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REVIEW

The Effect of Non-Stroke Cardiovascular Disease States on Risk for Cognitive Decline and Dementia: A Systematic and Meta-Analytic Review

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Abstract Cardiovascular disease is associated with increased risk for cognitive decline and dementia, but it is unclear whether this risk varies across disease states or occurs in the absence of symptomatic stroke. To examine the evidence of increased risk for cognitive decline and dementia following non-stroke cardiovascular disease we conducted two independent meta-analyses in accordance with PRISMA guidelines. The first review examined cardiovascular diagnoses (atrial fibrillation, congestive heart failure, periphery artery disease and myocardial infarction) while the second review assessed the impact of atherosclerotic burden (as indicated by degree of stenosis, calcification score, plaque morphology or number of plaques). Studies eligible for review longitudinally assessed risk for clinically significant cognitive decline and/or dementia and excluded stroke and cognitive impairment at baseline. Summary statistics were computed via the inverse variance weighted method, utilising Cox Proportional Hazards data (Hazard Ratios, HR). Both atrial fibrillation (n = 5, HR = 1.26, 95% CI [1.12, 1.43]) and severe atherosclerosis (n = 4, HR = 1.59, 95% CI [1.12, 2.26]) emerged as significant risk factors for cognitive decline and/or dementia. A small set of studies reviewed, insufficient for meta-analysis, examining congestive heart failure, peripheral artery disease and myocardial infarction suggested that these conditions may also be associated with an increased risk of cognitive decline/dementia. In the absence of stroke, patients with atrial fibrillation or generalised atherosclerosis are at heightened risk for cognitive deterioration. Nonetheless, this paper highlights the need for methodologically rigorous and prospective investigation of the relationship between CVD and dementia.

Keywords Cardiovascular disease · Dementia · Cognitive decline · Meta-analysis

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Introduction

A consistent link between cardiovascular disease (CVD) and dementia has been reported in the research literature. CVD and dementia share common risk factors, including age, obesity, physical inactivity, smoking, high blood pressure and elevated cholesterol (Alonso et al. 2009; Anstey et al. 2011; Anstey et al. 2007; Fillit et al. 2008; Kivipelto et al. 2002). CVD may manifest as cerebrovascular disease, including stroke, which is an independent predictor of cognitive dysfunction and vascular dementia (VaD) (Pinkston et al. 2009). The association between cardiovascular risk factors and dementia risk is further validated by autopsy studies. In a series of cases with pre-mortem clinical diagnosis of Alzheimer's dementia, at autopsy 50% displayed cerebrovascular pathology with only 30% displaying pure Alzheimer's disease pathology (Schneider et al. 2007). In a comparison sample of cases without a pre-morbid dementia diagnosis, at autopsy 24% of cases displayed pure AD pathology with 18% displaying cerebrovascular pathology (Schneider et al. 2007).

Although stroke is an established predictor of cognitive dysfunction and dementia, it is not clear whether other manifestations of CVD contribute independently to cognitive deterioration. In comparison to non-diseased counterparts, CVD patients display poorer performance on various cognitive tasks, including those of global cognition, attention, psychomotor speed, executive function, learning and memory (Knecht et al. 2008; Pressler et al. 2010; Silbert et al. 2007; Waldstein et al. 2003). In retrospective and cross-sectional studies, indices of both subclinical (atherosclerosis) (Hofman et al. 1997; Xiang et al. 2013) and clinical CVD (Debette et al. 2007; Jozwiak et al. 2006; Ott et al. 1997) have emerged as risk factors for cognitive impairment and dementia. In the small number of longitudinal studies, CVD risk factors and the presence of CVD at baseline have been shown to predict poorer cognitive performance, cognitive impairment and dementia at subsequent assessment (Elias et al. 2006; *Haring et al. 2013; *Newman et al. 2005; Qiu et al. 2006). In contrast, other studies report no association between various cardiovascular presentations and dementia (Kawabata-Yoshihara et al. 2012; Llewellyn et al. 2010; Rusanen et al. 2014).

Careful inspection of this literature however, reveals three important limitations. First, the majority of studies assess cognitive function at a single time point limiting the extent to which causal inferences can be made regarding the relationship between CVD, cognitive decline and dementia. Second, a large proportion of the studies examined treat CVD as a single diagnostic entity, precluding the capacity to determine the relative impact of each disease state on cognitive deterioration. Indeed, such information is of vital importance in terms of identifying the vascular bases of cognitive decline, and hence identifying patients most at risk of poor cognitive outcome. Finally, few studies account for the known effects of stroke on cognitive decline and dementia independent of underlying CVD. Whether each disease state, in the absence of stroke, serve as a risk factor for cognitive deterioration remains unclear.

The aims of this meta-analytic review are: (a) to determine whether cognitive deterioration secondary to CVD occurs in the absence of symptomatic stroke; and, (b) to determine the differential effects of CVD subtypes on cognitive deterioration. In order to disentangle the effect of cardiovascular pathology on cognitive decline and/or dementia, we conducted two independent systematic reviews and meta-analyses. The first review examined clinical cardiovascular disease states including atrial fibrillation, congestive heart failure, myocardial infarction and peripheral artery disease, while the second evaluated the risk associated with the presence and burden of atherosclerotic disease.

Method

Two independent reviews were performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Liberati et al. 2009; Moher et al. 2009). No institutional review board or ethics committee approval was required for this meta-analysis as no recruitment of participants was undertaken. KS undertook the literature searches and study selection. MS was consulted in cases of uncertainty, which were resolved by consensus. Specific details pertaining to the search strategy and study selection (i.e., number of articles screened/excluded, first identified reason/s for exclusion, risk of bias analysis) for each review can be found with the respective protocols (see supplementary materials).

Search Strategy & Selection

Electronic searches were performed using PubMed and ProQuest. ProQuest searches were limited to scholarly journals. As a means of capturing as much data as possible, no other restrictions (i.e., language, length of follow-up, year of publication) were specified.

