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The Relationship of Coronary Artery Calcium and Clinical Coronary Artery Disease with Cognitive Function: A Systematic Review and Meta-Analysis

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Aim: Coronary artery disease (CAD) and cognitive impairment are common in the elderly, with evidence for shared risk factors and pathophysiological processes. The coronary artery calcium (CAC) score is a marker of subclinical CAD, which may allow early detection of individuals prone to cognitive decline. Prior studies on associations of CAC and clinical CAD with cognitive impairment had discrepant results. This systematic review aims to evaluate the association of (sub)clinical CAD with cognitive function, cognitive decline, and diagnosis of mild cognitive impairment (MCI) or dementia.

Methods: A systematic search was conducted in MEDLINE, Embase, and Web of Science until February 2019, supplemented with citations tracking. Two reviewers independently screened studies and extracted information including odds ratios (ORs) and hazard ratios (HRs).

Results: Forty-six studies, 10 on CAC and 36 on clinical CAD, comprising 1,248,908 participants were included in the systematic review. Studies about associations of (sub)clinical CAD with cognitive function and cognitive decline had heterogeneous methodology and inconsistent findings. Two population-based studies investigated the association between CAC and risk of dementia over 6–12.2 years using different CAC scoring methods. Both found a tendency toward higher risk of dementia as CAC severity increased. Meta-analysis in 15 studies (663,250 individuals) showed an association between CAD and MCI/dementia (pooled OR 1.32, 95%CI 1.17–1.48) with substantial heterogeneity ($I^2=87.0\%$, $p<0.001$). Pooled HR of CAD for incident MCI/dementia over 3.2–25.5 years in six longitudinal studies (70,060 individuals) was 1.51 (95%CI 1.24–1.85), with low heterogeneity ($I^2=14.1\%$, $p=0.32$). Sensitivity analysis did not detect any study that was of particular influence on the pooled OR or HR.

Conclusions: Limited evidence suggests the CAC score is associated with risk of dementia. In clinical CAD, risk of MCI and dementia is increased by 50%, as supported by stronger evidence.

Key words: Coronary artery disease, Dementia, Coronary artery calcium, Mild cognitive impairment, Atherosclerosis

Introduction

Coronary artery disease (CAD) and dementia are common in the elderly. The prevalence of CAD and dementia is estimated to be 14.9% and 5.2%, respectively, among adults over 60 years of age^{1,2}. Mortality

of CAD has declined during the past decades because of improvement in disease management, resulting in an increasing number of CAD patients with a higher life expectancy¹. These patients, although they survive CAD, may develop other age-related diseases such as dementia in their late life. Mild cognitive impairment

(MCI) is an intermediate stage between age-related cognitive decline and clinically diagnosed dementia and may be a prodromal stage of Alzheimer's disease (AD) or other neurodegenerative disorders³. Potentially, early detection of MCI/dementia combined with preventive intervention could delay the progression to dementia. It is important to research the relationship between CAD and MCI/dementia in view of the possibility of measures to prevent dementia in CAD patients.

Epidemiological studies have shown that vascular risk factors are associated with cognitive decline and with incidence of MCI and dementia including AD^{4, 5}. There is evidence for shared pathophysiological mechanisms between cardiovascular disease and dementia: vascular risk factors and heart diseases might contribute to MCI and dementia through pathways including neurodegeneration, cerebral atherosclerosis, and cerebral hypoperfusion and hypoxia⁶. Vascular pathology such as intracranial atherosclerosis can convert low-grade AD to overt dementia⁷. Reviews and meta-analysis have found cardiovascular diseases such as atrial fibrillation and heart failure to be associated with increased risk of dementia^{8, 9}. However, so far, results on associations between clinical CAD and the risk of cognitive decline are inconsistent¹⁰⁻¹³. Caution is needed when summarizing evidence from longitudinal studies linking CAD to dementia; particularly, estimated effects may be distorted by study populations with prior invasive intervention¹⁴.

There is increasing interest to use coronary artery calcium (CAC) scoring as imaging biomarker for subclinical CAD to estimate cardiovascular disease risk^{15, 16}. Also, in population-based studies on calcium scoring, discrepant results on the relationship of CAC with cognitive function decline were found¹⁷⁻¹⁹. So far, there has been no systematic review of associations between CAC and cognitive impairment.

The aim of the current study was to systematically review the literature on the association of (sub) clinical CAD with cognitive function. To meet this aim, we addressed the following question: What is the association of CAC and clinical CAD with (1) cognitive function, (2) cognitive decline, and (3) risk of MCI or dementia?

Methods

This systematic review was performed in line

with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement²⁰ and Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement²¹.

Search Strategy

MEDLINE, Embase, and Web of Science were searched from inception to February 2019 without limits on publication dates. The search strategy included terms relevant to coronary atherosclerosis and cognitive impairment (see [Supplementary Table 1](#)). Additional appropriate articles were manually added when discovered by tracking citations. An experienced medical information expert checked the search strategy.

Selection Criteria

The following inclusion criteria were used to determine eligibility of a study: (1) all types of studies that examined both coronary atherosclerosis and cognitive function regardless of the study design concerned, that is, cross-sectional, case-control, or longitudinal cohorts (≥ 1 year follow-up); (2) coronary atherosclerosis as defined by clinical CAD events or by subclinical CAD as quantified by CAC scoring; (3) cognitive function based on either validated mental state examinations and neuropsychological testing or clinically diagnosed MCI or dementia; and (4) study sample size larger than 100.

Invasive interventions for CAD may have a negative effect on subsequent cognitive performance¹⁴. In addition, the effect of CAD on cognition may be distorted by atrial fibrillation, stroke, or heart failure because of different underlying pathophysiological mechanisms²². Therefore, we excluded studies (1) that clearly mentioned that participants had undergone invasive cardiac procedures prior to cognitive function testing; (2) that did not consider invasive intervention as a confounder for statistical analysis; and (3) that solely focused on patients with atrial fibrillation, stroke, or heart failure. We also excluded case reports, reviews, conference abstracts, editorials, or articles not published in English. In case of multiple articles that reported results based on the same cohort, we only included those articles that reported the largest sample size or that best addressed our research question.

Study Selection, Data Collection, and Quality Assessment

Two reviewers (C.X. and M.V.) independently performed the selection process and data extraction of included studies. Articles were first evaluated for eligibility on the basis of the selection criteria. A standardized data extraction form was used to collect the following information for eligible articles: publication details, study population characteristics, study setting, CAC measurements, determination of CAD and cognitive function, and description of results. Studies included for meta-analysis were evaluated for study quality. For observational studies including cohort and case-control studies, the Newcastle-Ottawa Scale (NOS) was used for the quality assessment²³, whereas for cross-sectional studies, an adapted NOS version was used²⁴. In case of a disagreement in article selection or data extraction, this was discussed between the two reviewers and consensus was obtained, or a third reviewer (R.V.) was consulted.

Data Analysis

This systematic review evaluates the relationship of CAC score and clinical CAD with cognitive function. For each part, the following three questions were evaluated: the association of CAC score or clinical CAD with (1) cognitive function, (2) changes of cognitive function over time/cognitive decline, and (3) risk of MCI or dementia. The strength of associations between CAC score or clinical CAD and MCI or dementia as dichotomous outcomes was estimated using either odds ratio (OR) or hazard ratio (HR) and 95% confident intervals (CIs). Meta-analysis was conducted if there were at least two studies that reported the same outcome of interest (MCI and/or dementia). If studies reported the results of myocardial infarction (MI) and angina pectoris (AP) separately, then only the results of the MI were used in this systematic review, and the AP results were excluded since MI is a harder endpoint of CAD. OR and HR (derived from a multivariable model in each study if available) were pooled separately using the inverse variance method with DerSimonian-Laird random-effects model despite inter-study heterogeneity. Pooled estimated effect was tested using the Z test. Heterogeneity was assessed using the Q statistic test and I^2 statistic. A two-tailed p value for Q statistic < 0.10 and $I^2 > 50\%$ was considered to indicate heterogeneity. Reporting biases or small-study effects were evaluated by visual evaluation of the funnel plot of each pooling analysis for symmetry. Egger's test for funnel plot asymmetry was performed only if the number of studies for pooling analysis was sufficient (≥ 10). Sensitivity analysis was conducted using the leave-one-out method to

detect any study that may be influential in the overall estimated effect. To explore potential source of heterogeneity across the studies, subgroup analysis was performed on the basis of study design. Statistical analysis was conducted using R (Package "meta," R Foundation, Vienna, Austria). A two-tailed value of $p < 0.05$ was considered as statistically significant except for the test of heterogeneity.

Results

Study Selection

The results of the search strategy and selection process are shown in **Fig. 1**. After removal of duplicates, 6,601 studies were screened on the basis of title and abstract. Finally, 46 studies (10 for CAC, 36 for clinical CAD), comprising 1,248,908 participants, were included for the systematic review. The main study characteristics are provided in **Supplementary Tables 2 and 3**. The main results of the studies are shown in **Supplementary Tables 4 and 5**, sorted by outcome: cognitive function, changes of cognitive function over time, and risk of MCI/dementia. Quality of studies that investigated the association between clinical CAD and diagnosis of MCI/dementia was variable (**Supplementary Tables 6–8**). Ten studies on clinical CAD had suboptimal ascertainment of exposure as determination of clinical CAD was self-reported or not described^{11, 25–33}.

