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SYSTEMATIC REVIEW AND META-ANALYSIS

Atrial Fibrillation and the Risk of Early-Onset Dementia: A Systematic Review and Meta-Analysis

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BACKGROUND: Recent studies have identified an increased risk of dementia in patients with atrial fibrillation (AF). However, both AF and dementia usually manifest late in life. Few studies have investigated this association in adults with early-onset dementia. The aim of this study was to investigate the relationship between AF and early-onset dementia.

METHODS AND RESULTS: We searched the PubMed/MEDLINE, Embase, and Scopus databases through April 15, 2022, for studies reporting on the association between AF and dementia in adults aged <70 years, without language restrictions. Two reviewers independently performed the study selection, assessed the risk of bias, and extracted the study data. We performed a meta-analysis of early-onset dementia risk according to occurrence of AF using a random-effects model. We retrieved and screened 1006 potentially eligible studies. We examined the full text of 33 studies and selected the 6 studies that met our inclusion criteria. The pooled analysis of their results showed an increased risk of developing dementia in individuals with AF, with a summary relative risk of 1.50 (95% CI, 1.00–2.26) in patients aged <70 years, and 1.06 (95% CI, 0.55–2.06) in those aged <65 years.

CONCLUSIONS: In this systematic review and meta-analysis, AF was a risk factor for dementia in adults aged <70 years, with an indication of a slight and statistically imprecise excess risk already at ages <65 years. Further research is needed to assess which characteristics of the arrhythmia and which mechanisms play a role in this relationship.

Key Words: Alzheimer dementia ■ atrial arrhythmia ■ atrial fibrillation ■ dementia ■ frontotemporal dementia

Atrial fibrillation (AF) is the most common clinically important cardiac arrhythmia worldwide. It is characterized by a rapid and irregular excitation of the atria, which occurs when a chaotic pattern of electrical activity replaces the normal sinus mechanism. AF is associated with increased mortality and morbidities, including a 5-fold increase in the risk for stroke, and it is a major cause of health care costs.[1,2] The prevalence of AF in the general population of Western countries tends to be between 1% and 2%. Age is the most important risk factor for AF, with a sharp increase in prevalence after the age of 65 years. Because of increased survival and progressive aging, models predict almost 18 million adults in Europe and 12 million adults in the United States will have dementia by 2050 to 2060.[3–5] Age and sex are major predictors of incident AF, but other important risk factors include hypertension, valvular heart disease, systolic dysfunction, obesity, and alcohol consumption.[1,6]

The term early-onset dementia (EOD) indicates dementia with symptom onset at a younger than usual age, usually arbitrarily set at 65 years but less frequently at 70 years or other age cut points. With a prevalence of ≈67 to 98 per 100 000, Alzheimer disease is the most frequent form of dementia, followed by frontotemporal dementia.[7,8] EOD attributable to Alzheimer disease

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CLINICAL PERSPECTIVE

What Is New?

- This article provides the first systematic review and meta-analysis that details the association between atrial fibrillation and the risk of dementia in adults aged <70 years.
- The data identify an increased risk of dementia in adults with atrial fibrillation, especially in those aged 60 to 69 years, although the risk is not as pronounced as that which has been identified in adults aged ≥70 years.

What Are the Clinical Implications?

- A timely diagnosis of atrial fibrillation and appropriate therapy may be warranted, even in adults who are aged <70 years.

Nonstandard Abbreviations and Acronyms

EOD	early-onset dementia

accounts for about 4% to 6% of all Alzheimer disease, with an annual incidence rate of ≈6 per 100 000 and a prevalence rate of about 24 per 100 000 people.[7,8] Alcohol consumption, cigarette smoking, traumatic brain injuries, cardiovascular and metabolic diseases, genetic susceptibility, neurotoxic agent exposure, like heavy metals and selenium, pesticides, and solvents are some of the factors involved in an increased risk of EOD, but the exact mechanisms of its pathophysiology are still uncertain. [9–12]

In a 1997 report from the Netherlands, an association was noted between AF and dementia risk,[13] and since then the association has been identified in many studies.[14–20] However, this association has been established for the overall risk of dementia and of dementia in elderly people, but limited evidence exists for the association between AF and EOD, and no systematic review and meta-analysis has been performed on this potential relationship.[21–23]

We performed a systematic review and meta-analysis on the association between AF and EOD, using an upper age cut point for symptom onset of 70 years given the low number of studies available on this topic.

METHODS

In performing this systematic review and meta-analysis, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 statement.[24] The Preferred Reporting Items for Systematic Reviews and Meta-Analysis checklist is reported in Data S1. We declare that this study review did not directly involve human subjects; thus, no informed consent was required. Finally, we declare that all supporting data are available within the article and its online supplementary files.

Study Identification

We conducted a systematic search in the PubMed/MEDLINE, Scopus, and Embase databases with no time restrictions up to April 15, 2022, using the following keywords: "atrial fibrillation," "heart atrium arrhythmia," "dementia," "amentia," "Alzheimer's dementia," and "frontotemporal dementia." Two authors (M.E.G. and T.F.) independently evaluated the retrieved studies to check eligibility for inclusion in our analysis. In case of disagreement, a third author (M.V.) was consulted to resolve conflicts. We made no preliminarily restrictions on language, on study design, and on diagnosis of AF and dementia. Our search was restricted to original research studies that had investigated the association between AF and dementia in adults aged <70 years, and excluded reviews, letters, commentaries, studies without a group control not affected by AF, studies with an outcome other than dementia or with an exposure other than AF, and studies that did not provide data stratified by age if the study population encompassed also individuals aged >70 years. Table S1 reports additional details of the search.

Risk of Bias

We assessed the quality of the selected studies using the Risk of Bias for Nonrandomized Studies of Exposure tool.[25] Table S2 reports the criteria for risk of bias evaluation. In this assessment, we considered 7 domains as having low, moderate, or high risk of bias: (1) bias attributable to confounding; (2) bias in selecting participants; (3) bias in exposure classification; (4) bias attributable to departures from intended exposures; (5) bias attributable to missing data; (6) bias in outcome measurement; and (7) bias in selection of reported results. The overall risk of bias was considered high or moderate if at least one domain was judged at high or moderate risk; otherwise, it was classified as having a low risk of bias.

