Atrial Fibrillation Is Associated with Cognitive Impairment, All-Cause Dementia, Vascular Dementia, and Alzheimer's Disease: a Systematic Review and Meta-Analysis

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BACKGROUND: Atrial fibrillation (AF) is a risk factor for cognitive impairment and dementia in patients with stroke history. However, the association between AF and cognitive impairment in broader populations is less clear.
OBJECTIVE: To systematically review and quantitatively synthesize the existing evidence regarding the association of AF with cognitive impairment of any severity and etiology and dementia.
METHODS: Medline, Scopus, and Cochrane Central were searched in order to identify studies investigating the association between AF and cognitive impairment (or dementia) cross-sectionally and longitudinally. Studies encompassing and analyzing exclusively patients with stroke history were excluded. A random-effects model meta-analysis was conducted. Potential sources of between-study heterogeneity were investigated via subgroup and meta-regression analyses. Sensitivity analyses including only studies reporting data on stroke-free patients, vascular dementia, and Alzheimer's disease were performed.
RESULTS: In total, 43 studies were included. In the pooled analysis, AF was significantly associated with dementia (adjusted OR, 1.6; 95% CI, 1.3 to 2.1; I^2, 31%) and the combined endpoint of cognitive impairment or dementia (pooled adjusted OR, 1.5; 95% CI, 1.4 to 1.8; I^2, 34%). The results were significant, even when studies including only stroke-free patients were pooled together (unadjusted OR, 2.2; 95% CI, 1.4 to 3.5; I^2, 96%), but the heterogeneity rates were high. AF was significantly associated with increased risk of both vascular (adjusted OR, 1.7; 95% CI, 1.2 to 2.3; I^2, 43%) and Alzheimer's dementia (adjusted HR, 1.4; 95% CI, 1.2 to 1.6; I^2, 42%).
CONCLUSION: AF increases the risk of cognitive impairment, all-cause dementia, vascular dementia, and Alzheimer's disease. Future studies should employ

interventions that may delay or even prevent cognitive decline in AF patients.

INTRODUCTION

Atrial fibrillation (AF) and dementia frequently coexist, affecting predominantly the elderly.[1] As global population aging is accelerated, the burden of both disorders is projected to increase dramatically. Specifically, the number of patients affected by dementia is expected to increase to 131 million by 2050, while the corresponding number for AF is more than 100 million individuals.[2–5] Prior studies have shown that AF is a risk factor for cognitive impairment and dementia in patients with stroke history, since AF-related brain infarcts may lead to a step-wise decline in cognitive function,[6, 7] as part of the vascular contributions to cognitive impairment and dementia.[8] Specifically, a previous meta-analysis by Kwok et al. showed that AF confers an increased risk of dementia not only in patients with stroke history, but also in broader populations.[9] At the same time, a number of recent observational studies examined the relationship between AF and cognitive impairment in stroke-free patients reporting equivocal results.[10–12] Interestingly, Saglietto et al., in their meta-analysis, pooled together adjusted data from separate studies, showing that AF increased the risk of dementia independently from prior history of cerebrovascular accident.[13] However, a more rigorous analysis including only studies with stroke-free patients would provide more solid conclusions. In this context, Liu et al.

attempted to explore the association of AF with dementia in patients without stroke at baseline, but the analysis may have led to overestimated results due to use of a fixed-effects instead of a random-effects model.[14] Additionally, no previous meta-analysis has systematically explored the association of AF with specific subtypes of dementia (i.e., vascular dementia and Alzheimer's disease). Filling this knowledge gap and examining whether an independent association exists between AF and cognitive impairment may help reduce the burden of both disorders on patients and healthcare systems.

With this study, we aim to systematically review and quantitatively synthesize the existing evidence regarding the association of AF with cognitive impairment of any severity and etiology, including dementia of any severity and etiology. Since dementia represents the more severely affected subgroup of individuals with cognitive impairment, a subgroup that may demonstrate unique associations with AF, we perform separate syntheses for dementia.

MATERIALS AND METHODS

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[15] and registered in Prospero (117069):

Data Sources—Search Strategy

The electronic databases Medline, Scopus, and Cochrane Central were searched for relevant studies by two independent reviewers (CAP, NZ). The complete search algorithm for each database is presented in Supplementary File 1. The search terms we used result in retrieving studies that include participants with various neurodegenerative dementias, vascular dementia, and mild cognitive impairment (retrievable since it contains "cognitive impairment," and VCID or VCI). Therefore, our use of the term cognitive impairment (CI) should not be confused with mild cognitive impairment (MCI). The reference lists of the included studies and relevant reviews were also examined for further eligible studies.

Study Selection

A study was deemed to be eligible for this systematic review if the following inclusion criteria were met: (i) investigating the association between AF and cognitive impairment (and/or dementia)[16]; reporting event rates or relative risk (RR)/odds ratio (OR) or hazard ratios (HR) for the comparison groups; (iii) all observational study designs were accepted (cohort, cross-sectional, prospective, retrospective); and (iv) published in any language up to December 2019. Studies encompassing and analyzing solely patients with stroke history were excluded. A summary of eligibility criteria can be found in Supplementary Table 1.

Two independent reviewers assessed the eligibility of the potentially included studies, according to the inclusion criteria (AAM, DGK). Disagreements were resolved by consensus.

Data Extraction and Quality Assessment

Pre-specified forms were used to extract the epidemiological and clinical data of the included studies. Data extraction was performed by two independent reviewers (CAP, CAT). Any discrepancies were resolved by the involvement of a third reviewer (LP). When duplicated populations were identified and the studies reporting on them used the same outcome measure, only the larger study was included in the analysis.

The assessment of risk of bias of the individual studies was performed independently by two investigators using the QUIPS tool (CAP, CAT).[17] Each of the following bias domains was critically appraised as low, moderate, or high risk: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, statistical analysis, and reporting. To rate the quality of evidence of individual studies, the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach was used.