Coronary Artery Calcium Score and Cognitive Function

Association with Cognitive Function

Three cross-sectional studies^{17, 34, 35} and two longitudinal cohort studies^{36, 37} examined the cross-sectional association between CAC and cognitive scores for different cognitive domains. Increasing severity of CAC was associated with worse performance of episodic memory^{34, 36}, semantic fluency³⁶, executive function^{17, 34–36}, and global cognition^{34, 37}.

Association with Cognitive Decline

One study examined the association between CAC and deterioration of cognitive function over 18 years of follow-up in patients with type 1 diabetes ($n = 1,045$). There was no difference in mean change of cognitive scores between diabetes patients with and without CAC³⁸.

Association with cognitive impairment or dementia

Four longitudinal studies reported the association between increased CAC at baseline and clinically relevant cognitive impairment or dementia^{18, 19, 39, 40}. The Rotterdam study in the elderly ($n = 2,326$) showed

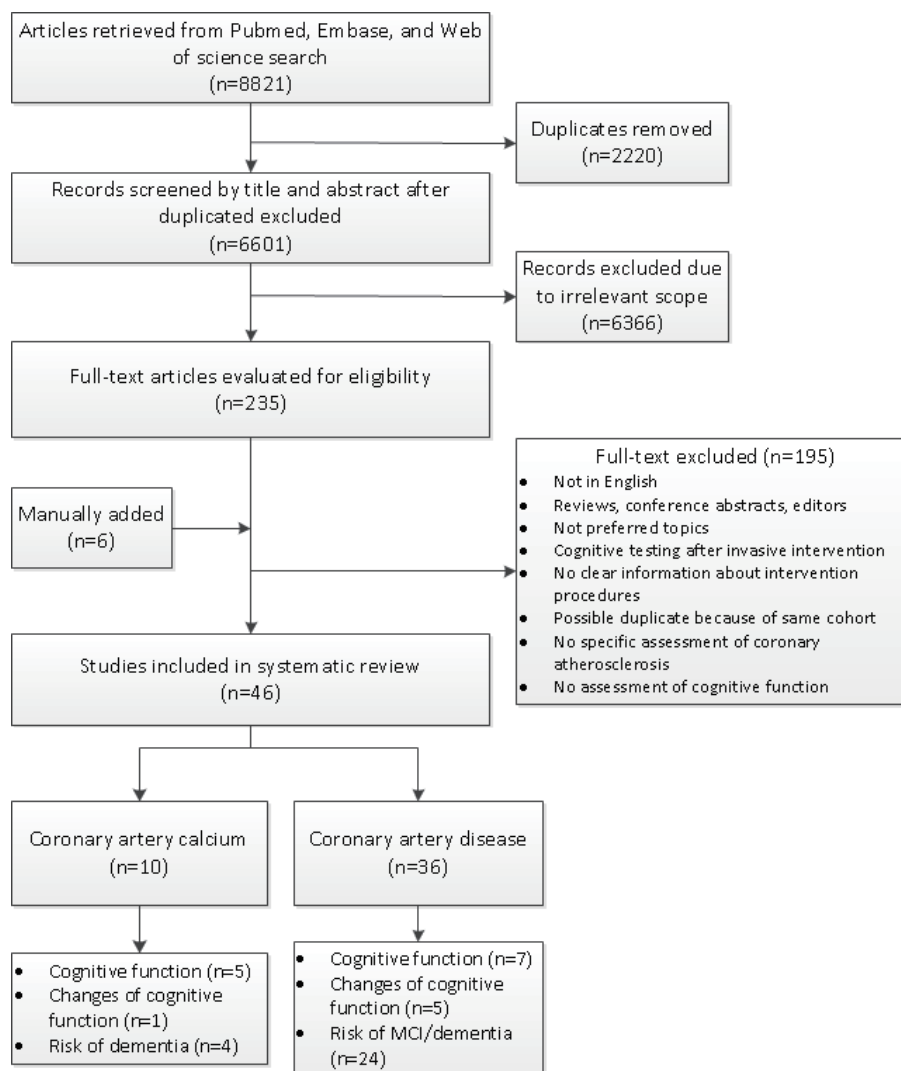


Fig. 1. Flowchart of literature search and selection

that increased CAC volume was associated with modestly increased risk of dementia after 6 years of follow-up¹⁸), but this result did not reach statistical significance (HR 1.05 per Ln(calcium volume + 1.0 mm³), 95%CI 0.80–1.36). On the other hand, in the Multi-Ethnic Study of Atherosclerosis (MESA) study, which includes a population with broader age range and different races/ethnicities ($n=6,293$), there was a statistically significant increased risk of dementia after a median of 12.2 years (HR 1.18 per log₂ (CAC score + 1), 95%CI 1.03–1.36)¹⁹. Because these two studies used different units to measure CAC, it was not possible to perform meta-analysis. A smaller study that mostly included women of ≥ 80 years ($n=311$) reported that white elderly women with CAC score > 400 had around three times higher risk of dementia after 10+ years, compared with those with CAC score of 0⁴⁰. An even smaller study in type 1 diabetes

patients ($n=148$) found significantly elevated risk of MCI with increasing CAC score categories after 14 years³⁹.

Clinical Coronary Artery Disease and Cognitive Function

Association with Cognitive Function

Seven studies reported the association between clinical CAD and cognitive function^{41–47}. Specifically, three cross-sectional studies ($n=516–478,557$) found that presence of CAD was associated with poorer cognitive scores in the domain of fluency⁴², memory⁴⁶, and global cognition⁴⁴. A case-control study ($n=446$) reported that the Mini Mental State Examination (MMSE) score of CAD cases was lower than that of controls, but this was not statistically significant⁴⁵. Furthermore, a prospective study ($n=616$) found that CAD patients had worse cognitive scores than had

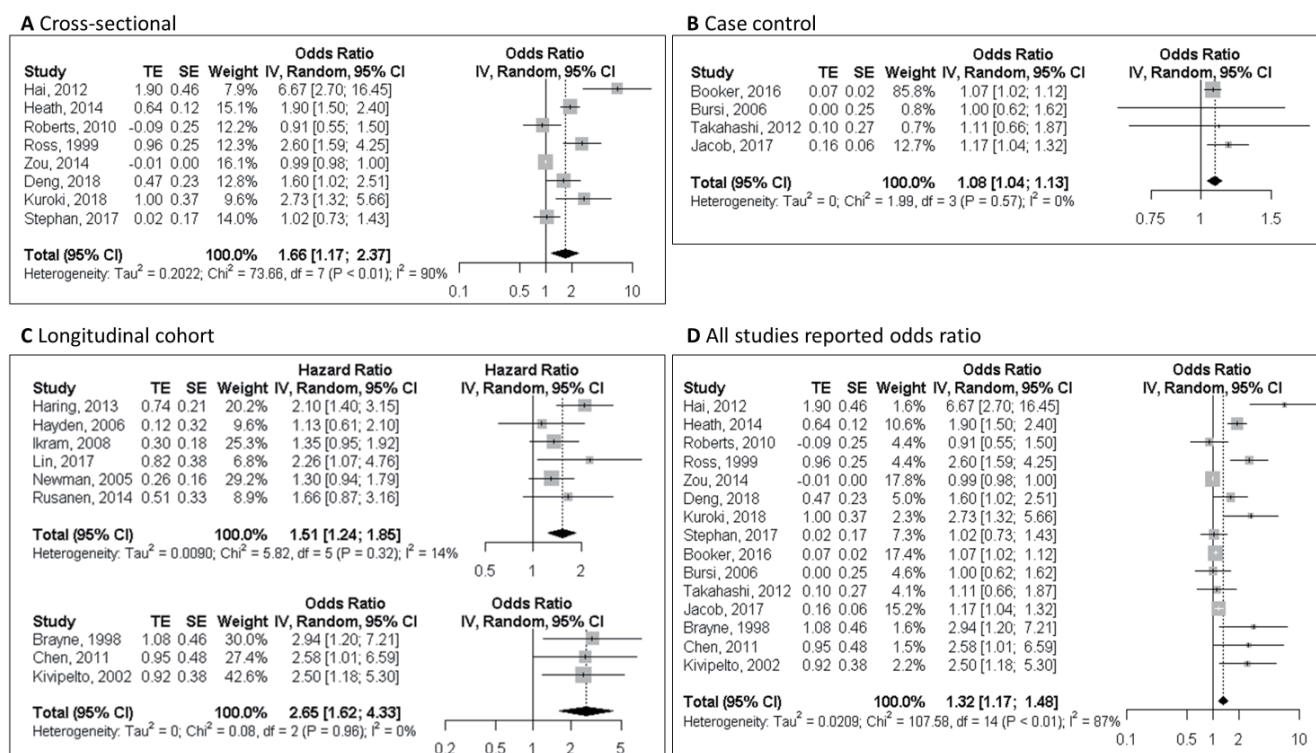


Fig. 2. Forest plot of the association between clinical coronary artery disease and mild cognitive impairment or dementia in cross-sectional studies. (A); in case-control studies (B); in cohort studies (C); and in all studies reporting odds ratio (D).

OR, odds ratio; HR, hazard ratio

controls at 1- and 5-year follow-up⁴⁷), and a study with longer follow-up (7 years, $n=380$) found that CAD was associated with worse information processing speed⁴¹. However, in a larger population-based cohort study in Norway ($n=5,033$), no association was found between CAD and cognitive test scores (12 word memory test, digit-symbol coding test, and tapping test)⁴³.