Data Extraction and Statistical Analysis

We extracted the following data from the included studies: (1) first author name, (2) publication year, (3) location, (4) exposure assessment, (5) outcome, (6) overall population and number of cases, (7) mean age, (8) age cutoff, (9) length of follow-up, (10) risk ratio (RR)

estimates with 95% CIs, and (11) adjustment factors. When >1 statistical model was available, we extracted the most adjusted estimates. When 95% CIs were not reported, we used *P* values to calculate them, according to established methods.[26]

We performed a meta-analysis of EOD risk according to AF occurrence using a random-effects model. We assessed the heterogeneity of the included studies using the I^2 statistic, considering the 25%, 50%, and 75% cut points to classify the set of studies as having low, moderate, and high inconsistency.[27] Because of the high heterogeneity, we used the random-effects model, as proposed by Paule and Mandel, for meta-analysis of dichotomous data.[28] We also explored the heterogeneity within stratified analyses whenever possible by cut point of EOD diagnosis, censoring for vascular dementia, and certainty of EOD diagnosis. Finally, we assessed the occurrence of small-study effects using visual inspection of funnel plots along with computation of the Egger regression asymmetry test for publication bias. We used "meta" routine of Stata 17.0 software (StataCorp, College Station, TX; 2021) for all statistical analysis.

RESULTS

The process of study selection is shown in Figure 1. Following duplicate removal, our preliminary literature search identified 1006 potentially eligible studies. After screening the title and abstract, we excluded 973 studies. We then retrieved the full text of the remaining 33 studies. Of these studies, 27 were excluded because they did not meet the inclusion criteria (15 did not provide data stratified by age, 2 investigated a population aged >70 years, and 10 analyzed outcomes or exposures other than AF and EOD). Six studies were therefore left for analysis, all characterized by a cohort design, published between 2015 and 2021. The Table describes the main characteristics of these studies.[21,22,29–32] Overall, they encompassed ≈1.6 million participants with a mean age at recruitment ranging from 42 to 85 years, with a dementia outcome in 3647 adults in the studies that studied those aged <70 years. Duration of follow-up ranged from 1 month to 8 years. The study outcome was incidence of dementia in participants with no history of AF and in those who had a previous history of AF or an AF

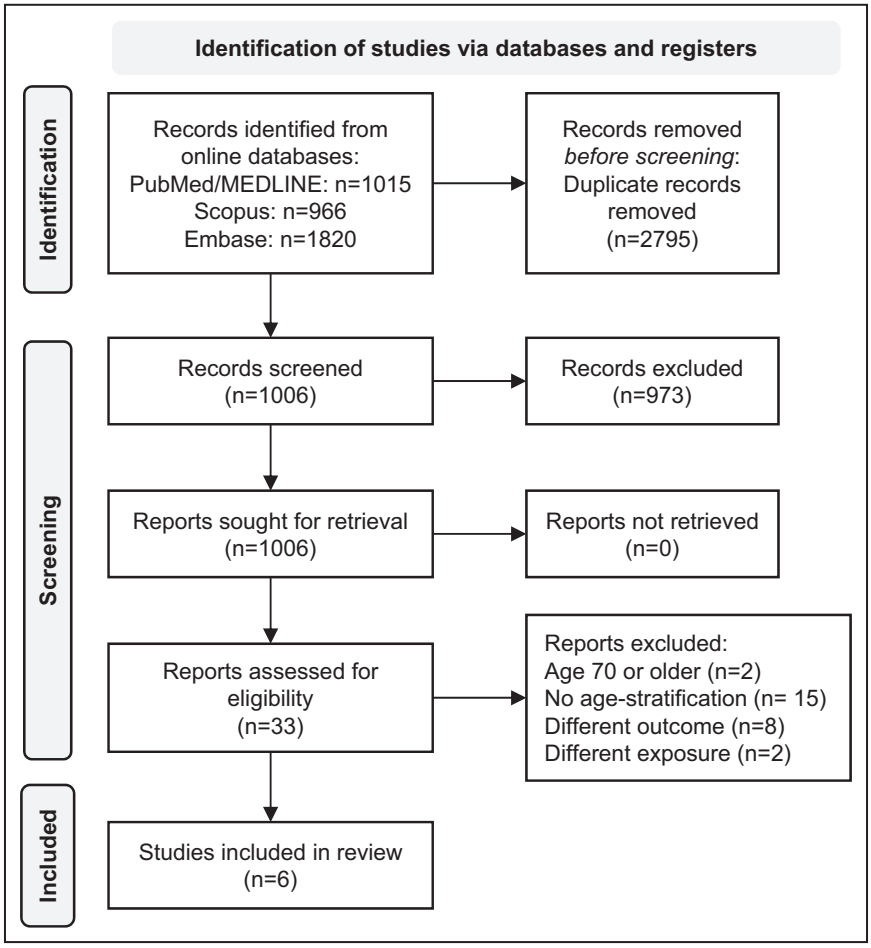

Figure 1. Flowchart of the literature search and study identification.

Table. Characteristics of Included Studies

Reference	Country	Period	Design	Total population (men/women)	Cases (men/women)	Outcome	Early-onset dementia cutoff, y	Age, mean±SD, y
Bunch et al 2010[21]	United States	Not reported	Cohort	37 025 (10 161 incident AF)	1535 cases of dementia (all ages); dementia for those aged <70 y not reported	Incidence of dementia	<70	60.6±17.9 (57.8±18.9 AF free; 68.1±12.2 AF)
Chen et al 2021[29]	Taiwan	Jan 2001–Dec 2013	Case-cohort AF and AF free	200 130 (100 065/ 100 065)	1897 (919/978)	Incidence of dementia (overall and for AD and VaD)	<65	72.5±12.5
de Bruijn et al 2015[22]	The Netherlands	Sept 2014–Apr 2015	Cohort	6194	932 cases of dementia (all ages); dementia for those aged <70 y not reported	Incidence of dementia	<67	68.3
Kim et al 2019[30]	South Korea	2005–2012	Cohort	262 611 (10 435 incident AF)	638	Incidence of dementia	<70	70.7±5.4 (AF); 71.7±5.7 (AF free)
Kim et al 2020[31]	South Korea	2005–2010	Cohort	428 262 (232 513/ 195 749)	1112 (955 censoring for stroke)	Incidence of AF and dementia	<65	61.7±9.9 (AF) 55.5±9.1 (AF free)
Liao et al 2015[32]	Taiwan	Jan 1996–Dec 2011	Case-cohort AF and AF free	665 330 (372 000/ 293 330)	56 901 cases of dementia (all ages); dementia for those aged <70 y not reported	Incidence of dementia	<65	70.3±13.0 (AF and AF free)

AD indicates Alzheimer dementia; AF, atrial fibrillation; and VaD, vascular dementia.

diagnosis at baseline. Three of these studies reported both the incidence of overall dementia at all ages and of EOD.[29–31] Diagnosis of AF was mainly identified by hospital discharge or admission records, or following such a diagnosis, confirmed on at least 2 occasions in an outpatient clinic (see Table S3 for detailed

