The Association between Carotid Intima-Media Thickness and Cognitive Impairment: A Systematic Review and Meta-Analysis

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Keywords

Cognitive impairment · Dementia · Carotid intima-media thickness · Meta-analysis

Abstract

Background: Emerging evidence suggests that cognitive impairment (CI) and different etiologies of dementia, including Alzheimer's disease (AD), are associated with vascular risk factors and atherosclerosis. In clinical practice, carotid intima-media thickness (CIMT) measured by ultrasonography may be a marker of atherosclerosis. Many studies report increased CIMT in patients with dementia and CI although a firm association has not yet been established. **Aim:** This systematic review and meta-analysis were conducted to study the relationship between CIMT, dementia, and CI. **Methods:** The literature search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and included the following databases: Medline, Embase, Cochrane Library, and Epistemonikos. The search spanned from 2000 to 2020 and was limited to English and Scandinavian languages. **Results:** The main analysis of CIMT in subjects with CI compared to subjects with no cognitive impairment (NCI) included 12 studies; 1,089 sub-

jects with CI and 5,223 with NCI. There was no significant difference in CIMT between the CI and NCI groups. However, subgroup analyses revealed significantly higher CIMT in the mild cognitive impairment (MCI) and dementia groups than the NCI group. In addition, patients with dementia had increased CIMT compared to patients with MCI, and patients with AD demonstrated higher CIMT than those with vascular cognitive impairment (VCI). **Conclusion:** CIMT may be higher in subjects with CI than in cognitively healthy subjects although no significant difference was observed in our main analysis. CIMT was higher in the dementia group than the MCI group and in the AD group compared to the VCI group.

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Introduction

Dementia is a syndrome of progressive decline in multiple cognitive domains such as memory, thinking, and behavior, sufficiently severe to affect activities of daily living [1]. Dementia has become a leading cause of disability and dependence in the elderly and results in enormous public burdens and family stress [2]. It is estimated that 50 million people suffer from dementia worldwide, and

this number is expected to increase to 75 million by 2030 [3]. The global cost for dementia was approximately US \$948 billion in 2016 [4]. At present, there is no effective treatment that prevents or retards disease progression in dementia [2].

Alzheimer's disease (AD) is the most common form of dementia and accounts for about 60–70% of dementia cases [2, 5]. Specific neuropathological hallmarks for AD are beta-amyloid (A β) plaques and phosphorylated tau neurofibrillary tangles [6]. Second only to AD, vascular dementia (VaD) causes 20% of dementia cases [5]. VaD is believed to result from processes that damage blood vessels leading to reduced blood flow in the brain, with strokes or white matter lesions as a result [7]. Mild cognitive impairment (MCI) is the term for patients who show objective evidence of CI, sometimes defined as <1.5 standard deviations (SD) on any cognitive test according to the Petersen criteria, with preserved activities of daily living [8].

It is well-known that atherosclerosis is involved in the development of VaD; however, increasing evidence shows that vascular pathology may also contribute to the development of AD [9]. Vascular pathology could possibly contribute to the development of AD through reduced cerebral blood flow resulting in the impairment of A β clearance [10] although the exact mechanisms are not yet known.

Carotid intima-media thickness (CIMT) investigation is a noninvasive procedure that uses ultrasound to measure atherosclerosis in clinical practice [11], usually on the far wall of the common or internal carotid arteries. Epidemiological studies have shown that atherosclerosis and vascular risk factors, including hypertension, diabetes, smoking, and hypercholesterolemia are associated with an increased risk of dementia [12]. However, the biomarkers that are currently available in clinical routine to assess the degree of atherosclerosis and vascular mechanisms in the pathogenesis of dementia and other forms of CI, for example, the Fazekas scale [13] in magnetic resonance imaging and computed tomography, are often examiner-dependent and not necessarily very sensitive. CIMT, being a precise and objective measurement, has therefore been suggested as a potentially useful marker to predict the risk of cognitive decline [11, 14, 15]. Increased CIMT has been reported as a risk factor for CI and poorer neuropsychological status in elderly patients [16, 17], as well as for VaD [18]. Moreover, a previous meta-analysis, focusing on atherosclerosis in patients with AD exclusively, found that CIMT may be related to AD [14].

