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Intracranial arterial calcification on computed tomography and risk of cognitive impairment or dementia: A systematic review and meta-analysis

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Short Title: Intracranial Arterial Calcification and Dementia

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Abstract

Introduction: Coronary arterial calcification on computed tomography (CT), or CT-CAC, is a widely studied risk factor for acute coronary events, but although intracranial arterial calcification on CT brain imaging (CT-IAC) is also a frequent finding in older individuals, there is no consensus on its prognostic significance, particularly whether its presence, severity, or site predict cognitive impairment or dementia. Given the clinical and mechanistic importance of any associations, we did a systematic review and meta-analysis.

Methods: Studies published before 30 January 2026 were identified from bibliographic databases, reference lists, and forward or backward screening. Inclusion criteria were: (1) Studies of adults linking CT-IAC/CAC with later cognitive impairment or dementia; (2) reporting adjusted effect measures with 95% confidence interval or p-values (or calculable); (3) calcification assessed by CT/CT angiography and cognition by recognised tests or expert evaluation. Studies were summarised qualitatively and pooled quantitatively depending on heterogeneity.

Results: Six cross-sectional studies and three longitudinal studies reported data on CT-IAC and cognitive status. Among five studies that reported associations for presence vs. absence of CT-IAC, presence of calcification was weakly associated with cognitive impairment or dementia (three cross-sectional studies – pooled adjusted odds ratio [aOR]=1.42, 0.88–2.28, p=0.15; two longitudinal studies – aOR=1.51, 1.03–2.22, p=0.033; all studies – aOR=1.48, 1.10–1.99, p=0.01). Among five studies that reported associations for more severe vs. milder CT-IAC, severe calcification was more strongly associated with the cognitive outcome (two cross-sectional studies – pooled aOR=2.29, 0.50–10.57, p=0.29; three longitudinal studies – aOR=1.84, 1.28–2.65, p=0.001; all studies – aOR=1.74, 1.28–2.36, p=0.0004), including in two longitudinal cohorts in patients with stroke/transient ischaemic attack (pooled aOR=1.73, 1.22–2.46, p=0.002). In two longitudinal studies, severity of vertebrobasilar CT-IAC also predicted dementia (pooled aOR=2.12, 1.06–4.21, p=0.033), and severity of medial/internal elastic lamina (IEL) CT-IAC was a stronger predictor of dementia (pooled aOR=2.35, 1.29–4.28, p=0.005) than severity of intimal CT-IAC (pooled aOR=1.29, 0.75–2.23, p=0.36). For coronary CT-CAC, three longitudinal cohorts revealed weak associations with dementia (per standard deviation increase in calcification measures – pooled adjusted hazards ratio=1.15, 1.02–1.30, p=0.025).

Conclusion: In longitudinal studies, presence and severity of CT-IAC are both independently associated with dementia, driven mainly by medial/IEL calcification, with weaker associations for intimal and coronary calcification. In cross-sectional studies, the associations for both CT-IAC measures were of a similar magnitude to the longitudinal analyses, but were not statistically significant. Future studies should determine age- and dementia-subtype specific associations.

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Introduction

Stroke and dementia are the most prevalent disabling neurological disorders in both high-income and low-income countries [1]. The two conditions often co-exist, each increasing the risk of the other, and they share several risk factors [2]. Both conditions are also strongly age-related, due partly to associations with vascular pathologies, including atherosclerosis and small vessel disease [3]. Arterial calcification also increases with age, and computed tomography (CT)-visualised coronary artery calcification (CT-CAC) has been shown in multiple studies to be a strong independent risk factor for acute coronary events [4, 5], with possible associations with stroke and dementia [6, 7].

Calcification of the intracranial arteries on CT brain imaging (CT-IAC) is also a frequent finding in older individuals, but there is less evidence on whether its presence, severity, or site predict cognitive impairment and dementia [8]. Following early reports from the Rotterdam Study [9, 10], several studies have reported cross-sectional associations between CT-IAC and co-existing cognitive decline or dementia [11-16], but there have been fewer longitudinal validations of the Rotterdam Study findings on the predictive value of CT-IAC for future risk of dementia adjusted for other vascular risk factors [17-21]. In addition, a recent longitudinal analysis within the Oxford Vascular Study (OXVASC) suggested that association between CT-IAC volume and dementia was non-linear, such that both presence and severity should be taken into account. Moreover, both the predictive value and the mechanism of development of CT-IAC might depend on the histological location of calcification. Calcification of the arterial intima is usually related to atheroma and thus inflammation and lipid deposition may therefore play a role [22-24, 18, 19]. Calcification of the media and internal elastic lamina (IEL) is more often associated with metabolic disorders including diabetes mellitus, chronic kidney disease, and parathyroid disorders, and is correlated with increased arterial stiffness and white matter hyperintensities, which might also explain an increased risk of dementia [22-24, 19]. Given that CT-IAC is a highly accessible and possibly treatable risk factor for dementia, particularly in patients with other vascular risk factors, and in the absence of a previous quantitative systematic review and meta-analysis, we performed a systematic review and meta-analysis of all eligible cross-sectional and longitudinal studies to determine whether the presence, severity, and site (intimal vs. medial/IEL) of CT-IAC are associated with dementia independently of vascular risk factors, both in patients with previous TIA or stroke and in the general population.

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Methods

We conducted a systematic review examining the association of CT-IAC with dementia and pooled previous longitudinal studies using meta-analysis depending on heterogeneity. This was conducted according to a pre-specified protocol registered on PROSPERO (CRD42024492864), which was initially focused on CT-IAC but was later expanded to include CT-CAC as a secondary, comparative analysis to enable comparisons between calcification at different vascular sites. The review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [25]. Eligibility criteria were defined to minimise clinical heterogeneity and to avoid selective inclusion based on study results, and were formulated using a structured framework addressing population, exposure, outcome, and study design, consistent with recommendations for prognostic factor meta-analyses [26].