Data Synthesis and Analysis

In the primary analysis, the combined endpoint of cognitive impairment or dementia was assessed. Given a lack of uniformity for criteria of cognitive impairment, a separate analysis for the better-defined outcome of dementia was also performed. Different effect measures (unadjusted OR/HR and adjusted OR/HR) were pooled separately. The adjusted effect measures were used as reported in the original studies, irrespective of the number and kind of confounders used in their multivariate analyses. When associations with cognitive impairment and dementia were both reported, the outcome for the larger population was included in the primary analysis (individuals with dementia comprise a subgroup of those with cognitive impairment). Potential sources of between-study heterogeneity were investigated via subgroup analysis (cross-sectional vs. cohort studies) and meta-regression analysis (explanatory variables: age, hypertension (HTN), coronary artery disease (CAD), diabetes mellitus (DM), and hyperlipidemia). Several sensitivity analyses were also performed: (i) including only studies with stroke-free patients, in order to assess whether AF is associated with CI/dementia for reasons other than inducing clinical strokes; (ii) including only studies with prospective design; (iii) including only studies that implemented sensitive neuropsychological testing for detection of cognitive impairment milder than dementia and did not rely solely on MMSE, since the latter is insensitive for detection of mild cognitive impairment (MCI) and even more so for subtle forms of cognitive impairment

due to ceiling effects.[18–20] Specifically, in this sensitivity analysis, we included studies that used a global score derived from scores of three or more sensitive neuropsychological tests for detection of cognitive impairment[21] [examples of tests that were combined for a global score were Delayed Word Recall Test (DWRT), Digit Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale–Revised, Word Fluency Test (WFT), logical memory immediate and delayed recall, incidental learning from the Wechsler Memory Scale-III, trail making test parts A and B, WAIS-R digits span backward, Boston naming test, and animal naming].[19, 20] We also included studies[22–24] that used singular sensitive diagnostic tests for detection of MCI, specifically, Montreal Cognitive Assessment (MoCA) or Modified Mini-Mental State Examination (3MS).[19, 20] Finally, studies that adopted the modified Petersen criteria for diagnosis of MCI were included in this analysis, since their implementation requires careful clinical review of cognitive symptoms and cognitive testing[25]; (iv) including only studies that implemented established criteria for diagnosis of dementia (such as the National Institute on Aging-Alzheimer's Association workgroups criteria; or the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences criteria; or the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; or the Diagnostic and Statistical Manual of Mental Disorders-IV criteria); or a single diagnostic tool with adequate sensitivity, such as the informant questionnaire on cognitive decline in the elderly (IQCODE). From this sensitivity analysis, we excluded studies which determined dementia diagnosis based on patient record (ICD-9/10) diagnoses, without direct assessment of patients; (v) including only studies reporting data for Alzheimer's dementia (AD); (vi) including only studies reporting data for vascular dementia (VaD); (vii) including only studies with a number of patients > 500. The random-effects model was used to account for heterogeneity within and between studies. Heterogeneity was assessed with the Higgins I-squared statistic (I2). Funnel plots were used to illustrate the publication bias risk, and the risk was quantified with the Egger's regression test. A forest plot was used to graphically display the effect size in each study as well as in the pooled estimate. To test the effect of study design (cross-sectional vs. cohort) on the outcome, a subgroup analysis was performed. A p value < 0.05 was considered significant. All statistical analyses were performed using Revman version 5.3 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014) and Comprehensive Meta-analysis version 3 (Englewood, NJ).
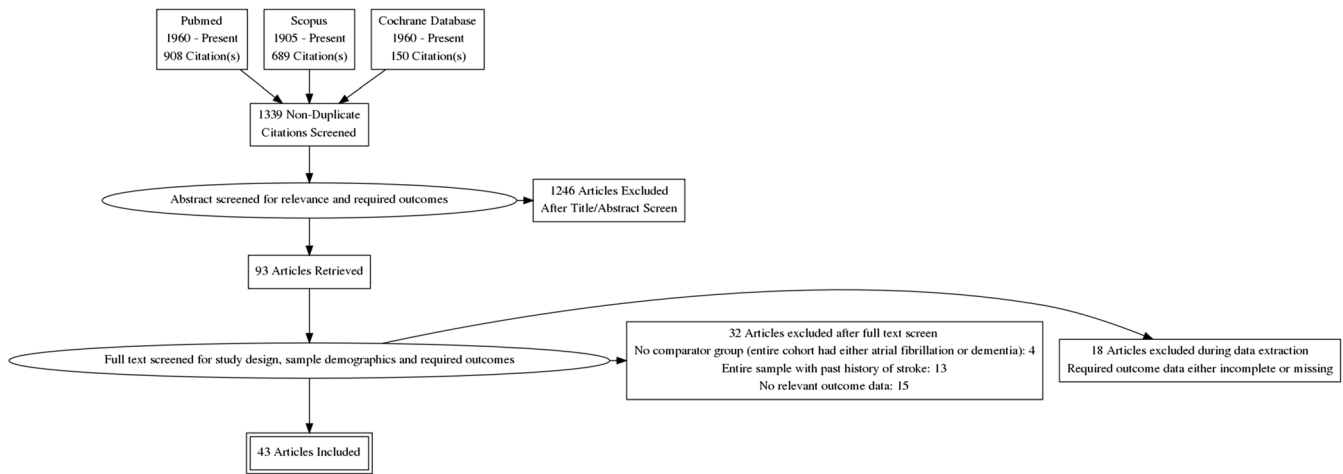
RESULTS