However, the association between CIMT and dementia has not been clearly established, and the contribution of vascular pathology in different forms of dementia and MCI is currently a matter of investigation [14, 18]. The present meta-analysis of existing studies was performed to evaluate the potential association between CIMT and different etiologies of dementia.

Methods

Search Strategy

The following databases were searched systematically by a trained information specialist to identify articles on dementia and CIMT from 2000 to 2020: Medline, Embase, Cochrane Library, and Epistemonikos. We used the following search terms: "cognitive screening," "cognition," "cognitive tests," "mental status," "cognitive function," dementia tests," "dementia," "Alzheimer's disease," "Alzheimer's dementia," "vascular dementia," "Lewy body dementia," "normal pressure hydrocephalus," "mixed dementia," "IMT," "carotid intima-media thickness," and "intima-media thickness measurements." The literature search was limited to studies in English or Scandinavian language. The full search strategy is shown in online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000518295.

Selection Criteria

The present systematic review and meta-analysis were performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. Reviewers applied eligibility criteria and independently screened titles and abstracts for inclusion after the removal of duplicated literature, followed by the assessment of full-text records according to the selection criteria. Eligible trials fulfilled the following prespecified criteria (PICOS): (1) population: persons with dementia or CI; (2) intervention: measurement of CIMT; (3) comparison: (a) persons without dementia if compared to persons with dementia, (b) persons without MCI or dementia if compared to persons with MCI, and (c) persons with VCI if compared to AD; (4) outcome: the association between CI and CIMT; and (5) observational studies.

Data Extraction and Analyses

Two investigators extracted data from the included articles independently of each other using a designed table and compared data to ensure accuracy. The general characteristics of included studies were obtained as follows: first author of the study, year of publication, country and setting of research, study design, number of patients included, patient demographics including age and sex distribution, location and side of CIMT measurement, and results from cognitive testing. Study investigators were not contacted for unreported data or additional details. The qualified studies included several subtypes of dementia. Data were extracted regarding the criteria used for diagnosing dementia and CI and for the measurement of mean and maximum CIMT.

Statistical Methods

Differences in CIMT between persons with (1) CI and NCI, (2) dementia and NCI, (3) dementia and MCI, (4) MCI and NCI, and

Fig. 1. PRISMA 2020 flow chart showing process of identification of studies. CIMT, carotid intima-media thickness; *n.*, number; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

(5) AD and VaD were analyzed. Values of mean CIMT with SD were extracted.

SD was calculated using the formula presented in the Cochrane Handbook for studies reporting confidence interval (CI) instead of SD [19]. Statistical analyses were carried out using RevMan 5.4.1 [20].

Quality Assessment and Risk of Bias

Two investigators independently assessed the quality of studies included in the meta-analyses using Critical Appraisals Skills Programme (CASP) [21] and Center for Evidence-Based Management (CEBM) checklists [22]. In assessing the studies included in this meta-analysis, the CASP checklists designed for case-control and cohort studies were used, and for cross-sectional studies, the CEBM critical appraisal checklist for cross-sectional studies was used. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) [23] tool was used to assess the overall confidence in the effect estimates across studies for each pooled outcome.

Disagreements between Individual Judgments

Any disagreements in study selection, data extraction, and quality assessment of studies were resolved by consensus.

Results

Literature Search

The process of identifying relevant studies is shown in Figure 1. In total, 102 relevant studies were identified after the removal of duplicates. After screening titles and abstracts, 68 records were excluded and 34 were reviewed in full text for eligibility. Finally, 12 studies met our inclu-

sion criteria and 22 were deemed ineligible; reasons for exclusion are shown in online suppl. Table 2.

Study Characteristics

The main characteristics of the 12 studies included in the meta-analyses, diagnosis and ascertainment of diagnosis, and CIMT values and location of CIMT measurements are shown in Tables 1–3, respectively. The included studies were published between 2009 and 2019. Of these, 5 were cross-sectional studies, 3 were prospective cohort studies, and 4 were case-control studies. The diagnostic criteria for dementia and MCI varied across studies. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [24] and the Mini-Mental State Examination [25] were the most frequently used instruments for diagnosing dementia and MCI, respectively.