Title and abstract screening, full text review, and data extraction of studies related to calcification and dementia on follow-up were performed and recorded on the Covidence online platform. The Ovid Medline (1946 to 30 January 2026) and Embase (1974 to 30 January 2026) databases were searched by one of the researchers (KL) using standard phrases (**Tables S1**). No restrictions were imposed on searching strategies. Searching reference lists of reviews, forward and backward screening were conducted as additional searching methods.

Inclusion criteria for the review were: (1) Studies of adult human subjects that examined the association between CT-IAC/CAC and cognitive impairment or dementia at follow-up. For CT-CAC, only longitudinal studies were included. (2) Studies that reported adjusted effect sizes, including but not limited to odds ratios (OR), hazard ratios (HR), or relative risks (RR), along with the corresponding 95% confidence intervals (CI) or *p*-values, or where these values could be calculated. (3) Use of CT or CT angiography to detect calcification. (4) Cognitive impairment or dementia on neuropsychological assessment or expert evaluations.

Exclusion criteria were as follows: (1) Short reports, including case reports, letters, conference proceedings, and viewpoints. (2) Studies that exclusively recruited subjects with metabolism-related conditions, such as hypoparathyroidism, renal insufficiency, diabetes mellitus, and Fahr's disease, or those that only included subjects undergoing vascular procedures. (3) If multiple studies with similar predictor and outcome variables were based on the same cohort, then only the study with most comprehensive and updated information on subjects, exposure, and outcome was included.

All articles retrieved from the initial search were screened by one reviewer (KL). Both reviewers (KL and OO) reviewed articles that passed screening to decide eligibility, and extracted data independently. The data extracted included study information (authors, study period, country/region), population characteristics (age, sex, inclusion/exclusion criteria, follow-up duration, and sample size), calcification measurements, cognitive outcomes with corresponding diagnostic criteria, number of participants with outcomes in each group, and effect sizes of calcification associated with outcomes along with their 95% CI).

The Newcastle-Ottawa scale (NOS) [27] was used for quality assessment of case-control or cohort studies by the two reviewers independently, and for cross-sectional studies the Appraisal tool for Cross-Sectional Studies (AXIS) was used [28]. On NOS, high, moderate, and low quality were defined as 8–9, 6–7, and 0–5 points, respectively [29]. AXIS getting favourable scoring for 15–20, 10–14 and 0–9 items were considered good, moderate and poor quality [30]. Disagreements were resolved by discussion between the reviewers.

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Certainty assessment was conducted with the online tool of Grading of Recommendations Assessment, Development and Evaluation (GRADE) (https://gdt.gradepro.org/app/).

Eligible studies were first summarised qualitatively. Given the high prevalence of ICA calcification in older individuals and the heterogeneous calcification measures across studies [19-21], some previous analyses involving ICA CT-IAC were stratified by mean age of participants (≥ or <65 years) and CT-IAC measures (continuous/ordinal, binary with high cutoff, or binary with low cutoff). Binary measures with high cut-off were defined as severe CT-IAC on qualitative scales or above the median on quantitative measures compared with milder CT-IAC. Estimates of the association between calcification measures and dementia were pooled using meta-analysis depending on the extent of heterogeneity between studies. Given that the OR in case-control studies nested in prospective cohorts approximates the rate ratio for the source population [31], estimates from studies using either of these methods were included for meta-analysis. Effect sizes reported as HR and RR were transformed to OR using previously published methods [32]. For results not available in the original study publications, authors were contacted to obtain the relevant data if available. Subgroup analysis was done for subtypes of CT-IAC (the intimal and the medial/IEL subtypes) if data were available. Sensitivity analysis was carried out by pooling studies using most similar calcification measures. Reporting biases of studies were not assessed due to the low number of eligible studies.

For the meta-analysis, adjusted OR (aOR) or adjusted HR (aHR) values of CT-IAC/CAC associated with future cognitive impairment or dementia, with respective 95% CI, were pooled. When a 95% CI was reported with an infinite upper or lower bound, we approximated the standard error of the log-transformed estimate using the other available bound. Meta-analysis was performed using random effects models if there are clinical or methodological differences in the included studies, otherwise fixed effects models were used. Heterogeneity of studies was assessed by I^2 statistic and the Q test.

Random-effects meta-regression was performed to examine whether mean age of the study population modified the association between CT-IAC and cognitive outcomes. Log-transformed adjusted odds ratios were used as the dependent variable, with mean age specified as the primary moderator. Meta-regression analyses were conducted separately for binary CT-IAC measures defined using high and low cutoff thresholds, to maximise use of available studies under each definition. Models were fitted using restricted maximum likelihood estimation. Bubble plots were used to visualise the relationship between effect size and mean age, with point size proportional to study precision. Statistical analyses were conducted with R 4.3.2.

Reasonable request for data supporting this study's findings will be considered by the chief investigator. For further details, please contact Professor Peter Rothwell (peter.rothwell@ndcn.ox.ac.uk).

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Results

Literature search and screening are summarised in **Figures S1–S2**, and eligible studies in **Tables 1–2 and S2**. CT acquisition, reconstruction, and assessment details of cross-sectional and longitudinal studies included in the systematic review were displayed in **Tables S3–S4**, respectively. Six cross-sectional studies on CT-IAC were found (**Table 1**). Nine reports derived from five eligible longitudinal cohorts on CT-IAC or CT-CAC and dementia were identified. Three of those reports remained in the systematic review and meta-analysis for CT-IAC (**Table 2**) and CT-CAC (**Table S2**) respectively after excluding reports from the same cohort. On quality assessment using the AXIS, the cross-sectional studies were of good quality (**Table S5**). The Tel-Aviv Brain Acute Stroke Cohort (TABASCO) study had moderate quality on NOS, with limitations in confounding adjustments, follow-up duration, and reporting of reasons for loss to follow-up. The reports from the Rotterdam Study, OXVASC, Multi-Ethnic Study of Atherosclerosis (MESA), and Cardiovascular Health Study Cognition Study (CHS-CS) were classified as high quality (**Tables S6–S7**).