Association with Cognitive Decline

Five longitudinal studies reported the relationship between clinical CAD and change in cognitive function over time⁴⁸⁻⁵². A relatively small study ($n=231$) found that the decline of global cognitive function over 2 years in patients with a history of CAD and normal heart function was not worse than that in patients without CAD⁴⁸. In contrast to this, a larger study in 889 elderly (70-90 years) found that CAD was associated with greater decline in memory over 2 years⁴⁹. Similarly, a study in elderly men ($n=353$) found that CAD increased cognitive decline over 3 years (OR 1.7, 95%CI 0.8-3.5)⁵¹. In addition, two other studies in 118 and 135 AD patients showed that CAD accelerated decline on both Clinical Dementia Rating scale and MMSE scores over $\geq 1-3$ years^{50, 52}.

Association with Cognitive Impairment or Dementia

Ten cross-sectional studies ($n=200-616,245$) reported on the association between CAD and clinically diagnosed MCI ($n=6$) or dementia ($n=4$)^{25-28, 53-58}. Five studies reported that CAD was significantly associated with MCI/dementia, with ORs varying from 1.60 to 6.76^{25-28, 57}. Four studies with MCI as outcome did not find an association or reported a tendency to an inverse association^{54-56, 58}. The largest study found an OR of ischemic heart disease for dementia of 1.9 (95%CI 1.5-2.4)²⁷. Meta-analysis was possible for eight studies^{25-28, 54, 56-58}. Pooled OR of CAD for MCI/dementia was 1.66 (95%CI 1.17-2.37), with significant heterogeneity between studies ($I^2=90.5\%$, $p<0.001$) (Fig. 2A). One study investigated coronary atherosclerosis confirmed by autopsy and found that an increased burden of intracranial atherosclerosis, but not coronary atherosclerosis, was associated with dementia⁵³.

Five case-control studies ($n=410-23,912$) evaluated the association between CAD and MCI/dementia^{10, 29-31, 59}. The largest studies found slight but significant positive associations, of which one focused on MCI (OR 1.17, 95%CI 1.04-1.32)³¹ and the other on dementia (OR 1.07, 95%CI 1.04-1.14)²⁹. The

three smaller studies found no significant association between CAD with dementia¹⁰, AD⁵⁹, or vascular dementia³⁰. Four studies could be included in the meta-analysis with a resulting pooled OR of 1.08 (95%CI 1.04–1.13) and no significant heterogeneity $I^2=0.0\%$, $p=0.57$ (Fig. 2B).

Nine prospective studies ($n=376-49,955$) with follow-up from 2.4 to 25.5 years addressed the association between CAD and risk of MCI/dementia^{11-13, 32, 33, 60-63}. Five studies showed that clinical CAD significantly increased the risk of dementia, with HRs of 2.1–2.9^{13, 32, 33, 60, 63}. In the Rotterdam study, unrecognized MI determined by electrocardiography was not related to dementia overall; however, there was a positive association in men (HR 2.23, 95%CI 1.24–4.01)⁶². Another two studies found that patients with MI, mostly based on self-report, tended to have a higher risk of dementia (HR 1.1–1.3)^{12, 61}. One study investigated the association of midlife CAD (diagnosed at or before baseline examination) and late-life CAD (diagnosed at or before first re-examination) with dementia and found that midlife CAD was not associated with dementia, whereas participants with late-life CAD tended to have a higher risk of dementia (HR 1.66, 95%CI 0.81–3.16)¹¹. Meta-analysis was conducted in studies that reported HRs^{11-13, 61-63} and studies that reported ORs^{32, 33, 60} separately. Pooled HR and pooled OR of CAD for MCI/dementia were 1.51 (95%CI 1.24–1.85, $I^2=14.1\%$, $p=0.32$) and 2.65 (95%CI 1.62–4.33, $I^2=0.0\%$, $p=0.96$), respectively (Fig. 2C). The funnel plot was symmetric (Supplementary Fig. 1C) for the pooled HR, whereas formal statistical testing was not performed because of insufficient number of studies. Sensitivity analysis did not detect any study that was of particular influence on the pooled HR.

Finally, an overall effect size of the association of CAD with MCI/dementia was calculated by including the data from all cross-sectional, case–control, and cohort studies ($n=15$). Pooled OR of CAD for MCI/dementia was 1.32 (95%CI 1.17–1.48), with significant heterogeneity between studies ($I^2=87.0\%$, $p<0.001$) (Fig. 2D). The funnel plot (Supplementary Fig. 1E) displayed asymmetry, with Egger's test p value <0.001 . Sensitivity analysis did not detect any study that was of particular influence on the pooled OR.

Discussion

This systematic review, including 46 studies, evaluated the current evidence of the association between (sub)clinical CAD and cognitive function. Prior studies about associations of (sub)clinical CAD with cognitive function and cognitive decline had het-

erogeneous methodology and inconsistent findings. Two population-based studies investigated the association between CAC and risk of dementia, both finding a tendency toward higher risk of dementia as CAC severity increased. Overall, cross-sectional, case–control, and longitudinal studies showed that clinical CAD was significantly associated with MCI/dementia, but high heterogeneity mainly caused by cross-sectional studies. In clinical CAD, risk of MCI and dementia was increased by 50%. Compared with two prior systematic review articles on the association between CAD and cognitive function^{64, 65}, our study has strengths that include the evaluation of subclinical CAD as assessed by CAC score in relation to dementia and restriction of clinical CAD studies to pre-cardiac intervention results.

Coronary Artery Calcium Score and Cognitive Function

The CAC score, a commonly used non-invasive imaging biomarker for subclinical CAD, is a robust predictor of cardiovascular events⁶⁶. To our knowledge, this is the first systematic review to assess the predictive value of CAC for cognitive outcomes. Two population-based longitudinal studies, MESA and Rotterdam study, found a tendency toward higher risk of dementia as CAC severity increased^{18, 19}. As they used a different CAC scoring method, meta-analysis could not be performed. Conversely, some studies showed that intracranial artery atherosclerosis, but not coronary atherosclerosis, was associated with MCI and dementia^{53, 67}. It is not irrational to presume that coronary atherosclerosis and intracranial artery atherosclerosis are likely to be concomitant. Another possible explanation is that both coronary atherosclerosis and dementia are age-related diseases sharing risk factors such as smoking, hypercholesterolemia, hypertension, and diabetes⁶. Although we tried to stratify the studies that used adjustment for risk factors, this was not feasible because considerable heterogeneity existed in the number and type of confounders that were included in the models across studies. However, after adjusting for covariates that may affect the effect estimates, CAC was still significantly associated with risk of dementia in the MESA study. Also, in clinical CAD studies with full adjustment for major cardiovascular risk factors, associations remained significant. These findings suggest a relationship between (sub)clinical CAD and dementia, beyond cardiovascular risk factors. Alternatively, the association between CAC and dementia may be explained by the potential mediating effect of cerebrovascular disease (e.g., stroke), since an association has been found between severity of CAC and risk of stroke⁶⁸. However, in MESA, after exclud-

ing interim stroke, associations between CAC score and risk of dementia remained statistically significant (HR 1.18, 95%CI 1.03–1.36)¹⁹), although associations between CAC volume and risk of dementia became statistically nonsignificant in the Rotterdam study (HR 1.05, 95%CI 0.80–1.36)¹⁸). Future studies need to clarify whether CAC merely reflects generalized atherosclerosis, confounded by shared risk factors, or whether coronary atherosclerosis is more directly related to MCI/dementia, and to which type of dementia. Even so, since the CAC score is increasingly used in cardiovascular risk stratification in cardiac asymptomatic individuals, our results can raise awareness of the elevated risk of dementia in individuals with increased CAC at a very early stage and thus allow for timely prevention of cognitive decline.

Clinical Coronary Artery Disease and Cognitive Function

By pooling results of all study types ($n=15$), we found a significant association between CAD and MCI/dementia, with a pooled OR of 1.32 (95%CI 1.17–1.48); however, substantial heterogeneity exists between studies ($I^2=87.0\%$, $p<0.001$). This heterogeneity likely has multiple causes. Many different study designs and patient samples were included. Also, differences in the definition and assessment of CAD may have contributed. For example, the definition of clinical CAD comprised MI or AP or both. Compared with the use of medical records and tests such as electrocardiography, a self-report strategy used by some studies for the diagnosis of CAD is less objective and may increase information bias. In addition, there was diversity in assessment of cognitive function and there may have been differences in percentage of dementia subtypes. Most studies used the Diagnostic and Statistical Manual of Mental Disorders for diagnosis of dementia without specifying subtypes; only a few studies clearly differentiated dementia subtypes^{25, 30, 61, 63}). Also, differences in duration of the follow-up period may play a role. For example, in the study by Hayden *et al.*, there was no significant association between clinical CAD and dementia after a relatively short follow-up period (about 3 years), whereas associations may only become manifest after a longer time⁶¹). Finally, differences in study populations may have contributed to heterogeneity. The majority of the studies in the meta-analysis was population based. The study of Haring *et al.* is an exception, as it consists of a cohort of postmenopausal women¹³).

With respect to reporting bias, the number of studies per study design was insufficient to be able to perform a formal statistical test; however, the funnel plots of cohort and case–control studies were visually

symmetric, indicating unlikely presence of bias. Nevertheless, pooling cohort and case–control studies together with cross-sectional studies indicated potential presence of bias. It may be due to high heterogeneity among cross-sectional studies, or it is likely that cross-sectional studies with a negative result were not published. This may lead to potential overestimation of the results. To deal with this issue, more longitudinal cohort studies are needed to validate the suggested association. As longitudinal cohort studies are assumed to have a higher level of evidence, we also pooled the results from these high-quality studies only. For these studies ($n=6$), we found that CAD is significantly associated with risk of dementia (pooled HR 1.51, 95%CI 1.24–1.85), and this time with minor inter-study heterogeneity ($I^2=14.1\%$, $p=0.32$).

