitive impairment. This analysis also highlights critical gaps in our knowledge about the mechanisms underlying the association between AF and cognitive impairment. The finding of this association warrants further well-designed longitudinal studies with better adjustment for potential confounders and with detailed information on subtypes of dementia, as well as clinical trials designed to evaluate interventions that may postpone or reduce the risk of cognitive impairment in patients with AF. On the basis of this systematic review and meta-analysis of all available data, future research should make a careful distinction between different types of dementia and investigators should consider cognitive function as a new outcome to be assessed in interventional studies for the treatment of AF.

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represent the official views of Harvard Catalyst, Harvard University and its affiliated academic health care centers, the National Center for Research Resources, or the National Institutes of Health.

Online Appendix 1

Search Strategy

Ovid MEDLINE(R) 1946 to Present with Daily Update

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations September 18, 2012

#1 mental processes/ or anticipation, psychological/ or exp cognition/ or executive function/ or intention/ or exp learning/ or exp perception/ or exp thinking/ or exp delirium, dementia, amnestic, cognitive disorders/ or exp amnesia/ or exp cognition disorders/ or exp consciousness disorders/ or exp delirium/ or exp dementia/ or exp dementia/ or alzheimer disease/ or exp dementia, vascular/ or exp frontotemporal lobar degeneration/ or lewy body disease/ or exp neurodegenerative diseases/ or Frontotemporal Dementia/ or exp Dementia, Multi-Infarct/ or exp memory disorders/ or exp amnesia/ or psychomotor agitation/ or (cognitive disorders or cognitive impairment or memory loss or amnesia or amnestic or delirium or dementia or Alzheimer or vascular dementia or frontotemporal lobar degeneration or lewy body disease or neurodegenerative diseases or frontotemporal Dementia or MultiInfarct Dementia).ti,ab. **1006376**

#2 exp atrial fibrillation/ or exp atrial flutter/ or (atrial fibrillation or atrial flutter or auricular fibrillation or auricular flutter or AFIB).ti,ab. **43836**

#1 AND #2 →**1094**

PsycINFO 1967 to September Week 2 2012

#1 exp cognitive ability/ or exp cognitive appraisal/ or exp cognitive assessment/ or exp cognition/ or exp cognitive impairment/ or exp cognitive processes/ or exp dementia/ or exp alzheimer's disease/ or exp neurodegenerative diseases/ or exp vascular dementia/ or exp delirium/ or exp dementia with lewy bodies/ or exp memory disorders/ or exp amnesia/ or (cognitive disorders or cognitive impairment or memory loss or amnesia or amnestic or delirium or dementia or Alzheimer or vascular dementia or frontotemporal lobar degeneration or lewy body disease or neurodegenerative diseases or frontotemporal Dementia or MultiInfarct Dementia).ti,ab. **390596**

#2 exp atrial fibrillation/ or exp auricular fibrillation/ or (atrial fibrillation or atrial flutter or auricular fibrillation or auricular flutter or AFIB).ti,ab. **562**

#1 AND #2 →**114**

EBM Reviews - Cochrane Database of Systematic Reviews 2005 to August 2012

EBM Reviews - Database of Abstracts of Reviews of Effects 3rd Quarter 2012

EBM Reviews - Cochrane Central Register of Controlled Trials September 2012

EBM Reviews - Cochrane Methodology Register 3rd Quarter 2012

#1 mental processes/ or anticipation, psychological/ or exp cognition/ or executive function/ or intention/ or exp learning/ or exp perception/ or exp thinking/ or exp delirium, dementia, amnestic, cognitive disorders/ or exp amnesia/ or exp cognition disorders/ or exp consciousness disorders/ or exp delirium/ or exp dementia/ or exp dementia/ or alzheimer disease/ or exp dementia, vascular/ or exp frontotemporal lobar degeneration/ or lewy body disease/ or exp neurodegenerative diseases/ or Frontotemporal Dementia/ or exp Dementia, Multi-Infarct/ or exp memory disorders/ or exp amnesia/ or psychomotor agitation/ or (cognitive disorders or cognitive impairment or memory loss or amnesia or amnestic or delirium or dementia or Alzheimer or vascular dementia or frontotemporal lobar degeneration or lewy body disease or neurodegenerative diseases or frontotemporal Dementia or MultiInfarct Dementia).ti,ab. **34076**

#2 exp Atrial Flutter/ or exp Atrial Fibrillation/ or (atrial fibrillation or atrial flutter or auricular fibrillation or auricular flutter or AFIB).ti,ab. **3289**

#1 AND #2 →**35**

CINAHL

#1“cognitive disorders” OR “cognitive impairment” OR “memory loss” OR “amnesia” OR “amnestic” OR “delirium” OR “dementia” OR “Alzheimer” OR “vascular dementia” OR “frontotemporal lobar degeneration” OR “lewy body disease” OR “neurodegenerative diseases” OR “frontotemporal Dementia” OR “MultiInfarct Dementia” **31461**

OR

#2 (MH “Delirium, Dementia, Amnestic, Cognitive Disorders+”) OR (MH “Cognition Disorders+”) OR (MH “Mental Processes+”) **162413**

AND

#3 (MH “Atrial Fibrillation”) OR (MH “Atrial Flutter”) OR “atrial fibrillation” OR “atrial flutter” OR “AFIB” OR “auricular fibrillation” OR “auricular flutter” **9153**