Three of the six eligible cross-sectional studies showed positive associations between CT-IAC and cognitive impairment or dementia (**Table 1**). Kao et al. found that ICA Agatston calcium score was significantly associated with cognitive impairment in patients undergoing CT for various neurological conditions (per 100-point increase – aOR=1.06, 1.00–1.13, p=0.04) [11]. An Ecuadorian study showed an association between ICA calcification based on the Woodcock scale and Montreal Cognitive Assessment (MoCA) score (severe calcification vs. none – β=-2.04, -3.76–-0.33, p=0.02) [13]. A Bolivian study revealed that more severe ICA or lenticulostriate artery calcification was associated with dementia compared to milder calcification (continuous vs. irregular or patchy ICA calcification – aOR=6.10, 1.23–30.4) [16]. The other three included cross-sectional studies did not find significant associations between CT-IAC and cognitive impairment or dementia [12, 14, 15].

Three eligible longitudinal studies on CT-IAC and dementia were identified (**Table 2**). The Rotterdam study reported that internal carotid artery (ICA) calcification predicted dementia risk at a median follow-up of 13.4 years (aHR=1.19, 1.01–1.40, for per standard deviation [SD]), as did vertebrobasilar artery (VBA) calcification (aHR=1.89, 1.00–3.59, for top vs. bottom volume tertile) [19]. In OXVASC study of patients with TIA or stroke, semi-automated quantitative volume of CT-IAC independently predicted dementia on follow-up for ICA calcification (top vs. bottom tertile – aOR=2.35, 1.33–4.16, p=0.003), VBA calcification (2.29, 0.58–9.06, p=0.24), and total CT-IAC (2.59, 1.43–4.68, p=0.002). The TABASCO study of patients with TIA or ischaemic stroke [18] reported data on calcification in ICA, vertebral artery (VA), and basilar artery (BA) combined, and found that the Agatston calcium score predicted cognitive impairment at 2-year follow-up (aOR=1.83, 1.01–3.35, for above vs below median). A fourth report, of a small case-control study of memory clinic participants [17], reported that the log-transformed Agatston calcium score/volume in ICA did not predict dementia (univariable OR=0.89, 0.74–1.07, p=0.21, and univariable OR=0.90, 0.85–1.08, p=0.27, respectively), but was not eligible for our review as only univariate analyses were reported, and the estimates could not be meta-analysed with the adjusted estimates from other studies.

Cross-sectional and longitudinal analyses on CT-IAC stratified by mean age of participants and CT-IAC measures were summarised in **Table S8**. For studies recruiting patients with a mean age of younger than 65 years, all types of CT-IAC measures were significantly associated with cognitive impairment (four out of four analyses). However, for studies recruiting patients with a mean age of older than 65 years, significant associations were mainly observed in analyses adopting continuous/ordinal or high cutoff binary CT-IAC

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measures (two out of three analyses and three out of five analyses, respectively), but not in analyses using binary CT-IAC measures with low cutoff (one out of six analyses).

In the meta-analysis, we first investigated whether presence of any calcification was associated with dementia. Pooled results showed that present ICA CT-IAC was not associated with cognitive impairment cross-sectionally (pooled aOR=1.42, 0.88–2.28, p=0.15; **Fig. 1**). However, the presence of ICA but not VBA calcification slightly increased risk of dementia on follow-up (ICA - pooled aOR=1.51, 1.03–2.22, p=0.033; VBA - pooled aOR=1.07, 0.81–1.40, p=0.63; **Fig. 1**). The association was stronger for the presence vs absence of medial/IEL ICA CT-IAC (pooled aOR=1.66, 1.05–2.63, p=0.030; **Fig. 2**), but weaker association for the atherosclerotic intimal subtype (pooled aOR=1.36, 0.94–1.98, p=0.10; **Fig. 2**). Pooling cross-sectional and longitudinal studies reporting effect sizes on presence of CT-IAC in ICA showed a significant association (pooled aOR=1.48, 1.10–1.99, p=0.01)

Regarding cross-sectional studies reporting severity measures, meta-analysis suggested higher odds of cognitive impairment among individuals with high CT-IAC, although the association did not reach statistical significance (pooled aOR=2.29, 0.50–10.57, p=0.29; **Fig. 3**). All three longitudinal studies reported data on severity of intracranial CT-IAC and risk of cognitive impairment or dementia, although there were small differences in methodology and analysis, which we attempted to circumvent in our pooled analyses (**Tables S9–S10)**. For example, the Rotterdam and OXVASC studies reported data on ICA calcification separately, whereas the TABASCO study combined ICA, VA, and BA calcification. However, since the vast majority of calcification volume across these vessels is derived from the ICA alone (98% in OXVASC), we pooled the TABASCO estimate with the ICA calcification estimates in the other two studies. Pooled analysis of estimates from the three studies showed a significant association between severe ICA calcification and dementia (pooled aOR=1.84, 1.28–2.65, p=0.001), with little heterogeneity between studies (I^2=0; **Fig. 3**).

Reclassification of CT-IAC measurements from OXVASC so as to match the estimates reported in the other studies as closely as possible yielded similar pooled estimates (OXVASC/TABASCO pooled aOR=1.73, 1.22–2.46, p=0.002; OXVASC/Rotterdam pooled aOR=1.85, 1.17–2.91, p=0.008; **Fig. S3**). Severity of VBA calcification was associated with increased risk of dementia on pooled analysis of the Rotterdam and OXVASC estimates (aOR=2.12, 1.06–4.21, p=0.033; **Fig. 3**).

Separate estimates of associations of severity of ICA CT-IAC with dementia risk for medial/IEL ICA CT-IAC vs. the atherosclerotic intimal subtype were reported in the Rotterdam and OXVASC studies (**Fig. 4**). The top vs. bottom tertile of medial/IEL ICA CT-IAC predicted dementia on pooled analysis (aOR=2.35, 1.29–4.28, p=0.005), whereas there was only a weak trend for the atherosclerotic intimal subtype (aOR=1.29, 0.75–2.23, p=0.36). Pooling cross-sectional and longitudinal studies that reported severity CT-IAC measures in ICA also showed a robust association (pooled aOR=1.74, 1.28–2.36, p=0.0004).