Meta-Analysis of Results

To evaluate the relationship between CIMT and CI, we explored the differences in mean CIMT between patients with CI and NCI. Subgroup analyses were performed to assess differences in CIMT between persons with MCI and NCI, dementia and MCI, dementia and NCI, and between AD and VCI.

Mean Difference of CIMT in Patients with and without CI

Of the 12 included studies [26–37], 9 [26–30, 32–34, 37], provided data for the main analysis of CIMT in pa-

Fig. 2. Forest plot showing MD in CIMT between persons with CI and NCI. CI, cognitive impairment; NCI, no cognitive impairment; SD, standard deviation; mm, millimeters; CIMT, carotid intima-media thickness; MD, mean difference.

Table 1. General characteristics of included studies

Author of publication	Study design	Country	Setting	N	Age, N (SD)	Sex, N (%)	Education
Park et al. [60]	1	South Korea	Community health centers	231	77 (4)	F: 186 (80.5)	Elementary school 72.7%; middle and high school 25.5%; college or more 1.7%
Matsumoto et al. [61]	1	Japan	University hospital	176	65 (10)	F: 98 (55.7)	Years of education, mean 14.5 (SD 3.0)
Rouch et al. [62]	2	France	University hospital	375	75 (7)	F: 246 (65.6)	University 49.6%; middle or high school 27.1%; primary school 23.3%
Cho et al. [63]	1	South Korea	University hospital outpatient clinic	53	NR	NR	NR
Tachibana et al. [64]	1	Japan	University hospital	76	NR	F: 43 (56.6)	NR
Casado Naranjo et al. [65]	3	Spain	University hospital	181	NR	F: 98 (54.1)	Education ≤ 6 years, 55.2% in the aMCI and 55.3% in the NCI group
Xiang et al. [66]	1	China	University hospital	2015	69	F: 981 (48.7)	NR
Chen et al. [67]	1	China	Hospital outpatient clinic	157	55 (7)	F: 76 (48.4)	NR
Dias Eda et al. [68]	1	Brazil	Specialized hypertension center	90	NR	F: 56 (62.2)	NR
Stefanova et al. [69]	1	Serbia	University hospital	533	NR	F: 269 (50.5)	NR
Viticchi et al. [70]	2	Italy	University hospital	117	76 (6)	F: 57 (48.7)	Years of education, mean 7.4 (SD 2.6)
Sander et al. [71]	2	Germany	University hospital and primary care	3,386	68	F: 2000 (59.1)	Lower elementary 90%; intermediary education level 7%; college or university 3%

Study design: 1 = cross-sectional, 2 = prospective cohort, 3 = case control. NR, not reported; SD, standard deviation; F, female; NCI, no cognitive impairment; aMCI, amnesic mild cognitive impairment.

tients with CI and NCI involving 6,312 subjects, 1,089 with CI, and 5,223 with NCI. Included studies had sample sizes ranging from 53 [37] to 3,386 [32]. The inverse variance model showed no statistically significant difference

of mean CIMT between the CI and NCI groups (mean difference [MD] = 0.22; 95% confidence interval, -0.07 to 0.52; $p = 0.14$). Since there was evidence of large heterogeneity, a random effects model was used to combine the

Fig. 3. Forest plot showing MD in CIMT between persons with MCI and NCI. MCI, mild cognitive impairment; NCI, no cognitive impairment; SD, standard deviation; mm, millimeters; CIMT, carotid intima-media thickness; MD, mean difference.