Deckers *et al.* and Wolters *et al.*^{64, 65}) also conducted systematic reviews to evaluate the association between CAD and dementia, and both studies found a significant association but with different estimated pooled effects. Deckers *et al.* performed a meta-analysis in seven longitudinal cohort studies resulting in an OR of 1.55 (95%CI 1.20–2.00), whereas Wolter *et al.* included nine population-based cohorts resulting in a pooled relative risk of 1.26 (95%CI 1.06–1.49)^{64, 65}). In our systematic review, we also found a significant association between the two diseases, with increased risk estimates very similar to the prior results. The difference in OR between the study of Deckers *et al.* and our study (1.55 vs 1.32) may be explained by the difference in selection criteria and consequent difference in studies included for the final analysis. The prior systematic reviews did not exclude studies that comprise patients with invasive coronary artery revascularization such as coronary artery bypass grafting before assessment of cognitive function. Invasive coronary interventions themselves may influence the association between CAD and cognitive function, as, for example, hypoperfusion during bypass surgery can impair the washout of microemboli, with potential subsequent brain ischemia and infarction, and increased long-term risk of dementia⁶⁹). Although there is no study that directly compared invasive coronary interventions with medical management regarding cognitive outcomes, many have reported that cardiac catheterization increases the risk of silent cerebral infarction, which is related to cognitive decline^{22, 70}). Furthermore, other cardiovascular diseases including stroke, atrial fibrillation, and heart failure can contribute to cognitive decline and dementia^{8, 9, 71}). We accounted for the effect of invasive interventions and the latter cardiovascular diseases on the association between clinical CAD and cognitive function in the selection of studies so that the magnitude of association would

not be distorted. Only studies with patient groups that had not undergone invasive treatment prior to cognitive function assessment or studies that had adjusted for these factors (invasive intervention and CAD complications) were included. This results in a more accurate estimate of the relationship of CAD itself with cognitive function. Furthermore, we investigated both subclinical and clinical CAD in our study.

Limitations

This systematic review has some limitations. First, although we made strict selection criteria in order to exclude the impact of potential confounders and interactions such as invasive coronary interventions, heart failure, atrial fibrillation, and stroke on cognitive outcomes, many studies did not report complications and/or invasive treatments in patients after developing CAD. This may have led to selection bias and could have impacted the magnitude of the association between CAD and cognition. On the other hand, because we excluded studies that specifically included patients with prior coronary intervention, perhaps the most severe CAD patient group was excluded. Second, although CAC severity was associated with risk of dementia, different CAC units were used. In clinical practice, the Agatston score is the most commonly used method for CAC quantification, although discussion exists whether better markers could be determined⁷². More data are needed to accurately estimate the effect size of Agatston-based CAC scores in predicting dementia. Furthermore, we did not perform meta-analysis per dementia subtype, since most studies reported syndrome diagnosis of dementia without clearly distinguishing subtypes, and only a limited number of studies focused on one specific dementia subtype, vascular dementia. Accurate differential diagnosis of dementia subtypes is a clinical challenge. In research studies, Alzheimer's dementia and vascular dementia are the most common subtypes of dementia, which are, however, supposedly different in pathophysiology. CAD may be strongly associated to vascular pathology than to neurodegenerative pathology. Nevertheless, as vascular pathology is frequently observed to be co-existent with AD, recently, an integrated approach to diagnosis, treatment, and prevention of dementia was proposed⁷³. More understanding of the association between CAD and dementia subtypes is important.

Conclusion

This systematic review and meta-analysis shows

an association between (sub)clinical CAD and cognitive function. Limited evidence suggests the CAC score is associated with risk of dementia. In clinical CAD, risk of MCI and dementia is increased by 50%, as supported by stronger evidence. These findings call for further investigation of whether and how coronary atherosclerosis is involved in the etiology and pathogenesis of cognitive decline and dementia and whether the relationship differs by type of dementia.

Acknowledgments

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Conflict of Interest

The PhD project of Congying Xia is part of the ImaLife project, which is funded by an institutional research grant from Siemens Healthineers and by the Ministry of Economic Affairs and Climate Policy by means of the PPP Allowance made available by the Top Sector Life Sciences & Health to stimulate public-private partnerships. Matthijs Oudkerk is involved in the company iDNA B.V. There are no other conflicts of interest to disclose.

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Supplementary Table 1. Literature search strategy

Search Strings
<p>Pubmed (“Myocardial Ischemia”[Mesh] OR “Atherosclerosis”[Mesh:Noexp] OR coronary atherosclerosis[tiab] OR coronary artery disease [tiab] OR coronary heart disease [tiab] OR coronary calcium[tiab] OR coronary calcification[tiab] OR coronary calcific[tiab] OR coronary calcified[tiab]) AND (“Dementia”[Mesh] OR “Cognitive Dysfunction”[Mesh] OR dementia [tiab] OR Alzheimer*[tiab] OR cognitive impairment[tiab] OR cognitive decline[tiab] OR cognitive function[tiab] OR cognitive disorder[tiab] OR cognitive performance [tiab] OR cognitive dysfunction[tiab]) NOT (“Animals”[Mesh] NOT “Humans”[Mesh])</p>
<p>EmBase (‘coronary artery disease’/exp OR ‘coronary artery calcium score’/exp OR ‘coronary atherosclerosis’:ab,ti OR ‘coronary artery disease’:ab,ti OR ‘coronary heart disease’:ab,ti OR ‘coronary calcium’:ab,ti OR ‘coronary calcification’:ab,ti OR ‘coronary calcific’:ab,ti OR ‘coronary calcified’:ab,ti) AND (‘mild cognitive impairment’/exp OR ‘dementia’/exp OR ‘dementia’:ab,ti OR ‘alzheimer disease’:ab,ti OR ‘mild cognitive impairment’:ab,ti OR ‘cognitive decline’:ab,ti OR ‘cognitive function’:ab,ti OR ‘cognitive disorder’:ab,ti OR ‘cognitive performance’:ab,ti OR ‘cognitive dysfunction’:ab,ti) NOT (‘animal’/exp NOT ‘human’/exp)</p>
<p>Web of Science #1 TS=(coronary artery disease) OR TS=(Coronary atherosclerosis) OR TS=(coronary artery calcium score) OR TS=(coronary calcium) OR TS=(coronary calcified) OR TS=(coronary calcific) OR TS=(coronary calcification) OR TS=(coronary heart disease) #2 TS=(dementia) OR TS=(mild cognitive impairment) OR TS=(alzheimer) OR TS=(cognitive function) OR TS=(cognitive dysfunction) OR TS=(cognitive disorder) OR TS=(cognitive performance) OR TS=(cognitive decline) #3 #1 AND #2</p>

Supplementary Table 2. Characteristics of included studies on the association between coronary artery calcium and cognitive function

Study, year	Study setting	Study population	No. of Participants	Age (Mean, SD), years	Female, %	Follow-up (Mean, SD), years
Topic 1: Association with cognitive function						
Cross-sectional						
Reis, 2013 ³⁵⁾	Cross-sectional analysis of coronary artery risk development in young adults (CARDIA) study	Multi-center, community based including black and white	2,510	Range 43-55 years	54.9	NA
Vidal, 2010 ¹⁶⁾	Cross-sectional analysis of the age, gene, environment susceptibility (AGES) - Reykjavik study	Residents in Reykjavik, Iceland	4,250	Range 74.5-78.0	75.0	NA
Suemoto, 2017 ³⁴⁾	Cross-sectional analysis of Brazilian Longitudinal Study of Adult Health (ELSD-Brasil) study	Residents in São Paulo Center, Brazil	4,104	50.9 ± 8.8	54.0	NA
Longitudinal						
Hugenschmidt, 2013 ³⁶⁾	Cross-sectional analysis of Diabetes Heart Study (DHS) –Mind	T2DM affected and unaffected siblings (European American, African American)	514 (T2DM affected $n=422$, T2DM unaffected $n=92$)	T2DM affected 67.8 ± 8.6, T2DM unaffected 67.0 ± 10.1	T2DM affected 46.2, T2DM unaffected 36.2	6.7 ± 1.6
Rossetti, 2015 ³⁷⁾	Cross-sectional analysis of Dallas heart study (DHS)	African American, white, Hispanic	1,154	50.9 ± 10.4	58.0	6
Topic 2: Association with changes of cognitive function over time (longitudinal)						
Jacobson, 2011 ³⁸⁾	Prospective cohort of Diabetes control and complications trial (DCCT)/ Epidemiology of diabetes interventions and complications (EDIC) study	Type 1 diabetes patients	1,144	45.7 ± 6.8	47.0	18.5
Topic 3: Association with MCI/dementia						
Longitudinal (risk of MCI/dementia)						
Bos, 2015 ¹⁷⁾	Prospective Rotterdam cohort	Residents in Rotterdam, The Netherlands	2,364 (2,212 censored for stroke)	69.4 ± 6.7	52.3	6
Fujiyoshi, 2017 ¹⁸⁾	Prospective cohort of Multi-Ethnic Study of Atherosclerosis (MESA)	12.2% Chinese, 26.1% black, 22.5% Hispanic, and 39.2% white	6,293 (6,120 excluded interim stroke)	68.4 ± 5.9	52.5	12.2 (Median)
Kuller, 2016 ⁴⁰⁾	Prospective cohort of Cardiovascular Health Study	Predominantly 80+ years (white, African-American, others)	311	≥ 80	65.0	10+
Guo, 2019 ³⁹⁾	Pittsburgh epidemiology of diabetes complications (EDC) study	Diagnosed with childhood-onset type 1 diabetes	148	37.2 ± 7.0	51.0	14.0 ± 3.5

SD, Standard Deviation; T2DM, Type 2 Diabetes Mellitus; NA, Not applicable.

