The association of atrial fibrillation and dementia incidence: a meta-analysis of prospective cohort studies

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Abstract

Objectives To assess and synthesize the prospective cohort studies published so far on the association between atrial fibrillation (AF) and dementia incidence.

Methods We searched PubMed, Web of Science, and the Cochrane Library for potential studies published in English previous to April 2018. Two independent reviewers screened the search results for prospective cohort studies reporting the association between AF and dementia incidence in patients with normal cognitive function at baseline and not suffering from an acute stroke. The Newcastle-Ottawa Scale was adopted to evaluate the quality of the included studies. The pooled hazard ratio (HR) of AF for dementia was calculated with the Comprehensive Meta-Analysis software, version 2. Heterogeneity and publication bias were assessed with the $I^2$ test and funnel plot, respectively.

Results We finally identified 11 prospective cohort studies covering 112,876 patients. All the included studies reported an adjusted HR obtained in multiple Cox regression models. The qualities of the included studies ranged from moderate to high. In pooled analysis with a fixed-effects model, AF was independently associated with dementia incidence (HR = 1.34, 95% CI: 1.24–1.44). Subgroup analysis of studies considering anticoagulation as an important confounding factor achieved a similar result. Based on the $I^2$ test and funnel plot, we did not detect obvious heterogeneity and publication bias in our study. Meta-regression on age did not find significant results.

Conclusions The results of our meta-analysis further confirmed that AF was an independent risk factor for dementia in patients with normal baseline cognitive function not suffering from acute stroke. Screening for dementia in AF patients and including dementia as an independent outcome in large AF treatment trials is warranted.

J Geriatr Cardiol 2019; 16: 298–306. doi:10.11909/j.issn.1671-5411.2019.03.006

Keywords: Atrial fibrillation; Arrhythmias; Cognitive impairment; Dementia; Meta-analysis

1 Introduction

As one of the most common arrhythmias, the incidence of atrial fibrillation (AF) increases with advancing age. More than 33 million individuals are reported to have AF worldwide, the majority of whom are elderly, and approximately 25% of individuals aged 40 years or older will develop AF during their lifetime.[1,2] Exclusive of age, AF also tends to increase with diabetes and hypertension.[3] In addition to well-known complications such as stroke, thromboembolism and heart failure, it also independently adds to total mortality in patients with and without cardiovascular disease.[4] Hypertensive and coronary heart diseases are the most common underlying disorders in AF patients. Similarly, the prevalence of dementia also increases with age. With aging of the population, it is estimated that approximately one-fifth of the population will be made up of older adults (aged ≥ 60 years) by 2050, and dementia will be an enormous burden on worldwide health care systems.[5] Therefore, it’s imperative to identify modifiable risk factors to formulate reasonable prevention strategies.

In consideration of the common clinical characteristics, it is reasonable to suspect a potential association between these two frequent conditions. It is widely recognized that AF and dementia share important risk factors such as hypertension and diabetes mellitus.[6,7] However, the association between dementia and AF is more than an epiphenomenon due to shared risk factors.[8] Other than the recognized vascular risk factors such as smoking and hypertension, growing evidence indicates that AF may also be independently associated with cognitive dysfunction ranging from mild cognitive impairment to dementia.[9] In addition, although the stroke caused by AF contributes to the occurrence of cognitive impairment and dementia, the association
between AF and dementia incidence appears to be independent of a history of stroke and other comorbidities.[10,11]

To verify the possible association, a number of studies discovered a significant association between AF and dementia incidence independent of a prior history of stroke, which was further verified by the higher incidence of dementia in anticoagulated patients for AF than in other conditions.[12–14] Although it is reported that AF is related to higher dementia incidence in most studies, findings on the association are inconsistent; AF was not associated with dementia incidence in the very old or in postmenopausal women.[15,16] Due to the conflicting results from different studies, a few meta-analyses have been performed to strengthen statistical power.[17,18] However, the former meta-analyses included both cross-sectional and prospective studies, which resulted in obvious heterogeneity. In view of this, we concentrated on prospective cohort studies, which have established that dementia occurs after the diagnosis of AF. As an effective means of stroke prevention, anticoagulation may influence the risk of dementia in AF patients. However, not all studies considered anticoagulant therapy as a confounding factor due to the diverse designs of the studies. To clarify the role of anticoagulation in the relationship, it was illuminating to probe the association in subgroup analysis. Furthermore, it was reported that AF was associated with an increased risk of dementia in patients aged < 67 years but not in older patients.[19] The studies included in the former meta-analyses varied significantly in the age of the population and failed to investigate the effect of age on the association. On balance, we expected to explore the association between these two diseases further and provide more reliable evidence for subsequent clinical studies.