Electronic searches were performed on April 4 and June 6 2016, respectively. Titles and abstracts were captured if they contained both a cardiovascular and cognition keyword (e.g., *cardiovascular disease* and *dementia*). Cardiovascular keywords for the first review included *cardiovascular*, *heart disease** or *cardiovascular disease risk*. Cardiovascular terms for the second review were *cardiovascular, cardiovascular disease*, cardiovascular disease risk*, *vascular disease**, *athero** and *arterio**. Cognition terms included *Alzheimer**, *dementia*, *mild cognitive impairment*, *MCI*, *vascular cognitive impairment*, *VCI* or *cognitive decline*.

Citations identified via electronic searches were subsequently exported into Endnote. Titles containing relevant cardiovascular keywords (see Supplements 1 and 2) were retained. Then after further review, studies with titles and abstracts pertaining to stroke/cerebrovascular disease, where the relation between cardiovascular disease/risk and cognition was not examined), or non-human studies, were excluded.

Subsequent to these searches, reference lists of appropriate review papers and commentaries were screened, and potentially relevant titles were sourced. Abstracts and/or full-texts were inspected as necessary. Additional sources were identified throughout the search and study selection process, which concluded on August 6, 2016. Inaccessible papers were requested from both the authors directly (via ResearchGate) and/or the university document delivery system. Additional information/data were requested on four occasions, without response.

Studies were eligible for review if they met the following criteria: (a) utilised a longitudinal design and randomised recruitment methods; (b) assessed the risk for clinically significant cognitive decline and/or dementia (at follow-up) associated with isolated cardiovascular disease states (at baseline);

and, (c) excluded patients with a history of symptomatic stroke, cognitive impairment or dementia at baseline.

- *Cognitive decline/dementia.* Evidence of cognitive decline and/or dementia using medical records, pathological evidence, and/or clinical diagnosis (as indicated by neuropsychologist or neurologist) was a requisite for inclusion. Studies utilising multiple sources of evidence were preferred, although this was not a requirement for inclusion. Meta-analyses were restricted to binary outcome data (i.e., presence or absence of clinically significant cognitive decline and/or dementia at follow-up). Studies examining associations between isolated disease states and cognitive performance measures were not eligible for inclusion, as such data introduces additional sources of heterogeneity in the meta-analysis. For example, test measures and cut-offs used differed substantially across studies.
- *Stroke.* Stroke is an established predictor of cognitive decline and dementia (Pinkston et al. 2009). In order to partial out these effects, only studies that: (a) identified a history of stroke (e.g., via self-report and/or medical records); and (b) excluded baseline stroke could be used.
- *Cardiovascular disease.* In the context of the first review, only studies confirming cardiovascular diagnoses (as indicated by medical records, self-report or cardiologist/medical practitioner) were included. The following cardiovascular conditions emerged: atrial fibrillation, congestive heart failure, myocardial infarction and peripheral artery disease.
- *Atherosclerosis of carotid, coronary and/or peripheral arteries.* For the second review, direct quantification of atherosclerotic load or severity was required, utilising one or more of the following methods: (a) severity of stenosis (degree of artery blockage, 0–100%); (b) calcification scores; (c) plaque morphology; or, (d) number of plaques. Indirect indices of atherosclerosis (e.g., carotid-intima thickness, pulse wave velocity and ankle to brachial blood pressure index) were deemed insufficient for inclusion.

Risk of Bias Assessment

Following the PRISMA guidelines (Liberati et al. 2009; Moher et al. 2009), we performed a risk of bias analysis, utilising an adapted version of the Cochrane Collaboration Tool for Assessing Risk of Bias in Randomised Trials (Higgins et al. 2011) (see Supplements 1 and 2; unmodified criteria obtained from http://www.handbook.cochrane.org/chapter_8/table_8_5_d_criteria_for_judging_risk_of_bias_in_the_risk_of.htm). Included studies were assessed over seven domains: (1) selection bias; (2) ascertainment of cardiovascular conditions; (3) ascertainment of cognitive impairment/dementia; (4) potential confounds; (5) attrition bias; (6) reporting bias; and, (7) other biases not otherwise specified. Studies were rated as "high risk", "low risk" or "unclear" and corroborated with evidence (e.g., direct quotation), by two independent authors (KS and MS). Discrepant results were deliberated and combined (see Section 8 of protocols).

Data Extraction & Eligibility for Meta-Analysis

KS was responsible for extracting and inspecting data. Studies were eligible for meta-analysis if they provided either (a) hazard ratios and their respective confidence intervals for each cardiovascular disease state (versus the absence of each cardiovascular disease state), or (b) sufficient information to calculate such values. However, the latter was not essential for either review as all studies included utilised Cox Proportional Hazards data. Values derived from the most conservative models (i.e., fully adjusted, sensitivity analyses) took precedence. The following information was extracted: (a) study population; (b) age of sample; (c) health characteristics of cardiovascular group (relative to cardiovascular-absent group); (d) assessment interval; and, (e) cognitive assessment methods.

Statistical Analyses

Meta-analyses were conducted using R statistical analysis package 'meta' (Schwarzer 2007). Random-effects models were utilised given the heterogeneity noted amongst study populations and methodologies (e.g., comorbidities, length of follow-up) (Borenstein et al. 2009). In addition, fixed-effects data are reported in Figs. 2 and 4, respectively.

Following the Tierney et al. (Tierney et al. 2007) guidelines for synthesising time-to-event data, the DerSimonian and Laird inverse variance weighted method was applied, using raw HRs and their respective confidence intervals. Raw HRs and confidence intervals were individually entered into Tierney et al.'s online Microsoft Excel spread sheet (see Tierney et al. 2007, additional file 1), which was used to compute the logarithm of each HR and the standard error of each logarithm from these values. Logarithmic data were subsequently imported into R to perform the meta-analysis. The total number of patients included in each meta-analysis was not computed, as some sample sizes (without stroke) were not reported. Indices of heterogeneity included I2 and Q statistics. In light of the small number of studies included in each meta-analysis, publication bias was not assessed (Lau et al. 2006).