Supplementary Table 3. Characteristics of included studies on the association between coronary artery disease and cognitive function

Study, year	Study setting	Study population	No. of Participants	Age (Mean, SD), years	Female, %	Follow-up (Mean, SD), years
Topic 1: Association with cognitive function						
Cross-sectional						
Verhaeghen, 2003 ⁴²⁾	Cross-sectional analysis of Berlin aging study (BASE) in Germany	Locally representative sample predominantly above 70 years old	516	84.9	50.0	NA
Elwood, 2002 ⁴⁴⁾	Cross-sectional analysis of the Caerphilly cohort in South Wales	Representative sample of men	Around 1,700	Range 55-69	0	NA
Lyall, 2017 ⁴⁶⁾	Cross-sectional analysis of baseline UK Biobank cohort	General population	478,557	56.4 ± 8.1	54.7	NA
Case control						
Ahto, 1999 ⁴⁵⁾	Case control study in Lieto, Finland	Residents	486 (patients with CHD 162, controls 324)	Range 64-85+	45.0	NA
Longitudinal						
Volonghi, 2013 ⁴⁷⁾	Longitudinal cohort of Oxford Vascular Study in UK	Population based	616 (ACS 216, TIA 182, Minor stroke 218)	ACS 68.1 ± 12.4, TIA 72.5 ± 11.7, Minor stroke 71.0 ± 12.5	ACS 27, TIA 55, Minor stroke 33	5
Reijmer, 2011 ⁴¹⁾	Hoorn Study, Netherland	Population based	380	Range 50-75	50.0	Cognitive function assessed 7 years after the assessment of CAD
Arntzen, 2011 ⁴³⁾	Tromsø Study in Norway	Population based	5,033	Men 58.8 ± 9.2, Women 58.2 ± 9.7	55.8	Cognitive function assessed 7 years after the assessment of CAD
Topic 2: Association with changes of cognitive function over time (longitudinal)						
Lipnicki, 2013 ⁴⁹⁾	Longitudinal cohort of Sydney Memory and Ageing Study (MAS) in Australia	Community based	889	78.6 ± 4.8	54.1	2
Kalmijn, 1996 ⁵¹⁾	Longitudinal cohort of the Zutphen Elderly Study in Netherlands	Men living in Zutphen	353	74.6 ± 4.2	0	3
Almeida, 2012 ⁴⁸⁾	Prospective case control, Heart Mind Community study in the western Australia	Community volunteers	231 (controls 81, CHD 73, CHF 77)	Controls 69.3 ± 11.3, CHD 67.8 ± 9.5, CHF 68.4 ± 10.2	Controls 67.9, CHD 33.3, CHF 16.9	2
Mielke, 2007 ⁵²⁾	Longitudinal cohort of Cache County Study on Memory, Health, and Aging (CCSMHA), Utah in the United States	Local residents with Alzheimer disease	135	84.2 ± 6.5	65.9	≥ 1

(Cont Supplementary Table 3)

Study, year	Study setting	Study population	No. of Participants	Age (Mean, SD), years	Female, %	Follow-up (Mean, SD), years
Bleckwenn, 2017 ⁵⁰⁾	Longitudinal cohort of Ageing, cognition, and dementia in primary care patients (AgeCoDe) in Germany	Patients with AD from primary health care	118	85.6 ± 3.3	74.6	3
Topic 3: Association with MCI or dementia						
Cross-sectional						
Wang, 2015 ⁵⁵⁾	Cross-sectional study in North China	Community based	3,136	Range 60-80 +	59.3	NA
Roberts, 2010 ⁵⁴⁾	Cross-sectional in Olmsted county, the United States	Residents	1,969	80.4	49.1	NA
Zou, 2014 ⁵⁶⁾	Cross-sectional study in China	Hospital and community based	597	Range 60 - 95	56.6	NA
Hai, 2012 ²⁶⁾	Cross-sectional study in China	Residents in Southwest China	202	82.5 ± 2.1	25.7	NA
Kuroki, 2018 ⁵⁷⁾	PROST (Project in Sado for Total Health) study in Japan	Outpatients	565	Range 62-79	48.7	NA
Stephan, 2017 ⁵⁸⁾	Cognitive Function and Ageing Study (CFAS) in UK	General population	2,050	~ 75 (estimated)	~ 63 (estimated)	NA
Heath, 2014 ²⁷⁾	Cross-sectional study in Scotland	Population based	616,245 (1,061 cases)	Range 40-64	49.5	NA
Ross, 1999 ²⁵⁾	Cross-sectional analysis of a Honolulu Heart Program, Honolulu-Asia aging study in Hawaii, the United States	Japanese American men	3,509 (Vascular dementia 68, stroke no dementia 106, no stroke no dementia 3,335)	Range 71-93	0	NA
Deng, 2018 ²⁸⁾	Cross-sectional study in Chongqing, China	Residents	1,781	≥ 60	60.5	NA
Dolan, 2010 ⁵³⁾	Cross-sectional analysis of Baltimore Longitudinal Study of Aging (BLSA) Autopsy Program in the United States	Predominantly white	200	87.6 ± 7.1 (age at death)	33.5	NA
Case control						
Jacob, 2017 ³¹⁾	Retrospective case control of the Disease Analyzer database (IMS Health) in Germany	German primary care patients	7,208 (3,604 patients with initial diagnosis of MCI; 3,604 controls without MCI)	75.2 ± 9.1	45.3	3 years of continuous follow-up prior to the index date of MCI
Bursi, 2006 ¹⁰⁾	Retrospective case control in Rochester, the United States	Local residents	1,832 (916 patients with dementia, 916 matched controls)	Median 82 range 38-102	72.0	NA
Massaia, 2001 ⁵⁹⁾	Retrospective case control study in the University of Torino, Italy	Consecutive patients and controls in the Geriatric Institute	456 (228 patients with AD and 228 cognitively intact controls)	AD patients 74.5 ± 7.0, controls 75.1 ± 7.7	NR	NA

(Cont Supplementary Table 3)

Study, year	Study setting	Study population	No. of Participants	Age (Mean, SD), years	Female, %	Follow-up (Mean, SD), years
Booker, 2016 ²⁹⁾	Retrospective case control of the Disease Analyzer database (IMS Health) in Germany	German primary care patients	23,912 (11,956 patients with initial diagnosis of dementia, 11,956 controls without dementia)	80.4 ± 5.3	61.0	10 years of continuous follow-up before index data of dementia
Takahashi, 2012 ³⁰⁾	Retrospective case control at Mayo Clinic in Olmsted County, USA	Patients living within Olmsted County received care at the Mayo Clinic	410 (205 cases of vascular dementia and 205 paired controls)	81.9 ± 7.8	59.0	NA
Longitudinal (risk of MCI/dementia)						
Newman, 2005 ¹²⁾	Longitudinal cohort of Cardiovascular Health Study (CHS) in US	Community based	2,539	Range 65-97	60.0	5.4
Rusanen, 2014 ¹¹⁾	Longitudinal cohort of Cardiovascular Risk factors, aging and dementia (CAIDE) study, Finland	Population based	1,510	50.3 ± 6.0 at baseline	62.4	25.5 ± 6.3 from baseline 7.8 ± 1 from first re-examination
Hayden, 2006 ⁶¹⁾	Cache County Study of Memory Health and Aging (CCSMHA), USA	Residents of Cache Country, Utah, USA	3,264	74.0 ± 6.4	58.2	3.2
Haring, 2013 ¹³⁾	Longitudinal cohort of Women's Health Initiative Memory Study (WHIMS) in the United States	Postmenopausal women	6,445	Range 65-79	100.0	8.4 median
Ikram, 2008 ⁶²⁾	Longitudinal cohort of Rotterdam Study in Netherland	Residents	6,347 (No MI 5578, Recognized MI 424, Unrecognized MI 345)	No MI 68.3 ± 8.5, Recognized MI 71.2 ± 8.2, Unrecognized MI 71.8 ± 8.8	No MI 61.4, Recognized MI 30.0, Unrecognized MI 53.9	10
Brayne, 1998 ⁶⁰⁾	A prevalence and incidence study of dementia in Cambridge city	Participants were from selected group general practices	376	≥ 75	63.6	2.4
Kivipelto, 2002 ³³⁾	Prospective FINMONICA study in Finland	Population based	1,287	Range 65-79	61.8	21.0 ± 4.9
Chen, 2011 ³²⁾	Prospective Anhui cohort study in China	Residents	1,307	≥ 65	NR	3.9 median
Lin, 2017 ⁶³⁾	Taiwan's National Health Insurance Research Database	Population based	49,955 (Depression 9,991 Non-depression 39,964)	Range 29-51	61.2	-7

CAD, Coronary Artery Disease; SD, Standard Deviation; ACS, Acute Coronary Syndrome; TIA, Transient Ischemic Attack; NA, Not Applicable; NR: not reported; CHD, Coronary Heart Disease; CHF, Chronic Heart Failure; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; MI, Myocardial Infarction.