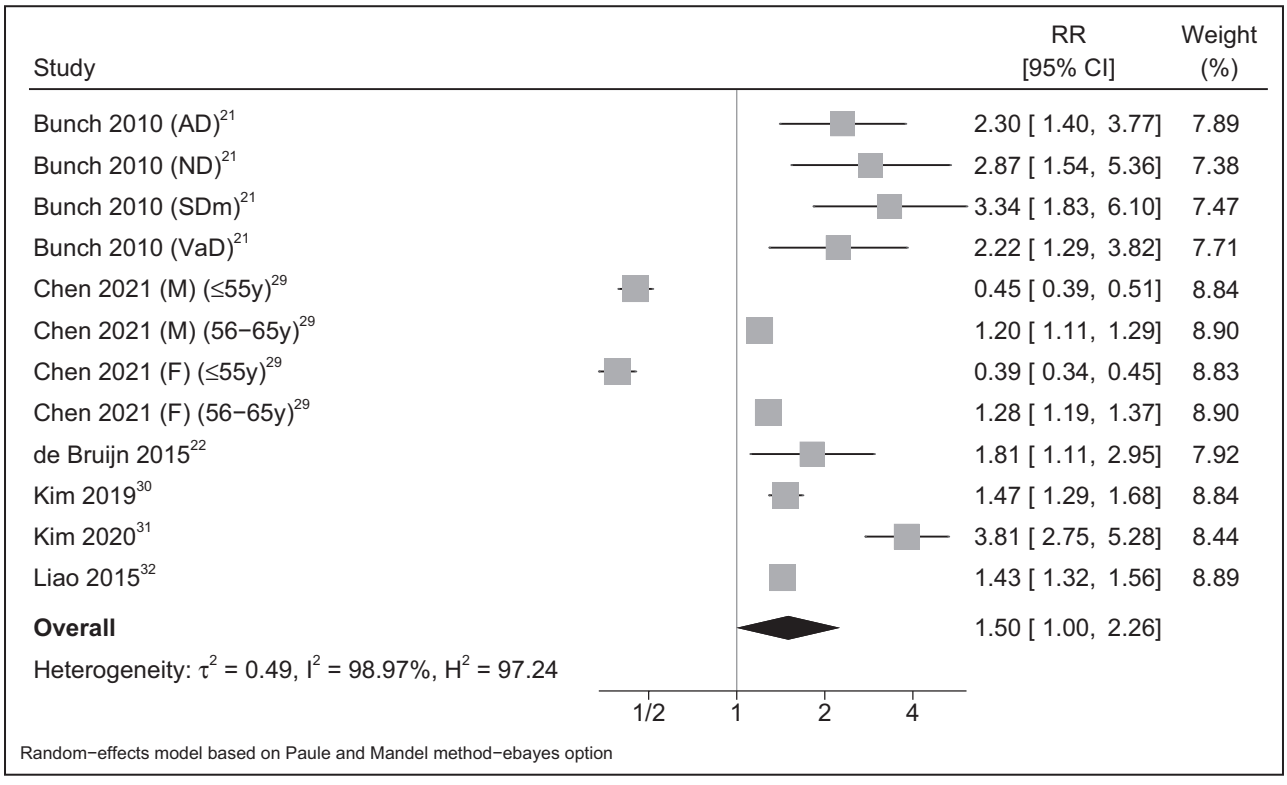

Figure 2. Forest plot for risk of early-onset (aged <70 years) dementia in association to atrial fibrillation in all studies.
AD indicates Alzheimer dementia; F, female; M, male; ND, nonspecified dementia; RR, risk ratio; SDm, senile dementia; and VaD, vascular dementia.

information). The studies differ in their assessment of dementia. Dementia diagnosis was identified through medical records, prescriptions of disease-specific medications (eg, donepezil and rivastigmine), clinical neuroimaging, hospital discharge records, diagnosis confirmation at least twice in outpatient clinic, and use of neuropsychological/cognitive tests. Concerning the 2 latter approaches to diagnosis, the Mini-Mental State Examination and the Geriatric Mental State Schedule were used. One study[29] confirmed the diagnosis of Alzheimer dementia through the combination of clinical diagnosis and documented use of Alzheimer disease medication, and that of vascular dementia through clinical neuroimaging (ie, positron emission tomography/single-photon emission computed tomography) (Table S3).

Assessment of AF as a risk factor for dementia was performed for those with different forms of dementia (ie, Alzheimer dementia, vascular dementia, senile dementia, or nonspecific dementia).[21,22,29–32] Results still showed an association of AF with incidence of dementia in study participants without a history of stroke, compared with the entire study population. Almost all of the studies exhibited a moderate risk of bias (Table S4), mainly because of a lack of adjustment for educational attainment (confounding domain). One study, however, was characterized by a low risk of bias.[22]

The meta-analysis of the results of these studies showed an increased EOD risk associated with presence of AF (summary RR, 1.50 [95% CI, 1.00–2.26]; Figure 2).[21,22,29-32] When we restricted the analysis using stroke-censored results or excluding vascular dementia, we found a similarly increased AF-related risk of EOD (summary RR, 1.38 [95% CI, 0.91–2.11]; Figure 3).[21,22,29-32] The only study with a low overall risk of bias reported an RR of EOD (defined as symptom onset at age <67 years) in individuals with a diagnosis of AF (RR, 1.81 [95% CI, 1.11–2.95]).[22]

In age-stratified analyses, we identified larger RRs with increasing age ranges (age group <65 years: summary RR, 1.06 [95% CI, 0.54–2.06[29,31,32]]; age group <67 years: summary RR, 1.81 [95% CI, 1.11–2.95[22]]; age group <70 years: summary RR, 2.13 [95% CI, 1.58–2.87[21,30]]) (Figure 4). However, one of the included studies that assessed the risk of dementia in younger adults affected by AF (≤55 years) yielded markedly different results in this specific age group (≤55 years group: RR, 0.45 [95% CI, 0.39–0.51] in men and RR, 0.39 [95% CI, 0.34–0.45] in women; 56–65 years group: RR, 1.20 [95% CI, 1.11–1.29] in men and RR, 1.28 [95% CI, 1.19–1.37] in women).[29] This latter study was also characterized by a wide range of follow-up (1 month–8 years), with the duration in those with the least follow-up being too short to allow a reliable assessment of the association between AF and incident dementia. A sensitivity analysis in which this study was excluded still identified an increased risk of dementia (summary RR, 2.16 [95% CI, 1.63–2.88]; Figure S1).[21,22,30–32] A sensitivity analysis