Study-level meta-regression showed no evidence that mean age of the study population modified the association between CT-IAC and cognitive outcomes. Using binary CT-IAC measures defined by a high cutoff, mean age was not associated with effect size (five studies – β=-0.014, -0.079−0.050, p=0.66), and similar results were observed using a low cut-off definition (five studies – β=-0.016, -0.079−0.046, p=0.61). Bubble plots showed no clear age-related trend in effect estimates across studies (**Fig. S4**; **Table S11**).

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Four prior longitudinal studies reported the association between the presence or severity of coronary artery calcification (CT-CAC) and risk of dementia[10, 33, 6, 34], which were from three independent cohorts[10, 6, 34], and thus three of them were included in our systematic review (**Table S2)**. Only MESA investigated the effect of presence vs. absence of any CT-CAC, but did not find a significant association with dementia [33]. Reports from MESA and CHS-CS showed associations between severity of CT-CAC and increased dementia risk,[33, 6, 34] while the Rotterdam cohort did not [10]. A pooled analysis was only possible for the MESA and Rotterdam studies, showing a weak association between CT-CAC and dementia (per SD increase in calcification measures – pooled aHR=1.15, 1.02–1.30, p=0.025; **Fig. S5**). Only the Rotterdam Study directly compared the predictive values of calcification at different sites (**Fig. S5**), showing that the association appeared to be stronger for CT-IAC than for CT-CAC.

The GRADE assessment indicated a high level of certainty regarding the longitudinal association between of severity of ICA calcification and risk of dementia, and a moderate level of certainty for the other calcification measures used in longitudinal studies due to imprecision. For cross-sectional studies, the level of certainty was low due to concerns on indirectness and imprecision.

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Discussion

Important early reports from the Rotterdam Study [9, 10, 19] and a previous qualitative review of calcification in various vascular beds [8] highlighted the potential of CT-IAC as a risk factor for dementia and other outcomes. Our systematic review now identified six eligible cross-sectional and three eligible longitudinal studies reporting associations between CT-IAC and cognitive impairment or dementia. Meta-analysis showed that both presence and severity of CT-IAC were associated with cognitive outcomes in longitudinal studies, with similar trends in stroke/TIA patients and the general population, driven mainly by medial/IEL CT-IAC. In cross-sectional studies, pooled effect estimates for both CT-IAC measures were of a similar magnitude to those observed in longitudinal studies but did not reach statistical significance.

Given that age is a major determinant of both CT-IAC burden and cognitive outcomes, we explored its potential role using age-stratified analyses and meta-regression. Age-stratified descriptive analyses suggested that severe CT-IAC tended to be associated with cognitive impairment or dementia in both older and younger individuals, whereas presence versus absence of CT-IAC appeared more consistently associated with cognitive outcomes in younger populations. Formal meta-regression did not identify mean study age as a statistically significant moderator of the pooled effect estimates, which indicated that the observed relationship between CT-IAC and cognitive outcomes was not driven by differences in age across studies, thereby supporting the robustness of the pooled estimates. The meta-regression was necessarily restricted to studies with comparable binary exposures and outcomes and therefore largely reflected populations aged ≥65 years (**Fig. S4**). Overall, these findings suggest that CT-IAC is associated with adverse cognitive outcomes across a wide age range, while the discriminatory value of different CT-IAC measures might vary according to baseline calcification prevalence across age groups. Further studies are needed to validate this observation.

Although the association between CT-IAC and dementia appeared to be independent of vascular risk factors, a causal link cannot necessarily be assumed. However, there is some evidence of plausible mechanisms. For example, in mouse models, arterial stiffness due to carotid calcification led to compromised resting cerebral blood flow and cerebral autoregulation, increased pulsatility of flow, and increased blood-brain barrier permeability, and Aβ40/Aβ42 ratio [35, 36]. The finding of a stronger association with dementia for CT-IAC of the medial/IEL type vs. CT-IAC of the atherosclerotic intimal type potentially supports mediation by arterial stiffness rather than hypoperfusion and micro-embolism [19]. In addition, the Bolivian cross-sectional study showed stronger associations than most studies, and their patients had predominant circular and continuous CT-IAC consistent with medial calcification [16]. Indeed, although CT-IAC is probably also an independent predictor of ischaemic stroke [37], the associations with dementia in the Rotterdam Study and in OXVASC were independent of stroke recurrence [19-21]. Findings from previous reports [10, 38] (**Fig. S5**) that calcification of the aortic arch and of the extracranial or intracranial ICA appear to be more strongly related to future cognitive decline and dementia than coronary artery calcification would also be consistent with greater predictive value of medial/IEL vs. atherosclerotic intimal calcification.

Distinguishing intimal from medial/IEL calcification in vivo is methodologically challenging. Accordingly, current studies included in this systematic review rely on validated CT-based morphological surrogates (e.g. circularity, thickness, and continuity) [39]. Although this approach is indirect, histology-correlated data support its reasonable validity and reproducibility [39]. At present, visual distinction of intimal from medial/IEL calcification therefore represents the most practical approach for clinical and epidemiological

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studies, while more standardised quantitative and automated methods are expected to develop incrementally as complementary tools.