Table 2. Diagnosis and diagnostic criteria

Author	Diagnosis (CI group)	Diagnosis (control group)	Diagnostic criteria (CI group)	Diagnostic criteria (control group)
Park et al. [60]	MCI	NCI	K-MMSE, interview, neuropsychological assessment	Same as for CI group
Matsumoto et al. [61]	CI	NCI	MMSE, the clock drawing test, subjective forgetfulness, the WMS-R logical memory test according to ADNI	Same as for CI group
Rouch et al. [62]	Dementia	MCI	DSM-IV, MMSE, cognitive battery	Petersen's criteria
Cho et al. [63]	MCI and dementia	NCI	MCI: Petersen's criteria, MMSE, cognitive evaluation battery dementia: neuroimaging, MMSE, CDR, SNSB	No signs of CI
Tachibana et al. [64]	AD and VaD	NCI	Clinical and radiological diagnosis. DSM-V and/or NINCDS-ADRD (AD), NINDS-AIREN (VaD)	MMSE ≥ 26
Casado Naranjo et al. [65]	MCI	NCI	MMSE and neuropsychological testing	MMSE ≥ 27
Xiang et al. [66]	CI	NCI	MMSE < 24	MMSE
Chen et al. [67]	MCI	NCI	MoCA < 26	MoCA
Dias Eda et al. [68]	CI	NCI	MMSE < 24	MMSE
Stefanova et al. [69]	AD	VCI	NINCDS-ADRD and DSM-IV	NINDS-AIREN
Viticchi et al. [70]	AD	MCI	Modified DSM-IV and NINCDS-ADRD	Petersen's criteria; MMSE > 24
Sander et al. [71]	CI	NCI	6CIT	6CIT

CI, cognitive impairment; NCI, no cognitive impairment; MCI, mild cognitive impairment; AD, Alzheimer's disease; VaD, vascular dementia; VCI, vascular cognitive impairment; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th edition; MMSE, Mini-Mental State Examination; K-MMSE, Korean Mini-Mental State Examination; WMS-R, Wechsler Memory Scale-Revised; ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR, Clinical Dementia Rating Scale; SNSB, Seoul Neuropsychological Screening Battery; MoCA, Montreal Cognitive Assessment; NINCDS-ADRD, National Institute of Neurological and Communicative Disorders and Stroke/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; 6CIT, Six-Item Cognitive Impairment Test.

data. The forest plot for the MD in CIMT between the CI and NCI groups is shown in Figure 2.

Subgroup analyses revealed higher mean CIMT in subjects with MCI (MD = 0.12; 95% confidence interval, 0.07–0.16; $p < 0.01$) and dementia (MD = 0.11; 95% con-

fidence interval, 0.00–0.23; $p = 0.05$) than NCI subjects and is shown in Figures 3 and 4, respectively. In addition, mean CIMT was higher in subjects with dementia compared to MCI (MD = 0.07; 95% confidence interval, 0.00–0.13; $p = 0.05$) as well as in subjects with AD com-

Fig. 4. Forest plot showing MD in CIMT between persons with dementia and NCI. NCI, no cognitive impairment; SD, standard deviation; mm, millimeters; CIMT, carotid intima-media thickness; MD, mean difference.

Table 3. CIMT measurements in a CI group compared to a NCI group

Author	Location of CIMT measurement	Mean CIMT (CI group)	Mean CIMT (NCI group)
Park et al. [60]	Left CCA between 1 cm and 5 cm proximal the carotid bulb	0.90 (0.2)	0.79 (0.1)
Matsumoto et al. [61]	Far wall of ICA and CCA bilaterally	^a 2.0 (1.0)	1.7 (0.6)
Rouch et al. [62]	Far wall of the middle segment of CCA bilaterally	0.85 (0.13) (dementia)	0.82 (0.13) (MCI)
Cho et al. [63]	Far wall of CCA	0.74 (0.23) (MCI); 0.81 (0.01) (dementia)	0.64 (0.12)
Tachibana et al. [64]	Far wall of CCA bilaterally	0.89 (0.23) (AD); 0.89 (0.30) (VaD)	0.84 (0.18)
Casado Naranjo et al. [65]	Bilateral CCA	1.03 (0.27)	0.85 (0.22)
Xiang et al. [66]	Far wall of CCA, carotid bifurcations, and first 2 cm of ICA bilaterally at plaque-free sites	1.57 (0.15)	0.77 (0.15)
Chen et al. [67]	Near and far walls of distal CCA bilaterally, and far wall of carotid bifurcation and first 1.5 cm of ICA bilaterally	0.87 (0.16)	0.69 (0.1)
Dias Eda et al. [68]	Anterior and posterior walls of carotid arteries bilaterally	0.99 (0.2)	^b 0.79 (0.14) left thickest
Stefanova et al. [69]	Far wall of CCA and ICA. Side not specified	1.15 (0.18) (AD)	1.11 (0.20) (VCI)
Viticchi et al. [70]	Near and distal wall of CCA bilaterally	1.04 (0.16) (AD)	0.92 (0.15) (MCI)
Sander et al. [71]	Distant wall of CCA. Side not specified	0.82 (0.24)	0.79 (0.28)

CIMT, carotid intima-media thickness; CI, cognitive impairment; NCI, no cognitive impairment; MCI, mild cognitive impairment; AD, Alzheimer's disease; VaD, vascular dementia; VCI, vascular cognitive impairment; CCA, common carotid artery; ICA, internal carotid artery. ^a Mean max CIMT. ^b Left, highest value.

pared to VaD (MD = 0.04; 95% confidence interval, 0.00–0.07; $p = 0.03$), shown in Figures 5 and 6, respectively.