(#1 OR #2) AND #3 →**292**

EMBASE

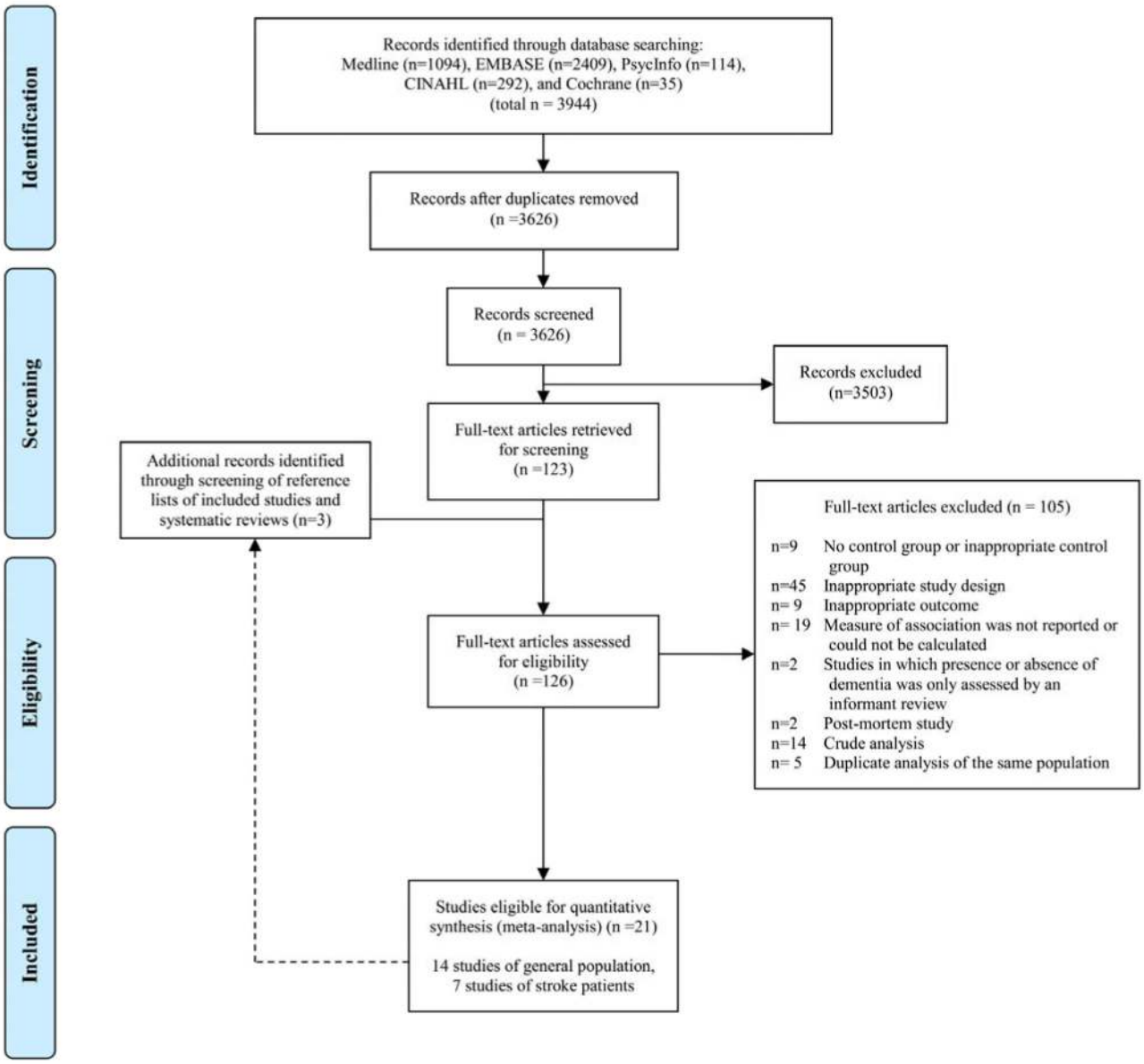
#1’cognitive disorders’:ab,ti OR ’cognitive impairment’:ab,ti OR ’memory loss’:ab,ti OR ‘amnesia’:ab,ti OR ‘amnestic’:ab,ti OR ‘delirium’:ab,ti OR dementia:ab,ti OR ‘alzheimer’:ab,ti OR ‘vascular dementia’:ab,ti OR ‘frontotemporal lobar degeneration’:ab,ti OR ‘lewy body disease’:ab,ti OR ‘neurodegenerative diseases’:ab,ti OR ‘frontotemporal dementia’:ab,ti OR ‘multiinfarct dementia’:ab,ti OR ‘memory’/exp OR ‘cognition’/exp OR ‘executive function’/exp OR ‘learning’/exp OR ‘perception’/exp OR ‘delirium’/exp OR ‘dementia’/exp OR ‘alzheimer disease’/exp OR ‘degenerative disease’/exp OR ‘lewy

body'/exp OR 'multiinfarct dementia'/exp OR 'frontotemporal dementia'/exp OR 'amnesia'/exp OR 'cognitive defect'/exp AND [humans]/lim AND [embase]/lim **772,728**

#2 'heart atrium fibrillation'/exp OR 'heart atrium fibrillation' OR 'heart atrium flutter'/exp OR 'heart atrium flutter' OR 'atrial fibrillation':ab,ti OR 'atrial flutter':ab,ti OR 'auricular fibrillation':ab,ti OR 'auricular flutter':ab,ti OR afib:ab,ti AND [humans]/lim AND [embase]/lim **50,150**

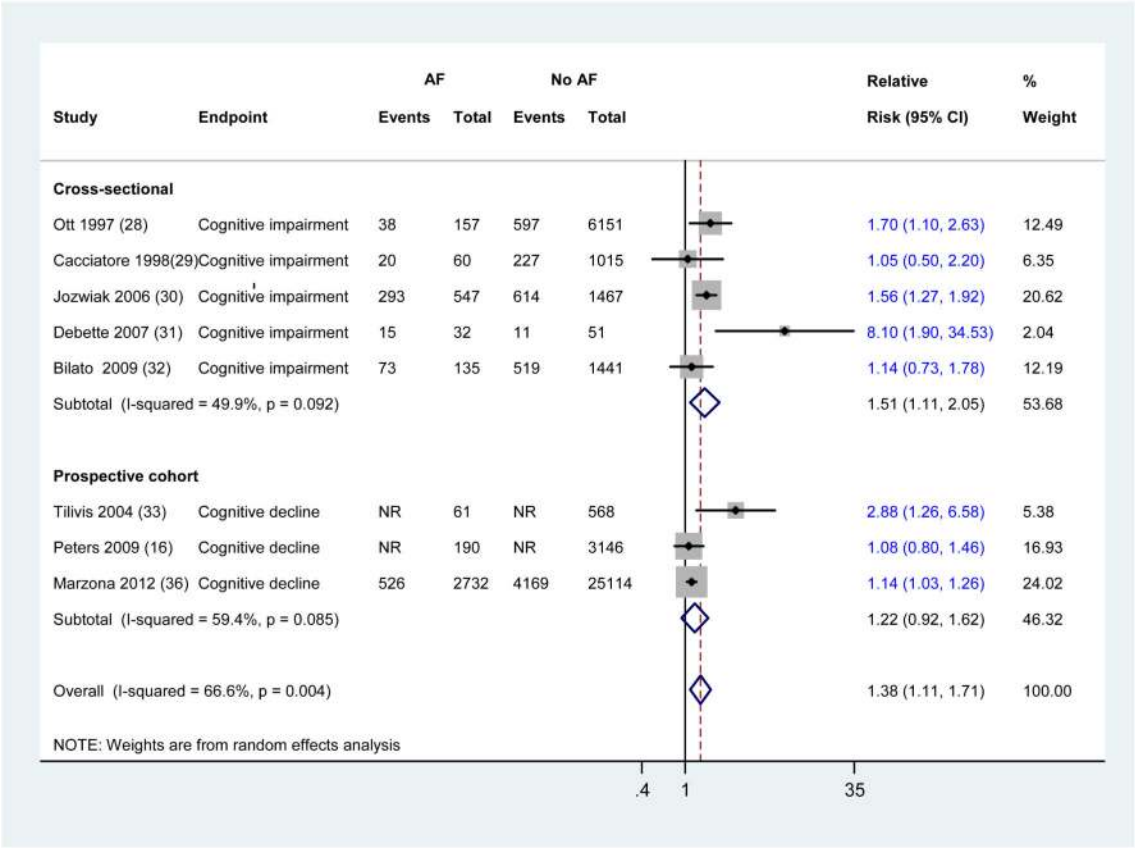
#1 AND #2 →**2,409**

Total=3944



Appendix Figure 1.