While the findings strengthen the evidence base on the associations between the presence/severity of CT-IAC and cognitive impairment or dementia, and provide some hints on the sources of heterogeneity in the current literature, our systematic review and meta-analysis have some limitations. First, for prediction of future risk of dementia only three eligible longitudinal studies of CT-IAC were available. Second, none of studies included in the review were able to fully account for all potentially confounding factors, including by medications, such as loop diuretics [40, 41], warfarin [42], and angiotensin receptor blockers [43, 44], which are potentially related to both vascular calcification and dementia. Third, the Rotterdam and OXVASC cohorts are predominantly white, and so the findings might not be fully generalisable. Indeed, in the South American Tsimane population, the prevalence of ICA and VA CT-IAC was 95.7% and 98.2%, respectively, with a predominance of circular and continuous calcification patterns consistent with medial calcification [16], which rates are significantly higher than those in reported in European populations [19-21]. Fourth, although intracranial arterial calcification can also be present in distal intracranial vessels such as the middle, anterior, and posterior cerebral arteries, we did not identify any studies meeting our eligibility criteria that specifically examined calcification in these vessels in relation to cognitive outcomes. As a result, the present review was necessarily limited to major intracranial arteries. Future studies using whole-brain [45] or vessel-specific approaches may help clarify the potential independent relevance of calcification in distal intracranial arteries. Finally, there was methodological heterogeneity across studies in exposure definition (e.g. presence versus severity and different quantitative or categorical CT-IAC measures), outcome ascertainment (continuous cognitive scores versus categorical dementia diagnoses), and duration of follow-up. Accordingly, random-effects models were used throughout. However, most studies were rated as good or high quality, and the main associations were generally consistent across studies of satisfactory quality. Although the limited number of studies precluded formal statistical tests for publication bias, there was no clear indication that the findings were driven by studies at higher risk of bias. Future high-quality studies should apply more standardised approaches to the assessment of both intracranial arterial calcification and cognitive outcomes.

Our findings have some clinical implications. First, both the presence and severity of CT-IAC could be used to identify individuals at higher risk of adverse cognitive outcomes, with severity of CT-IAC being of most use at older ages and presence vs. absence potentially being informative in younger individuals. Indeed, CT-IAC, especially that of the medial subtype, could be reported routinely and integrated into dementia prediction models in both patients with stroke/TIA and more general population. Second, stronger associations for medial/IEL CT-IAC highlight mechanisms other than atherosclerosis including renal insufficiency, parathyroid dysfunction, and vitamin D metabolism disorders and could guide participant selection in future studies investigating the role of CT-IAC as a potentially treatable risk factor for dementia.

In conclusion, although larger studies are needed to further elucidate associations in different age groups, to determine dementia-subtype associations, and to better understand underlying mechanisms and potential therapeutic implications, routine reporting of severe CT-IAC as a risk factor for dementia could be justified in the meantime.

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Statement of Ethics

Ethical approval and informed consent were not sought for this article because it is a systematic review based on published literature and does not report on or involve the use of any animal or individual human data or tissue that were not covered by previous published studies.

Conflict of Interest Statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author Contributions

KL and PMR conceived the study and developed the protocol. KL and OO assessed eligibility and quality of identified studies. KL aggregated and analysed the data and PMR supervised the study. KL, PMR, and OO interpreted the data. KL wrote the first draft of the manuscript. PMR and OO refined and complemented the manuscript for critical review. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Data Availability Statement

The data supporting the findings of this study are available within the article and its supplementary materials. Further enquiries can be directed to Professor Peter Rothwell (peter.rothwell@ndcn.ox.ac.uk).

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Figure Legends

Fig. 1. Pooled adjusted odds ratio between presence vs. absence of ICA or VBA calcification and cognitive impairment or dementia. Participants with recurrent stroke on follow-up in OXVASC were excluded to match the estimates reported in the Rotterdam Study. CI, confidence interval; ICA, internal carotid artery; OR, odds ratio; OXVASC, Oxford Vascular Study; Rotterdam, The Rotterdam Study; SE, standard error; VBA, vertebrobasilar artery.

Fig. 2. Pooled adjusted odds ratio between presence vs. absence of ICA calcification of the atherosclerotic intimal or medial/IEL subtype and dementia in longitudinal studies. CI, confidence interval; ICA, internal carotid artery; IEL, internal elastic lamina; OR, odds ratio; OXVASC, Oxford Vascular Study; Rotterdam, The Rotterdam Study; SE, standard error; VBA, vertebrobasilar artery.

Fig. 3. Pooled adjusted odds ratio between severity of ICA or VBA calcification and cognitive impairment or dementia. In the study by Golüke et al., the predictor variable was severe vs. absent ICA calcification on Woodcock scale, and the outcome variable was dementia. In the study by Gatz et al., the predictor variable was more severe vs. dot/absent ICA calcification, and the outcome variable was cognitive impairment. In the Rotterdam Study and OXVASC, the predictor variables were top vs. bottom tertile ICA or VBA calcification volume in participants with prevalent ICA or VBA calcification on semi-automated software, and the outcome variables were dementia. Participants with recurrent stroke on follow-up in OXVASC were excluded to match the estimates reported in the Rotterdam Study. In TABASCO, the predictor variable was above vs. below the 50th percentile of Agatston calcium score in ICA, VA, and BA (which would approximate the same measure in ICA alone), and the outcome variable was post-stroke cognitive impairment or dementia. CI, confidence interval; ICA, internal carotid artery; OR, odds ratio; OXVASC, Oxford Vascular Study; Rotterdam, The Rotterdam Study; SE, standard error; TABASCO, Tel-Aviv Brain Acute Stroke Cohort; VBA, vertebrobasilar artery.

Fig. 4. Pooled adjusted odds ratio between severity of ICA calcification of the atherosclerotic intimal or medial/IEL subtype and dementia in longitudinal studies. CI, confidence interval; ICA, internal carotid artery; IEL, internal elastic lamina; OR, odds ratio; OXVASC, Oxford Vascular Study; Rotterdam, The Rotterdam Study; SE, standard error; VBA, vertebrobasilar artery.