Supplementary Table 4. Exposure and outcomes of included studies on the association between coronary artery calcium and cognitive function

Study, year	CT type	Type of Calcium score	Data type of input variable	Outcomes	Adjustments for confounders	Main results
Topic 1: Association with cognitive function						
Cross-sectional						
Reis, 2013 ³⁵⁾	MDCT	Agatston score	Categorical (0, 1-99, 100-399, ≥ 400)	Cognitive performance assessed with the DSST, Stroop Test, and RAVLT.	Age, sex, race, educational level, study center, BMI, smoking status, alcohol use, dyslipidemia, hypertension, and diabetes	Higher CAC was significantly associated with lower DSST score.
Vidal, 2010 ¹⁶⁾	MDCT	Agatston score	Quartiles of CAC calculated separately by gender	Prevalence of dementia and cognitive scores of separate cognitive domains	Age, education level presence of depressive symptoms and cardiovascular risk factors including ever smoker, prevalent coronary heart disease, current hypertension and diabetes, and midlife systolic pressure and total cholesterol	Increasing quartile of CAC associated with lower cognitive scores of speed of processing, executive function, and increased percentage of dementia.
Suemoto, 2017 ³⁴⁾	MDCT	Agatston score	Binary (CAC < 100: absent or mild atherosclerosis, CAC \geq 100; moderate to severe atherosclerosis)	Cognitive function was assessed by using DWRT, CFT, TMT by trained examiners	Age, sex, race, marital status, education income, hypertension, diabetes, LDL-cholesterol, HDL-cholesterol, smoking, alcohol use, physical activity, BMI, depression and thyroid function status	Participants with CAC \geq 100 had worse cognitive performance in global cognition, DWRT TMT scores, compared to those with CAC < 100.
Longitudinal						
Hugenschmidt, 2013 ³⁶⁾	NA	Agatston score	Natural log transformed	Cognitive performance tested with a battery of tests including DSST, RAVLT and Semantic Fluency Task.	Age sex and education	Higher burden of coronary calcification was significantly associated with worse cognitive performance on DSST, RAVLT, and semantic fluency task after a mean of 6.7 years, in participants with T2DM.
Rossetti, 2015 ³⁷⁾	EBT	Agatston score	Binary (CAC > 10 Agatston units were defined as positive)	MoCA Scores	NA	Mean of MoCA total score (SD) after about 6 years was 23.69 (3.87) for CAC \leq 10, and 22.35 (4.40) for CAC > 10, <i>p</i> -value 0.038.
Topic 2: Association with changes of cognitive function over time (longitudinal)						
Jacobson, 2011 ³⁸⁾	NA	Agatston score	Binary (0 versus > 0)	Deterioration of cognitive scores on 8 cognitive domains	Sex, baseline age, baseline education level, painful neuropathy reported at follow-up, visual acuity, length of follow-up, the number of interval cognitive tests taken	No evidence supporting the association between presence of coronary calcification and rapid decline of cognitive scores in T1DM patients.

(Cont Supplementary Table 4)

Study, year	CT type	Type of Calcium score	Data type of input variable	Outcomes	Adjustments for confounders	Main results
Topic 3 : Association with MCI/dementia						
Longitudinal (risk of MCI/dementia)						
Bos, 2015 ¹⁷⁾	MDCT	Volume score	Ln(calcification + 1.0 mm ³)	Incidence of dementia was diagnosed according to DSM-III-R	Age, sex and education level	CAC score was not significantly associated with risk of dementia: HR 1.05 (95% CI 0.80, 1.36), of AD: HR 1.09 (95%CI 0.81, 1.46) censored for stroke.
Fujiyoshi, 2017 ¹⁸⁾	EBT, MDCT	Agatston score	Log2 (CAC score + 1)	Incidence of dementia was diagnosed based on ICD10 codes	Age, sex, race, education level, having health insurance, physical activity, smoking, obesity, hypertension, medications for hypertension or dyslipidemia, systolic blood pressure, non-HDL cholesterol, diabetes, APOE epsilon-4 genotype	log2 (CAC score + 1) was significantly associated with risk of dementia (HR 1.18; 95% CI 1.03, 1.36) after multivariable adjustment and exclusion of interim stroke.
Kuller, 2016 ⁴⁰⁾	EBT	Agatston score	Categorical (0, 1-10, 11-100, 101-400, >400)	Incidence of dementia basis NA of standard criteria	NA	White women with a CAC score >400 had around 3 times higher risk of dementia than those with CAC score=0.
Guo, 2019 ³⁹⁾	EBT	Agatston score	Categorical (0, 1-100, 101-300, >300)	Cognitive impairment defined as having two or more of cognitive test scores ≥ 1.5 SD worse than norms	Education, sex, age, diabetes duration, APOE epsilon-4, ever smoking, BMI, HbA1c, cholesterol (HDL and non-HDL), triglycerides, urinary albumin excretion rate, hypertension, proliferative retinopathy, distal symmetric polyneuropathy, and statin use were offered for model selection.	Compared to CAC score=0, OR (95%CI) of MCI for CAC score 1-100, 101-300 and >300 were 1.4 (0.6, 3.6), 2.3 (0.6, 9.7), and 7.9 (1.6, 38.5), respectively.

CAC, Coronary Artery Calcium ; CT, Computed Tomography; MDCT, Multi-detector Computed Tomography; EBT, Electron Beam Tomography; SD, Standard Deviation; BMI, Body Mass Index; LDL, Low-density Lipoprotein; HDL, High-density Lipoprotein; DSST, Digit Symbol Substitution Task; RAVLT, Rey Auditory-verbal Learning Task; MoCA, Montreal Cognitive Assessment; DWRT, Delayed Word Recall Test; CFT, Category Fluency Test; TMT, Trail Making Test; T2DM, Type 2 Diabetes Mellitus; HR, Hazard Ratio; CI, Confidence Interval; ICD10, International Statistical Classification of Diseases and Related Health Problems 10th version; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders Version III Revised; AD: Alzheimer's Disease; NA, not available; APOE, apolipoprotein E

Supplementary Table 5. Exposure and outcomes of included studies on the association between coronary artery disease and cognitive function

Study, year	Ascertainment of exposure	Outcomes	Adjustments for confounders	Main results
Topic 1: Association with cognitive function				
Cross-sectional				
Verhaeghen, 2003 ⁴²⁾	In order to ascertain MI and CHD diagnoses, medical history, physical examination, resting ECG results, interview with family doctor were considered	Cognitive performance including perceptual speed, episodic memory, fluency and knowledge was assessed using cognitive test battery separately	Age, sex, social-economic status	Prevalent of CHD associated with worse cognitive performance on fluency.
Elwood, 2002 ⁴⁴⁾	Medical history of IHD including previous MI, ECG ischemia, angina recorded via interviews as well as ECG testing	Tests of cognitive function including AH4, CAMCOG, MMSE and the Choice Reaction Time were performed	Age, education level, mood at the time of testing	Compared with men without disease, decrements in men with IHD was 16% SD for the AH4, 13% SD for the MMSE, 14% SD for the CAMCOG and 17% SD for the CRT.
Lyllal, 2017 ⁴⁶⁾	CAD defined as history of physician-diagnosed angina and/or MI.	Cognitive abilities were tested by three tests including verbal-numerical reasoning, visual memory test and reaction time test.	Age, sex, ethnicity, depression, education, Townsend deprivation score, smoking status, alcohol intake, medication use and BMI	Presence of CAD associated with poorer cognitive scores, for reasoning (effect size -0.107, 95%CI -0.135, -0.079), log reaction time (effect size 1.005, 95%CI 1.004, 1.007), log memory error scores (effect size 1.017, 95%CI 1.011, 1.023).
Case control				
Ahto, 1999 ⁴⁵⁾	MI ascertained by checking medical records or ECG results. AP defined as chest pain on effort fulfilling the Rose questionnaire's criteria.	Cognitive impairment defined as total MMSE scores under 23 tested by 2 trained nurses.	NA	MMSE score (mean \pm SD) among Men: CAD 26.5 \pm 4.9, Controls 27.0 \pm 3.6 (<i>p</i> -value 0.70); among Women: CAD 26.5 \pm 3.4 Controls 26.9 \pm 3.1 (<i>p</i> -value 0.35).
Longitudinal				
Reijmer, 2011 ⁴¹⁾	IHD defined as Minnesota codes on ECG or self-reported history of MI	Neuropsychological test battery was used for cognitive assessment	Age and sex	Presence of IHD significantly associated with lower information processing speed.
Arntzen, 2011 ⁴³⁾	Definition of CHD was history of MI and/ or prevalent AP	Cognitive performance assessed by the twelve word memory test, digit-symbol coding test and tapping test.	Age, education, physical activity, smoking systolic blood pressure, total cholesterol, HDL-cholesterol, BMI, diabetes, depression	No evidence supporting CHD correlated with lower cognitive scores
Volonghi, 2013 ⁴⁷⁾	ACS defined as ST elevation and non-ST elevation MI, or unstable angina, according to currently accepted criteria	Cognitive function assessed using MMSE, TICSm, and MoCA by trained research nurses.	NA	ACS patients had worse cognitive function than those with TIA

(Cont Supplementary Table 5)