2 Methods

2.1 Search strategy

We performed a comprehensive search in PubMed, Web of Science and the Cochrane library without date and language restriction. The search strategy is listed in Table 1.

2.2 Inclusion criteria and study selection

We selected prospective cohort studies that appraised the relationship between AF and subsequent occurrence of dementia. The specific inclusion criteria were as follows: (1) published in English, (2) prospective cohort study, (3) participants had normal cognitive function at baseline and were not suffering from an acute stroke, (4) the studies estimated the risk for dementia with hazard ratio (HR), 95% CI of patients with AF compared to those without AF, and (5) the reported HR was derived from a multivariate Cox regression analysis adjusted for all possible confounders. Regarding the studies of the same population, the longest follow-up or the largest number of patients was included. Two independent reviewers (Daoshen Liu and Jing Chen) scanned titles and abstracts according to the inclusion criteria; the full text was retrieved for further inspection if a study potentially met the inclusion criteria.

2.3 Data extraction and quality assessment

Two independent reviewers (LIU DS and CHEN J) extracted the study information about population, follow-up, relevant outcomes, and confounder adjustment onto a spreadsheet. If there was any discrepancy, the article was discussed to reach an agreement. The study quality of the included studies was evaluated according to the Newcastle-Ottawa Scale (NOS) scoring from 0 to 9. In regard to the follow-up time in the NOS, we stipulated that not less than five years would score a point in view of the lengthy onset of dementia.

2.4 Statistical analysis

We used the Comprehensive Meta-Analysis software, version2 (Biostat, Inc.) to conduct the data analysis. The adjusted HR of each study was imported in the spreadsheet

Table 1. Search strategy.

| Databases | Search terms |
|-----------|--------------|
| PubMed    | (“Atrial Fibrillation” [MeSH] or “Auricular Fibrillation” [All Fields] or “atrial flutter” [All Fields] or “auricular flutter” [All Fields] or “Atrial Fibrillation” [All Fields]) and (“cognition” [MeSH] or “cognitive disorders” [All Fields] or “cognitive impairment” [All Fields] or “cognitive ability” [All Fields] or “dementia” [MeSH]) |
| Web of Science | (“Atrial Fibrillation” or “Auricular Fibrillation” or “Atrial Flutter” or “Auricular Flutter”) and (“Cognition” or “Cognitive disorders” or “Cognitive impairment” or “Cognitive ability or dementia”) |
| Cochrane Library | (“Atrial Fibrillation” or “Auricular Fibrillation” or “Atrial flutter”) and (“Cognition” or “Cognitive impairment” or “Dementia”) |

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as computed effect sizes to produce a pooled adjusted HR. Statistical heterogeneity was evaluated by using the $I^2$ statistic, with $I^2$ values below 25% representing a low level of heterogeneity; 25%–50%, moderate; and above 75%, high.\[20]\] Potential publication bias was assessed using the funnel plots and Egger’s test. Statistical tests were two-sided and used a significance threshold of $P < 0.05$.

3 Results

3.1 Study selection

The procedure of study selection is shown in Figure 1. Just as the figure shows, the search strategy yielded 1930 records, which contained 322 duplicates. After reading titles and abstracts, we eliminated 1495 records, leaving 113 articles. Eleven studies were left after screening the full texts according to the inclusion criteria. The studies excluded by reason of other study types contained seven case-control studies, nine cross-sectional studies and three retrospective cohort studies. Ultimately, 11 studies, involving 112,876 patients, were included in the meta-analysis.\[14–16,19,21–28\]

3.2 Qualitative findings

Table 2 exhibits the primary characteristics of the 11 studies included in the meta-analysis. All the studies had a prospective cohort study design and evaluated the association between AF and risk of dementia incidence. All studies included a population of older patients (mean age: 50.3–75.7 years). In accordance with the inclusion criteria, no patient had an acute stroke at baseline. Through meticulously exploring the characteristics of the included studies, we discovered some qualitative heterogeneity in population and baseline characteristics.