Results

Review One: Cardiovascular Disease and Risk for Cognitive Decline and/or Dementia

The first electronic search yielded a total of 6579 citations, of which 1597 titles contained a cardiovascular term and were

retained (Figure 1). Sixty-one review articles were identified, from which 56 full-texts/abstracts were sourced and inspected. A further 18 articles were identified via additional sources, although only 1 article was eligible for meta-analysis. From the entire search, 5 citations could not be retrieved in English and 3 were inaccessible (including one reference list from a review paper). A total of six studies met criteria, five of which were included in the meta-analysis. Refer review protocol (Supplement 1) for a detailed explanation of this process.

Given the small number of studies assessing each disease state, a sufficient number of studies for meta-analysis were identified only for atrial fibrillation. Results from the risk of bias analysis are presented in eTable 1. Sample characteristics and data extracted from each study are presented in Table 1 and Table 2.

Atrial Fibrillation

Patients with atrial fibrillation are at elevated risk for clinically significant cognitive decline and/or dementia. The pooled estimate of 5 studies returned a significant hazard ratio of 1.26, 95% CI [1.12, 1.43], $z = 3.81$, $p < .001$, in patients with atrial

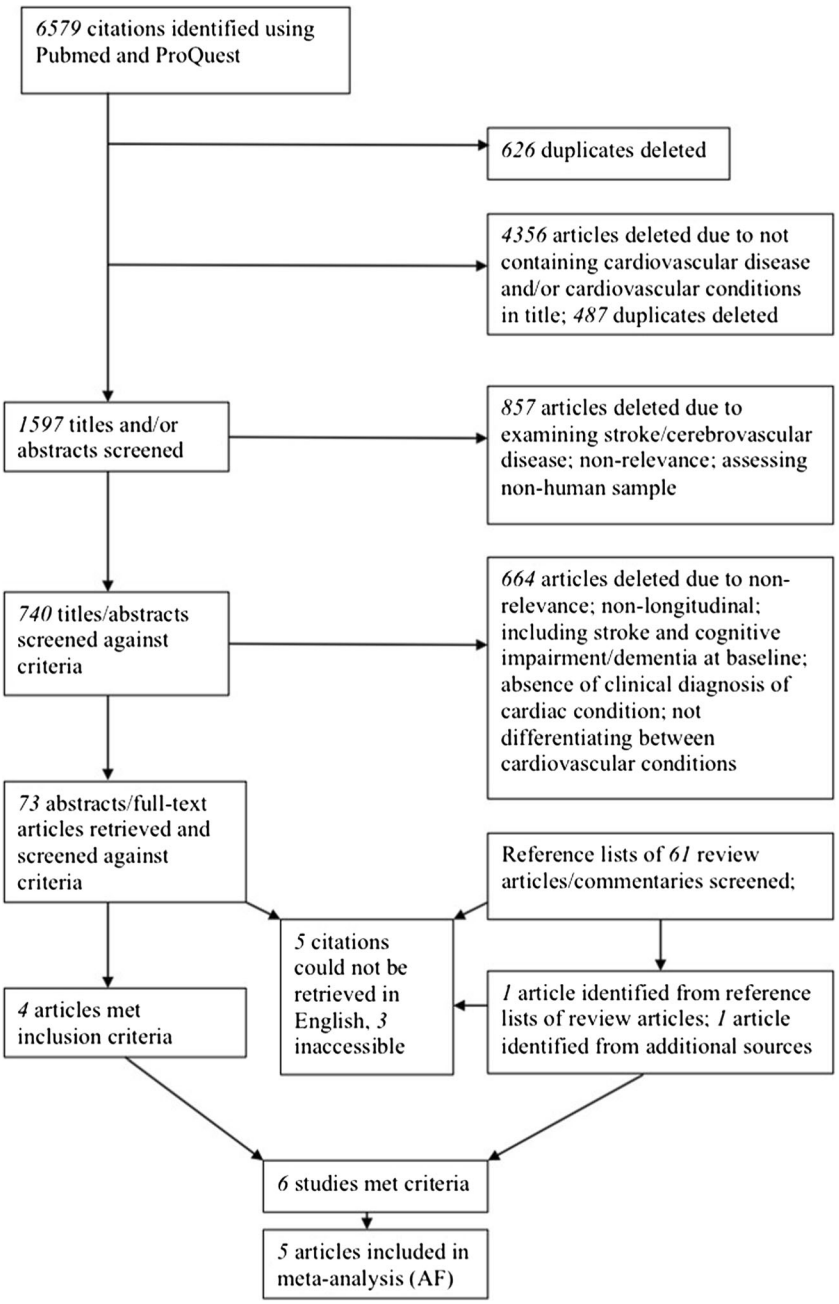

Fig. 1 Search strategy flow diagram for cardiovascular diagnosis meta-analysis

Table 1 Study and sample characteristics for review one

Study	Population (*N*)	Cardiovascular Condition	Health characteristics of cardiovascular group (relative to condition-absent group)	Assessment Interval (person-years/mean years)	Cognitive Assessment
*de Bruijn et al. (2015)	Netherlands Rotterdam Study *N* = 6314 (note: excluding stroke patients)	Atrial fibrillation	Present: 75.7 (8.1) years Absent: 68.3 (8.5) years Greater proportion of individuals using blood pressure-lowering medication, ever use of oral anticoagulant treatment, lower total cholesterol, lower high-density lipoprotein cholesterol levels, greater proportion of diabetes mellitus, coronary heart disease and heart failure diagnoses (note: including stroke patients)	81,483 person-years (note: including stroke patients) (81,483/6314 = 12.9 years)	Cognitive/dementia screening: medical records, Mini-Mental State Examination score < 26 or Geriatric Mental State Schedule organic level > 0. Suspected cases: Cambridge Examination for Mental Disorders of the Elderly, neuropsychological assessment and/or neuroimaging Panel (including neurologist). Dementia as per *Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised* and criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association
*Dublin et al. (2011)	Washington Adult Changes in Thought (ACT) Study, Group Health *N* = 3045	Atrial fibrillation	Present: 76.5 (71.6–82.6) years Absent: 74.2 (70.3–79.4) years (note: median interquartile range reported only) Greater proportion of cardiovascular risk factors/conditions (e.g., coronary heart disease, congestive heart failure, treated hypertension), warfarin use	20,806 person-years 6.8 years	Cognitive/dementia screening: Cognitive Abilities Screening Instrument (< 86) Suspected cases: comprehensive neuropsychological assessment and/or cranial imaging Possible and probable AD or dementia Multidisciplinary panel. Dementia as per *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.* Possible and probable AD as per criteria of National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).
*Haring et al. (2013)	US postmenopausal women Women's Health Initiative Memory Study (WHIMS), Women's Health Initiative Hormone Trials (WHI HTs)	Atrial fibrillation, congestive heart failure, myocardial infarction	65 years and older at baseline (note: means and standard deviations for present vs. absent not reported) Greater proportion of smokers (current), depression cases, hypertensive cases, and aspirin use, hypercholesterolaemia or diabetes treatment, persons with higher body mass index (note: participants with any CVD)	Median 8.6 years (including interim stroke) (note: person-years not reported. Mean follow-up years for each condition reported on p.8 of paper)	Cognitive/dementia screening: Modified Mini-Mental State Examination (3MSE), modified Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery, informant interview, medical history. MCI or probable dementia Specialised physician and panel (including two neurologists and

