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SYSTEMATIC REVIEW AND META-ANALYSIS

Intima Media Thickness and Cognitive Function Among Adults: Meta-Analysis of Observational and Longitudinal Studies

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BACKGROUND: Carotid structural changes measured by intima media thickness (IMT) have been related to cognitive complaints during aging. Therefore, the aims of this meta-analysis were (1) to elucidate the relationship between vascular status, measured as IMT, and cognitive domains distinguishing between global cognition, executive functions, memory and attention; and (2) to explore whether demographic (ie, age and sex), clinical (ie, body mass index and IMT baseline values), and procedure characteristics influence this association.

METHODS AND RESULTS: We performed a systematic review of MEDLINE (via PubMed), Scopus, and Web of Science databases from their inception to June 2021. Studies meeting the following inclusion criteria were included: (1) the participants were adults; (2) the exposure was carotid IMT; (3) the outcome was cognitive function, including global cognition, executive function, memory, and attention measured using standardized tests; and (4) the study design was cross-sectional or longitudinal including unadjusted and adjusted analyses. A total of 19 cross-sectional and 15 longitudinal studies were included and demographic (age and sex), clinical (body mass index and baseline IMT values), and procedure characteristics were analyzed as potential mediator or moderators of the association.

CONCLUSIONS: Our data support negative associations between IMT and cognitive function in cross-sectional studies. The association between IMT and cognition lost significance in longitudinal studies and when controlling for covariates in cross-sectional studies. Finally, the strength of these associations seems not to be modified by age, sex, body mass index, and baseline IMT values. This systematic review and meta-analysis adds to the evidence supporting the use of IMT as a measure for identifying patients at risk of cognitive decline.

Key Words: aging ■ carotid intima-media thickness ■ cognition ■ cognitive impairment

According to World Health Organization estimates, by the end of 2020, the number of people aged >60 years might outnumber children younger than 5 years and reach 22% of the global population by 2050.[1] As population life expectancy continues growing worldwide, health systems, social systems, and governments have to face the aging-related burden of chronic diseases.[2] Among the needs of elderly people are changes in several physical and mental health domains (eg, somatic diseases, physical function aging, and psychological and cognitive changes). In particular, cognitive complaints are among the most common reasons for consultation with older patients and their primary caregivers and have been described as a predictor of cognitive decline.[3]

To date, cognitive decline lacks effective treatment, and the search for approaches to prevent or delay its progression and the onset of cognitive impairment has

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CLINICAL PERSPECTIVE

What Is New?

- A cross-sectional negative association between intima media thickness (IMT) and global cognition, executive functions, and memory has been identified.
- This association is not supported for longitudinal studies and when controlling for covariates in cross-sectional studies.
- In addition, variables including age, sex, body mass index, and baseline IMT values do not seem to modify the strength of this association.

What Are the Clinical Implications?

- The results of this systematic review and meta-analysis do not support a strong association between IMT and longitudinal change in cognitive function.
- Although IMT could be used as a measure for identifying patients at risk of cognitive decline, future work is needed to address the association of IMT with the onset of cognitive impairment.

Nonstandard Abbreviations and Acronyms

ES	effect size
IMT	intima media thickness

become an important clinical target.[4,5] The concept of cognitive decline as a vascular disease is being increasingly accepted,[6] together with the evidence that the early detection and treatment of classical cardiovascular risk factors could reduce the impact of cognitive decline.[7-9] In this framework, the monitoring of subclinical cardiovascular risk markers may have an important role in detecting individuals at risk to develop cognitive impairment[9] and in tracking changes induced by treatments.[10] A number of structural alterations that are an expression of vascular aging, reflecting the integrated burden of known and unknown cardiovascular risk factors on the vasculature, such as large artery stiffness[11-13] and carotid structural changes,[14,15] have been associated with a steeper cognitive decline. Among subclinical cardiovascular risk markers, carotid structural changes have been specifically associated with chronic cerebral hypoperfusion, silent micro- and macrocerebrovascular disease, and cortical atrophy, silent cerebral small vessel lesions,[16-18] which in turn are associated with reduced cognitive function.