One study included a mixed population of patients with normal cognition and mild cognitive impairment, in which we restricted the analysis to patients with normal cognitive function.\[21\] The study by Marenzoni, et al.\[15\] evaluated the risk factors in community-dwelling elderly people. The study by Haring, et al.\[16\] focused on the association between cardiovascular diseases and cognitive decline in postmenopausal women. Two studies (Peters, et al.\[22\] and Marzona, et al.\[24\]) were randomized controlled trials on antihypertensive treatment in patients with normal cognitive function at baseline who had longitudinal assessment of cognitive status. Three studies included patients in the health system, namely, the Intermountain Healthcare System,\[28\] the Group Health System,\[23\] and the British civil service.\[26\] The participants of the remaining studies came from a large population-based cohort, that is, the Cardiovascular Risk Factors, Aging, and Dementia study;\[25\] the Rotterdam Study;\[19\] and, the Atherosclerosis Risk in Communities Neurocognitive Study.\[27\] As shown in Table 2, the quality scores of all the included studies ranged from 5 to 8, indicating moderate to high quality. All studies adopted one kind of reliable method such as ECG, medical records, or common standards to ascertain AF or dementia, except the study by Haring, et al.\[16\] which used self-report questionnaires to ascertain AF. In addition, the follow-up time of the studies ranged from 1.8 to 26.6 years. All the aforementioned factors may have introduced heterogeneity to a certain degree.

3.3 Meta-analysis and publication bias

The adjusted HRs and adjustment of confounders of the included studies are listed in Table 3. After inspection, we achieved a result of $I^2 = 0$, which indicated that the statistical heterogeneity between studies was almost negligible. Therefore, we finally adopted the fixed-effects model to perform the meta-analysis. As shown in Figure 2, the meta-analysis reached a pooled adjusted HR = 1.34 (95% CI: 1.24–1.44), which showed that the patients with AF, compared with non-AF patients, had a 34% higher risk of developing dementia during follow-up. The publication bias assessed in the funnel plot is presented in Figure 3, and does

Figure 1. Flow diagram of the article selection procedure for meta-analysis.

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Examination. aOnly patients without cognitive impairment were included in the meta-analysis. rived at similar results (not suggest obvious publication bias. The Egger’s test ar-

Table 2. Characteristics of the studies included in the meta-analysis.

| Study                | Year | Population | No.   | Inclusion criteria                                                                 | Exclusion criteria                                                                 | AF ascertainment                                         | Dementia ascertainment                  | Follow-up yrs | NOS score |
|----------------------|------|------------|-------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|----------------------------------------------------------|------------------------------------------|--------------|-----------|
| Forti, et al.[23]    | 2006 | Elderly outpatients without dementia | 431a  | Patients ≥ 60 yrs seeing medical advice for cognitive complaints                    | Patients with psychiatric disorders, Parkinson’s disease, epilepsy, substance abuse | Medical history and clinical evaluation                   | MMSE and neuropsychological tests        | 3.8 ± 0.7      | 5         |
| Peters, et al.[22]   | 2009 | Patients in the HYVET trial        | 3336  | Patients ≥ 80 yrs with hypertension                                                | Patients with dementia                                                            | Not specified                                            | DSM-IV                                   | 1.8           | 5         |
| Bunch, et al.[29]    | 2010 | Patients in the Inter-mountain Heart Collaborative Study | 37025 | Patients in the Inter-mountain Healthcare System database                          | Patients with dementia                                                            | ICD codes                                                | ICD codes                                | 5             | 7         |
| Dublin, et al.[23]   | 2011 | ≥ 65 yrs community-dwelling adults of GH members | 3045  | Patients with dementia, prior stroke                                              | ICD codes                                                                         | DSM-IV                                                  | 6.8           | 7         |
| Marengoni, et al.[15] | 2011 | ≥ 75 yrs community-dwelling elderly people | 685   | Patients ≥ 75 yrs without dementia                                                | Not specified                                                                      | Medical history and clinical evaluation                  | DSM-III                                  | 4             | 6         |
| Marzona, et al.[24]  | 2012 | Participants from the ONTARGET and TRANSCEND trials | 31506 | Patients ≥ 55 yrs, history of cardiovascular disease or diabetes with end-organ damage | Patients with heart failure, substantial valvular disease, or uncontrolled hypertension | ECG and medical records                                  | MMSE                                     | 4.7           | 6         |
| Haring, et al.[20]   | 2013 | Postmenopausal women in the WHIMS   | 6455  | Patients ≥ 65 yrs without dementia                                                | Not specified                                                                      | Self-report questionnaires                               | DSM-IV                                   | 8.4           | 6         |
| Rusanen, et al.[25]  | 2014 | Participants in the CAIDE study     | 1510  | Patients ≥ 65 yrs without dementia                                                | Not specified                                                                      | Medical records                                          | DSM-IV                                   | 7.8           | 7         |
| Bruijn, et al.[19]   | 2015 | Participants in the Rotterdam Study | 6154  | Patients ≥ 55 yrs without dementia                                                | Patients with dementia                                                            | ECG and medical records                                  | DSM-III                                  | 20            | 8         |
| Singh-Manoux, et al.[26] | 2017 | Participants in the Whitehall II study | 10214 | ≥ 69 yrs without dementia                                                          | Not specified                                                                      | ECG or medical records                                   | Cognitive decline and medical records    | 26.6          | 7         |
| Chen, et al.[27]     | 2018 | Participants in the ARIC study      | 12515 | Without dementia                                                                   | Non-black or white, prevalent AF, prevalent dementia or lowest 5th percent cognitive scores | ECG and medical records                                  | National Institute on Aging–Alzheimer’s Association work groups and DSM-V or telephone cognitive status–modified score, and informant interview, and ICD codes | 20.2          | 8         |