Study Selection and Study Characteristics

In total, 43 studies were included in this systematic review.[1, 10–12, 16, 21–58] A detailed flow diagram is presented in Figure 1. Nineteen studies reported cross-sectional analyses,[1, 22–28, 32, 33, 35, 36, 38, 40, 41, 43, 44, 49, 58] 20 studies had prospective design,[10–12, 16, 21, 34, 37, 39, , 45–48, 50–53, 55–57] and four were retrospective.[29–31, 54] The number of enrolled patients ranged from 57 to 1,627,631 among the included studies. Hypertension (HTN), coronary artery disease (CAD), and diabetes rates among different studies ranged from 1 to 99%, 3.3 to 74.6%, and 4.4 to 37.2%, respectively. The percentage of patients with stroke history was reported in 23 studies (231.564 patients) and ranged from 1 to 24.7%,[10, 12, 16, 21, 25–27, 29–31, 33, 34, 36, 40, 45, 47–50, 52–54, 56] while 14 studies reported data on stroke-free patients[10–12, 23, 24, 28, 32, 34, 37, 41, , 51, 55, 57] (325.494 patients). Although different diagnostic methods were used to identify AF and cognitive impairment, electrocardiogram and Mini-Mental State Examination (MMSE) were the most commonly used tests. The baseline characteristics of the included studies are presented in Table 1 and Supplementary Table 2. The overall risk of bias was found to be low or moderate in most studies. The most common cause of bias was related to the measurement of outcome (i.e., cognitive impairment and dementia). Details for risk of bias assessment of individual studies are shown in Supplementary Table 3. Details for the GRADE rating of individual studies can be found in Supplementary Table 3. Egger's test (p = 0.01) and visual inspection of the funnel plot (Fig. 2) indicated that publication bias may exist due to potentially unpublished small studies.

Synthesis of Individual Results

Composite Endpoint of Dementia or Cognitive Impairment.
In total, 31 studies reported unadjusted OR for the combined endpoint of dementia or cognitive impairment.[1, 10–12, 21–26, 28, 29, 31–33, 35–38, 40–46, 49–52] In the pooled analysis, AF was associated with increased risk for the combined endpoint (pooled unadjusted OR, 1.6; 95% CI, 1.4 to 1.9; df = 30) with significant between-study heterogeneity (I^2, 97%) (Supplementary Figure 1). When adjusted effect measures were pooled together, AF was found to be a strong predictor of the combined endpoint with low between-study heterogeneity (15 studies: pooled adjusted OR, 1.5; 95% CI, 1.4 to 1.8; df = 14; I^2, 34%; Supplementary Figure 2 and 18 studies: pooled adjusted HR, 1.4; 95% CI, 1.2 to 1.5; df = 17; I^2, 92%; Supplementary Figure 3). The test for subgroup differences showed that there was no statistically significant subgroup effect (p = 0.24), suggesting that study design did not affect the outcome (Supplementary Figure).

Figure 1 PRISMA flow chart. The selection process is reported according to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

The results of meta-regression analysis can be found in Supplementary file 2.

Dementia. Sixteen studies reported unadjusted data on the association of AF with dementia.[10–12, 16, 21, 30, 32, 36, 38, 39, 41, 44–46, 51, 52] In the pooled analysis, AF was strongly associated with dementia (pooled unadjusted OR, 1.5; 95% CI, 1.2 to 1.9; df = 15) with significant between-study heterogeneity (I^2, 98%) (Fig. 3). The association remained significant, after pooling together adjusted effect measures (8 studies: adjusted OR, 1.6; 95% CI, 1.3 to 2.1; df = 7; I^2, 31%; Supplementary Figure 5; and 17 studies: adjusted HR, 1.4; 95% CI, 1.2 to 1.5; df=16; I2, 92% Supplementary Figure 6).

Sensitivity Analysis. Studies with Stroke-Free Patients. In total, 325.494 patients without stroke at baseline were included in the analysis. Among the 14 studies that reported data on stroke-free patients,[10–12, 23, 24, 28, 32, 34, 37, 41, , 51, 55, 57] AF was associated with a higher risk of cognitive impairment or dementia (11 studies: unadjusted OR, 2.2; 95% CI, 1.4 to 3.5; df = 10; I^2, 96%; Supplementary Figure 7, 7 studies: adjusted HR, 1.4; 95% CI, 1.1 to 1.7; df = 6; I^2, 87%; Supplementary Figure 8).

Studies with Prospective Design. Significant results were yielded for the combined endpoint of cognitive impairment and/or dementia, even when the analysis was limited to prospective studies (15 studies: adjusted HR, 1.3; 95% CI, 1.2 to 1.5; df = 14; I^2, 94%) (Fig. 4).

Studies with Comprehensive Cognitive Testing. Among the 9 studies with comprehensive cognitive testing,[21–25, 36, 41, 52, 57] AF was associated with higher risk of cognitive dysfunction (unadjusted OR, 1.8; 95% CI, 1.2 to 2.6; I^2, 88%) (Supplementary Figure 9).

Studies with Comprehensive Dementia Diagnosis. AF was found to be an independent predictor of dementia, when the analysis was restricted to studies that used high-quality criteria for the diagnosis of dementia and reported adjusted data (9 studies: adjusted HR, 1.3; 95% CI, 1.2 to 1.4; I^2, 0%) (Supplementary Figure 10).

Alzheimer's Dementia and Vascular Dementia. Thirteen studies provided data for the association of AF with AD[1, 10, 11, 25, 26, 30, 31, 34, 36, 38, 46, 56] and 5 studies for the association with VaD.[1, 26, 31, 36, 38] AF was associated with an increased risk for both types of dementia (7 studies: adjusted HR for AD, 1.4; 95% CI, 1.1 to 1.6; df = 6; I^2, 42%; Supplementary Figure 11, adjusted OR for VaD, 1.7; 95% CI, 1.2 to 2.3; df = 4; I^2, 43%; Supplementary Figure 12)

Studies with Number of Patients > 500. Among the 11 studies that included in their analysis more than 500 patients and reported adjusted data, AF was significantly associated with the combined endpoint of cognitive impairment or dementia (adjusted pooled OR, 1.5; 95% CI, 1.4 to 1.7; df = 10; I^2 = 25%) (Supplementary Figure 13).