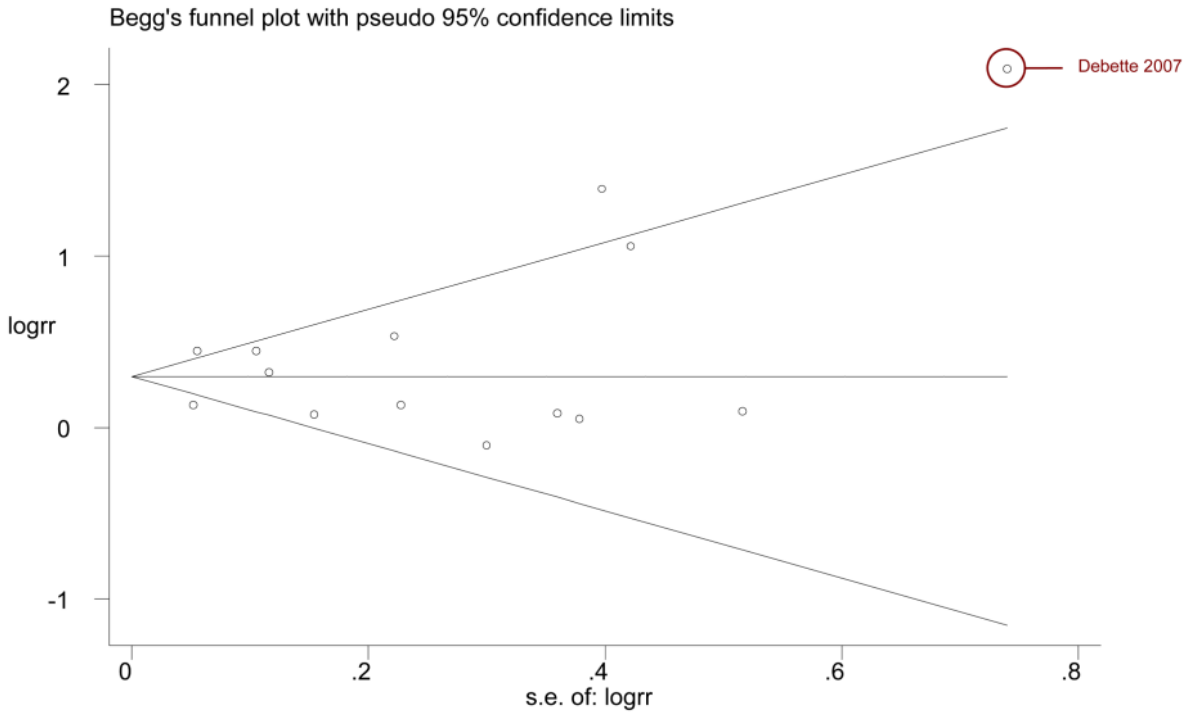
Flow diagram of selection process.



Appendix Figure 2.

Meta-analysis of the association between atrial fibrillation and Mini-Mental State Examination (MMSE) score ≤24 or MMSE decline ≥3 points

Studies are sorted by publication year. Diamond represents the pooled risk estimate. NR: not reported.



Appendix Figure 3.

Funnel plot for assessment of publication bias among the 14 studies evaluating patients with or without history of stroke

Appendix Table 1

Characteristics of the 14 included studies evaluating the association between atrial fibrillation and cognitive impairment in patients with or without history of stroke

Author Year	Design & Settings (Comparison Groups)	N	Female,%	Age, Mean (SD)	CVA Exclusion	Country
Ott 1997 (28)	Cross-sectional community cohort (cognitive impairment vs. no cognitive impairment, and dementia vs. no cognitive impairment)	6584	59.2	69.2 (9.1)	No*	The Netherlands
Cacciatore 1998 (29)	Cross-sectional community survey (MMSE <24 vs. MMSE ≥24)	1075	55.3	73.9 (6.2)	Yes	Italy
Tilivis 2004 (33)	Prospective cohort with up to 10 yrs of follow-up (change in cognitive function over time, in patients with AF vs. no AF)	650†	73.61	Age at entry 75 (37%) 80 (32.7%) 85 (30.2%)	No	Finland
Elias 2006 (13)	Prospective cohort of the Framingham	1011	0	No AF:60.5 (9.4) AF: 68.1 (7.0)	Yes	United States

Author Year	Design & Settings (Comparison Groups)	N	Female,%	Age, Mean (SD)	CVA Exclusion	Country
	Offspring Heart Study with assessment of cognitive function an average of 8 mos after the AF surveillance period (chronic or paroxysmal AF vs. no AF followed for development of dementia)					
Jozwiak 2006 (30)	Cross-sectional study (4 comparison groups : AF alone; AF with FNDs; FNDs alone; neither AF nor FNDs)	2314‡	65	76§ (71- 81) ‖	Yes¶	Poland
Debette 2007 (31)	Cross-sectional study of HF patients with LVEF ≤45% (MMSE <24 vs. MMSE ≥24)	83	30.1	62§ (17-98) **	No	France
Forti 2007 (34)	Prospective cohort with 3 and 4 yrs of follow-up for patients with MCI and normal cognitive function, respectively (evaluating conversion to dementia, comparing converters vs. nonconverters)	Normal:431 MCI: 180	Normal: 63 MCI: 51	Normal: 75.2 (9.0) MCI: 75.7 (8.3)	No	Italy
Bilato 2009 (32)	Cross-sectional assessment of participants in the Progetto Veneto Anziani (Pro.V.A.) study (comparing cognitive impairment in patients with AF vs. no AF)	1,576	61.5	Men: 77 (8) Women: 76 (7)	No	Italy
Marengoni 2009 (14)	Prospective cohort with 6 yrs of follow-up (AF vs. no AF)	685	75.6 ††	83.6 (4.1) ††	Yes‡‡	Sweden
Peters 2009 (16)	Prospective cohort of hypertensive elderly with mean follow-up of 2 yrs (development of dementia in patients with AF vs. no AF)	3336	60.4	>=80	No	United Kingdom
Bunch 2010 (11)	Prospective cohort with mean follow-up of 5 yrs (development of dementia in patients with AF vs. no AF)	37,025	39.9	60.6 (17.9)	No	United States
Dublin 2011 (12)	Prospective cohort of community-dwelling adults with mean follow-up of 6.8 yrs (development of dementia in AF vs. No AF)	3,045	60	75.3 (6.18) ††	Yes	United States

Author Year	Design & Settings (Comparison Groups)	N	Female,%	Age, Mean (SD)	CVA Exclusion	Country
Li 2011 (35)	Prospective cohort of patients with MCI with mean follow-up of 5 yrs (evaluating conversion to AD)	837[§§]	Convertors: 62.8 Non-convertors: 54.5	66.5 (7.12) [††]	No	China
Marzona 2012 (36)	Prospective cohort (post-hoc analysis of two randomized controlled trials) with median follow-up of 56 mos (AF vs. no AF)	31,506	29.7	66.5 (7.2)	No[*]	40 countries

Studies are ordered based on the publication year.

SD: Standard Deviation; CVA: Cerebrovascular Accidents; MMSE: Mini-mental State Examination; AF: Atrial fibrillation; FND: Focal Neurologic Deficit; HF: Heart Failure; LVEF: Left Ventricular Ejection Fraction; MCI: Mild Cognitive Impairment; AD: Alzheimer's disease

[*] Excluded patients with stroke history in a secondary analysis.

[†] Only 629 were included in the analysis.

[‡] Including patients in all the four comparison groups.

[§] Median age.

[‖] Inter-quartile range.

[¶] Two comparison groups for this meta-analysis were: AF alone vs. neither AF nor focal neurologic deficits.

[**] Age range.

[††] Per contact with the author.

[‡‡] Only excluded patients with history of stroke at baseline and did not exclude incident stroke cases during the follow up.