AF: atrial fibrillation; DSM: Diagnostic and Statistical Manual of Mental Disorders; ICD: International Classification of Diseases; MMSE: Mini-Mental State Examination. aOnly patients without cognitive impairment were included in the meta-analysis.

not suggest obvious publication bias. The Egger’s test arrived at similar results ($P = 0.99$, two-tailed).

3.4 Subgroup analysis

As an important means of therapy, anticoagulation may influence the risk of dementia in AF patients. Accordingly, the Framingham Heart Study discovered that the risk of dementia associated with AF declined over three decades (from the 1970s to the early 2010s); it was speculated that improved anticoagulation might contribute to the tendency. Moreover, emerging evidence suggested that anticoagulation was an effective measure to prevent dementia in AF patients. Because of this, we performed a subgroup analysis according to whether anticoagulation was considered an important confounding factor. In the 11 studies, the studies by Marengoni, et al.[15] Marzona, et al.[24] Bruijn, et al.[19] and Singh-Manoux, et al.[26] included anticoagulation as an important confounding factor in multivariable analysis. As shown in Figure 4, the pooled HR [1.35 (95% CI: 1.21–1.51)] suggested a positive result with $P < 0.01$, which was close to the overall HR [1.34 (95% CI: 1.24–1.44)].

3.5 Meta-regression on age

Other risk factors that trigger neurodegeneration become more important in the very old population, so the effect of AF on dementia incidence may be more significant in relatively
### Table 3. Study outcomes (reported as adjusted HR) and adjusted confounders.

| Study                  | Adjusted HR (95% CI) | Adjusted confounders                                                                 |
|------------------------|-----------------------|-------------------------------------------------------------------------------------|
| Forti, et al.[21]      | 1.10 (0.40–3.03)      | Age, sex, education, baseline MMSE score, diastolic blood pressure, BMI and serum folate |
| Peters, et al.[22]     | 1.03 (0.62–1.72)      | Sex, previous CVA, HF, diabetes, total cholesterol, HDL cholesterol, creatinine glucose hemoglobin, education, antihypertensive treatment, systolic blood pressure, BMI. |
| Bunch, et al.[28]      | 1.36 (1.13–1.63)      | Age, gender, hypertension, hyperlipidemia, diabetes, renal failure, smoking, family history, myocardial infarction, previous CVA, HF, drug therapy |
| Dublin, et al.[23]     | 1.38 (1.10–1.73)      | Sex, education, diabetes mellitus, hypertension, systolic and diastolic blood pressure, incident stroke, CHD, and HF |
| Marengoni, et al.[25]  | 0.90 (0.50–1.70)      | Age, gender, education, baseline MMSE score, hypertension, antithrombotic medications, and ApoE. |
| Marzona, et al.[24]    | 1.30 (1.14–1.49)      | Age; level of education; sex; MMSE; systolic blood pressure, previous CVA, hypertension, diabetes, and myocardial infarction; levels of microalbuminuria, macroalbuminuria, creatinine; drug therapy, smoking, BMI, physical activity, sleep apnea; and alcohol consumption. |
| Haring, et al.[14]     | 1.12 (0.59–2.14)      | Age, education, race, MMSE, alcohol intake, smoking status, physical activity, diabetes, sleep hours, hypertension, BMI, depression, waist–hip ratio, hypercholesterolemia, and aspirin use. |
| Rusanen, et al.[25]    | 2.61 (1.05–6.47)      | Gender and education. Systolic blood pressure, cholesterol, BMI, ApoE, smoking, physical activity, diabetes or impaired glucose tolerance. |
| Bruijn, et al.[19]     | 1.33 (1.02–1.73)      | Age, sex, diabetes, total and HDL cholesterol, lipid-lowering medication, systolic and diastolic blood pressure, blood pressure–lowering medication, BMI, education, anticoagulant medication, CHD, HF, ApoE. |
| Singh-Manoux, et al.[26]| 1.87 (1.37–2.55)      | Sex, education, ethnicity, alcohol consumption, smoking, physical activity, diet, diabetes, hypertension, HF, CVA, and drug therapy. |
| Chen, et al.[27]       | 1.31 (1.11–1.55)      | Age, sex, education, occupation, ApoE, smoking, BMI, systolic blood pressure, diastolic blood pressure, antihypertensive medication, diabetes, CHD, and HF |