Table 1 (continued)

Study	Population (*N*)	Cardiovascular Condition	Health characteristics of cardiovascular group (relative to condition-absent group)	Assessment Interval (person-years/mean years)	Cognitive Assessment
	N = 6455 (note: including interim stroke patients)				1 geriatric psychiatrist) Comprehensive neuropsychological assessment by specialised physician. MCI as per CERAD norms (deficit in at least one cognitive domain or functional impairment as indicated by informant). Probable dementia as per *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* and/or non-contrast computed tomography brain scan/blood tests.
*Marengoni et al. (2011)	Stockholm The Kungsholmen Project *N* = 685	Atrial fibrillation	75 years and older at baseline (note: means and standard deviations for present vs. absent not reported) Cardiovascular group comparisons not reported	3058 person- years 4.0 years	Cognitive/dementia screening: Mini-Mental State Examination (MMSE), comprehensive neuropsychological assessment. Dementia as per *Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised* 2 physicians (senior physician consulted in cases of uncertainty) and/or medical records/death certificate
*Marzona et al. (2012)	40 countries ONTARGET and TRANSCEND trials *N* = 31,506 (note: excluding baseline and interim stroke, *N* = 23,655)	Atrial fibrillation	Present: 70.3 (6.9) years Absent: 66.3 (7.2) years Greater proportion of e.g., stroke/transient ischemic attack, hypertension cases	Median follow-up 56 months (56/12 = 4.67 years) (note: person-years years not reported)	Cognitive/dementia screening: Mini-Mental State Examination Dementia as per diagnosis, severe cognitive impairment reported or Mini-Mental State Examination score ≤ 23
*Newman et al. (2005)	Four US communities Cardiovascular Health Study (CHS) Cognition Study *N* = 2539	Myocardial infarction, peripheral artery disease	65 to 97 years at baseline (note: means and standard deviations for present vs. absent not reported) Cardiovascular group comparisons not reported	13,900 person-years 5.4 years	Cognitive/dementia screening: Mini-Mental State Examination, Digit Symbol Substitution Test, Modified Mini-Mental State Examination score < 80 (decrease ≥5 points), Telephone Interview for Cognitive Status score < 28 or Informant Questionnaire on Cognitive Decline in the Elderly score > 3.6, incident stroke, medical records (i.e., diagnosis), nursing home residence. Neurological/ neuropsychological assessment and/or medical records, informant

Table 1 (continued)

Study	Population (*N*)	Cardiovascular Condition	Health characteristics of cardiovascular group (relative to condition-absent group)	Assessment Interval (person-years/mean years)	Cognitive Assessment
					interview and physician questionnaires. Panel including neurologists and psychiatrists. Differential diagnosis of dementia as per magnetic resonance imaging and criteria of National Institute of Neurological and Communicative Diseases and Stroke – Alzheimer Disease and Related Disorders Association for Alzheimer's Disease and the State of California Alzheimer's Disease Diagnostic and Treatment Centers for VaD.

fibrillation, relative to individuals with no atrial fibrillation (see Fig. 2 and Table 2). Tests of heterogeneity indicated consistency in findings across studies, I^2 = 0%, 95% CI [0.0, 60.4], Q(4) = 2.10, p = 0.717.

Congestive Heart Failure

Only one study concerning congestive heart failure was eligible for review (*Haring et al. 2013). This study indicated a non-significant risk for MCI/probable dementia, based on 67 patients with congestive heart failure and 6057 non-diseased controls (HR = 1.54). The generalizability of these findings are questionable given the wide confidence intervals and that the sample was comprised only of postmenopausal women.

Myocardial Infarction

Two studies indicated a greater risk of clinically significant cognitive decline and dementia in patients with a history of myocardial infarction: HRs 1.98 and 1.30, respectively (*Haring et al. 2013; *Newman et al. 2005). However, one study examined a sample of only postmenopausal women (*Haring et al. 2013) with the other study reported a confidence interval encapsulating one (*Newman et al. 2005).