DISCUSSION

This was a systematic review and meta-analysis of 43 observational studies that examined the association of AF with CI and dementia. To the best of our knowledge, this is the most updated meta-analysis on the topic with the largest patient population (more than 3.5 million patients), providing for the first time separate analyses and pooled data for the association of AF with VaD and AD, as well. The main finding of our study is that the presence of AF is associated with an increased risk of cognitive impairment and dementia. Interestingly, this

Table 1   Baseline Demographics and Baseline Characteristics of Included Studies (AF/no AF)

Author/ Year	Country	No. of patients	Study design	Follow-up, years (Mean)[a]	Age, years (Mean)	Stroke History (%)	AF ascertainment	Cognitive impairment ascertainment	Dementia ascertainment	Comprehensiveness of assessment for cognitive impairment/ dementia
Ott 1997[c]	Netherlands	6584 (157/6151)	Cross-sectional	NA	NA	NA	EKG	MMSE	MMSE; Geriatric Mental Schedule; CAMDEN; DSM III; brain MRI; examination by neurologist; medical records; criteria with a subdiagnosis of Alzheimer's disease based on NINCDS-ADRDA; criteria with subdiagnosis of vascular dementia in accordance with NINDS-AIREN	Cognitive impairment: No Dementia: Yes
Cacciatore 1998	Italy	1075 (88 vs 987)	Cross-sectional	NA	73.9 (NA)	0	NA	MMSE	NA	Cognitive impairment: No Dementia: NA
Tilvis 2004	Finland	629 (61/568)	Prospective	5	NA	8.6 (NA)	History, medical records	MMSE	CDR	Cognitive impairment: No Dementia: No
Debette 2006	France	83 (32 /51)	Cross-sectional	NA	62 (NA)	NA	NA	MMSE	NA	Cognitive impairment: No Dementia: NA
Joswiak 2006	Poland	2314 (547/1467)	Cross-sectional	NA	76	NA	EKG	MMSE	NA	Cognitive impairment: No Dementia: NA
Forti 2007	Italy	431 (13/418)	Prospective	4	75 (NA)	NA	History	MMSE	NINCDS-ADRDA criteria, CDR, Petersen criteria for MCI	Cognitive impairment: No Dementia: Yes
Rastas 2007	Finland	339 (72/267)	Prospective	3.5	88 (NA)	20 (NA)	Medical records	MMSE	DSM-III Revised criteria, neurologist's clinical examination, MMSE, and Short Portable Mental Status Questionnaire tests; CDR, Actives of Daily Living, and Instrumental Activities of Daily Living scales; delirium excluded; history/interviews; consensus by two neurologists needed	Cognitive impairment: No Dementia: Yes
Bilato 2009	Italy	1576 (135/1441)	Retrospective	4	76 (79/74)	4.5 (8.8/4.2)	EKG	MMSE, clock drawing tests	NA	Cognitive impairment: No Dementia: NA
Peters 2009	UK	3369	Prospective	1.8	84	6.5	NA	NA	NA	

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Table 1. (continued)

Author/ Year	Country	No. of patients	Study design	Follow-up, years (Mean)[a]	Age, years (Mean)	Stroke History (%)	AF ascertainment	Cognitive impairment ascertainment	Dementia ascertainment	Comprehensiveness of assessment for cognitive impairment/ dementia
		(190/3146)			(NA)	(NA)			MMSE, clock drawing tests; DSM-IV criteria; brain CT assessed by two neuroradiologists and modified ischaemic score/Hachinski ischaemic score	Cognitive impairment: NA; Dementia: Yes
Bunch 2010[b]	USA	37025 (10161/26864)	Retrospective	5	60.7 (68/58)	3.6 (4.7/3.2)	Medical Records, ICD-9 codes	NA	Medical Records, ICD-9 codes	Cognitive impairment: NA; Dementia: No
Dublin 2011	USA	3045 (132/2913)	Prospective	6.8	74.1 (77/74)	0	ICD Codes	NA	Cognitive Abilities Screening Instrument, DSM-IV, NINCDS-ADRDA	Cognitive impairment: NA; Dementia: Yes
Marengoni 2011	Sweden	685 (68/617)	Prospective	4	78 (NA)	NA	ICD codes, history, medical records	MMSE	DSM-III	Cognitive impairment: No; Dementia: Yes
Marzona 2012	USA	31506 (27864/3068)	Prospective	4.7 (median)	66.5 (66.3/69.4)	21[d] (27.6/20.5)	EKG	MMSE	MMSE, reported dementia	Cognitive Impairment: No; Dementia: No
Yoshihara 2012	Brazil	1524 (37/1487)	Cross-sectional	NA	72.2 (77.7/72.1)	NA	EKG	NA	DSM-IV, Diagnostic tool developed by the 10/66 Dementia Research Group and validated for low income countries, community screening instrument for dementia (CSI-D), modified version of the CERAD ten word list, community directed version of the geriatric mental state	Cognitive Impairment: NA; Dementia: Yes
Polidoro 2013	Italy	140 (70/70)	Cross-sectional	NA	79.2 (79.3/79,1)	21.4 (22.9/20)	EKG	MMSE	NA	Cognitive impairment: No; Dementia: NA
Bellomo 2012	Italy	57 (26/31)	Cross-sectional	NA	71.8 (71.4/72.1)	0	EKG	MMSE	NA	Cognitive impairment: No; Dementia: NA
Habeych 2015	USA	17062 (898/16164)	Case-control	NA	NA	NA	NA	NA	ICD-9 codes	Cognitive impairment: NA; Dementia: No
Haring 2013	USA	6433 (255/6178)	Prospective	8.6	NA	0	NA	3MSE	Modified Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery of neuropsychological tests	Cognitive impairment: Yes; Dementia: Yes

Table 1. (continued)