ApoE: apolipoprotein E; BMI: body mass index; CHD: coronary heart disease; CVA: cerebrovascular accident; HDL: high-density lipoprotein; HF: heart failure; MMSE: Mini-Mental State Examination.

### Figure 2. Forest plot of meta-analysis.

![Forest plot of meta-analysis](image)

### Figure 3. Funnel plot of meta-analysis.

![Funnel plot of meta-analysis](image)

As our study shows, AF significantly increased the risk of dementia in patients with normal cognition at baseline younger individuals. Therefore, we looked through the population of the included studies, which all included older patients (mean age range: 50.3–75.7 years). To explore the potentially important role of age in the association, we performed a meta-regression on age (Figure 5), which did not show significant results.

### 4 Discussion

As our study shows, AF significantly increased the risk of dementia in patients with normal cognition at baseline...
not suffering from acute stroke. The 11 prospective cohort studies, further demonstrated that AF was independently associated with dementia incidence, with an additional 34% risk of developing dementia compared with non-AF patients. To eliminate the interference of anticoagulation, subgroup analysis reached a similar result even after taking anticoagulation into consideration. In light of the diversity of patients, we performed a meta-regression on age, which did not show significant results. Furthermore, the heterogeneity of the meta-analysis was rather small after verification; all the aforementioned analyses warranted the validity of our results.

In consideration of the recent published results of several prospective cohort studies, we updated the meta-analysis of the present set of prospective cohort studies to verify further the association of AF and dementia. In contrast to our results, the study by Kwok, et al.\(^{[17]}\) concluded that there was considerable uncertainty regarding a link between AF and dementia in patients not suffering from an acute stroke. However, our findings were consistent with the studies by Santangeli, et al.\(^{[18]}\) and Kalantarian, et al.\(^{[19]}\) We differed from the former meta-analyses, by excluding the studies by Tilvis, et al.\(^{[20]}\) and Elias, et al.\(^{[21]}\) in our analysis because of the ambiguous definition of dementia in the two studies. In the meantime, our analysis contained the recently published studies by Haring, et al.\(^{[16]}\) Rusanen, et al.\(^{[22]}\) Bruijn, et al.,\(^{[19]}\) Singh-Manoux, et al.\(^{[26]}\) and Chen, et al.\(^{[27]}\) Due to the rigorous inclusion criteria, we did not detect significant heterogeneity in our analysis. In the former meta-analyses, publication bias was only evaluated in the study by Kalantarian, et al.\(^{[18]}\) which discovered obvious heterogeneity. Through the Egger’s test and funnel plot, the possibility of publication bias in our study was rather small. The lower heterogeneity and publication bias guaranteed the credibility of our study. Besides, it was reported that AF might be an important risk factor for dementia in less elderly individuals, but the meta-regression on age did not find significant results; we speculated that it was partially because the population of most studies included those aged < 70 years.