Peripheral Artery Disease

The one eligible study reported peripheral artery disease to be a significant risk factor for dementia. Specifically, this study found that patients with PAD were 2.4 times more likely to develop dementia at follow-up compared to those without PAD (*Newman et al. 2005).

Review Two: Atherosclerotic Burden and Risk for Cognitive Decline/Dementia

A total of 11,123 citations were obtained for the second review, of which 1367 titles contained a relevant cardiovascular keyword and were subsequently screened. Seventy-six review articles/commentaries were screened with 76 full-text (or abstracts as necessary) identified from these and reviewed. An additional 25 articles were noted as potentially relevant during the screening process, although none of these were eligible for meta-analysis. Overall, ten citations could not be retrieved in English. A total of four studies met criteria for inclusion. The number of articles screened and extracted at each stage can be located in Fig. 3.

A total of 4 studies met criteria for the second review, all being eligible for meta-analysis. Risk of bias assessments can be found in eTable 2, while sample characteristics and data extracted from each study can be located in Table 3 and Table 4.

Table 2 Hazard ratios for clinically significant cognitive decline, Mild Cognitive Impairment (MCI) and/or dementia per cardiovascular condition

Study	Cardiovascular Condition (*n* present vs. absent)	MCI/Dementia Cases (*n* present vs. absent)	Hazard Ratio (HR)	HR 95% CI	Log HR	Log HR standard error (SE)
Atrial fibrillation present vs. absent						
*de Bruijn et al. (2015)[a]	*n* censored for stroke not specified	844	1.33	(0.99, 1.78)	0.29	0.15
*Dublin et al. (2011)[b]	132 (vs. 2913)	103 (vs. 469)	1.38	(1.10, 1.73)	0.32	0.12
*Haring et al. (2013)[c]	230 (vs. 5873)	19 (vs. 360)	1.25	(0.78, 2.00)	0.22	0.24
*Marengoni et al. (2011)[d]	68 (vs. 617)	18 (vs. 152)	0.90	(0.50, 1.70)	−0.11	0.31
*Marzona et al. (2012)[e]	Not specified	Not specified	1.21	(1.01, 1.45)	0.19	0.09
Congestive heart failure present vs. absent						
*Haring et al. (2013)[c]	67 (vs. 6057)	8 (vs. 375)	1.54	(0.75, 3.16)	NA	NA
Myocardial infarction present vs. absent						
*Haring et al. (2013)[c]	191 (vs. 5933)	24 (vs. 359)	1.98	(1.29, 3.04)	NA	NA
*Newman et al. (2005)[f]	Not specified	Not specified	1.30	(1.0, 1.90)	NA	NA
Peripheral artery disease present vs. absent						
*Newman et al. (2005)[f]	Not specified	Not specified	2.40	(1.40, 4.0)	NA	NA

[a] Covariates: age, sex, diabetes mellitus, smoking, total cholesterol and high-density lipoprotein cholesterol levels, lipid-lowering medication, systolic and diastolic blood pressure, blood pressure-lowering medication, body mass index, educational level, ever use of oral anticoagulant medication, coronary heart disease, heart failure, and apolipoprotein E ε4 carrier status

[b] Covariates: age (time scale), interim stroke, stratified by study cohort, gender, education, diabetes, hypertension, systolic and diastolic blood pressure, coronary heart disease and congestive heart failure. Time-dependent variables: atrial fibrillation, interim stroke, coronary heart disease and congestive heart failure

[c] Sensitivity analyses: excluding interim stroke/transient ischemic attack. Covariates: age, education, race, hormone trial randomization arm, baseline 3MSE, alcohol intake, smoking status, physical activity, diabetes status, sleep hours, hypertension status, body mass index, depression, waist–hip ratio, hypercholesterolemia, and aspirin use

[d] Covariates: age, gender, education, baseline Mini-Mental State Examination score, hypertension, antithrombotic medications and apoliproptein E genotype. Follow-up duration (time scale)

[e] Covariates: age, education, sex, baseline Mini-Mental State Examination score, systolic blood pressure at baseline; stroke/transient ischemic attack history, hypertension, diabetes and myocardial infarction, levels of microalbuminuria, macroalbuminuria, and creatinine, statin use, β-blockers, angiotensin-converting enzyme inhibitors, antiplatelet therapy or oral anticoagulants; changes in systolic blood pressure during follow-up, smoking, body mass index, physical activity level, sleep apnea and ation

[f] Covariates: age at baseline, race (black), education, income, apolipoprotein e-4 allele, and Modified Mini-Mental State Examination score at magnetic resonance imaging scan

The studies included in the meta-analysis used different methods for assessing atherosclerosis, but all considered atherosclerosis of the carotid artery. Three studies categorised persons on the basis of disease severity. For example, one study examined the risk of cognitive deterioration subsequent to no plaques, unilateral or bilateral plaques. To maximise consistency across studies, we extracted hazard ratios concerning the most severe form of atherosclerosis reported

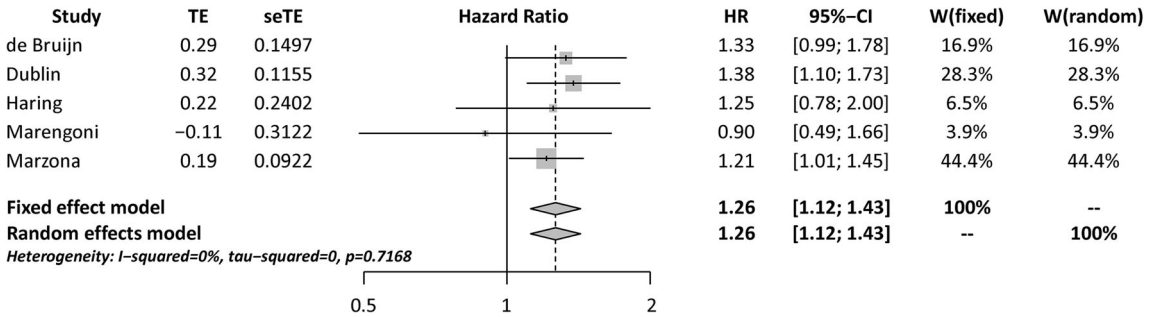

Fig. 2 Pooled estimate for the risk of clinically significant cognitive decline and/or dementia secondary to atrial fibrillation (TE = log HR, seTE = standard error log HR, HR = hazard ratio, W = weighting, grey square = study weighting, grey diamond = model summary estimates, – = summary estimate derived from random effects model)