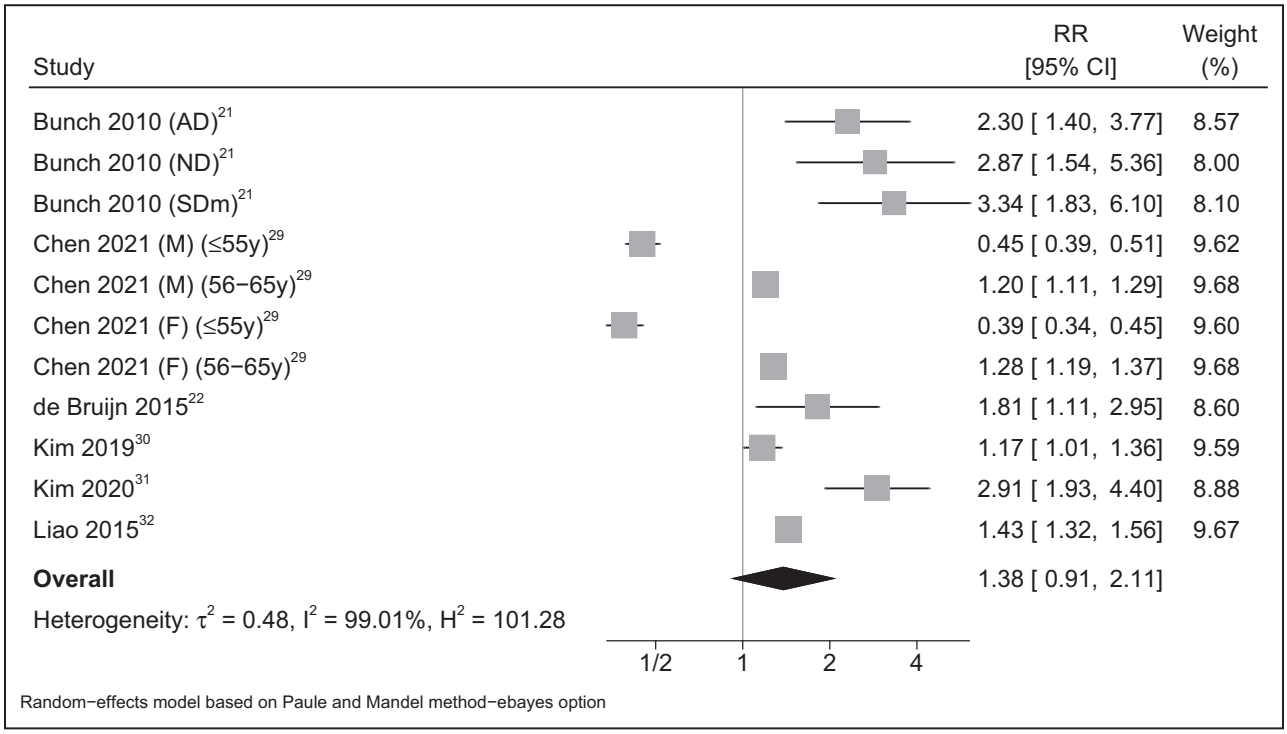

Figure 3. Forest plot for the risk of early-onset (aged <70 years) dementia in association with atrial fibrillation in studies using stroke-censored data or excluding vascular dementia (VaD).
AD indicates Alzheimer dementia; F, female; M, male; ND, nonspecified dementia; RR, risk ratio; and SDm, senile dementia.

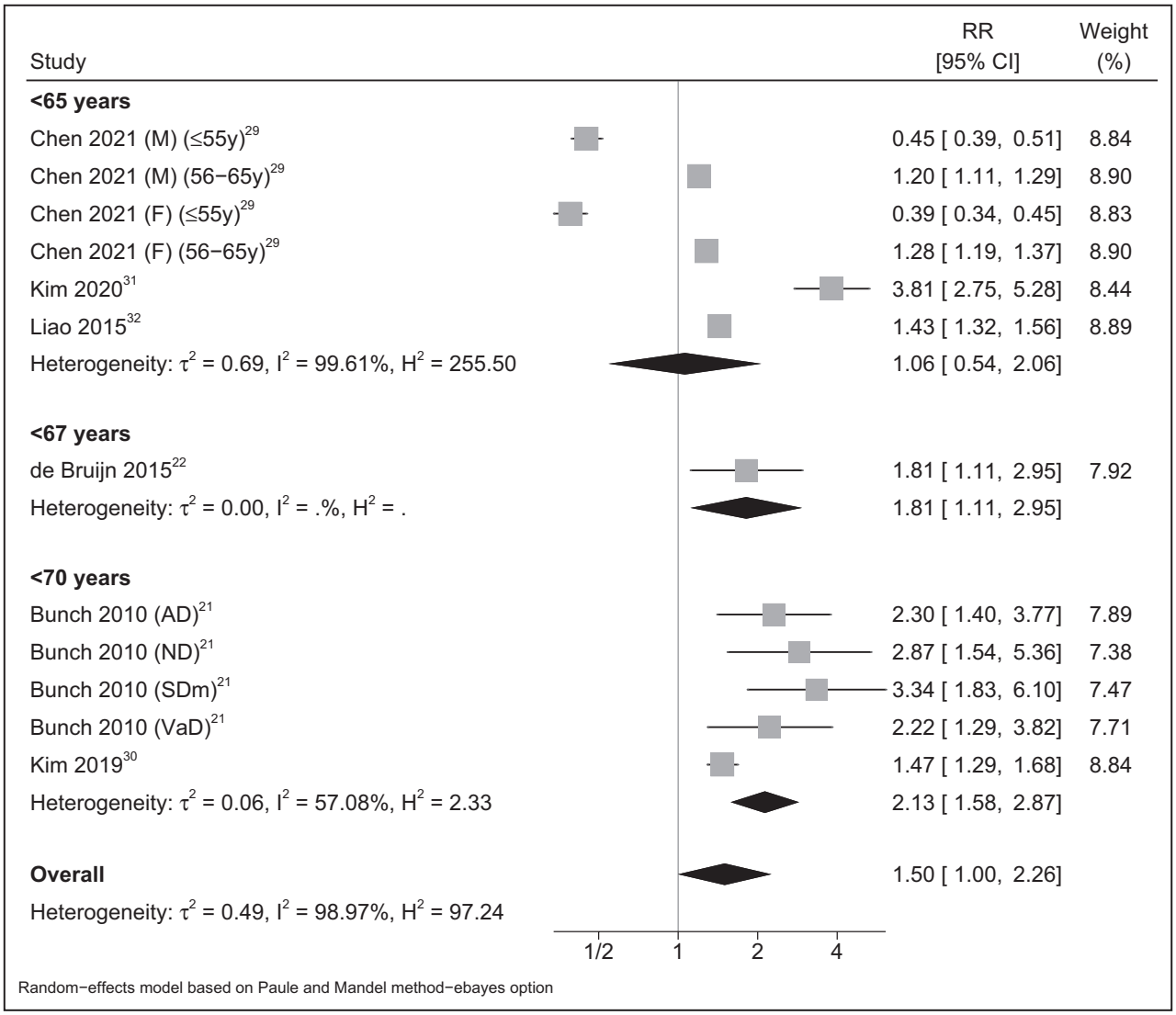

Figure 4. Forest plot for risk of early-onset dementia associated with atrial fibrillation, according to age categories of the populations studied.
AD indicates Alzheimer dementia; F, female; M, male; ND, nonspecified dementia; RR, risk ratio; SDm, senile dementia; and VaD, vascular dementia.