[§§] 638 completed the follow-up.

Appendix Table 2

Results, multivariate models, methods of AF, stroke and outcome ascertainments in 14 studies of patients with or without a history of stroke

Author Year	Outcomes	Outcome ascertainment	AF ascertainment	Stroke ascertainment	Results	Variables in multivariate mod
Ott 1997 (28)	Cognitive impairment without dementia, total Dementia, AD, VD	Cognitive impairment by MMSE score<26 Dementia by MMSE and Cambridge Examination for mental Disorders of elderly combined with an informant interview and brain MRI, diagnosis confirmed by neurologists or neuropsychologist based on DSM-III criteria. AD by NINCDS-ADRDA criteria VD by NINDS-AIREN criteria	Standard 12-lead ECG analyzed with the Modular ECG Analysis System (MEANS) software	Interviewing participants or the informants and inquiring about a history of clinically overt stroke, verified by medical records	Significant association between AF and cognitive impairment: OR [95%CI] =1.7 [1.1-2.6] Significant association between AF and total dementia: OR [95%CI] =2.0 [1.2-3.4] No significant association between AF and either VD or AD in multivariate adjusted analysis	Age, sex, myocardial infarction, blood pressure, peripher atherosclerosis, diabetes mellitus, education, antihypertensives, beta-blocker, digoxin, verapamil, anticoagulants, thyroid drugs

Author Year	Outcomes	Outcome ascertainment	AF ascertainment	Stroke ascertainment	Results	Variables in multivariate mod
Cacciatore 1998 (29)	Cognitive impairment	Italian MMSE score <24	Physical examination	Medical history and clinical assessment by trained physician	No significant association between AF and cognitive impairment (multivariate adjusted OR [95%CI] =1.05 [0.5, 2.19])	Age, sex, congestive heart failure, diabetes, hypertension, education, GDS score, alcohol consumption, smoking, heart rat blood pressure
Tilivis 2004 (33)	Cognitive impairment and cognitive decline	Cognitive impairment was defined as MMSE score <24. Cognitive decline was determined by a minimum of 4-point decrease in MMSE score or an increase in CDR class	NR*	NR*	Significant association between AF and 5 yr cognitive decline: Multivariate RR[95% CI]=2.88 [1.26–6.06]	Age and baseline MMSE score
Elias 2006 (13)	Global cognitive ability and several sub-domains	A battery of multiple neurologic tests evaluated by Framingham Study neuropsychological review panel	ECG or Holter reading confirmed by a Framingham cardiologist	Repeated screening of all participants for stroke by physical examination, repeated CT or MRI in suspected patients	Significant association between AF and performance at or below the 25th percentile (OR [95%CI] = 4.01 [1.84, 8.74])	Age, education, blood pressure, cigarettes/day, alcohol, BMI, tota cholesterol, depressed mood, electrocardiograp left ventricular hypertrophy, diabetes, cardiovascular disease, and antihypertensive treatment
Jozwiak 2006 (30)	General cognitive function	MMSE score ≤23	Physical examination and resting ECG	Medical history and detailed neurologic examination in all patients, CT in a subset of patients	Significant association between AF and cognitive impairment (multivariate OR [95% CI] = 1.56 [1.27–1.92])	Age, sex
Debette 2007 (31)	Overt cognitive impairment	MMSE score <24	NR (a history of AF was considered in all patients)	Medical history (defined by WHO criteria)	Significant association between AF and risk of overt cognitive impairment (multivariate OR [95% CI] = 8.1 [1.9–34.6])	Age, sex, schooling>8 y, NYHA class IV, Plasma hemoglobin<12.3 cause of heart failure (ischemic, nonischemic, undetermined)
Forti 2007 (34)	Conversion from MCI to dementia, conversion from normal cognition to dementia	MMSE and an extensive neuropsychological battery by two examiners with third examiner for discrepancies for diagnosis of MCI. Incident dementia diagnosed by follow up clinical and neuropsychological evaluations. NINCDS-ADRDA criteria for AD	Medical history confirmed by clinical evaluation, and previous medical records (when available)	NR (all participants were interviewed and underwent physical examination)	In patients with MCI, there was a significant association between AF and dementia (multivariate HR [95% CI] = 4.63 [1.72-12.46]) but such an association was not present in the cognitively normal	Age, sex, educatio baseline MMSE score, blood pressure, BMI, serum folate

Author Year	Outcomes	Outcome ascertainment	AF ascertainment	Stroke ascertainment	Results	Variables in multivariate mod
					group (multivariate HR [95% CI] = 1.10 [0.40-3.03])	
Bilato 2009 (32)	Cognitive impairment	MMSE<24	10 Sec ECG evaluated by 2 cardiologists and validated by a third cardiologist	NR (Medical record review and general physical examination)	Cognitive impairment was significantly more prevalent in patients with AF but the association was not significant in multivariate model (multivariate adjusted OR [95%] CI = 1.14 [0.73–1.80])	Age, sex, heart failure, myocardia infarction, angina pectoris, diabetes mellitus, peripher artery disease, disability in basic activity daily living, strok chronic obstructive pulmonary diseas
Marengoni 2009 (14)	Total dementia, AD	MMSE for global cognitive function, DSM-III criteria for dementia	Physician diagnosis (by auscultation) medical records, medical drug use, and ICD-9 code	ICD-9 and ICD-10 codes for incident stroke from Stockholm Inpatient Register	No significant association between AF and dementia (multivariate HR [95%CI]=0.9 [0.5, 1.7]) No significant association between AF and AD (multivariate HR [95%CI]= 0.8 [0.4, 1.5])	Age, sex, educatio baseline MMSE score, hypertension, anti thrombotic medications, and APO-E genotype
Peters 2009 (16)	Dementia, cognitive decline	DSM-IV criteria for dementia diagnosis Cognitive decline was defined as decrease in MMSE score to <24 or by >3 points annually	Reported by the investigators at the baseline visit after taking an ECG from the patient †	Previous stroke was ascertained by local investigators via patient interview and medical records. †	Multivariate HR [95% CI] for the association between AF and dementia: 1.031 [0.619, 1.718] Multivariate HR [95% CI] for the association between AF and cognitive decline : 1.08 [0.798, 1.463]	Sex, geographic recruitment area, BMI, randomized trial treatment group, previous stroke, heart failu diabetes mellitus, total cholesterol, HDL cholesterol, creatinine, glucose, hemoglobin
Bunch 2010 (11)	VD, AD, SD, ND, total dementia	ICD-9 codes to identify dementia and its subtypes	Diagnostic ICD-9 codes, ECG database of all Intermountain Healthcare hospitals	Patients records from inpatients and outpatients clinical visits	Significant association between AF and total dementia (Multivariate OR[95% CI] 1.56[1.40-1.74]), and between AF and VD (multivariate OR [95% CI]=1.73 [1.27-2.36])† Significant association between AF and AD only in patients younger than 70 yo (multivariate OR=2.30 [1.40-3.79])	Confounding variables included in the models were chos based on 10% change in hazard ratios ar all models include history of cerebrovascular accidents †