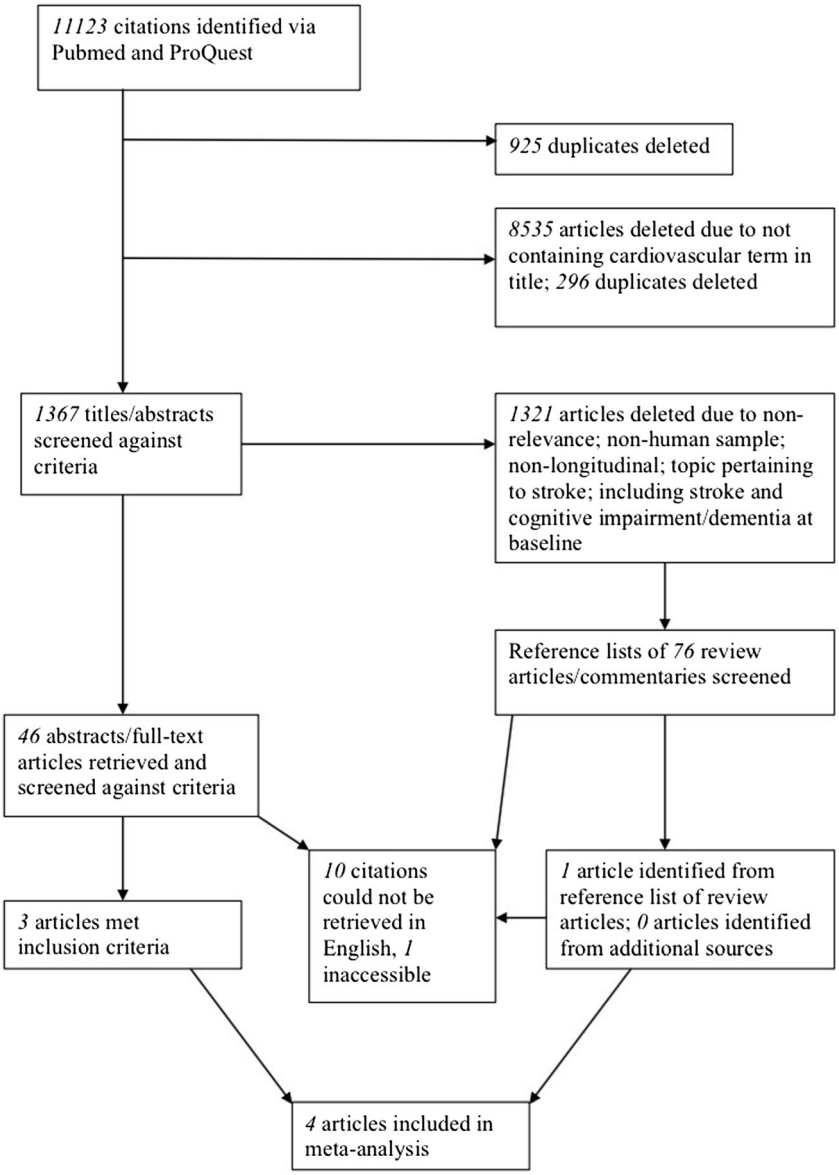

Fig. 3 Search strategy flow diagram for atherosclerotic burden meta-analysis

in each study (accordingly, data concerning bilateral plaques took precedence over unilateral plaques). One study examined dementia risk per standard deviation increase in atherosclerosis of the carotid artery (as indicated by calcification volume) (*Bos et al. 2015).

Atherosclerosis of the carotid artery serves as a risk factor for clinically significant cognitive decline/dementia. A meta-analysis of four studies indicated individuals with severe atherosclerosis of the carotid artery are 1.6 times more susceptible to cognitive deterioration in comparison to those with no/little atherosclerotic burden, HR = 1.59, 95% CI [1.12, 2.26], $z = 2.59$, $p = .01$. Tests of consistency indicated little/moderate heterogeneity in findings, I^2 = 44.2% 95% CI [0.0, 81.4], although Q(3) = 5.38 did not significantly differ from zero, $p = 0.146$ (refer to Figure 4).

Sensitivity Analysis: Atherosclerosis

The magnitude of one HR (*Carcaillon et al. 2015) was notably large relative to the remaining data. As such, we performed a second analysis excluding this potential outlier. A significant risk associated with atherosclerosis still emerged, HR = 1.38, 95% CI [1.09, 1.74], $z = 2.72$, $p = .007$, $I^2 = 0\%$, 95% CI [0.0, 87.1], Q(2) = 1.61, $p = .446$.