confined to those in whom there was certainty of an EOD diagnosis (dementia onset before 65 years) also identified an increased risk of dementia (summary RR, 1.14 [95% CI, 0.64–2.05]), although the estimate was imprecise (Figure S2).[21,22,29–32]

Funnel plot analysis for small-study bias showed an asymmetric distribution in line with results using the Egger test, yielding an indication of presence of small-study effect (4.21 [95% CI, 1.18–7.25]; Figure 5).[21,22,29–32]

DISCUSSION

To the best of our knowledge, this systematic review and meta-analysis is the first to assess the relationship between AF and dementia in studies of adults aged <70 years. It provides evidence that adults with AF experience an increase in the risk of developing dementia before the age of 65 to 70 years. Our findings are consistent with the overall association between AF and dementia risk.[17–19] The biological mechanisms underpinning an excess EOD risk in adults with AF are unclear. Cerebral hypoperfusion and altered cerebral blood flow inducing brain atrophy could play a role, as could a decrease in cardiac output in patients with AF, secondarily to the loss of atrial systole and atrioventricular synchrony.[33–36] A low or high ventricular rate response, leading to an important reduction or marked variability in cardiac output, could play a role in the development of dementia in individuals affected by AF.[37,38] Another potential mechanism could be

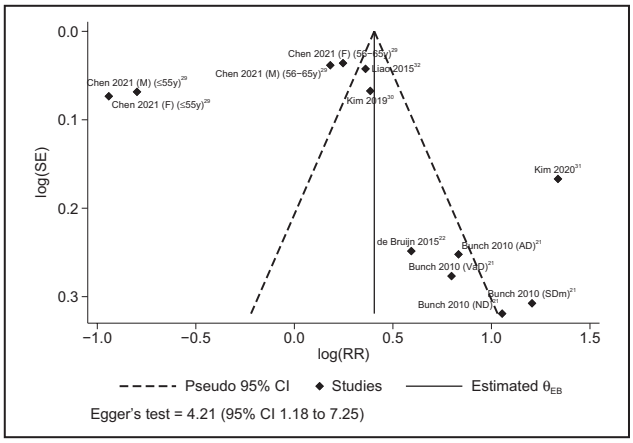

Figure 5. Funnel plot for publication bias and small-study effects.
AD indicates Alzheimer dementia; F, female; M, male; ND, nonspecified dementia; RR, risk ratio; SDm, senile dementia; and VaD, vascular dementia.

vascular inflammation, leading to damage of the blood-brain barrier and adversely affecting the brain.[39] Both the hemodynamic alterations and the vascular inflammation could favor amyloid beta-protein accumulation and the phosphorylation of tau protein in patients with Alzheimer dementia.[39–41] In addition, blood stasis in the atrium may lead to development of thrombi and consequently increase the risk of strokes and silent cerebral infarct.[42] Last, genetic factors, such as the AF-related gene *PITX2*, whose expression results in both structural and electrical remodeling of the atrium, may be associated with an increased risk of ischemic cerebral events and resulting dementia.[43–46]

A causal link between AF and dementia in all age groups is also supported by findings of studies that have investigated the effect of AF therapy in dementia prevention. In particular, an association between oral anticoagulants and a reduced risk of dementia and cognitive impairment in patients with AF has been suggested.[47–50] In addition, the capacity of rhythm-control therapy by means of catheter ablation to reduce the risk of dementia has recently been suggested, further supporting a causal link between AF and dementia onset.[51,52] In young adults (aged ≤55 years), AF does not seem to correlate positively with dementia, as a decreased risk was reported.[29] This negative association could be attributable to the low AF and dementia incidence before 55 years,[53] or by better adherence to anticoagulant therapy with a relatively low number of comorbid conditions in younger compared with older adults.[54,55] As a consequence, we observed a stronger association between AF and dementia after removing the study with young participants from our analysis (summary RR, 2.16 [95% CI, 1.63–2.88]).

Our systematic review and meta-analysis had several limitations. Because the number of studies available for analysis was limited, we could not conduct subgroup analyses that stratified for geographical area. Interestingly, the quality of the included studies, although generally belonging to the intermediate category (ie, showing a moderate risk of bias), did not appear to influence the results of our meta-analysis. In fact, our summary estimate for the RR of developing dementia was similar to the RR reported in the only study with a low risk of bias (RR, 1.81 [95% CI, 1.11–2.95]).[22]

Our results were generally affected by high heterogeneity. For this reason, we used a random-effects model that can be considered more robust when implementing meta-analysis of dichotomous data.[28] We also explored possible sources of heterogeneity in several stratified and sensitivity analyses. We noted a somewhat diminished heterogeneity in the stratified analysis by age of study participants, as well as in our sensitivity analysis in which the study with younger participants was excluded.[29] The remaining heterogeneity may have resulted from various reasons, including the different methods used for dementia assessment (ie, drug prescription, medical records, Mini-Mental State Examination, or Geriatric Mental State Schedule) and the different covariates that were considered in the multivariable analyses, although we systematically used the most adjusted estimates in our meta-analysis. Unfortunately, the limited number of studies hampered the implementation of stratified analyses for some of the previously mentioned sources of heterogeneity. In addition, our findings could have been partially affected by the moderate to substantial small-study effect, with some potential for publication bias that suggests caution in evaluating our results. We were also unable to assess whether AF type (paroxysmal, persistent, or permanent) and duration may contribute differently to the risk of developing dementia, because none of the available studies reported such details, and the role of comorbidities could not be investigated in detail. Last, the lack of information on concurrent treatments, and specifically anticoagulant therapy following the occurrence of AF, did not allow us to assess the effects of the specific pharmacological therapy for AF on EOD risk.

ARTICLE INFORMATION

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Disclosures

G.B. received small speaker's fees from Boston and Daiichi-Sankyo outside of the submitted work.