Study, year	Ascertainment of exposure	Outcomes	Adjustments for confounders	Main results
Topic 2: Association with changes of cognitive function over time (longitudinal)				
Lipnicki, 2013 ⁴⁹⁾	CAD defined as previous diagnosis of MI or angina.	Cognitive performance assessed by a battery of neuropsychological tests	Age and sex	CAD associated with greater decline in memory.
Kalmijn, 1996 ⁵¹⁾	History of MI and AP obtained from a standardized questionnaire	Cognitive decline defined as a decrease in MMSE of above 1 SD from 1990 to 1993	Age, education and baseline MMSE score	History of CAD increased the risk of cognitive decline with OR 1.7 (95%CI 0.8, 3.5).
Almeida, 2012 ⁴⁸⁾	Clinical and biochemical evidence of past MI with normal left ventricular function and no clinical symptoms of congestive heart failure	CAMCOG scores	Age, sex and CAMCOG scores at baseline	No difference between CAD and control groups on changes of CAMCOG.
Mielke, 2007 ⁵²⁾	Information on previous MI obtained via proxy and self-report	Decline as reflected by scores of MMSE and CDR	Age, sex, education, dementia duration, APOE epsilon-4, depression, baseline MMSE score	MI and AP predicted cognitive decline (MMSE scores) in patients with AD.
Bleckwenn, 2017 ⁵⁰⁾	Diagnosis of CHD or MI reported by GPs	Decline of cognitive function in patients with AD assessed by MMSE and the CDR	Age, sex, education, and time since dementia diagnosis	Presence of CHD related to rapid decline of cognition in patients with AD.
Topic 3: Association with MCI or dementia				
Cross-sectional				
Wang, 2015 ⁵⁵⁾	CHD checked through medical history	Diagnostic criteria of MCI was according to the proposal of Petersen et al.	Not clarified	CHD was not associated with MCI (effect size not reported).
Roberts, 2010 ⁵⁴⁾	Ascertainment and criteria described in reference, in brief the assessment was based on medical history, diagnostic test, and ICD codes.	Prevalent MCI including amnesic and non-amnesic subtypes diagnosed according to published criteria	Age, sex, years of education, diabetes, hypertension, stroke, BMI, depression, dyslipidemia, APOE genotype	OR of MI for MCI was 0.91 (95%CI 0.55, 1.49).
Zou, 2014 ⁵⁶⁾	History of coronary heart disease including silent MI, AP, MI, or ischemic cardiomyopathy, assessed by ECG and color doppler ultrasound	MCI diagnosed according to patients complains and MMSE and CDR scores.	Age, gender and education	OR of CHD for MCI, OR 0.988 (95%CI 0.981, 0.996).
Hai, 2012 ²⁶⁾	History of CHD ascertained by interview	MCI diagnosed following the criteria proposed by Petersen et al.	Not clarified	OR of CHD for MCI 6.76 (95%CI 2.74, 16.67).
Kuroki, 2018 ⁵⁷⁾	Medical history of IHD obtained from clinical records	MMSE score < 24 considered to indicate MCI.	Age, sex, smoking and drinking habit, number of teeth	OR of IHD for MCI 2.73 (95% CI 1.32, 5.67)
Stephan, 2017 ⁵⁸⁾	CHD composite variable incorporating the presence of self-reported heart attack (single question asking about the presence or absence of the condition) or angina based on the Rose Diagnostic Scale.	MMSE score < 24 considered to reflect MCI.	Age, sex, years of education, disease comorbidity	OR of CHD for MCI 1.02 (95%CI 0.71-1.40).

(Cont Supplementary Table 5)

Study, year	Ascertainment of exposure	Outcomes	Adjustments for confounders	Main results
Heath, 2014 ²⁷⁾	Information of IHD extracted using electronic medical records	Diagnosis of dementia fulfilled DSM-IV	Age, sex, neurodegenerative disorder, learning disability, socioeconomic status	OR of IHD for dementia 1.9 (95%CI 1.5, 2.4)
Ross, 1999 ²⁵⁾	Prevalent CHD defined as MI or AP without describing ascertainment method	Vascular dementia diagnosed based on the criteria proposed by California Alzheimer Disease Diagnostic and Treatment Centers	Age	OR of CHD for vascular dementia 2.60 (95%CI 1.59, 4.25).
Deng, 2018 ²⁸⁾	CHD ascertained by questionnaire	Dementia diagnosis based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders	Living area, age, marital status, smoking, exercise, social activities, BMI, hypertension, depression	OR of CHD for dementia 1.596 (95%CI 1.017–2.506)
Dolan, 2010 ⁵³⁾	Coronary atherosclerosis examined postmortem	Diagnosis of dementia based on DSM-III-R and the pathology assessed by autopsy	Age, sex	No association between coronary atherosclerosis and dementia
Case control				
Jacob, 2017 ³¹⁾	CHD diagnosed based on ICD codes I20-I25	MCI diagnosed based on ICD 10 codes by neurologists or psychiatrists	Disorders including, anxiety, depression, hyperlipidemia, obesity, hypertension, diabetes	OR of CHD for MCI 1.17 (95%CI 1.04, 1.32).
Bursi, 2006 ¹⁰⁾	MI defined based on ICD codes 410-414	Dementia diagnosed according to DSM-IV	NA	OR of MI for dementia 1.00 (95%CI 0.62, 1.62)
Massaia, 2001 ⁵⁹⁾	History of acute MI	AD diagnosed according to DSM-III and the NINCDS-ADRDA work group criteria	NA	No significant difference between AD and controls regarding a history of acute MI
Booker, 2016 ²⁹⁾	CHD diagnosed in primary care based on ICD codes I20-I25	Dementia diagnosed based on ICD codes.	Diabetes, hypertension, obesity, hyperlipidemia, medications	OR of CHD for dementia 1.07 (95%CI 1.04, 1.14).
Takahashi, 2012 ³⁰⁾	History of angina and diagnosis of	Clinically documented diagnosis of definite vascular dementia based upon the NINDS-AIRE criteria	Not adjusted	ORs of angina and previous MI for vascular dementia 1.22 (95%CI 0.79, 1.88) and 1.11 (95%CI 0.66, 1.87) respectively.
Longitudinal (risk of MCI/dementia)				
Newman, 2005 ¹²⁾	Prevalent MI and AP assessed by self-report and confirmed by medical records, test results, medication use.	Incidence of dementia diagnosed based on clinical criteria	Age, race, education, income, APOE epsilon-4, modified MMSE score	HR of MI for dementia 1.3 (95%CI 1.0, 1.9) and HR of AP for incident of dementia 1.3 (95%CI 1.0, 1.7)
Rusanan, 2014 ¹¹⁾	CAD based on ICD codes, ascertained by self-reported history of MI or AP	Incidence of dementia diagnosed according to the DSM-IV	Sex, education, systolic blood pressure, cholesterol, BMI, APOE, smoking, physical activity, diabetes or impaired glucose tolerance	HR of CAD diagnosed midlife (at or before baseline) and late-life (at or before first reexamination) for dementia 0.80 (95%CI 0.38, 1.67) and 1.66 (95%CI 0.87, 3.16), respectively

(Cont Supplementary Table 5)

Study, year	Ascertainment of exposure	Outcomes	Adjustments for confounders	Main results
Hayden, 2006 ⁶¹⁾	History of MI obtained by interview	Dementia diagnosed according to DSM-III-R, the NINCDS-ADRDA criteria was used for AD diagnoses. Vascular dementia was identified with the NINDS-AIREN criteria.	Age, sex, education, APOE epsilon-4, hypertension, high cholesterol, diabetes, obesity	HR of MI for dementia 1.13, (95%CI 0.59, 2.03), for AD 1.11, (95%CI 0.49, 2.26) and for vascular dementia 1.06, (95%CI 0.34, 2.93)
Haring, 2013 ¹³⁾	MI defined as reported history of clinical MI, or ECG results with evolving Q-wave	Measures for incidence of MCI or probable dementia based on DSM-IV	Age, education, race, smoking, alcohol intake, physical activity, diabetes, sleep hours, hypertension, BMI, depression, waist-hip ratio, hypercholesterolemia, aspirin use	HR of MI for dementia 2.18 (95%CI 1.19, 3.99), for MCI 2.56 (95%CI 1.64, 4.01) and for MCI or dementia 2.10 (95%CI 1.40, 3.15)
Ikram, 2008 ⁶²⁾	MI including unrecognized, Q-wave and recognized subtypes screened by interview and then confirmed by clinical data and ECG characteristics	Incident dementia ascertained following a 3-step protocol and diagnosed based on DSM-III-R	Age, sex, APOE epsilon-4, systolic blood pressure, diastolic blood pressure, BMI, diabetes, atrial fibrillation, current smoking, intima media thickness, total cholesterol and HDL cholesterol	HR of unrecognized MI for dementia 2.23, (95%CI 1.24, 4.01) in men, in women 1.17, (95%CI 0.74, 1.83), and in total 1.35, (95%CI 0.95, 1.92).
Brayne, 1998 ⁶⁰⁾	History of heart attack ascertained from informants	Incidence of dementia ascertained based on the clinical criteria	Age, sex	OR of history of MI for dementia 2.94 (95%CI 1.2, 7.21)
Kivipelto, 2002 ³³⁾	History of MI assessed with a self-administrated questionnaire	Dementia diagnosed according to the criteria of the DSM-IV	Age, APOE epsilon-4, education level, sex, smoking, alcohol consumption	OR of MI for AD or vascular dementia 2.5 (95%CI 1.2, 5.4)
Chen, 2011 ³²⁾	Doctor-diagnosed angina recorded	Dementia diagnosis based on DSM-III	Age, sex, BMI, urban-rurality, socio-economic status, smoking, social network, psychosocial factors	OR of Angina for dementia 2.58 (95%CI 1.01, 6.59).
Lin, 2017 ⁶³⁾	ICD-9-CM used for diagnosis coding, further specified for CHD	Vascular dementia (ICD-9-CM code 290.4x) diagnosed by a psychiatrist or a neurologist	Age, sex, comorbidities like hypertension, diabetes, dyslipidemia; urbanization level, monthly income level, depressive disorder	HR of CHD for vascular dementia in patients with and without depression 2.26 (95%CI 1.07, 4.75)