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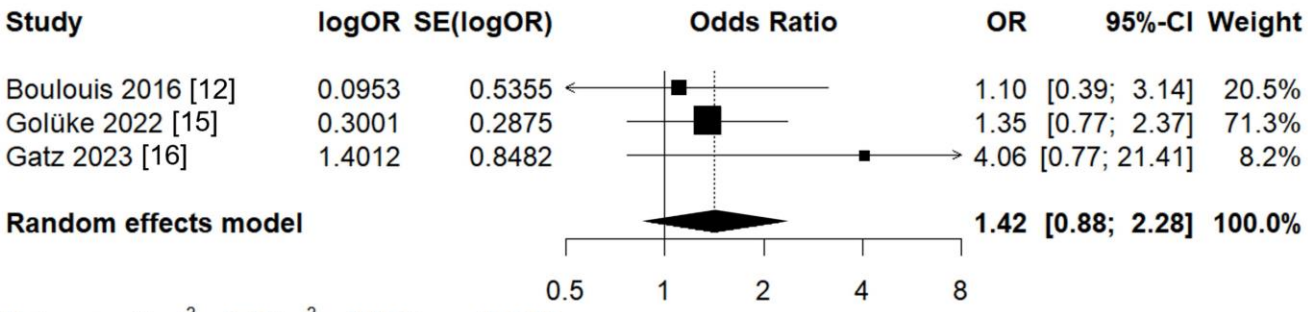
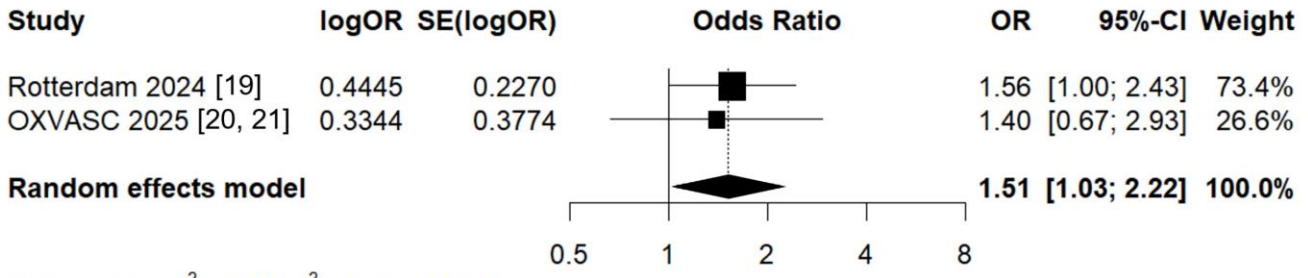
Presence vs. absence of ICA calcification (cross-sectional studies)



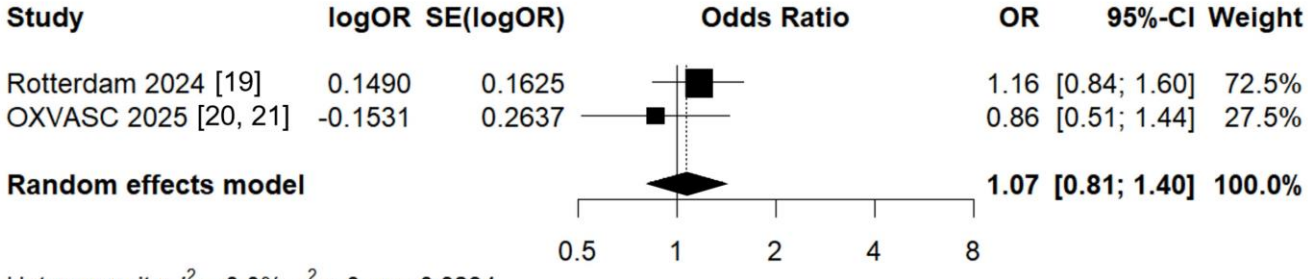
Heterogeneity: $I^2 = 0.0\%$, $\tau^2 < 0.0001$, $p = 0.4082$

Presence vs. absence of ICA calcification (longitudinal studies)



Heterogeneity: $I^2 = 0.0\%$, $\tau^2 = 0$, $p = 0.8026$

Presence vs. absence of VBA calcification (longitudinal studies)



Heterogeneity: $I^2 = 0.0\%$, $\tau^2 = 0$, $p = 0.3294$

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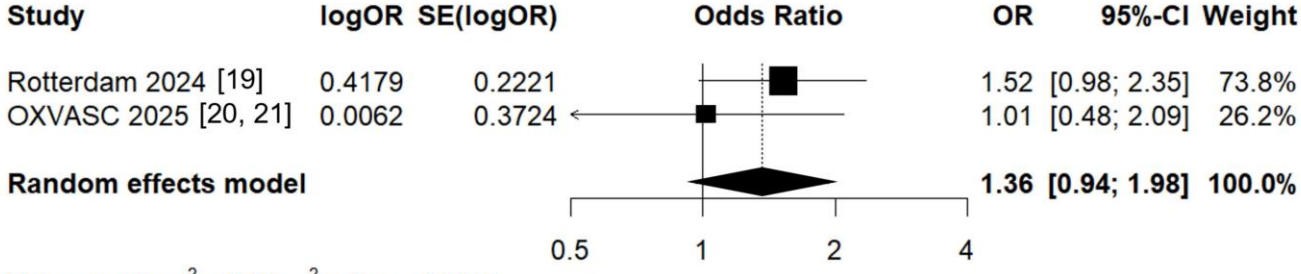
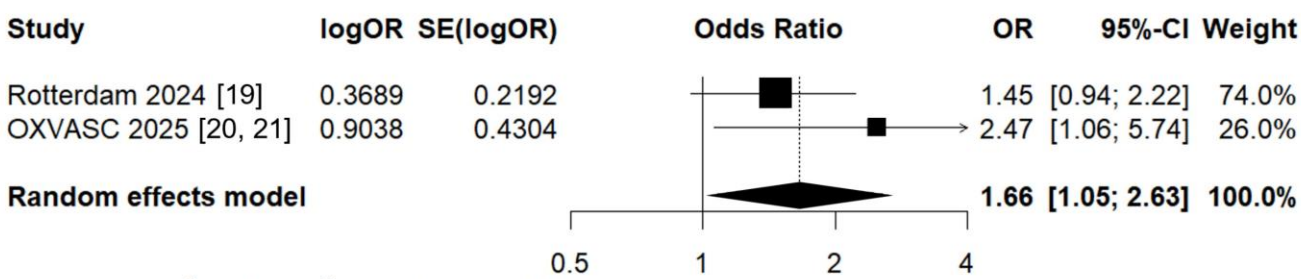
Presence vs. absence of ICA calcification (atherosclerotic subtype)