Supplemental Material

Data S1

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SUPPLEMENTAL MATERIAL

Data S1.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	P1,P3,P6
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	See below
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P5-6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Table S1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P6-7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	P7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	P6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	P7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	P7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	P7-8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	P7-8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	P8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	P6-7, Table S2
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not assessed

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	P8-9, Tables 1 and S3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table S4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figures 2-4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	P8-9, Table S4
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	P9-10, Figure 2-5
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	P9-10
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	P9-10, Fig.3-4
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Table S4
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P10-11
	23b	Discuss any limitations of the evidence included in the review.	P11-12
	23c	Discuss any limitations of the review processes used.	P12
	23d	Discuss implications of the results for practice, policy, and future research.	P12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Not available
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P13
Competing interests	26	Declare any competing interests of review authors.	P13
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	P6, P8

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	no
Synthesis of results	6	Specify the methods used to present and synthesise results.	yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	yes
Interpretation	10	Provide a general interpretation of the results and important implications.	yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	no
Registration	12	Provide the register name and registration number.	no

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Table S1. Literature search on online databases.

Database	Search
Pubmed	('Atrial fibrillation [Mesh] OR 'heart atrium arrhythmia' OR 'arrhythmia, atrial' OR 'atrial arrhythmia' OR 'atrium arrhythmia' OR 'heart atrial arrhythmia' OR 'heart atrium arrhythmia' OR 'atrial fibrillation' OR 'atrial fibrillation' OR 'atrium fibrillation' OR 'auricular fibrillation' OR 'auricular fibrillation' OR 'cardiac atrial fibrillation' OR 'cardiac atrium fibrillation' OR 'fibrillation, heart atrium' OR 'heart atrial fibrillation' OR 'heart atrium fibrillation' OR 'heart fibrillation atrium' OR 'non-valvular atrial fibrillation' OR 'nonvalvular atrial fibrillation') AND ('dementia' [Mesh] OR 'dementia' OR 'amentia' OR 'dementia' OR 'demention' OR 'Alzheimer' OR 'frontotemporal dementia')
Scopus	'Atrial fibrillation' AND (dementia OR 'Alzheimer Disease' OR 'frontotemporal dementia')
Embase	('heart atrium arrhythmia'/mj OR 'arrhythmia, atrial' OR 'atrial arrhythmia' OR 'atrium arrhythmia' OR 'heart atrial arrhythmia' OR 'heart atrium arrhythmia' OR 'atrial fibrillation'/mj OR 'atrial fibrillation' OR 'atrium fibrillation' OR 'auricular fibrillation' OR 'auricular fibrillation' OR 'cardiac atrial fibrillation' OR 'cardiac atrium fibrillation' OR 'fibrillation, heart atrium' OR 'heart atrial fibrillation' OR 'heart atrium fibrillation' OR 'heart fibrillation atrium' OR 'non-valvular atrial fibrillation' OR 'nonvalvular atrial fibrillation') AND ('dementia'/mj OR 'amentia' OR 'dementia' OR 'demention')

Table S2. Criteria adopted for risk of bias assessment using Risk of Bias for in Non-randomized Studies of Exposures (ROBINS-E) tool.

Domains	Criteria
Bias due to confounding	Studies are considered at **moderate** risk of bias if they considered age in the confounding factors. Studies are considered at **low** risk of bias if they considered the educational attainment in the adjustment factors. Studies are considered at **high** risk of bias if adjusting factors are not reported.
Bias in selecting participants in the study	Studies are considered at **low** risk of bias if selection of eligible dementia cases was independent of the diagnosis of atrial fibrillation. Studies are considered at **moderate** risk of bias if selection of cases from a population at higher risk of dementia (e.g. mild cognitive impairment. Studies are considered at **high** risk of bias if the modality of selection of participants is not specified.
Bias in exposure classification	Studies are considered at **low** risk of bias if the assessment of atrial fibrillation was through electrocardiography (ECGs) at baseline and at each follow-up examination or through medical records, with a discharge diagnosis or at least confirmed twice. Studies are considered at **moderate** risk of bias if exposure assessment was performed relying on self-reports, but afterwards the exposure was confirmed through medical records. Studies are considered at **high** risk of bias if they relied only on self-report for exposure classification or criteria are not reported.
Bias in departure from intended exposure	This domain should not of concerns since the exposure is presence of atrial fibrillation, thus departure from the intended exposure is not an issue. As consequence, all studies are considered at low risk of bias for this domain.
Bias due to missing data	Studies are considered at **low** risk of bias if less than 10% of participants were excluded to missing data, while at **moderate** risk of bias if less than 20%. Studies with higher proportion (≥20%) are considered at **high** risk of bias.
Bias in outcome measurement	Studies are considered at **low** risk of bias if outcome assessment was based on a discharged diagnosis or at least on two consecutive diagnoses in outpatient clinic consultation. Studies are considered at **moderate** risk of bias if outcome assessment was based on the use of the Mini-Mental State Examination or the Geriatric Mental State Schedule, while they are still considered at low risk if this first diagnosis was confirmed with a subsequent clinical analysis. Studies are considered at **high** risk of bias if outcome assessment was based on self-report only without external validation or if information about outcome assessment was missing.
Bias in selection of reported results	Studies are considered at **low** risk of bias if they reported a prior publication of the protocol or data are made available in a public and accessible repository. Studies are considered at **moderate** risk of bias if they presented outcome measures and analyses consistent with a priori plan outlined in the manuscript. Studies are considered at **high** risk of bias if no protocol was available and the a priori plan was not outlined
Overall risk of bias	If at least one domain was found at **high** risk of bias, the overall risk was considered **high**. If at least one domain was found at **moderate** risk of bias, the overall risk was considered **moderate**. If all domains were at **low** risk of bias, the overall risk was considered **low**.

Table S3. Additional characteristics of the included studies.