Author Year	Outcomes	Outcome ascertainment	AF ascertainment	Stroke ascertainment	Results	Variables in multivariate mod
Dublin 2011 (12)	All-cause dementia and possible or probable AD	DSM-IV criteria for dementia (by a multidisciplinary committee) and NINDS-AIREN criteria for AD	At least 2 documented ICD-9 codes within 12 mos	Self-reported history of stroke; ICD-9 codes and self-report for incident stroke	Significant association between AF and all-cause dementia (adjusted HR [95% CI]=1.38 [1.10-1.73] as well as AF and AD (adjusted HR [95% CI]=1.50 [1.16–1.94])	Age, incident stroke, sex, education, diabetes mellitus, hypertension, bloo pressure, coronary heart disease, and congestive heart failure
Li 2011 (35)	Conversion from MCI to AD	Modified DSM-IV for dementia. NINCDS-ADRDA criteria for AD NINDS-AIREN criteria for VD Demented patients were further evaluated with CT or MRI	ICD-9 codes	CVD defined by history, presence of focal neurologic signs or brain imaging including strategic or multiple lesions, or diffuse white matter lesions, or TIA	No significant association between AF and conversion to AD (Multivariate adjusted HR [95% CI]=1.088 [0.538–2.201])	Age, sex, educatio occupation, depressive symptoms, APO E4, baseline MMSE, ADL score
Marzona 2012 (36)	Cognitive decline, dementia	Cognitive decline: a decrease in MMSE score ≥3 Dementia: defined as new dementia diagnosis, reported severe cognitive impairment or MMSE ≤23	12-lead ECG‡	History of stroke was determined by using patient reports. Incident stroke was determined by an adjudication committee	Significant association between atrial fibrillation and cognitive decline (multivariate HR [95%CI]=1.14 [1.03, 1.26) Significant association between atrial fibrillation and dementia (multivariate HR [95%CI]=1.30 [1.14,1.49])	Age; education; sex; baseline MMSE score; blood pressure; history of stroke c transient ischemic attack, hypertension, diabetes and myocardial infarction; levels microalbuminuria macroalbuminuria and creatinine; statins beta-blockers, angiotensin-converting enzym inhibitors, antiplatelets or ora anticoagulants; changes in systolic blood pressure during follow-up; smoking; BMI; physical activity; sleep apnea; and alcoho consumption

Studies are ordered based on the publication year.

AF: Atrial Fibrillation; AD: Alzheimer's Disease; VD: Vascular Dementia; MMSE: Mini-mental State Examination; DSM: The Diagnostic and Statistical Manual of Mental Disorders; NINCDS-ADRDA: The National Institute of Neurological and Communicable Disease and Stroke- Alzheimer's Disease and Related Disorders Association; NINDS-AIREN: National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences; ECG: Electrocardiogram; OR: Odds Ratio; CI: Confidence Interval; GDS: Geriatric Depression Scale; CDR: The Clinical Dementia Rating; NR: Not Reported; RR: Relative Risk; CT: Computed Tomography ; MRI: Magnetic Resonance Imaging; WHO: World Health Organization; NYHA: The New York Heart Association Functional Classification; MCI: Mild Cognitive Impairment; HR: Hazard Ratio; BMI: Body Mass Index; ICD: The International Classification of Diseases; HDL: High Density Lipoprotein; SD: Senile Dementia; ND: Non-specific Dementia; CVD: Cerebrovascular Diseases; TIA: Transient Ischemic Attack; ADL: Activities of Daily Living.

* At entry all participants underwent physical examination by a neurologist and a cardiologist and the patient records were collected.

† Per contact with the authors.

‡ Data obtained from rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) trials (53).

Appendix Table 3

Characteristics of the 7 included studies evaluating the association between atrial fibrillation and post-stroke cognitive impairment or dementia

Author Year	Design & Settings	N	Female,%	Age, Mean (SD)	Country
Inzitari 1998 (37)	Prospective cohort of stroke patients with dementia assessment 1 year after stroke	339*	47.9	Dementia: 76.2 (9.4), No-dementia: 70.0 (11.5)	Italy
Barba 2000 (38)	Prospective cohort of patients with either ischemic or hemorrhagic stroke with 3 mos of follow-up	251†	47	69 (13)	Spain
Altieri 2004 (39)	Prospective cohort of patients with hemorrhagic or ischemic stroke with mean (SD) follow-up of 45.3 (9.2) mos	191	30.9	71.3 (8.9)	Italy
Zhou 2004 (40)	Prospective cohort of patients with ischemic stroke with 3 mos of follow-up	434	47.2	Dementia: 73.8 (7.5) No dementia: 65.3 (6.8)	China
Tang 2006 (41)	Prospective cohort of patients with first-ever or recurrent stroke with 3 mos of follow-up	179‡	44.1	73 (7.5)	China
Mizrahi 2012 (42)	Cross-sectional study of patients with ischemic stroke admitted to stroke rehabilitation with assessment of cognitive function within 1 week of admission	707	42.9	74.11 (9.29)	Israel
Khan 2012 (43)	Cross-sectional study of patients with ischemic or hemorrhagic stroke admitted to Aga Khan University Hospital with assessment of cognitive function within 1 to 12 mos of admission	309	62.1	61.75 (21-90) §	Pakistan

Studies are ordered based on the publication year.

* Number alive for interview at 1 year follow-up (>10% lost to follow-up).

† Available for interview at three month follow-up (>10% lost to follow-up).

‡ Number included in the final analysis (>10% lost to follow-up).

§ Inter-quartile range.

Appendix Table 4

Results, multivariate models, methods of AF, stroke and outcome ascertainments in 7 post-stroke studies

Author Year	Outcomes	Outcome ascertainment	AF ascertainment	Stroke ascertainment	Results	Variables included in the multivariate model
Inzitari 1998 (37)	Post-stroke dementia	ICD-10 codes and interview with a proxy informant (method was validated in two	Chronic AF by at least one ECG and/or clinical verification	Stroke was defined by WHO criteria and every stroke	Significant association between	Age> 72 yrs, ,Prestroke