Assessment of Quality of the Included Studies

Assessments according to the CASP and CEBM checklists are presented in Table 4. Assessments of our confidence in the pooled estimates according to GRADE are presented in Table 5. The confidence in the effect estimates was assessed as low or very low, implying that further research is very likely to affect the results.

Discussion

This systematic review and meta-analysis were performed to investigate the relationship between CIMT and CI including dementia and MCI. The meta-analysis showed that CIMT of the CI and NCI groups did not differ significantly. However, the subgroup analyses, generated by analyzing MCI and dementia separately, revealed a significant difference with higher CIMT in the MCI and dementia groups than the NCI group. Also, subjects with dementia had significantly higher CIMT than subjects

Fig. 5. Forest plot showing MD in CIMT between persons with dementia and MCI. MCI, mild cognitive impairment; SD, standard deviation; mm, millimeters; CIMT, carotid intima-media thickness; MD, mean difference.

Fig. 6. Forest plot showing MD in CIMT between persons with AD and VCI. AD, Alzheimer's disease; VCI, vascular cognitive impairment; SD, standard deviation; mm, millimeters; CIMT, carotid intima-media thickness; MD, mean difference.

with MCI, and CIMT was higher in subjects with AD compared to VCI.

A number of studies have explored the relationship between CIMT and CI, reporting diverging results [16, 17, 38]. Higher CIMT has been associated with lower MMSE scores [39], reduced cognitive function [40], and has been shown to predict impaired cognitive function later in life when measured in middle-aged persons [41]. A recent longitudinal study that followed 462 individuals for 20 years found that higher CIMT in midlife increases the risk of cerebral small vessel disease and even subsequent all-cause dementia [18]. Three additional prospective studies – the Cardiovascular Health Study [42], the Rotterdam Study [43], and the Baltimore Longitudinal Study of Aging [44] – have reported a significant and independent association between CIMT and dementia. These results were not reproduced in our main analysis of CIMT and CI although a nonsignificant trend toward higher CIMT in CI subjects was observed. This nonsignificant association was supported by the subgroup analyses in which both the dementia and MCI groups demonstrated significantly higher CIMT than the NCI group. CIMT was treated as a continuous variable in our analy-

ses, and studies reporting only dichotomous measurements of CIMT were excluded. This may be important since the 3 aforementioned longitudinal studies found increased hazard ratios of dementia only for the highest quintile of CIMT [42, 43], or when CIMT was defined as a dichotomous variable [44], suggesting a “threshold effect.”

In contrast, the Three-City study, a longitudinal study including 6,025 subjects, reported that carotid plaques, but not mean CIMT, predicted subsequent dementia [38]. The Three-City study measured CIMT in a plaque-free zone, while the Cardiovascular Health Study and the Rotterdam Study measured CIMT in all carotid segments. Therefore, the association with CIMT and dementia could instead reflect an association with carotid plaques per se. This was also observed in the current meta-analysis, where CIMT values ranged from 0.82 to 2.0 mm in the CI group, and from 0.64 to 1.7 mm in the NCI group, where the higher values could represent heterogeneity due to measurement in areas with plaque. A postmortem study found that carotid stenosis was associated with increased odds for dementia, while CIMT showed no such association [45].