Author/Year	Country	No. of patients	Study design	Follow-up, years (Mean)[a]	Age, years (Mean)	Stroke History (%)	AF ascertainment	Cognitive impairment ascertainment	Dementia ascertainment	Comprehensiveness of assessment for cognitive impairment/dementia
Author/Year	Country	No. of patients	Study design	Follow-up, years (Mean)[a]	Age, years (Mean)	Stroke History (%)	AF ascertainment	Cognitive impairment ascertainment	Dementia ascertainment	Comprehensiveness of assessment for cognitive disorder/dementia and standardized interviews, DSM-IV Dementia ascertainment
Salehi 2013	Iran	189 (93/96)	Prospective	1 (overall)	71.2 (71.1/71.3)	0	EKG	NA	DSM-IV	Cognitive impairment: NA Dementia: yes
Horstmann 2014	Germany	718 (165/623)	Cross-sectional	NA	66.8 (75.5/64.5)	0	History, EKG, holter monitoring	IQCODE >3.44	IQCODE ≥4	Cognitive impairment: Yes Dementia: Yes
Alosco 2015	USA	187 (60/127)	Cross-sectional	NA	68.5 (70.9/67.3)	0	History	Modified MMSE, Trail making test A and B, Digit symbol coding, boston naming test, Animal fluency test, CVLT-II long delay free recall and total recognition hits	NA	Cognitive Impairment: yes Dementia: NA
Annweiler 2015	France	267 (58/209)	Cross-sectional	NA	83.3 (NA)	19.9 (NA)	EKG, History	MMSE	NA	Cognitive impairment: No Dementia: NA
Rusanen 2014	Finland	1510 (NA)	Prospective	25.5	50.3 (NA)	7.2 (NA)	ICD codes	MMSE	MMSE, Finnish version of CERAD	Cognitive impairment: NA Dementia: Yes
Ding 2018	Sweden	2658 (243/2442)	Prospective	9	73.1 (80.9/72.3)	4.3[d] (13.2/3.4)	ICD codes	MMSE	DSM-IV, NINCDS-ADRDA, NINDS-AIREN	Cognitive function: No Dementia: Yes
Elias 2006	USA	1011 (59/952)	Prospective	30	61.4 (68/61)	0	EKG, holter monitoring, history	Multiple tests from the Wechsler adult intelligence scale and Halstead-Reitan Battery for the assessment of multiple cognitive domains	NA	Cognitive impairment: Yes Dementia: NA
De Bruijn 2015[c]	Netherlands	6514 (318/6196)	Prospective	20 (overall)	68.6 (75.7/68.3)	3[d] (NA)	EKG	NA	Cambridge Examination for Mental Disorders of the Elderly	Cognitive impairment: NA Dementia: Yes
Di Nisio 2015	Italy	309 (103/206)	Cross-sectional	NA	77.5 (77.7/77.4)	4.5 (24.3/12.2)	EKG	MMSE, Rey Auditory Verbal Learning Test, Rey-Osterrieth Complex Figure, Corsi block-tapping task,	DSM-IV, NINDS-ADRDA, NINDS-AIREN criteria	Cognitive impairment: Yes Dementia: Yes

Table 1. (continued)

Author/Year	Country	No. of patients	Study design	Follow-up, years (Mean)[a]	Age, years (Mean)	Stroke History (%)	AF ascertainment	Cognitive impairment ascertainment	Dementia ascertainment	Comprehensiveness of assessment for cognitive impairment/dementia
								digit span test, verbal span test, Babcock's story, Raven's progressive matrices and attentive matrices		
Jefferson 2015	USA	9720 (583/9137)	Cross-sectional	NA	NA	0	EKG	Petersen criteria, CDR, MMSE, Digit Span Forward, Digit Symbol, Trail Making Test (A, B), Digit Span Backward, Boston Naming Test, Animal Naming, Vegetable Naming, Logical Memory (Immediate/Delayed Recall)	NA	Cognitive impairment: Yes Dementia: NA
Liao 2015	Taiwan	665330 (332665/332665)	Prospective	12	70.3 (70.3/70.3)	24.7 (32.3/17.2)	ICD-9 codes	NA	ICD-9 codes	Cognitive impairment: NA Dementia: No
Bunch 2016[b]	USA	6030 (3000/3030)	Retrospective	7.1 (median)	69.3 (69.3/69.3)	5.1 (5.2/4.9)	EKG	NA	MMSE	Cognitive impairment: NA Dementia: No
Coma 2016	Spain	881 (187/794)	Cross-sectional	NA	72.6 (NA)	12 (14 11.5)	NA	MMSE	NA	Cognitive impairment: No Dementia: NA
Dugger 2016	USA	17008 (1003/16005)	Cross-sectional	NA	NA	NA	NA	NA	Uniform Data Set (UDS), composed of standardized clinical evaluations at Alzheimer's Disease Centers (ADCs) funded by the National Institute of Aging	Cognitive impairment: NA Dementia: Yes
Ma 2016	China	5067 (174/4893)	Cross-sectional	NA	72.1 (NA)	24.1 (NA)	History	Modified Petersen criteria	NA	Cognitive impairment: Yes Dementia: NA
Marzona 2016	Italy	1627631 (27431/1600200)	Prospective	12	75.3 (78.4/75.2)	1 (7.3/0.9)	EKG	NA	ICD-9 codes	Cognitive impairment: NA Dementia: No
Pulignano 2016	Italy	331 (98/233)	Prospective	1	78 (78/77)	10 (11.2/9.4)	EKG	MMSE	NA	Cognitive impairment: No Dementia: NA
	USA	1044 (141/903)	Cross-sectional	NA	77.8 (NA)	5.4 (9.9/4.7)	EKG	NA	Petersen criteria for MCI	Cognitive impairment:NA

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Table 1. (continued)