CAD, Coronary Artery Disease; IHD, Ischemic Heart Disease; ECG, electrocardiogram; CHD, Coronary Heart Disease; MI, Myocardial Infarction; SD, Standard Deviation; CAMCOG, Cambridge Cognitive Examination of the Elderly Revised; MoCA, Montreal Cognitive Assessment; MMSE, Mini Mental State Examination; AP, Angina Pectoris; ACS, Acute Coronary Syndrome; BMI, Body Mass Index; HDL, High-density Lipoprotein; TICSm, Telephone Interview for Cognitive Status-modified; TIA, Transient Ischemic Attack; OR, Odds Ratio; CI, Confidence Interval; CDR, Clinical Dementia Rating; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; GP, General Practitioner; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders Version III Revised; HR, Hazard Ratio; ICD, International Statistical Classification of Diseases and Related Health Problems NINCDS-ADRDA : National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NINDS-AIREN: National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences; NA, not available; APOE, apolipoprotein E

Quality assessment

Supplementary Table 6. Quality assessment of cross-sectional studies included in the meta-analysis

Study, author	Selection				Comparability (maximum two stars)	Outcome	
	Representative- ness of the sample	Sample size	Non- respondents	Ascertainment of the exposure (risk factor) (maximum two stars)	The subjects in different out- come groups are comparable, based on the study design or analysis. Confounding fac- tors are controlled	Assessment of the outcome (maximum two stars)	Statistical test
Ross 1999	★	★			★★	★★	★
Roberts 2010	★	★		★	★★	★★	★
Hai 2012		★	★			★★	★
Zou 2014		★	★	★	★	★★	
Heath 2014	★	★			★★	★★	★
Stephen 2017	★	★		★	★★	★★	★
Kuroki 2018		★		★	★★	★★	★
Deng 2018	★	★			★★	★	★

Star is rewarded for each item when the study presents the feature of quality. Each study can be rewarded a maximum of one star for each item except a maximum of two stars can be given to the items including ascertainment of the exposure (risk factor), comparability and assessment of the outcome. In brief, the quality criteria were defined as follows: representativeness of the sample: all subjects or random sampling; sample size: justified and satisfactory; non-respondents: response rate is satisfactory, characteristics between respondents and non-respondents were comparable; ascertainment of exposure (risk factor): validated measurement tool=2 stars, non-validated measurement tool, but the tool is available or described=1 star; comparability: study controls for most important factor (defined as age and sex) (1 star) and control for any additional factor (defined as cardiovascular risk factors) (1 star); assessment of the outcome: was independent blind assessment or record linkage=2 stars, self-report=1 star; statistical test: clearly described and appropriate, and the measurement of the association is presented including confidence intervals and the p value.

Supplementary Table 7. Quality assessment of case-control studies included in the meta-analysis

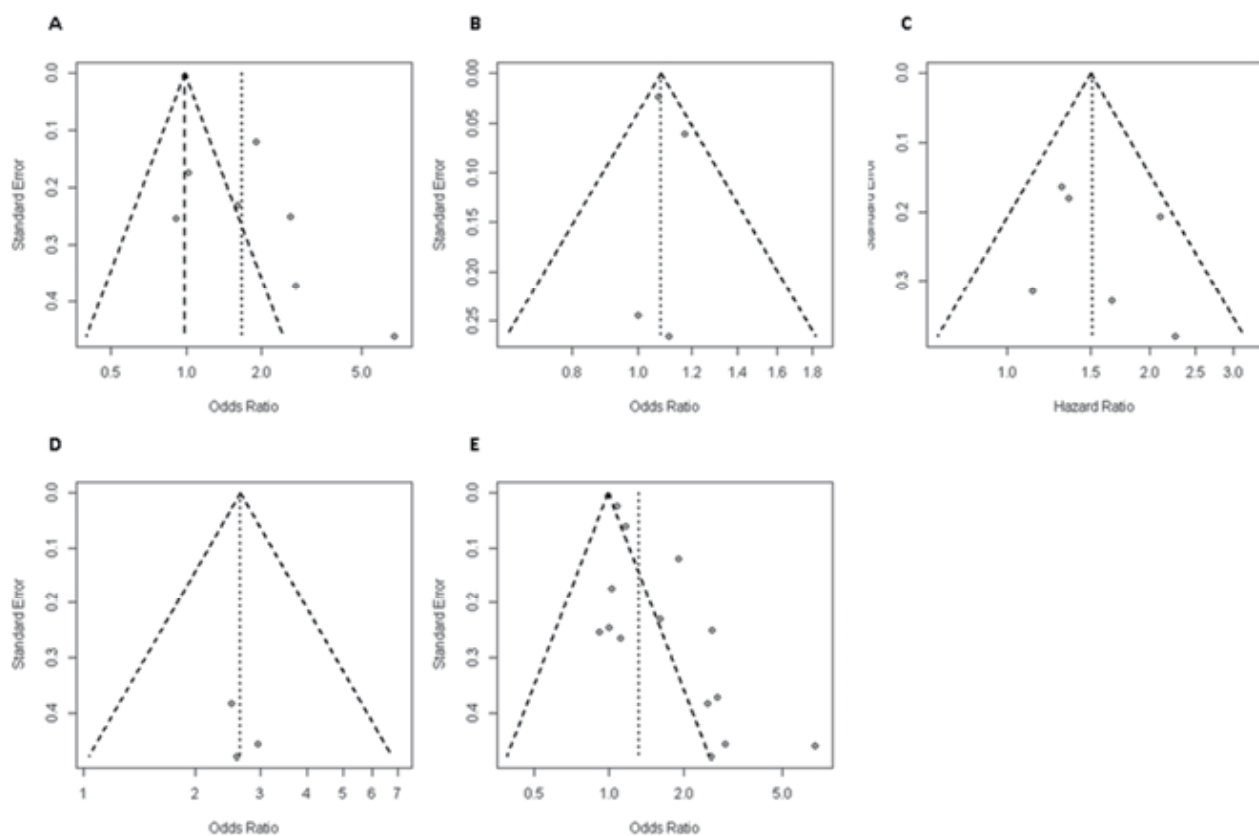
Study, author	Selection				Comparability (maximum two stars)	Outcome		
	Is the case definition adequate?	Representa- tiveness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertain- ment of exposure	Same method of ascertainment for cases and controls	Non- response rate
Bursi 2006	★	★	★	★		★	★	
Booker 2016		★		★			★	
Takahashi 2012	★	★		★			★	
Jacob 2017		★		★			★	

Star is rewarded for each item when the study presents the feature of quality. Each study can be rewarded a maximum of one star for each item except a maximum of two stars can be given to the item comparability. In brief, the quality criteria were defined as follows: is the case definition adequate: yes with independent validation; representativeness of the cases: consecutive or obviously representative series of cases; selection of controls: community controls; definition of controls: no history of disease(endpoint); comparability: study controls for age and sex (1 star) and controls for cardiovascular risk factors (1 star); ascertainment of exposure: secure record or structured interview where blind to case/control status; same method of ascertainment for cases and controls: yes; non-response rate: same rate for both groups.

Supplementary Table 8. Quality assessment of longitudinal cohort studies included in the meta-analysis

Study, author	Selection			Comparability (maximum two stars)		Outcome		
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of the outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Rusanen 2014	★	★		★	★★	★	★	
Newman 2005	★	★	★	★	★★	★	★	
Hayden 2006	★	★	★	★	★★	★		
Haring 2013		★	★	★	★★	★	★	
Ikram 2008	★	★	★	★	★★	★	★	★
Lin 2017	★	★	★	★	★★	★	★	★
Brayen 2006		★	★	★	★★	★		
Chen 2011	★	★			★★	★		
Kivipelto 2002	★	★			★★	★		

Star is rewarded for each item when the study presents the feature of quality. Each study can be rewarded a maximum of one star for each item except a maximum of two stars can be given to the item comparability. In brief, the quality criteria were defined as follows: representativeness of the exposed cohort: truly or somewhat representative of the population based community; selection of the non-exposed cohort: draw from the same community as the exposed cohort; ascertainment of exposure: secured record or structured interview; demonstration that outcome of interest was not present at start of study : yes; comparability: study controls for age and sex (1 star) and controls for cardiovascular risk factors (1 star); assessment of outcome: independent blind assessment or record linkage; was follow-up long enough for outcomes to occur: yes, at least 5 years; adequacy of follow up cohorts: complete follow up all subjects accounted for or subjects lost to follow up unlikely to introduce bias: small number (5%) lost follow up or description provided of those lost.



Supplementary Fig. 1. Funnel plots of the association between coronary artery disease and mild cognitive impairment or dementia in cross-sectional studies. (A), in case-control studies (B), in cohort studies that reported hazard ratio (C), in cohort studies that reported odds ratio (D), and in all studies reported odds ratio (E).