Heterogeneity: I^2 = 0.0%, τ^2 = 0, p = 0.3423

Presence vs. absence of ICA calcification (medial/IEL subtype)



Heterogeneity: I^2 = 18.5%, τ^2 = 0.0265, p = 0.2680

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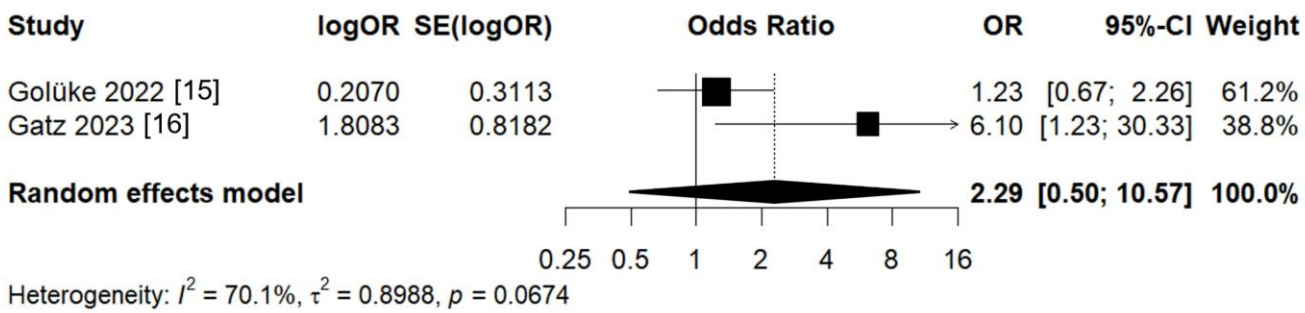
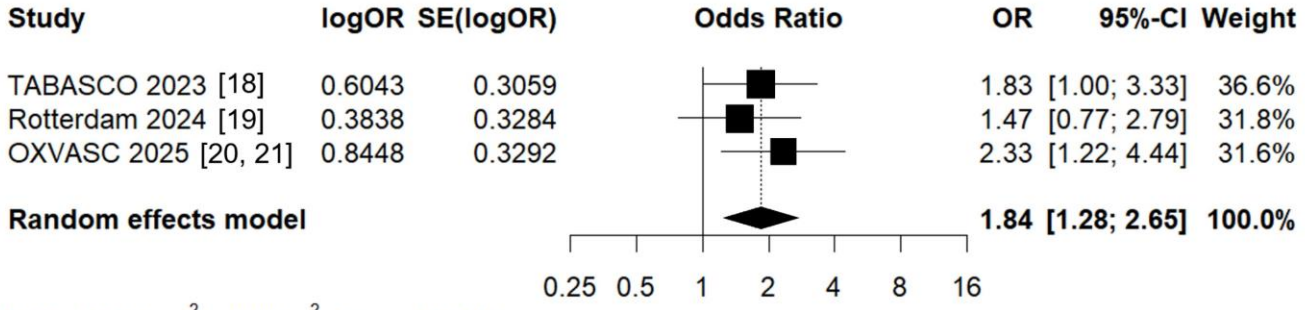
High vs. low ICA calcification volume (cross-sectional studies)



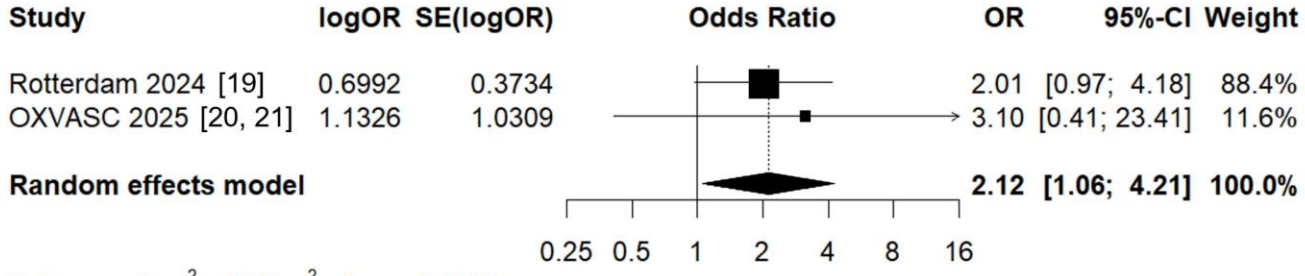
Heterogeneity: I^2 = 70.1%, τ^2 = 0.8988, p = 0.0674

High vs. low ICA calcification volume (longitudinal studies)



Heterogeneity: I^2 = 0.0%, τ^2 = 0, p = 0.6115

High vs. low VBA calcification volume (longitudinal studies)