Table 4. Assessments according to CASP (Q 1–6, 9–11 for case-control and Q 1–5, 9–11 for cohort studies) and CEBM (Q 1–6, 8–10, 12 for cross-sectional studies) checklists for included studies

Study	Did the study address a clearly focused issue?	Did the authors use an appropriate method to answer their question?	Were the cases recruited in an acceptable way?	Were the controls selected in an acceptable way?	Was the exposure accurately measured to minimize bias?	Have the authors taken account of potential confounding factors in the design and/or in their analysis?	Do you believe the results?	Will the result help locally?	Do the result fit with other available evidence?	Overall appraisal
<i>CASP checklist case-control studies</i>										
Casado Naranjo et al. [65]	+	+	?	+	+	?	+	+	+	?
Cho et al. [63]	+	+	+	?	+	?	+	+	+	?
Tachibana et al. [64]	+	+	?	+	+	+	+	+	+	?
Matsumoto et al. [61]	+	+	+	+	+	+	?	–	–	–
<i>CASP checklist cohort studies</i>										
Viticchi et al. [70]	+	+	+	+	+	+	+	+	+	+
Rouch et al. [62]	+	+	+	+	+	+	+	+	+	+
Sander et al. [71]	+	+	+	+	+	+	+	+	+	+
<i>CEBM checklist cross-sectional studies</i>										
Stefanova et al. [69]	+	+	+	+	+	–	?	+	?	–
Dias Eda et al. [68]	+	+	+	–	?	?	+	+	+	–
Chen et al. [67]	+	+	+	+	–	+	+	+	+	–
Xiang et al. [66]	+	+	+	+	+	?	?	+	+	?
Park et al. [60]	+	+	+	+	+	?	+	+	+	?

CASP, Critical Appraisals Skills Programme; CEBM, center for evidence-based management; +, yes; –, no; ?, cannot tell; Q, question(s).

Table 5. Showing the GRADE evidence profile with assessments of our confidence in the estimates

Certainty assessment			Patients, <i>n</i>			Effect		Certainty	Importance	
studies, <i>n</i>	study design	risk of bias	inconsistency	indirectness	imprecision	other considerations	CIMT in CI, dementia, or MCI	CIMT in control groups	relative (95% CI)	absolute (95% CI)
<i>CI compared to NCI</i>										
9	Observational studies	Serious	Not serious	Not serious	Serious	Dose response gradient	1,089	5,223	–	MD 0.22 mm higher (0.07 lower–0.52 higher)
<i>MCI compared to CI</i>										
4	Observational studies	Serious	Not serious	Not serious	Serious	Dose response gradient	286	303	–	MD 0.12 mm higher (0.07 higher–0.16 higher)
<i>Dementia compared to NCI</i>										
2	Observational studies	Not serious	Not serious	Not serious	Serious	Dose response gradient	41	35	–	MD 0.11 mm higher (0–0.23 higher)
<i>Dementia compared to MCI</i>										
3	Observational studies	Not serious	Not serious	Not serious	Serious	Dose response gradient	140	377	–	MD 0.07 mm higher (0–0.13 higher)
<i>AD compared to VCI</i>										
2	Observational studies	Serious	Not serious	Not serious	Serious	Dose response gradient	227	260	–	MD 0.04 mm higher (0–0.07 higher)
CI, confidence interval; CI, cognitive impairment; MD, mean difference; CIMT, carotid intima-media thickness; mm, millimeters; NCI, no cognitive impairment; MCI, mild cognitive impairment; VCI, vascular cognitive impairment; GRADE, Grading of recommendations, Assessment, Development and Evaluations; AD, Alzheimer's disease. ⊖ Low: our confidence in the estimate is low; ⊖⊖ Very low: our confidence in the estimate is very low. Statistically significant differences in CIMT thickness between groups is reported in bold (<i>p</i> ≤ 0.05)										

CI, confidence interval; CI, cognitive impairment; MD, mean difference; CIMT, carotid intima-media thickness; mm, millimeters; NCI, no cognitive impairment; MCI, mild cognitive impairment; VCI, vascular cognitive impairment; GRADE, Grading of recommendations, Assessment, Development and Evaluations; AD, Alzheimer's disease. ⊖ Low: our confidence in the estimate is low; ⊖⊖ Very low: our confidence in the estimate is very low. Statistically significant differences in CIMT thickness between groups is reported in bold ($p \leq 0.05$)

On the other hand, other longitudinal studies have, in accordance with our analysis of dementia and NCI, demonstrated that CIMT, as a continuous variable, is associated with an increased risk of MCI and dementia [17, 18]. As for dementia, previous studies that have explored the relationship between CIMT and MCI have showed diverging results [34, 46, 47]. Also, no agreement has been reached regarding the role of CIMT as a predictor of conversion from MCI to dementia [17, 35, 37]. Data from our subgroup analyses revealed that dementia patients had higher CIMT values than MCI patients, which could provide support for studies suggesting a link between CIMT and conversion from MCI to dementia [17, 36].