Author Year	Outcomes	Outcome ascertainment	AF ascertainment	Stroke ascertainment	Results	Variables included in the multivariate model
		different studies) Minimum required duration for memory and intellectual deficit was 6 mos		diagnosis was confirmed by a neurologist	AF and post-stroke dementia multivariate OR [95% CI] = 2.33 (1.09–4.98)	Rankin>2, Previous stroke, Aphasia, Urinary incontinence
Barba 2000(38**)**	Post-stroke dementia	DSM-IV criteria for post stroke dementia, DSM-III-R criteria for previous dementia and dementia stage, and NINDS-AIREN criteria for VD, cognitive status assessment with SS-IQCODE	Clinical diagnosis and ECG after the acute phase	Clinical diagnosis based on presence of acute focal signs and cerebral dysfunction lasting ≥24 hrs, with CT scan available for 93% of cases	Significant association between AF and post-stroke dementia: multivariate OR [95% CI]= 4.4 [1.4 -14.3]	Age, AF, Nephropathy, Psychiatric disease, Canadian neurological scale, SS-IQCODE
Altieri 2004 (39**)**	Post-stroke dementia	ICD-10 codes for dementia NINCDS-ADRDA for AD NINDS-AIREN for VD	NR	Clinical diagnosis based on presence of acute focal signs and cerebral dysfunction lasting ≥24 hrs, confirmed by CT or MRI	No significant association between AF and post-stroke dementia : Multivariate HR[95% CI] = 2.3 [0.9–5.7]	Age, cortical atrophy, multiple lesions, education, subcortical atrophy, leukoariosis
Zhou 2004 (40**)**	Post-stroke dementia	Modified DSM-IV criteria plus several neuropsychological tests	NR (based on previous AF diagnosis or treatment)	Clinical diagnosis based on presence of acute focal signs and cerebral dysfunction lasting ≥24 hrs and CT or MRI	Significant association between AF and stroke-related dementia : OR[95% CI] = 3.45 [1.584–7.512]	Age, educational level, drinking, prior stroke, dysphasia, and left carotid territory infarction
Tang 2006 (41**)**	Post-stroke cognitive impairment	Not meeting DSM-IV criteria for dementia but scoring ≤the boundary score on the MMSE	ECG	Clinical presentation or brain CT	Significant association between AF and post-stroke cognitive impairment after adjustment for potential confounders: OR [95% CI]= 9.363 [1.012-86.622]	Sex, NIHSS dysarthria score , Urinary incontinence , Education Cerebral atrophy index , Prestroke IQCODE score
Mizrahi 2012 (42**)**	Post-stroke cognitive impairment	MMSE score <24	ICD-9	Clinical diagnosis based on presence of acute focal signs and cerebral dysfunction lasting ≥24 hrs confirmed by CT or MRI	AF was significantly associated with post-stroke cognitive impairment (multivariate adjusted OR [95%CI] =1.6 [1.03, 2.47])	Age, sex, ischemic heart disease, hypertension, diabetes mellitus, hyperlipidemia, dementia, Parkinson's disease, previous stroke
Khan 2012(43**)**	Post-stroke dementia	Blessed Dementia Scale (BDS)	NR	Stroke was defined by the WHO definition and	AF was significantly associated	Not explicitly mentioned (variables with biological

Author Year	Outcomes	Outcome ascertainment	AF ascertainment	Stroke ascertainment	Results	Variables included in the multivariate model
				diagnosis was supported by CT or MRI	with post-stroke dementia (multivariate adjusted OR [95%CI] =5.12 [1.9, 13.3])	significance and *P* value< 0.25 in the univariate analysis were included in multivariate logistic regression model)

Studies are ordered based on the publication year.

AF: Atrial Fibrillation; ICD: The International Classification of Diseases; ECG: Electrocardiogram; WHO: World Health Organization; OR: Odds Ratio; CI: Confidence Interval; DSM: The Diagnostic and Statistical Manual of Mental Disorders; NINDS-AIREN: National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences; VD: Vascular Dementia; SS-IQCODE: Shortened Spanish version of the Informant Questionnaire on Cognitive Decline in the Elderly; CT: Computed Tomography; NINCDS-ADRDA: The National Institute of Neurological and Communicable Disease and Stroke-Alzheimer's Disease and Related Disorders Association; AD: Alzheimer's Disease; NR: Not Reported; MRI: Magnetic Resonance Imaging; HR: Hazard Ratio; MMSE: Mini-mental State Examination; NIHSS, National Institutes of Health Stroke Scale; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly.

Appendix Table 5

Assessment of selected quality criteria in 14 studies of patients with or without a history of stroke

Author Year	Was AF the primary exposure of interest?	Inclusion & exclusion criteria clearly stated?	Was ECG used as one of the methods for AF ascertainment?	Method of Outcome ascertainment	Temporality clear?	Lost to follow up, %	Adjustment	Number of quality criteria met *
Ott 1997 (28)	Yes	Yes	Yes	Superior†	No	N/A	Multivariate	5
Cacciatore 1998 (29)	No	Yes	No	Acceptable	No	N/A	Multivariate	2
Tilivis 2004 (33)	No	No	Unclear	Acceptable	Yes	> 10%	Minimal	1
Elias 2006 (13)	Yes	Yes	Yes	Superior	Yes	Unclear	Multivariate	6
Jozwiak 2006 (30)	Yes	Yes	Yes	Acceptable	No	N/A	Minimal	3
Debette 2007 (31)	No	Yes	Unclear	Acceptable	No	N/A	Multivariate	2
Forti 2007 (34)	Yes	Yes	No	Superior	Yes	Unclear	Multivariate	5
Bilato 2009 (32)	Yes	Yes	Yes	Acceptable	No	N/A	Multivariate	4
Marengoni 2009 (14)	Yes	Yes	No	Superior	Yes	>10%	Multivariate	5
Peters 2009 (16)	No	Yes	Yes‡	Superior†	Yes	Unclear	Multivariate	5
Bunch 2010 (11)	Yes	Yes	Yes§	Acceptable	Yes	Unclear	Multivariate	5
Dublin 2011 (12)	Yes	Yes	No	Superior	Yes	<10%‡	Multivariate	6
Li 2011 (35)	No	Yes	No	Superior	Yes	>10%	Multivariate	4
Marzona 2012 (36)	Yes	Yes	Yes	Acceptable	Yes	<10%	Multivariate	6

Studies are ordered based on the publication year.

* The purpose of the numbers reported in this column is to provide an overview of how studies compare to each other in terms of methodological quality. We made every effort to include the most comprehensive and relevant quality criteria; however, there is no standard basis for quality assessment of observational studies. Although we find it unlikely that the

classification of studies would dramatically change by using different quality criteria. It should be kept in mind that these numbers could vary depending on the items chosen for quality assessment (54, 55). Therefore, readers are encouraged to focus on each individual quality criterion rather than the overall quality scores in the assessment of bias.

† Superior for dementia acceptable for cognitive impairment.

‡ Per contact with the author.

§ ECG database of all Intermountain Healthcare hospitals and ICD-9 codes were used for AF diagnosis.

Appendix Table 6
Assessment of selected quality criteria in 7 studies of post-stroke cognitive impairment or dementia

Author Year	Was AF the primary exposure of interest?	Inclusion & exclusion criteria clearly stated?	Was ECG used as one of the methods for AF ascertainment?	Method of Outcome ascertainment	Temporality clear?	Lost to follow up, %	Adjustment	Number of quality criteria met*
Inzitari 1998 (37)	No	No	Yes	Superior	Yes	>10%	Multivariate	4
Barba 2000 (38)	No	Yes	Yes	Superior	Yes	>10%	Multivariate	5
Altieri 2004 (39)	No	Yes	Unclear	Superior	Yes	<10%	Multivariate	5
Zhou 2004 (40)	No	Yes	Unclear	Superior	Yes	>10%	Multivariate	4
Tang 2006 (41)	No	Yes	Yes	Acceptable	Yes	>10%	Multivariate	4
Mizrahi 2012 (42)	Yes	Yes	No	Acceptable	No	N/A	Multivariate	3
Khan 2012 (43)	No	Yes	Unclear	Acceptable	No	N/A	Multivariate	2

Studies are ordered based on the publication year.

* The purpose of the numbers reported in this column is to provide an overview of how studies compare to each other in terms of methodological quality. We made every effort to include the most comprehensive and relevant quality criteria; however, there is no standard basis for quality assessment of observational studies. Although we find it unlikely that the classification of studies would dramatically change by using different quality criteria. It should be kept in mind that these numbers could vary depending on the items chosen for quality assessment (54, 55). Therefore, readers are encouraged to focus on each individual quality criterion rather than the overall quality scores in the assessment of bias.