Discussion

The aim of this review was to determine the longitudinal and relative impact of isolated cardiovascular disease states on clinically significant cognitive decline and/or dementia,

Table 3 Study and sample characteristics for review two

Study	Population (*N*)	Atherosclerosis Assessment	Health Characteristics of severe atherosclerosis group (relative to no atherosclerosis group)	Assessment Interval (person-years/mean years)	Cognitive Assessment
*Bos et al. (2015)	Netherlands Rotterdam Study *N* = 2212 (note: excluding stroke patients)	Atherosclerotic calcification (Syngo Calcium Scoring) (coronary arteries, aortic arch and extracranial carotid arteries. Intracranial carotid arteries (semiautomated scoring)	69.4 years (note: means and standard deviations for severe vs. none not reported) Cardiovascular group comparisons not reported	13,397 person- years 6.0 years (note: including stroke patients)	Cognitive/dementia screening: Mini-Mental State Examination score < 26 or Geriatric Mental State Schedule organic level > 0. Cambridge Examination for Mental Disorders in the Elderly, medical history/ records, informant interview, and/or neuropsychological assessment, neuroimaging Panel including neurologist. Dementia as per *Diagnostic and Statistical Manual of Mental Disorders, version III, Revised* and criteria of the National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)
*Carcaillon et al. (2015)	France The Three-City Study *N* = 6025 (note: including baseline stroke) (6025–391 stroke cases = 5634)	Number of sites with carotid plaques (0, 1 or ≥≥2)	Severe: 75.0 (5.0) years None: 72.4 (4.5) years Cardiovascular group comparisons not reported	35,530 person years 5.4 years (note: including baseline and interim stroke patients)	Cognitive/dementia screening: Mini-Mental State Examination score and Isaac's set test, neuropsychological assessment Panel of neurologists. Dementia as per *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* and criteria of the Clinical Dementia Rating Scale and/or magnetic resonance imaging data Differentiation of dementia types as per criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), and on the basis of medical history, neurovascular disease status, neurological examination, Hachinski score, computed tomography scan and/or magnetic resonance imaging data, and National Institute of Neurological Disorders and Stroke Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN)
*Newman et al. (2005)	Four US communities Cardiovascular Health Study (CHS) Cognition Study *N* = 2539	Carotid artery stenosis % (normal; 1–24; 25–49; ≥≥50)	65 to 97 years at baseline (note: means and standard deviations for severe vs. none not reported) Cardiovascular group comparisons not reported	13,900 person-years 5.4 years	Cognitive/dementia screening: Mini-Mental State Examination, Digit Symbol Substitution Test, Modified Mini-Mental State Examination score < 80 (decrease ≥≥5 points), Telephone Interview for Cognitive Status score < 28 or

Table 3 (continued)

Study	Population (*N*)	Atherosclerosis Assessment	Health Characteristics of severe atherosclerosis group (relative to no atherosclerosis group)	Assessment Interval (person-years/mean years)	Cognitive Assessment
					Informant Questionnaire on Cognitive Decline in the Elderly score > 3.6, incident stroke, medical records (i.e., diagnosis), nursing home residence. Neurological/ neuropsychological assessment and/or medical records, informant interview and physician questionnaires. Panel including neurologists and psychiatrists. Differential diagnosis of dementia as per magnetic resonance imaging and criteria of National Institute of Neurological and Communicative Diseases and Stroke – Alzheimer Disease and Related Disorders Association for Alzheimer's Disease and the State of California Alzheimer's Disease Diagnostic and Treatment Centers for VaD.
Wendell et al. (2012)	Baltimore Longitudinal Study of Aging *N* = 364 (364–35 baseline and interim stroke cases = 329)	Presence of carotid plaque (none, unilateral, or bilateral)	73.6 (8.3) years (note: means and standard deviations for severe vs. none not reported Cardiovascular group comparisons not reported	364 × 14 = 5096 person-years 14.0 years	Dementia diagnosis as per *Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised* MCI or dementia Multidisciplinary panel. MCI diagnosis as per impairment present in single or multiple domains in the absence of functional impairments Differentiation of dementia types as per criteria of the National Institute of Neurological and Communication Disorders-Alzheimer's Disease and Related Disorders Association

Table 4 Hazard ratios for clinically significant cognitive decline, Mild Cognitive Impairment (MCI) and/or dementia per atherosclerotic index

Study	Atherosclerosis Index (*n* present vs. absent)	MCI/Dementia Cases (*n* present vs. absent)	Hazard Ratio (HR)	HR 95% CI	Log HR	Log HR standard error (SE)
Extracranial carotid calcification (per SD increase)						
*Bos et al. (2015)[a]	Not specified	77 (vs. 2135)	1.32	(1.02, 1.71)	NA	NA
Intracranial carotid calcification (per SD increase)						
*Bos et al. (2015)[a]	Not specified	77 (vs. 2135)	1.34	(1.01, 1.78)	0.29	0.14
Carotid plaque (≥2 sites vs. no plaque)						
*Carcaillon et al. (2015)[b]	Not specified	Not specified	3.22	(1.41, 7.31)	1.17	0.42
Bilateral plaque (vs. no plaque)						
Wendell et al. (2012)[c]	Not specified	Not specified	2.02	(1.05, 3.89)	0.70	0.33
Severity of carotid artery stenosis (≥50% vs. normal)						
Newman et al. (2005)[d]	Not specified	Not specified	1.20	(0.70, 2.0)	0.18	0.27

[a] Covariates: age, sex and education

[b] Covariates: sex, study centre, education, apolipoprotein e-4 allele, obesity, hypertension, hypercholesterolemia, diabetes mellitus, smoking, history of cardiovascular disease (myocardial infarction and stroke)

[c] Covariates: age, sex, race, education, systolic and diastolic blood pressure, total and high-density lipoprotein cholesterol, cardiovascular disease, diabetes mellitus and smoking

[d] Covariates: age at baseline, race (black), education, income, apolipoprotein e-4 allele, and Modified Mini-Mental State Examination score at magnetic resonance imaging scan

independent of clinical stroke. Data from two independent reviews indicate that in the absence of stroke, individuals with atrial fibrillation or severe atherosclerosis of the carotid artery display a significantly increased risk for subsequent cognitive decline and dementia. Unfortunately, a lack of data precluded analysis of the pooled estimates for risk of cognitive decline associated with congestive heart failure, myocardial infarction, peripheral artery disease, or other manifestations of atherosclerotic CVD.