Reference	Databases	Assessment of AF and dementia	Follow-up duration	Exclusion criteria	Types of dementia	Outcomes	Main findings	Adjustments
Bunch et al. 2010[21]	Database Registry of the Intermountain Heart Collaborative Study	(ICD-9); AF: hospital discharge or admission for AF or electrocardiographic database of all Intermountain Healthcare hospitals. Dementia: medical records (ICD9)	5 y	incomplete medical information about dementia screening or follow-up on dementia diagnosis; prevalent dementia;	VaD, Senile, Alzheimer's and non-specific dementia	incidence of dementia	AF independently associated with all types of dementia and the highest risk of AD was in the younger AF group	Age, sex, hypertension, hyperlipidemia, diabetes mellitus, renal failure, smoking, family history, MI, CVA, heart failure, statin, ACE inhibitor, ARB, beta-blockers, diuretic*
Chen et al. 2021[29]	NHIRD released by the Taiwan NHRI	(ICD-9-CM) AF and dementia: discharge diagnosis or more than two consecutive clinic visits; further analysis of AD and VaD with AD medications (i.e., donepezil, rivastigmine, memantine and galantamine) and PET/SPECT imaging	3.5 ± 3.4 y (F) 3.4 ± 3.3 (M) y	patients with incomplete demographic data, age < 20 years, rheumatic heart disease, hyperthyroidism, past valvular heart surgery, and a history of dementia.	Alzheimer's dementia, VaD	incidence of dementia stratified by age and by sex; differences between incidence of AD and VaD	higher incidence in women than in men in all groups older than 55; higher incidence in women than in men only in the age groups between 56-85 if considering only AD	Age, sex, monthly income (USD), urbanization level, hypertension, diabetes mellitus, ischemic heart disease, dyslipidemia, gout, COPD, peripheral arterial disease, renal function status, abnormal liver function, traumatic brain injury, alcohol abuse, systemic thromboembolism (excluding ischemic stroke), myocardial infarction, stroke, heart failure, history of depression or bipolar disorder, use of anticoagulant, antiplatelet, ACEi/ARB, dihydropyridine CCB, don-dihydropyridine CCB, beta-blockers, statins, DPP4 inhibitors, biguanides, sulfonylurea, thiazolidinedione, insulin
de Bruijn et al. 2015[22]	The Rotterdam Study	AF: ECGs and hospital discharges; dementia: MMSE and GMS, subsequent interview with eventually further neuropsychological testing if dementia was suspected and, if necessary, clinical neuroimaging.	Up to 20 y	preexisting AF or dementia	Alzheimer's dementia and overall dementia	incidence of dementia	atrial fibrillation is associated with an increased risk of dementia, independent of clinical stroke; association strongest in the younger	Age, sex, diabetes mellitus, smoking, total cholesterol, high density lipoprotein cholesterol levels, lipid-lowering medication, systolic and diastolic blood pressure, blood pressure-lowering medication, BMI, educational level, ever use of oral anticoagulant medication, coronary heart disease, heart failure, apolipoprotein E ε4 carrier status.

Kim et al. 2019[30]	Korean NHIS-HEALS database	(ICD-10) AF: discharge diagnosis or at least confirmed twice; dementia: ICD-10 with prescription of dementia drugs (rivastigmine, galantamine, memantine, or donepezil)	AF group 96 months, IQR 86-101 months); AF-free group 93 months, IQR 84-100 months)	valvular heart disease, TIA/stroke, hemorrhagic stroke, dementia, prevalent AF	Alzheimer's dementia, VaD	incidence of AF and dementia	after censoring for stroke, the cumulative incidence of dementia was higher in the incident-AF group	Age, sex, hypertension, diabetes mellitus, dyslipidemia, heart failure, previous myocardial infarction, peripheral artery disease, osteoporosis, chronic kidney disease, chronic obstructive pulmonary disease, malignant neoplasm, liver disease, CHA2DS2-VASc score, cardiovascular medications, economic status, alcohol consumption, smoking status, exercise habits, follow-up duration, body mass index, systolic and diastolic blood pressure, blood glucose, total cholesterol, and blood hemoglobin level.
Kim et al. 2020[31]	Korean NHIS-Senior database	(ICD-10) AF and dementia: ICD10 diagnosis confirmed if secondary to a hospital discharge or at least confirmed twice in outpatient department.	AF group 86 months, IQR 62-96 months); AF-free group 85 months, IQR 58-95 months)	valvular heart disease (mitral stenosis or prosthetic heart valves or with insurance claims for valve replacement or valvuloplasty), ischemic stroke or TIA, hemorrhagic stroke, pre-existing dementia or AF	Alzheimer's dementia, VaD	incidence of dementia	higher incidence of dementia in AF participants, independently of stroke	Age, sex, and clinical variables, including hypertension, diabetes mellitus, previous MI, heart failure, peripheral artery disease, dyslipidemia, osteoporosis, CKD, COPD, liver disease, history of malignant neoplasm, economic status, cardiovascular medications (aspirin, P2Y12 inhibitor, statin, anticoagulant, beta-blocker, ACEi or ARB, calcium channel blocker, digoxin, diuretics), body mass index, systolic and diastolic blood pressure (BP), blood glucose level, total cholesterol, and alcohol and smoking habits.
Liao et al. 2015[32]	NHIRD released by the Taiwan NHRI	(ICD-9-CM) AF: discharge diagnosis or at least confirmed twice; dementia: registered by the physicians responsible for the treatment (medical records).	NR	preexisting dementia, age <20 years old	presenile and senile dementia, VaD Alzheimer's dementia	incidence of dementia and usefulness of CHADS2 and CHA2DS2-VASc scores in predicting dementia	the cumulative incidence of dementia was higher in the incident-AF group, even in patients without comorbidities; CHADS2 and CHA2DS2-VASc scores higher in patients with dementia	Age, sex, hypertension, diabetes mellitus, heart failure, vascular diseases, dyslipidemia, CVA, ESRD, COPD, malignancy, autoimmune diseases, the use of aspirin, clopidogrel, warfarin, ACEi/ARB, statin, Charlson index, income level, and systemic diseases

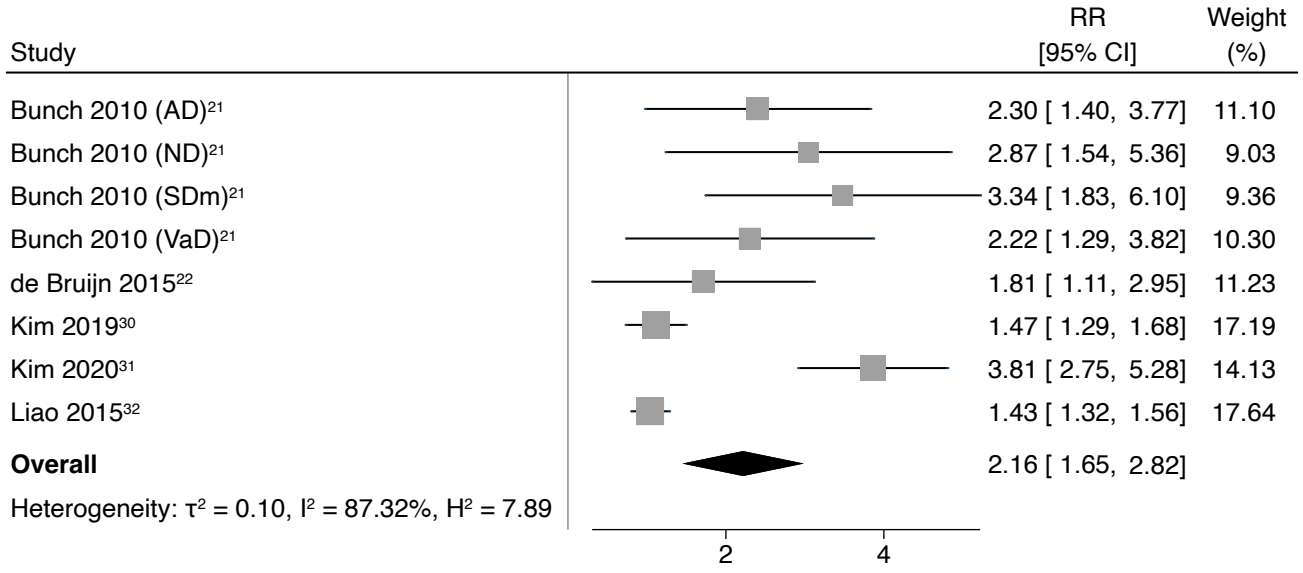
Abbreviations: ACEi: angiotensin-converting enzyme inhibitor; AD: Alzheimer's dementia; AF: atrial fibrillation; ARB: angiotensin II-receptor blocker; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CVA: cerebral vascular accident; CHADS2: Congestive heart failure, Hypertension, Age >75 years, Diabetes mellitus, prior Stroke 2 or transient ischemic attack, or thromboembolism; ESRD: end-stage renal disease; ICD: International Classification of Diseases; MI: myocardial infarction; NHIRD: National Health Insurance Research Database; NHRI: National Health Research Institutes; NR: not reported; TIA: transient ischemic stroke; VaD: vascular dementia.