Author/Year	Country	No. of patients	Study design	Follow-up, years (Mean)[a]	Age, years (Mean)	Stroke History (%)	AF ascertainment	Cognitive impairment ascertainment	Dementia ascertainment	Comprehensiveness of assessment for cognitive impairment/dementia
Graff-Radford 2016										Dementia:No
Walters 2016	UK	800013 (24763/775250)	Retrospective	5 (median)	65.6 ±6.1(NA)	4.9(NA)	Medical records	NA	ICD-10	Cognitive impairment: NA Dementia: No
Alonso 2017[c]	USA	6432 (611/5821)	Cross-sectional	NA	76.2 (79/76)	4.5 (10/4)	EKG during study visit or any prior visit, or ICD-9 code at any point	NA	NIA-AA and NINDS-AIREN criteria	Cognitive impairment: NA Dementia: Yes
Yang 2017	China	188 (72 /116)	Cross-sectional	NA	66.3 (68.9/64.6)	0	History	The Beijing version of MoCA	NA	Cognitive impairment: Yes Dementia: NA
Singh-Manoux 2017	UK	7428 (414/7014)	Prospective	14.7	55.7 (58.8/55.5)	15 (NA)	EKG, ICD codes	Cognitive test battery, comprising of the following cognitive tests: 20-word free recall for memory, Alice Heim 4-1 for reasoning, measures of phonemic and semantic fluency. A global cognitive score was calculated based on the above	ICD-10 codes	Cognitive impairment: Yes Dementia: No
Pavel 2018	Russia	100 (48/50)	Cross-sectional	NA	77 (78/76)	NA	EKG	MoCA, FCSRT	MoCA, FCSRT	Cognitive impairment: Yes Dementia: No
Chen 2018[c]	USA	12515 (2106/10409)	Prospective	20.2	56.9 (59.3/56,4)	2 (1/2)	EKG, ICD-9 codes	Cognitive battery comprising of delayed word recall (DWR), digit symbol substitution (DSS), subtest of the Wechsler Memory Scale-Revised, first letter word fluency	DSM-V, NIA-AA, ICD-9 codes	Cognitive impairment: Yes Dementia: Yes
Dongmin Kim 2019	Korea	262611 (10435/252176)	Prospective	8 (overall)	70.7 (71.7/70.7)	0	NA	NA	KDSQ, ICD-10 codes	Cognitive impairment: NA Dementia: No

[a]Unless otherwise specified
[b]Studies with overlapping population
[c]Studies with overlapping population
[d]Data for stroke-free patients were also reported

CAD Coronary Artery Disease; CDR Clinical Dementia Rating; CVLT-II California Verbal Learning Test-II; EKG Electrocardiogram; FCSRT Free and Cued Selective Reminding Test; GMS Geriatric Mental Schedule; HLD Hyperlipidemia; HTN Hypertension; ICD International Classification of Diseases; IQCODE Informant Questionnaire on Cognitive Decline in the Elderly; KDSQ Korean Dementia Screening Questionnaire; MMSE Multi-Mental State Exam; MoCA Montreal Cognitive Assessment; NA Not Applicable
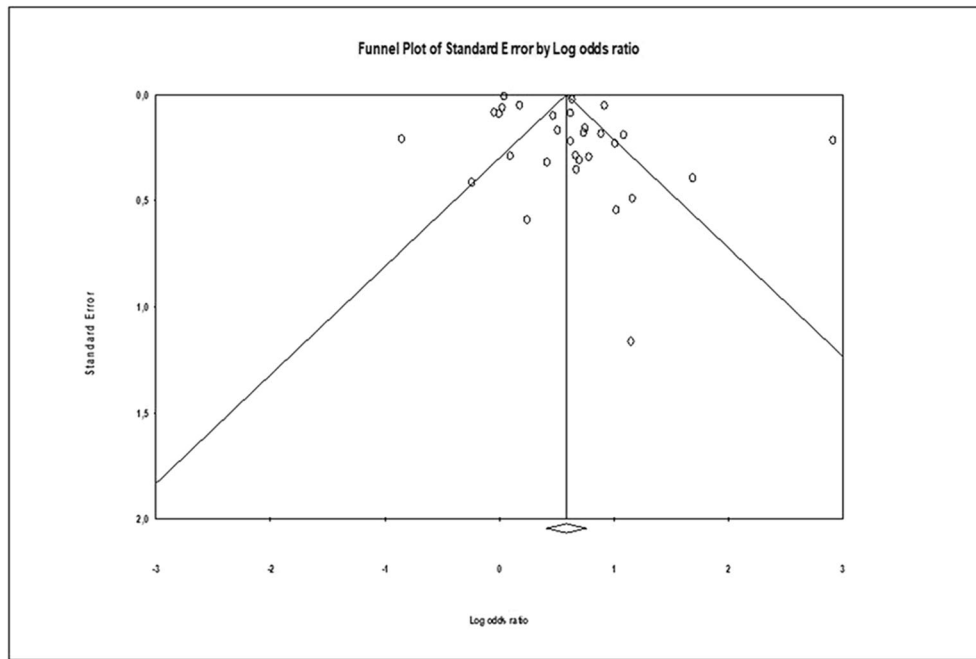
Figure 2 Publication bias assessment. Funnel plot with pseudo 95% confidence limits. Log, logarithm.

association remained significant even when data from prospective studies were pooled together. Moreover, the sensitivity analyses for the association of AF with vascular dementia and Alzheimer's disease yielded significant results for both subtypes of dementia. Finally, given the great heterogeneity in the methods used to ascertain CI and dementia across the included studies, we performed separate analyses including only studies that implemented sensitive neuropsychological testing for detection of cognitive impairment and established criteria for diagnosis of dementia. These sub-analyses allow drawing more solid conclusions on the association of AF with CI and dementia. In light of the high incidence of AF, our findings have important implications for patients and

healthcare systems given the morbidity and quality-of-life implications, as well as the economic and social burden associated with poor cognitive outcomes during aging.