Heterogeneity: I^2 = 0.0%, τ^2 = 0, p = 0.6927

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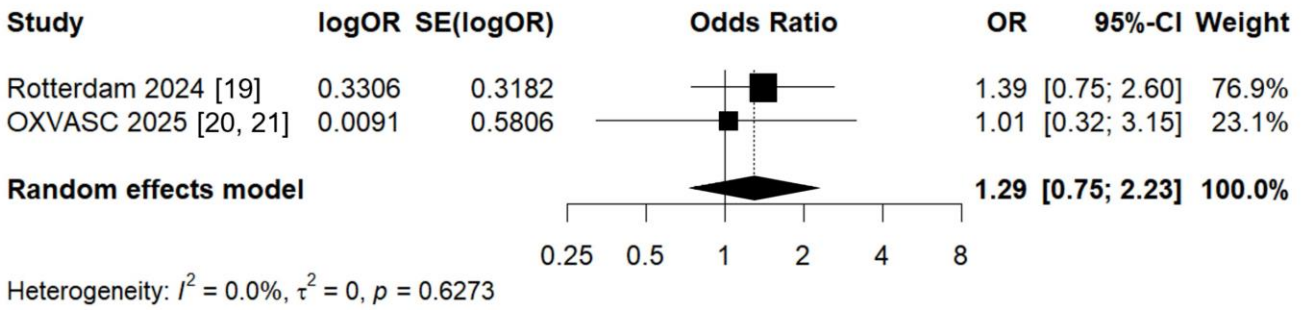
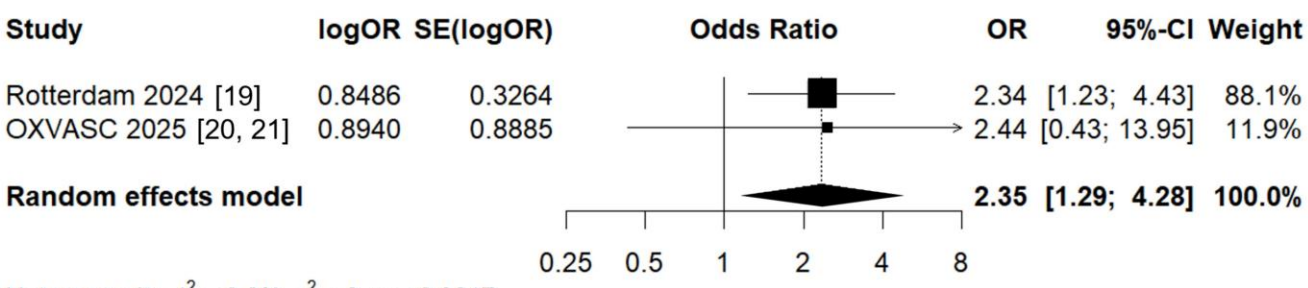
Top vs. bottom tertile of ICA calcification volume (atherosclerotic subtype)



Heterogeneity: $I^2 = 0.0\%$, $\tau^2 = 0$, $p = 0.6273$

Top vs. bottom tertile of ICA calcification volume (medial/IEL subtype)



Heterogeneity: $I^2 = 0.0\%$, $\tau^2 = 0$, $p = 0.9617$

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Table 1. Eligible cross-sectional studies on intracranial arterial calcification and cognitive impairment or dementia.

Study and region	Cases/ non-cases	Age (years)	Female	Subject features	Artery	Predictor variable	Outcome variable	Adjusted effect sizes (95% confidence interval)	Outcome diagnosis
Tri-Service General Hospital, Taiwan [11]	178/401	Mean 62	61.5%	Patients who had CT for various reasons	ICA	Agatston calcium score/100	Cognitive impairment (4 grades)	**OR=1.06 (1.00–1.13)**	MMSE
Massachusetts General Hospital, USA [12]	38/305	Mean 71.2 (SD 12.7)	51.6%	Patients with primary symptomatic ICH	ICA	Present vs. absent CT-IAC	Dementia	OR=1.1 (0.38–3.1)	Clinical records
The Atahualpa project, Ecuador [13]	584 in total	Mean 60 (SD 12)	58%	Participants from a population cohort	ICA	Mild, moderate, and severe CT-IAC vs. none	MoCA score	**β_1=-1.34 (-2.23–-0.44)** **β_2=-1.73 (-2.68–-0.78)** **β_3=-2.04 (-3.76–-0.33)**	MoCA
University of Munich, Germany [14]	162 in total	Mean 74.25 (SD 9.02)	58.0%	Patients from memory clinic	ICA and VA	Total calcified plaque score	MMSE score	r=-0.086, p=0.280	MMSE
Tergooi Hospital, The Netherlands [15]	939/1053	Mean 80 (SD 12)	59.7%	Patients from memory clinic	ICA	Mild, moderate, and severe CT-IAC vs. none	Dementia	OR_1=1.07 (0.60–1.89) OR_2=1.35 (0.81–2.50) OR_3=1.23 (0.67–2.27)	DSM-IV
					BA	Present vs. absent CT-IAC		OR=0.87 (0.62–1.23)	
The Tsimane Health and Life History Project, Bolivia [16]	35/89	Not given, range 60-93	48.5%	Participants from a population cohort	ICA	More severe vs. dot/absent ICA CT-IAC Continuous vs. irregular/patchy CT-IAC	Cognitive impairment	OR_1=4.06 (0.77–∞) **OR_2=6.10 (1.23–30.4)**	DSM-V
					LSA	More severe vs. dot/absent LSA CT-IAC		**OR=4.77 (1.04–22.0)**	

BA, basal artery; CT, computed tomography; CT-IAC, CT-visualised intracranial arterial calcification; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-V, The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ICA, internal carotid artery; ICH, intracerebral haemorrhage; LSA, lenticulostriate artery; MMSE, mini-mental state examination; MoCA, Montreal Cognitive Assessment; SD, standard deviation; USA, United States of America; VA, vertebral artery.

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Table 2. Eligible longitudinal studies on intracranial arterial calcification and risk of cognitive impairment or dementia on follow-up.

Study and region	Cases/non-cases	Age (years)	Female	Subject features	Relevant exclusion criteria	Artery	Outcome variable	Follow-up (years)	Outcome diagnosis
TABASCO, Israel [18]	105/426	Mean 67.6 (SD 10.0)	59.5%	Patients with first-ever stroke or TIA	Haemorrhagic stroke; prevalent cognitive impairment or dementia	ICA, VA, and BA	Cognitive impairment or dementia	2.0	Cognitive tests and expert consensus
Rotterdam, The Netherlands [19]	281/ 2058	Mean 69.5 (SD 6.7)	52.2%	Participants from a general population cohort	Prevalent stroke; prevalent dementia	ICA and VBA	Dementia	Median 13.4	Cognitive tests and DSM-III-R
OXVASC, UK [20, 21]	200/200	Mean 78.0 (SD 9.3)	53.5%	Patients with stroke or TIA from a population-based cohort	Prevalent dementia	ICA, VA and BA	Dementia	Median 7.9	Cognitive tests and DSM-IV

BA, basal artery; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ICA, internal carotid artery; IQR, interquartile range; OXVASC, Oxford Vascular Study; SD, standard deviation; Rotterdam, The Rotterdam Study; TABASCO, Tel-Aviv brain acute stroke cohort; TIA, transient ischaemic attack; UK, United Kingdom; VA, vertebral artery; VBA, vertebrobasilar artery.

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