Note: *data obtained from Table 1 of the original study [20].

Table S4. Risk of bias assessment of the included studies.

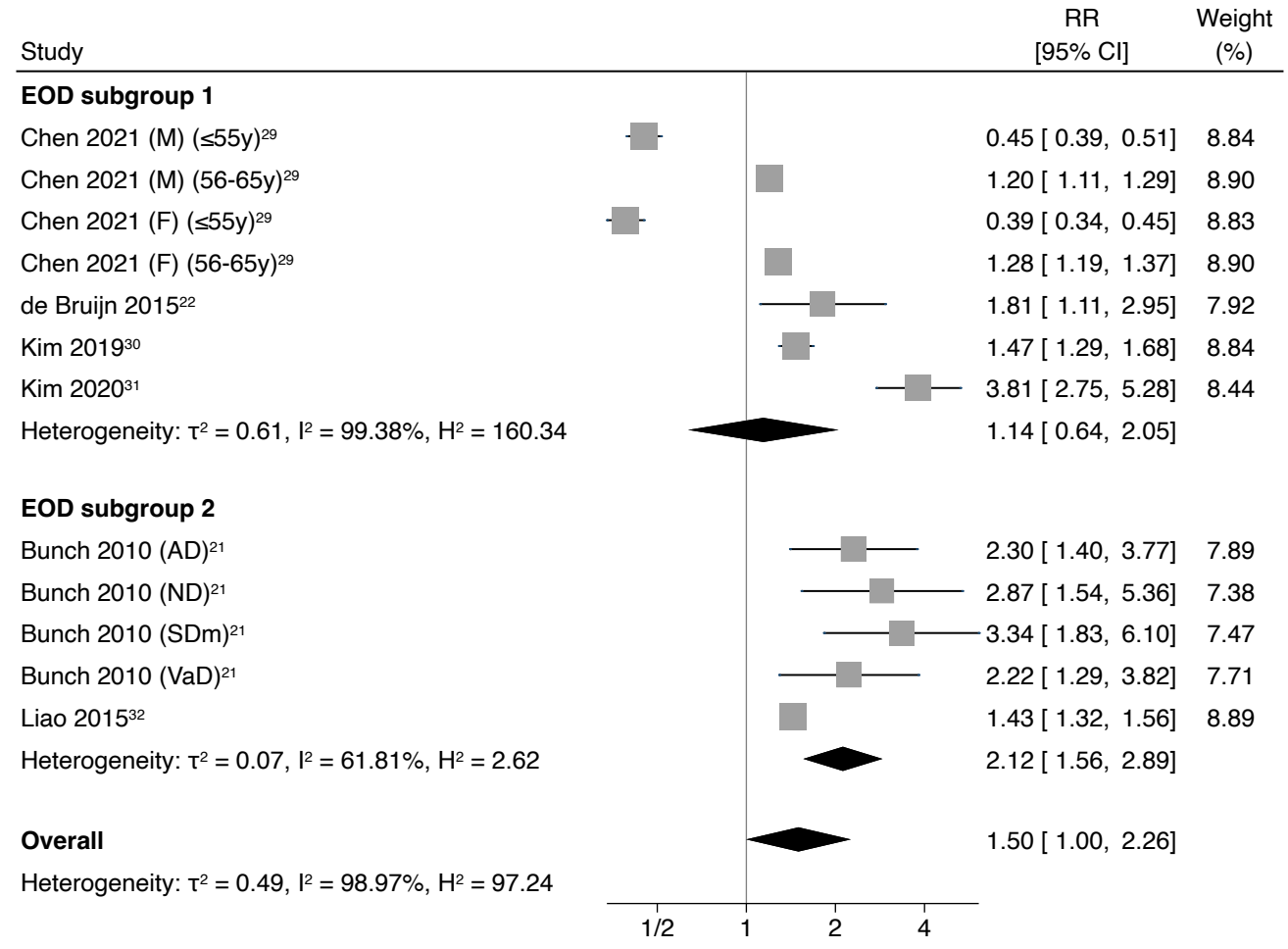
Reference	Bias due to confounding	Bias in selecting participants in the study	Bias in exposure classification	Bias in departure from intended exposure	Bias due to missing data	Bias in outcome measurement	Bias in selection of reported results	Overall risk of bias
Bunch et al. 2010[21]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Chen et al. 2021[29]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
de Bruijn et al. 2015[22]	Low	Low	Low	Low	Low	Low	Low	Low
Kim et al. 2019[30]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Kim et al. 2020[31]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Liao et al. 2015[32]	Moderate	Low	Low	Low	Low	Low	Low	Moderate

Figure S1. Forest plot for risk of early-onset (<70 years) dementia in association to atrial fibrillation; sensitivity analysis after exclusion of Chen et al. 2021 study.[29] AD, Alzheimer's dementia; F, female; M, male; ND, Nonspecified dementia; SDm, senile dementia; VaD, vascular dementia.



Random-effects model based on Paule and Mandel method-ebayes option

Figure S2. Forest plot for risk of early-onset (<70 years) dementia in association to atrial fibrillation; sensitivity analysis stratified by certainty of EOD diagnosis: dementia onset before 65 years (EOD subgroup 1) and unclear exact age of onset (EOD subgroup 2). AD, Alzheimer's dementia; F, female; M, male; ND, Nonspecified dementia; SDm, senile dementia; VaD, vascular dementia.



Random-effects model based on Paule and Mandel method-ebayes option