However, some of the analyses of our study were limited by a high degree of heterogeneity. Even if we tried to adjust for them, by using a random-effects model, performing multiple subgroup, sensitivity, and meta-regression analyses, there was still significant heterogeneity in the analyses. We think the reason for that was mainly the different status and management of patients with AF among the different studies. Prior studies have shown that anticoagulation has a positive impact in decreasing the risk for dementia and cognitive impairment in patients with AF. We were not able to adjust for the
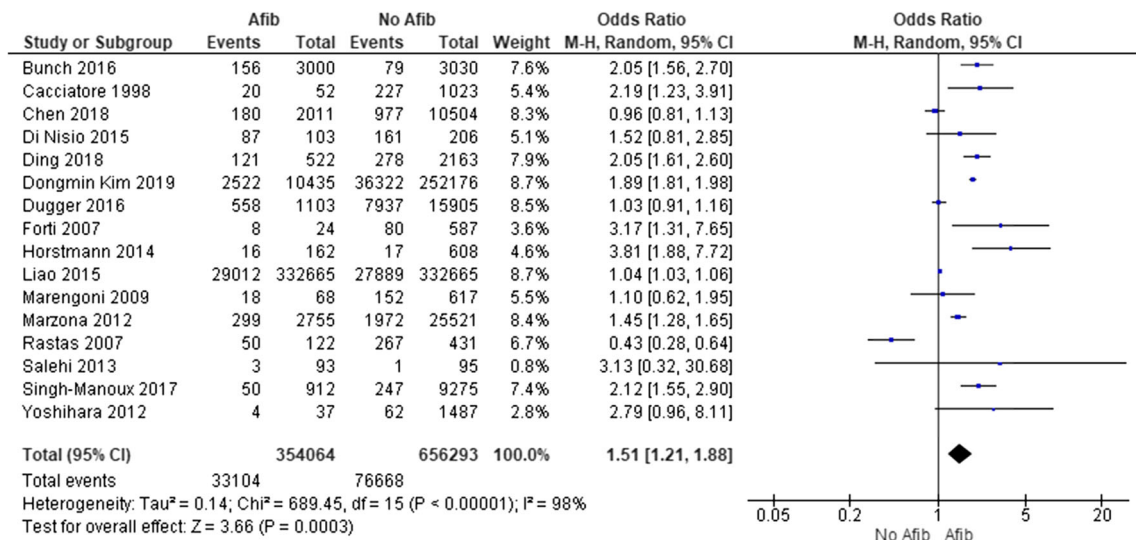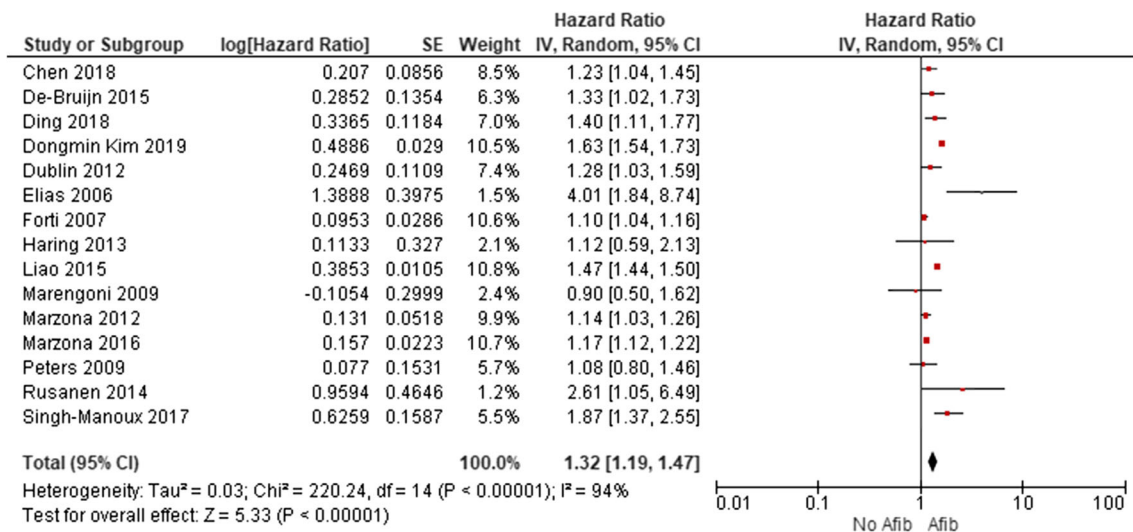

Figure 3 Meta-analysis results. Forest plot demonstrating pooled unadjusted odds ratio for dementia. Afib, atrial fibrillation; CI, confidence interval.

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Chen 2018	0.207	0.0856	8.5%	1.23 [1.04, 1.45]
De-Bruijn 2015	0.2852	0.1354	6.3%	1.33 [1.02, 1.73]
Ding 2018	0.3365	0.1184	7.0%	1.40 [1.11, 1.77]
Dongmin Kim 2019	0.4886	0.029	10.5%	1.63 [1.54, 1.73]
Dublin 2012	0.2469	0.1109	7.4%	1.28 [1.03, 1.59]
Elias 2006	1.3888	0.3975	1.5%	4.01 [1.84, 8.74]
Forti 2007	0.0953	0.0286	10.6%	1.10 [1.04, 1.16]
Haring 2013	0.1133	0.327	2.1%	1.12 [0.59, 2.13]
Liao 2015	0.3853	0.0105	10.8%	1.47 [1.44, 1.50]
Marengoni 2009	-0.1054	0.2999	2.4%	0.90 [0.50, 1.62]
Marzona 2012	0.131	0.0518	9.9%	1.14 [1.03, 1.26]
Marzona 2016	0.157	0.0223	10.7%	1.17 [1.12, 1.22]
Peters 2009	0.077	0.1531	5.7%	1.08 [0.80, 1.46]
Rusanen 2014	0.9594	0.4646	1.2%	2.61 [1.05, 6.49]
Singh-Manoux 2017	0.6259	0.1587	5.5%	1.87 [1.37, 2.55]
Total (95% CI)			100.0%	1.32 [1.19, 1.47]

Heterogeneity: Tau² = 0.03; Chi² = 220.24, df = 14 (P < 0.00001); I² = 94%
Test for overall effect: Z = 5.33 (P < 0.00001)

Figure 4 Sensitivity analysis. Forest plot demonstrating pooled adjusted hazard ratio including only prospective studies. Afib, atrial fibrillation; CI, confidence interval.

anticoagulation status (and type) in our analysis. Similarly, prior studies have shown that higher CHADS2 and CHA2DS2-VASc scores are associated with dementia risk in AF patients.[37, 45] The amount of time that patients spent in AF vs sinus rhythm and the overall left ventricular function are likely associated with the risk for cognitive decline, given the increased risk for thromboembolic events and the decreased cardiac output.[59]