Consistent with previous meta-analyses (Kalantarian et al. 2013; Kwok et al. 2011) these data favour an association between atrial fibrillation and risk for cognitive decline and dementia. Such effects are typically attributed to three key mechanistic clusters, including shared CVD risk factors, hemodynamic/vasoreactivity disturbances, and cerebrovascular disease (*de Bruijn et al. 2015; *Dublin et al. 2011; Kalantarian et al. 2013). These findings complement the extant literature, indicating that atrial fibrillation itself confers an increased risk for subsequent cognitive decline and dementia. As such, it is possible that mechanisms other than symptomatic stroke, such as cerebral micro- and macro-circulatory dysfunction, may underlie cognitive deterioration secondary to non-stroke atrial fibrillation. For instance, cardiac insufficiency (i.e., varied or reduced cardiac output) is a characteristic feature of AF. A persistent reduction in systemic blood flow may result in cerebral hypoperfusion and impaired cerebrovascular function, which may then lead to subclinical brain injury (e.g., white matter hyperintensities) (de la Torre 2012; Flück et al. 2014; Jefferson et al. 2011). We do recognise that interim stroke or the presence of mutual risk factors, such as hypertension and hypercholesterolaemia, may also explain the relationship between AF and cognitive decline. However, these explanations seems

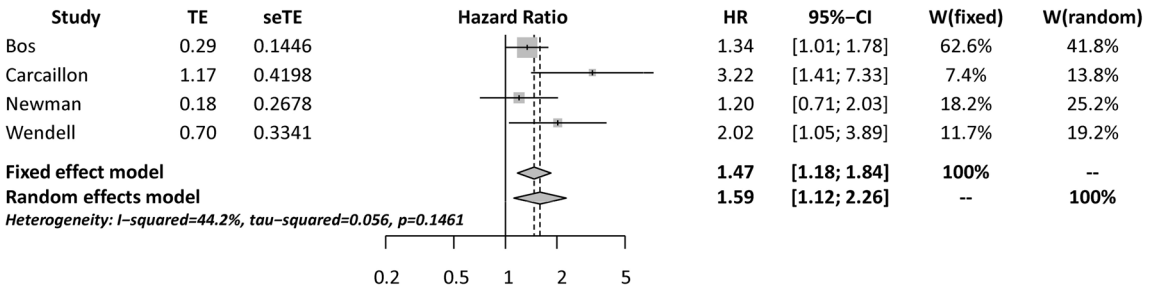

Fig. 4 Pooled estimate for the risk of clinically significant cognitive decline and/or dementia secondary to severe atherosclerotic burden (TE = log HR, seTE = standard error log HR, HR = hazard ratio, W = weighting, grey square = study weighting, grey diamond = model summary estimates, – = summary estimate derived from random effects model)

less likely as we utilised data derived from the most conservative models, which typically accounted for such confounds (e.g., via exclusion or statistical adjustment).

That atherosclerosis in the absence of baseline and interim stroke emerged as a significant predictor of cognitive decline and dementia strengthens this perspective. Compared to individuals without atherosclerosis, individuals with atherosclerosis of the carotid artery (who presented with the most severe form of atherosclerosis within each study) were almost 1.6 times more likely to develop cognitive decline/dementia at follow-up. Given that such effects emerged in the absence of symptomatic stroke, and irrespective of cardiovascular disease status, supports the potential role of hemodynamic disturbances and chronic cerebral hypoperfusion in the pathogenesis of dementia. Conceivably, the nature of impairment could vary depending on: (a) the brain's capacity to compensate for disturbances in blood flow (e.g., autoregulatory mechanisms); and, (b) the nature and severity of hypoperfusion (e.g., chronicity, diffuse vs. focal) (Cohen 2010). Nonetheless, further research assessing the trajectory of cerebral perfusion in patients with each disease state is required to test this possibility. Whether the aforementioned mechanisms are likely to have a synergistic or additive impact on cognitive deterioration also warrants further investigation.

We employed a number of stringent criteria in order to gauge the relative impact of each cardiovascular disease state on cognitive outcome. In particular, studies that met inclusion criteria for meta-analysis all excluded the presence of stroke at baseline and were found to have used comprehensive neuropsychological assessment in determining cognitive outcomes. That the findings were homogeneous across the majority of studies is also reassuring. Nonetheless, three limitations do deserve mention. First, few studies were eligible for inclusion. Second, studies differed in length of follow-up and the number of confounding factors they considered. While the use of a random-effects model may combat such forms of heterogeneity, it is still important to consider these limitations in interpreting the findings from each meta-analysis. Finally, although all directly quantified atherosclerotic load, the methods used to assess atherosclerotic severity varied substantially across studies. Unfortunately, because we could not combine data into a common metric, we could not assess whether the risk of cognitive decline/dementia varied as a function of atherosclerotic severity. The lack of data also precluded statistical comparison of the form and location (e.g. arteriosclerosis and atherosclerosis or atherosclerosis of the carotid artery versus the aorta).

The paucity of studies meeting eligibility criteria for this review highlights the need for methodologically rigorous and longitudinal studies of the relationship between individual cardiovascular disease states, cognitive decline and dementia. In particular, investigation of large cohorts identified via randomised recruitment methods (and importantly, not on the basis of cardiac disease status) is needed. Further, comprehensive assessment of cognitive and cardiovascular health at baseline (including stroke/cerebrovascular pathology), and exclusion of pre-existing cognitive impairment, is imperative in terms of determining the magnitude of decline secondary to each disease state.

Nonetheless, this review of existing data indicates that patients with atrial fibrillation in the absence of symptomatic stroke, are at increased risk of clinically significant cognitive decline. Further, individuals with severe carotid atherosclerosis without symptomatic stroke may be as susceptible to clinically significant cognitive deterioration, irrespective of the presence of another cardiovascular condition.

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CA: made critical revisions of the manuscript for key intellectual content.

KG: made critical revisions of the manuscript for key intellectual content.

MS: conceived and designed the research, performed statistical analyses, acquired the data, drafted the manuscript.

Compliance with Ethical Standards

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