The vascular alterations indicated by increased CIMT could possibly be involved in the development of CI through multiple mechanisms. First, increase in CIMT can reduce blood flow to the brain, thereby affecting different cognitive domains [48, 49]. In addition, increased CIMT is associated with vascular pathologies such as hypertension and atherosclerosis that could be related to structural changes in the brain, including white matter lesions associated with cerebral small vessel disease, and atrophy, that may in turn affect cognition [50, 51]. Moreover, white matter lesions caused by silent brain micro infarcts and brain micro hemorrhages could contribute to CI [33, 52]. Interestingly, our analyses revealed that CIMT was higher in the AD than the VCI group that included both VaD and vascular MCI. Although this association was only statistically significant and not necessarily of clinical significance, it may support the growing evidence that vascular pathology is involved not only in the development of VaD but even in AD [9, 53]. Vascular risk factors measured in midlife, including hypertension, diabetes, smoking [54], and hypercholesterolemia [55] have been associated with the risk of AD, and might accelerate AD progression [56]. Indeed, the association between CIMT and AD is supported in a previous meta-analysis [14]. Vascular risk factors have been associated with higher levels of brain A β deposition measured using positron emission tomography [57]. A possible mechanism for this association, a dysfunctional glymphatic system with abnormal arterial impulse propagation compromising brain clearance of A β , has recently been demonstrated in vivo in patients with AD [58]. Furthermore, hypoperfusion and hypoxia have been associated with increased A β deposition in the brain and oxidative stress that could contribute to CI [59].

The limitations of this meta-analysis include that some of the reported studies had small sample sizes and that our subgroup analyses only included between 2 and 4

studies. Moreover, due to the large heterogeneity of studies, a random effects model was used for our analyses. There is a risk that some studies in the literature were overlooked since we did not include conference abstracts in the article selection process or contact the authors when data were missing or only presented as odds ratios. An additional limitation is the heterogeneity in study samples, with some studies measuring CIMT in midlife and others in late life (age >65 years). This could be important since some major vascular risk factors have been associated with an increased risk of dementia when they occur in midlife in particular, but not necessarily later in life [57]. However, studies that measured CIMT in late life have also reported increased hazard ratios of all-cause dementia [43, 44]. When MCI or dementia is diagnosed in persons included in research studies, researchers may sometimes follow-up of these persons more carefully than controls without CI, which may lead to a bias in the sample studied. Finally, diagnostic criteria for CI varied across the included studies. Some of the strengths of the present meta-analysis is that the systematic literature search was performed by a trained information specialist as well as the presentation of a transparent methodology of sorting, including, and assessing studies.

In conclusion, the results from the current systematic review and meta-analysis suggest that CIMT may be higher in subjects with CI than cognitively healthy subjects although no significant difference was observed in our main analysis. This potential association is supported by subgroup analyses which showed that CIMT was significantly higher in subjects with MCI and dementia than subjects with NCI. In addition, the dementia group had significantly higher CIMT than the MCI group, and CIMT was also higher in subjects with AD than those with VCI. However, many of the studies had methodological weaknesses affecting our confidence in the results. Therefore, further research with larger, high-quality studies is needed to clarify the potential association between CI and CIMT.

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Statement of Ethics

All investigations were conducted in accordance with the Declaration of Helsinki. The study followed the ethical guidelines of the Regional Ethics Committee of Uppsala, Sweden and is exclusively based on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

D.F. and B.F. conceived and designed the study, and A.M., M.H., and S.B. helped to establish the final PICOS criteria. D.F. and B.F. performed the data extraction, quality assessment of studies, and meta-analyses. D.F. wrote the first draft of the manuscript and revisions of drafts. B.F. reviewed and contributed to revision of all the drafts. All authors revised the manuscript critically for important intellectual content.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online suppl. material files. Further inquiries can be directed to the corresponding author.

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