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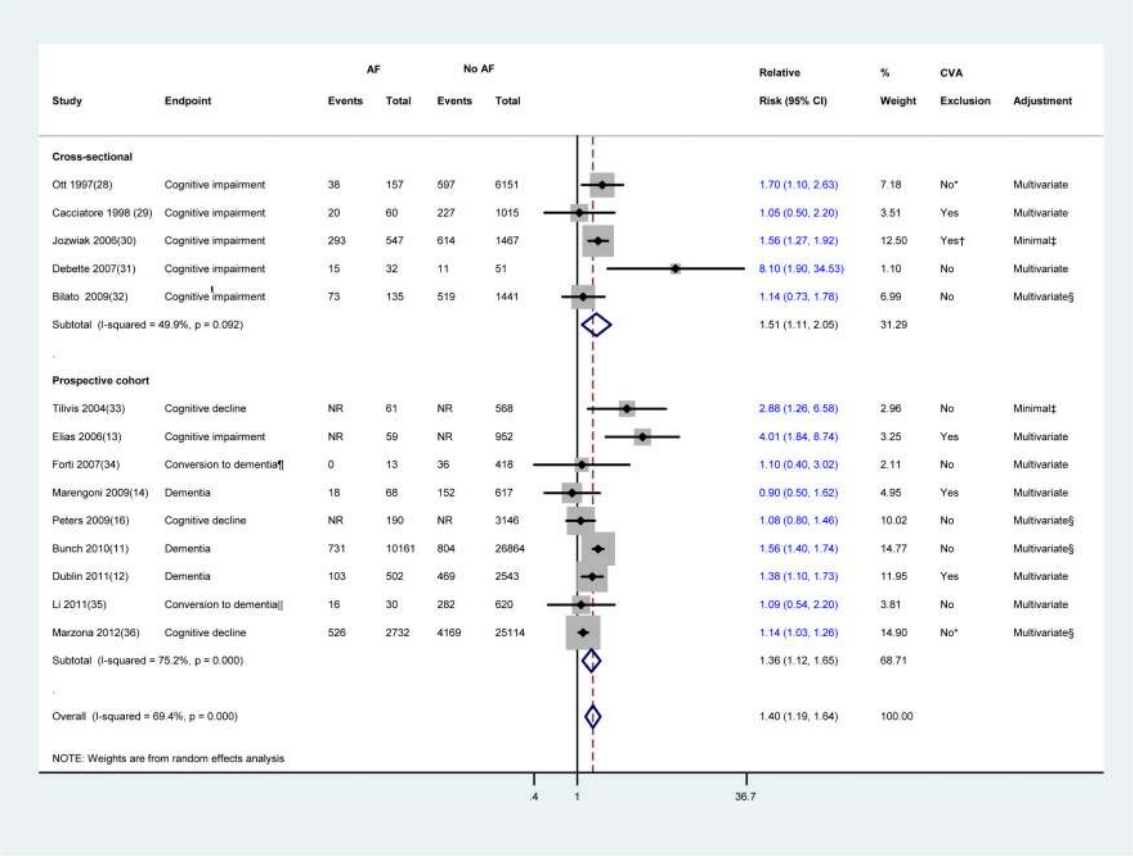

Figure 1.

Meta-analysis of 14 studies evaluating the association between atrial fibrillation and cognitive impairment in patients with or without history of stroke

Studies are sorted by publication year. Diamond represents the pooled risk estimate. NR: not reported.

* Patients with history of stroke were excluded in a subgroup analysis.

† Patients with no focal neurologic deficits (i.e. previous strokes, head injuries, head neurosurgery, tumors of the central nervous system, and so forth) were only considered for this meta-analysis.

‡ Minimal adjustment should include at least adjustment for age.

§ History of stroke was included as a covariate in the multivariate adjusted model.

¶ Conversion from normal cognition to dementia.

‖ Conversion from mild cognitive impairment to dementia.

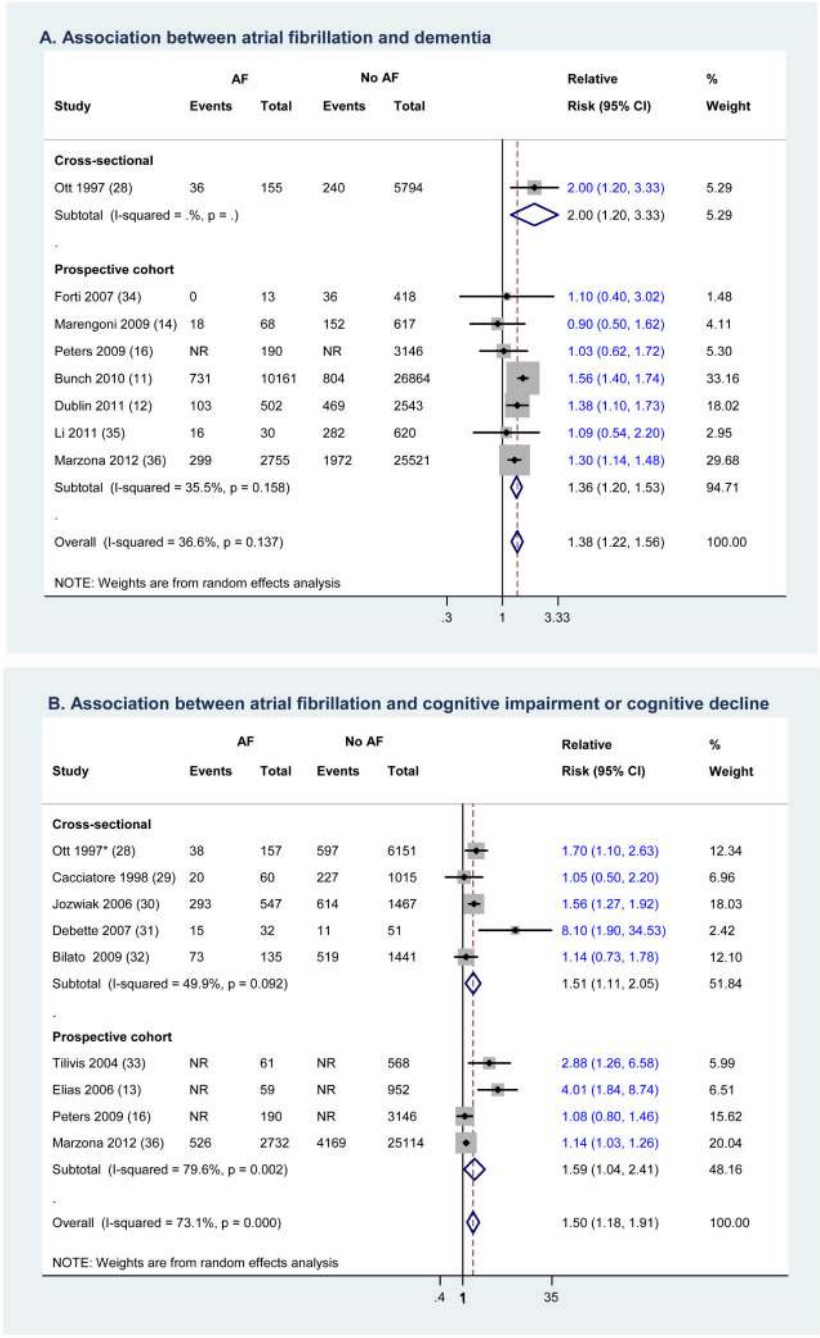

Figure 2.