In accord with most of the previous studies, our meta-analysis further validated the association between AF and dementia incidence. Despite the shared common risk factors prevailing in elderly patients, it was reasonable to suspect that potential mechanisms might underlie the association considering the strong and reproducible results.\(^{[33]}\) To elucidate the association between AF and dementia, several potential mechanisms have been proposed. The recently published reviews and expert consensus argued that silent cerebral lesion, cerebral hypoperfusion, and systematic inflammation might account for the higher risk of dementia in AF patients.\(^{[9,33,34]}\) First, silent cerebral lesion, mainly silent stroke, may be the principal factor in the independent association between AF and dementia incidence. The study by Gaita, et al.\(^{[35]}\) reported that worse cognitive performance in AF patients was significantly associated with the extent of silent stroke. Some studies even held that AF without silent stroke did not increase the risk of cognitive impairment.\(^{[36–38]}\) In the second place, cerebral hypoperfusion due to AF may also be involved in the relationship. In AF patients, both ejection fraction and cerebral blood flow, evaluated by transcranial Doppler ultrasonography, were lower, and an association between cerebral blood flow and cognitive performance was found.\(^{[39]}\) Third, systemic inflammation may
be a potential mechanism underlying the association. It was reported that inflammatory markers, including C-reactive protein and interleukin-6 (IL-6), were elevated in both AF and dementia patients.\textsuperscript{40,41} In addition, other factors, such as genetic variants and brain atrophy may also play a role in the increased risk of dementia in AF patients.\textsuperscript{42} In spite of the existing evidence, it is still necessary to investigate the impact of individual mechanisms to confirm the potential mechanisms involved in the association.

Despite insufficient understanding of the mechanisms involved in the association between AF and dementia incidence, targeted therapies were considered possible effective measures to prevent cognitive dysfunction in AF patients. Although our subgroup analysis achieved similar results with overall HR, the effect of anticoagulation in reducing dementia risk could not be neglected. Emerging evidence suggested an effective measure of anticoagulation to prevent dementia in AF patients. In support of the role of anticoagulation in reducing AF-related dementia, the study by Mongkhon, et al.\textsuperscript{40} reported a protective effect of anticoagulant therapy in reducing dementia risk in AF patients, and that a lower time in the therapeutic range in warfarin-treated AF patients significantly increased the risk of incident dementia.\textsuperscript{14,43,44} In addition, catheter ablation was reported to contribute to lower dementia incidence in AF patients by rhythm control.\textsuperscript{45} However, catheter ablation could increase the risk of both clinically overt stroke and silent cerebral lesions; cognitive decline was found in 13% of AF patients after catheter ablation, compared to 0 in controls without ablation.\textsuperscript{46} Other probable measures included rhythm control by pharmaceuticals or anti-inflammation by statin therapy and risk factor management.\textsuperscript{9,47} In spite of these possible measures mentioned above, randomized data exploring the efficacy of therapies and in particular individualized management to prevent dementia in AF patients is still lacking.

The strengths of our study should be highlighted. First, we included only prospective cohort studies that investigated dementia incidence in patients with normal baseline cognitive function not suffering from an acute stroke, which could be regarded as the strongest evidence yet about the association between AF and dementia incidence. Second, we performed a subgroup analysis to evaluate the risk in anticoagulant patients. Third, statistical tests revealed no significant heterogeneity and publication bias in our study, and the meta-regression on age excluded the confounding effects of age on the results. Last but not least, the meta-analysis covered recently published studies and reflected real-world situations.

Our meta-analysis also has limitations. First, the included studies were different in terms of the age of the population and the study design; despite the proven low heterogeneity, the results should be interpreted with caution. Second, we only included the studies published in English, which might introduce selective bias. Third, we only investigated the association between AF and dementia; the results could not be generalized to the relationship between AF and the complete range of cognitive disorders. In addition, although we appraised the quality of studies carefully, some degree of subjectivity was inevitable due to the various methods adopted by the studies to ascertain AF and dementia.

5 Conclusion

The results of our meta-analysis further demonstrated that AF was an independent risk factor for dementia in patients with normal baseline cognitive function not suffering from acute stroke. Screening for dementia in AF patients and including dementia as an independent outcome in large AF treatment trials is warranted. The precise mechanisms involved in the association of AF and dementia need to be explored further in well-designed large cohort studies.

Acknowledgements

This meta-analysis was supported by a grant from the National Natural Science Foundation of China (Grant No. 81471197) and the National Key Research and Development Program of China (2017YFC0907703). The authors declare that no conflicts of interest exist.

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