Our findings are in agreement with most of the previous studies. A recent study demonstrated an independent association between AF and cognitive impairment but included only patients with previous history of stroke, which is per se a known risk factor for cognitive decline.[60] Whether AF is independently associated with cognitive impairment and dementia in the absence of known cerebrovascular accident history had remained an unanswered question for many years, with several studies reporting conflicting results.[38,] This important question was not addressed by a recently published meta-analysis by Islam et al., since a subgroup analysis including only studies with stroke-free patients was not performed.[61] Seven years ago, a large meta-analysis published in 2013 demonstrated that patients with AF had approximately 40% higher risk to develop cognitive impairment regardless of the presence of history of clinical stroke or not.[62] Contrary to our meta-analysis, the impact of clinically important moderator variables (e.g., age, hypertension, diabetes) on study effect measure was not explored. Since then, several population-based studies have been published. A recent study by Kim et al., which was included in our meta-analysis, was performed on a population-based cohort with more than 10,000 participants and showed that incident AF increased the risk of dementia (HR, 1.52; 95% CI, 1.43 to 1.63). The results remained significant after censoring for stroke (HR, 1.27; 95% CI, 1.18 to 1.37).[11] Our work expands previous knowledge by exploring the independent association between AF

and cognitive decline in a much larger patient population (more than 3.5 million patients) of whom the vast majority had no prior history of clinical stroke. Another intriguing finding of our meta-analysis was that AF was independently associated with an increased risk of AD, supporting the hypothesis that there may be a causality link between vascular disease risk factors and AD.[63]

The underlying mechanisms that could explain an association between AF and cognitive impairment independent of clinical stroke have not been elucidated, but the leading hypothesis is that chronic AF may lead to silent strokes that gradually deteriorate brain function.[64] Apart from cardioembolic events, AF may lead to cerebral hypoperfusion due to the irregular rhythm and subsequent decrease in cardiac output predisposing to silent strokes and cognitive decline.[,64] Despite the fact that the data on the association of AF with cognitive dysfunction are observational, and thus causality cannot be established, it is tempting to hypothesize that the prevention and aggressive treatment of these pathogenic mechanisms may be beneficial for AF patients. Interestingly, in a randomized trial, patients with restored sinus rhythm after AF ablation had significantly lower rates of dementia, compared to those who remained in AF.[65] Additionally, a previous study by Cacciatore et al. demonstrated that both low (< 50 beats per minute) and fast (> 90 beats per minute) ventricular rate responses were significant predictors of dementia in patients with AF.[32] Taking these lines of evidence together, a reasonable strategy for patients with AF would be to aim at maintaining heart rate within normal range in order to reduce the risk for cognitive impairment. Prospective randomized controlled clinical trials are needed to clarify whether aiming for lower heart rates than those currently

recommended by guidelines (< 110 beats per minute), or even converting to sinus rhythm, may provide incremental benefit to patients at higher risk for cognitive impairment (i.e., stroke patients).[66]

The effect of anticoagulation on cognition in patients with AF is equivocal. A meta-analysis of three observational studies showed that the incidence rates of dementia were not different in the group treated with anticoagulants (pooled OR, 0.89; 95% CI, 0.47 to 1.69).[67] In contrast, a recent large study by Kim et al. showed that AF patients taking oral anticoagulants had lower risk for dementia, compared to the no-anticoagulation group (HR, 0.61; 95% CI, 0.54 to 0.68).[11] Another important finding of this study was that the risk for dementia gradually increased with rising CHA_2DS_2-VASc score (HR, 1.11; 95% CI, 1.07 to 1.14; for each 1-point increment of the score). This finding suggests that patients with higher scores should be closely monitored for signs of cognitive decline. Whether high CHA_2DS_2-VASc scores can guide initiation of anticoagulation without a diagnosis of AF is a hypothesis that should be further investigated in the future.

STRENGTHS AND LIMITATIONS

This is the largest meta-analysis to date on this topic, and the only study with detailed subgroup analyses across the whole spectrum of cognitive impairment and dementia subtypes. By following the most rigorous guidelines for data extraction and analysis, the results of this analysis may be considered as statistically robust. However, our study has also a number of limitations. First, this was a meta-analysis of population-based cross-sectional and cohort-based/case control studies and thus should be interpreted within the context of observational research and its inherent limitations (e.g., some studies included a small percentage of patients with stroke history). Second, some of the studies were not designed to study the impact of AF on dementia and cognitive impairment and this might have led to less than rigorous ascertainment of dementia diagnosis and cognitive impairment or in their reporting in the original investigations. Third, ascertainment for AF, cognitive impairment, and dementia relied on widely different methods and definitions across studies. Fourth, the adjusted effect measures used in our meta-analysis were adjusted for different covariates across the original studies. Fifth, many of the analyses were limited by high degrees of heterogeneity which we tried to address by using a random-effects model, analyzing separately unadjusted and adjusted OR/HR, and performing multiple subgroup, sensitivity, and meta-regression analyses. In the stroke-free sub-analysis, where a high degree of heterogeneity was reported, a meta-regression analysis was limited by the fact that most of the included studies

did not provide sufficient data for this patient population. Finally, despite the meticulous search of the existing literature by two independent reviewers, a reference librarian was not involved in the study selection process.

CONCLUSION

Our findings suggest that AF may be associated with an increased risk of both cognitive impairment and dementia in a broad population including mainly stroke-free patients and studies with very low rates of stroke. Physicians should be particularly alert to identify early clinical manifestations of cognitive decline in this patient population. If such symptoms are present, an interdisciplinary approach (heart-stroke team with cardiologists, neurologists, and geriatricians) may be required to effectively manage and treat these patients. Future studies should explore the effect of interventions that may delay or even prevent cognitive decline in AF patients.

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Declarations:

Conflict of Interest: The authors declare that they do not have a conflict of interest.

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