Separating dementia outcomes from cognitive impairment

Studies are sorted by publication year. Diamond represents the pooled risk estimate. NR: not reported.

* Patients with dementia were excluded.

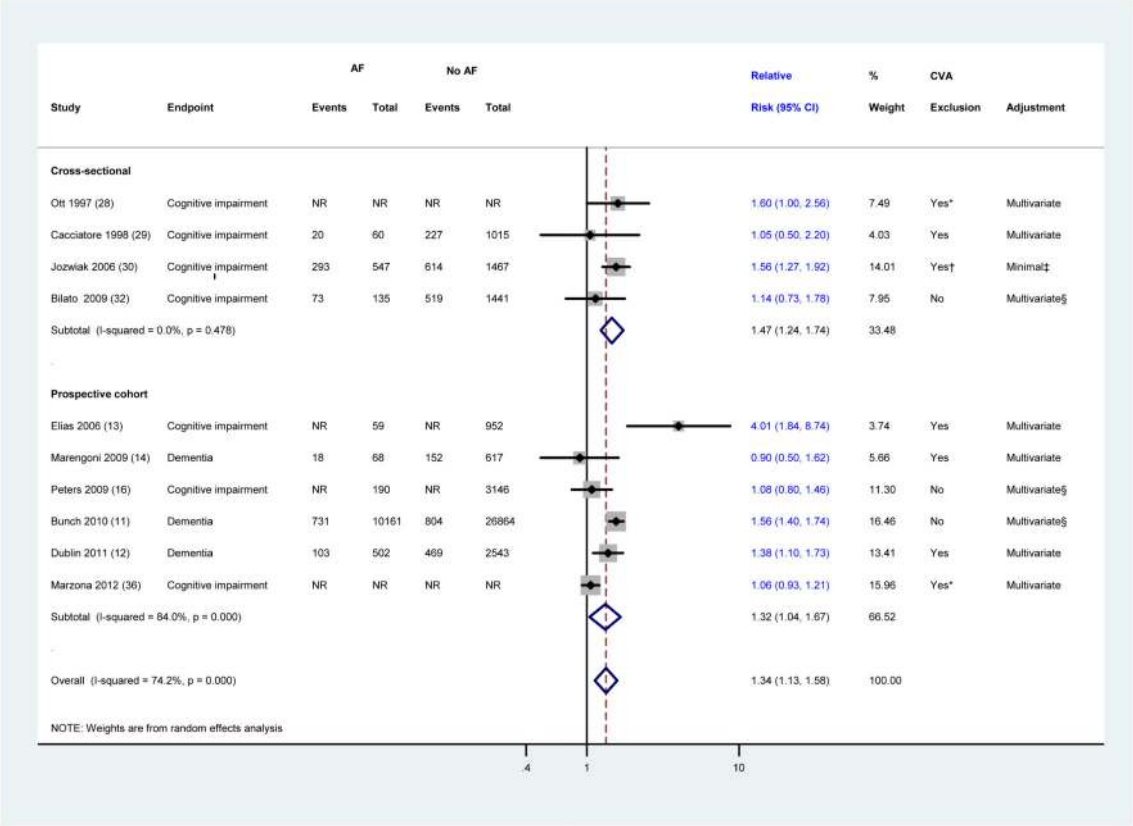

Figure 3.

The association between atrial fibrillation and cognitive impairment independent of stroke history

Studies are sorted by publication year. Diamond represents the pooled risk estimate. NR: not reported.

* Patients with history of stroke were excluded in a subgroup analysis.

† Patients with no focal neurologic deficits (i.e. previous strokes, head injuries, head neurosurgery, tumors of the central nervous system, and so forth) were only considered for this meta-analysis.

‡ Minimal adjustment should include at least adjustment for age.

§ History of stroke was included as a covariate in the multivariate adjusted model.

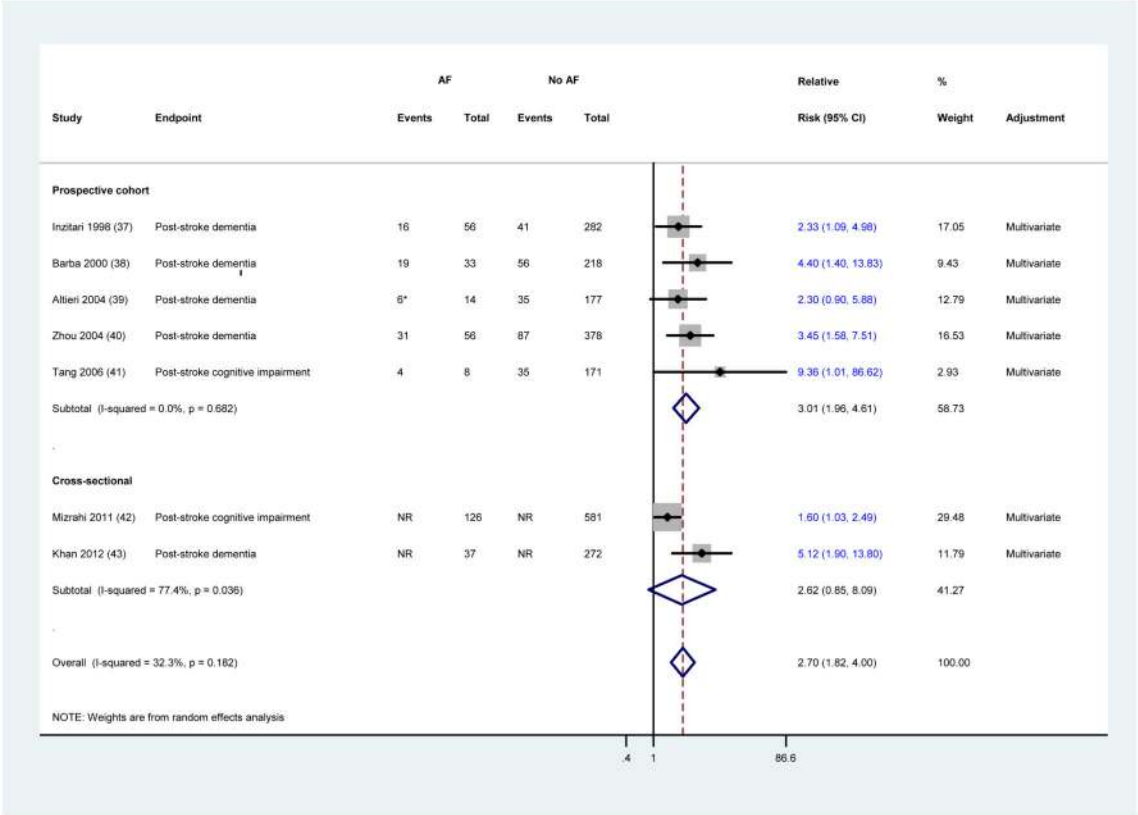

Figure 4.

Meta-analysis of 7 studies evaluating the association between atrial fibrillation and post-stroke cognitive impairment in patients with recurrent or first-ever stroke

Studies are sorted by publication year. Diamond represents the pooled risk estimate. NR: not reported.

* During the follow-up 5 additional patients developed atrial fibrillation (2 were diagnosed with post-stroke dementia)