The utility of the measurement of carotid structural changes by intima media thickness (IMT) has been debated; these subclinical biomarkers of vascular aging are currently not recommended in international guidelines for risk stratification,[19] though recent meta-analyses demonstrate that the extent of intervention effects on carotid IMT predicted the degree of cardiovascular diseases reduction, thus supporting the usefulness of IMT as surrogate biomarkers in interventional trials.[20] Furthermore, a relationship between IMT and cognitive performance has been demonstrated in many cross-sectional and longitudinal studies.[21-23] Discrepancies among studies, including differences in the design and population characteristics and the measurement of a wide variety of cognitive domains, make the evidence of this relationship inconsistent. Furthermore, not every cognitive domain is equally affected during aging, because the brain does not age uniformly, and several factors could protect or damage specific cognitive functions.[24,25]

Therefore, the aims of this meta-analysis were the following: (1) to elucidate the relationship between vascular status, measured as IMT, and cognitive domains distinguishing between global cognition, executive functions, memory, and attention; and (2) to explore whether demographic (ie, age and sex), clinical (ie, body mass index (BMI) and baseline IMT values), and procedure characteristics influence this association.

METHODS

This systematic review and meta-analysis was conducted following the Cochrane Collaboration Handbook[26] and was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis of Observational Studies in Epidemiology statement.[27] The protocol for this systematic review and meta-analysis was previously registered on PROSPERO. The methods used in the analysis, and materials used to conduct the research are available to other researchers upon request.

Data Sources and Searches

Studies on the association between carotid IMT and cognitive function in adults were searched on Medline (via PubMed), Web of Science, and Scopus from database inception to June 2021. The search strategy included the following terms: "endothelial function," "atherosclerosis," "IMT," '"intima thickness," "intima media thickness," "carotid plaque," "cognition," "executive," "executive function," "cognitive control," "memory," "attention," "metacognition," "life skills," "goal setting," "problem solving," "self-regulation," "brain development," and "brain health". We completed the search by screening previous systematic reviews and meta-analyses in the field and checking the reference lists of the included studies.

Study Selection

This systematic review includes studies on the relationship between vascular status, measured by IMT, and cognitive function in adults. The inclusion criteria were as follows: (1) the participants were adults, (2) the exposure was carotid IMT, (3) the outcome was cognitive function, including global cognition, executive function, memory and attention, measured using standardized tests, and (4) the study design was cross-sectional or longitudinal including unadjusted and adjusted analyses.

Studies were excluded when they were (1) focused on children or adolescents, (2) focused on patients with dementia, or (3) written in languages other than English, French, Portuguese, or Spanish.

Data Extraction and Risk of Bias Assessment

The main characteristics of the included studies are summarized in Table 1 and Table S1, including information on (1) subject characteristics (sample size, percentage of women, mean age, BMI, systolic blood pressure, and diastolic blood pressure; (2) exposure (technique used to measure IMT); and (3) outcome information (test used to measure cognitive function and cognitive domain measured).

The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used to evaluate the risk of bias.[57] This tool evaluates 14 criteria for longitudinal studies. For cross-sectional designs, only 11 were applied. Each criterion could be scored as "yes" when the study achieves the criterion, "no" when the study does not achieve the criterion, and "not reported" when the studies do not clearly report the required information. Following this risk of bias tool, studies could be rated as good (ie, at least 11 criteria for longitudinal studies and 8 criteria for cross-sectional studies were met), fair (ie, from 6–10 criteria for longitudinal studies and 4–7 criteria for cross-sectional studies were met), or poor (ie, from 1–5 criteria for longitudinal studies and 1–3 criteria for cross-sectional studies were met).

The literature search (inter-rater agreement Kappa[58,59] index 0.93 [95% CI, 0.99–0.95]), data extraction (inter-rater agreement Kappa index 0.89 [95% CI, 0.87–0.91]), and risk of bias assessment (inter-rater agreement Kappa index 0.92 [95% CI, 0.90–0.94]) were independently performed by 2 researchers (C.A.-B. and I.C.-R.), and disagreements were solved by consensus or involving a third researcher (V.M.V.).

Data Synthesis and Statistical Analysis

To perform the meta-analysis, 4 cognitive domains were considered: (1) global cognition, (2) executive functions, (3) memory, and (4) attention. Separate analyses were conducted for unadjusted and adjusted estimations of cross-sectional and longitudinal associations. For cross-sectional associations, effect sizes (ESs) and 95% CIs were calculated for each observed correlation and regression coefficient using Cohen's d index. A pooled ES was estimated for each cognitive domain using a random-effects model based on the Der Simonian and Laird method.[60] Random effects models were used as they provide more conservative results than fixed effects models and assume that each sample comes from a different population and that the effects in these populations may also differ.[61,62] The ES was interpreted following Cohen's suggestions; d=0.2 was considered a "small" ES, 0.5 represented a "medium" ES, and 0.8 a "large" ES. The Cochran's Q statistics were used to estimate the between-study heterogeneity in ES.[63] The proportion of the total variation across studies because of heterogeneity was assessed using the I^2 statistic, whose values were not important (0% to <30%), moderate (≥30% to <50%), substantial (≥50% to <75%), or considerable (≥75% to 100%).[63] Moreover, the corresponding *P* values were also considered.[58] Following similar procedures, we estimated the pooled ES for the longitudinal associations between the baseline IMT and the pre–post change in the cognitive domains. The *Z* scores and corresponding *P* values against the hypothesis that IMT has no effect on cognitive function were also reported.

The following methodological considerations for data collection and analysis should be noted. When longitudinal studies reported baseline associations between IMT and cognitive function, these reports were included in the cross-sectional pooled ES estimates. When studies provided ≥2 measurements for the same cognitive domain, these measurements were combined to calculate a single pooled ES for the corresponding domain. For unadjusted analyses, those associations including the shortest number of covariates were considered, and for the adjusted analyses, those associations including the largest number of covariates were considered. Finally, when studies reported mean value trends by groups or associations using regression models or correlation coefficients, ES values were calculated.

Sensitivity analyses were performed excluding all the studies 1 at a time from the pooled estimates to evaluate whether any particular study modified the original summary estimate. Subgroup analyses were performed based on characteristics of the procedures to measure IMT, including (1) manual, automated, or not specified measurements; (2) right, left, or bilateral carotid artery measurement; and (3) frequency of the ultrasound (defined as a range, >7 or not specified). Additional subgroup analyses were performed based on the method used to measure cognitive function

Table 1. Characteristics of the Studies Included in the Systematic Review and Meta-Analysis on the Association Between Cognition Parameters and IMT

	Subjects characteristics						Exposure		Outcome	
References	n, female (%)	Age	BMI	SBP	DBP	Depressives (%)	IMT device	IMT average	Cognitive measurement	Cognitive construct
Al Hazzouri et al, 2015[28]	2618 (57.1)	45.3 (3.6)	NR	NR	NR	16.2%	GE-Logiq-700	0.8 (0.1)	Rey AVLT Digit Symbol Substation Stroop Interference	Delayed verbal memory Processing speed Executive function
Arntzen et al, 2012[23]	4371 (51.5)	M: 58.6 (9.3) W: 59.5 (9.9)	M: 26.1 (3.1) W: 25.8 (4.2)	M: 143.1 (19.2) W: 142.4 (22.9)	NR	M: 2.1% W: 5.5%	High- resolution B-mode ultrasonography	M: 0.88 (0.18) W: 0.81 (0.16)	12-word memory Test Digit Symbol-Coding Test Finger tapping Test	Immediate free recall Psychomotor speed, attention, and mental flexibility. Psychomotor tempo
Casado-Naranjo et al, 2016[29]	181 (45.9)	MCI: 77.5 (4.6) C: 75.3 (5.2)	NR	NR	NR	MCI: 18.1% C: 4.0%	Philips HD 11	MCI: 1.03 (0.27) C: 0.85 (0.32)	MMSE	Global cognitive
Cohen-Manheim et al, 2016[30]	507 (32.3)	49.9 (0.8)	24.7 (3.6)	112.0 (10.0)	68.0 (9.0)	Depressive symptoms score (HADS 0–21): 3.6 (2.9)	Philips IU22	0.63 (0.11)	Digit arithmetic problems Go-NoGo, Stroop and Catch Game Abstract spatial ability test Immediate and delayed memory tests	Global cognitive Attention Information processing speed Executive Visual spatial processing Memory
Cohen et al, 2009[31]	88 (NR)	72.2 (7.7)	NR	129.3 (19.5)	68.5 (10.1)	Exam Score Beck Depression Inventory: 4.2 (2.5)	Agilent 5500 machine	0.88 (0.13)	MMSE, Dementia Rating Scale BNT, Animals Block Design, Hooper Visual Organization, Rey Complex Figure Test- Copy California Verbal Learning delayed, Rey Complex Figure Test delayed, Brief Visual Memory Test–Revised Stroop, TMT A-B, controlled oral Word association, Letter search, Digit Symbol Coding, Digit Span and Pegs-D	Global cognitive Language Visual-spatial Learning and memory functions Attention-executive-psychomotor functions
Del Brutto et al, 2020[24]	561 (58)	57.8 (11.9)	NR	NR	NR	10%	Terason Smart 3300 NexGen	NR	MoCA	Global cognition

(*Continued*)

Table 1. Continued

	Subjects characteristics						Exposure		Outcome	
References	n, female (%)	Age	BMI	SBP	DBP	Depressives (%)	IMT device	IMT average	Cognitive measurement	Cognitive construct
Feinkohl et al, 2013[32]	831 (48.3)	67.7 (4.2)	31.3 (5.6)	132.5 (15.9)	69.0 (8.9)	HADS Depression: 3 (1–5)	Sonoline Elegra Ultrasound Imaging System	1.0 (0.2)	Borkowski Verbal Fluency Test Logical Memory Faces Subtest TMT-B Digit Symbol Coding Letter-Number Sequencing Matrix Reasoning Mill Hill Vocabulary Scale MMSE	Executive function Immediate and delayed memory Nonverbal memory Mental flexibility and Executive function Speed of information processing Working memory Nonverbal reasoning Vocabulary abilities Global cognition
Frazier et al, 2014[33]	251 (46.0)	78.0 (6.4)	NR	NR	NR	NR	High-resolution B-mode ultrasound	0.9 (0.1)	Dementia Rating Scale Initiation-perseveration subscale, Wechsler Memory Scale Memory Scale-Revised Digit and Visual Span backwards, COW-Fluency Task Word List Learning Test, short and long delayed recall	Executive function Verbal memory
Gardener et al, 2018[34]	1166 (60.0)	70. 0 (9.0)	28.0 (5.0)	NR	NR	NR	GE LogIQ 700	0.9 (0.1)	List-learning, Delayed Recall, Delayed Recognition Color Trail Test, Odd-man-out subtest Grooved Pegboard Task, Color Trial test, Visual–motor Integration BNT, Animal Naming, Phonetic fluency test	Episodic memory Executive function Processing speed Semantic memory
Gatto et al, 2009[35]	504 (38.9)	60.8 (9.9)	28.1 (5.0)	129.6 (16.9)	80.8 (10.4)	7.3%	High-resolution B-mode ultrasound	0.75 (0.15)	Symbol Digit Modalities, Trial-B, Letter-Number Sequencing, Judgment of Line Orientation, Block design, Shipley Institute of Living Scale California Verbal Learning Test, immediate recall and delayed recall Paragraph recall- immediate recall and delayed recall Faces I and II Category fluency and BNT	Executive function Verbal learning Logical memory Visual memory Semantic memory Global cognitive
Geijselaers et al, 2016[36]	722 (44.9)	60.0 (8.0)	27.2 (4.4)	137.0 (19.0)	77.0 (11.0)	3.9%	MyLab 70	0.85 (0.15)	Verbal Learning Test Stroop Colour/Word, Concept Shifting Test Part A and B, Letter-Digit Substitution Test Stroop Colour-Word, Concept Shifting	Immediate and delayed recall Processing speed Executive function and attention

(*Continued*)

Table 1. Continued

	Subjects characteristics						Exposure		Outcome	
References	n, female (%)	Age	BMI	SBP	DBP	Depressives (%)	IMT device	IMT average	Cognitive measurement	Cognitive construct
Haley et al, 2007[37]	109 (43.0)	69.2 (7.43)	NR	NR	NR	NR	High- resolution B-mode ultrasonography	0.88 (0.13)	MMSE, Dementia Rating Scale BNT, Category Fluency for Animals HVOT, WAIS-III Block Design Subtest, CFT copy CVLT, CFT immediate recall, delayed recall, and recognition discrimination, BVMT-R, recognition discrimination TMT (A and B), Stroop Word/Color, COW-Association Test, Letter Search, WAIS-III Block Coding Subtest, WAIS-III Digit Span Subtest, Grooved Pegboard Dominant Hand	Global cognitive functioning Language Visual–spatial Memory Attention-executive-psychomotor
Imran et al, 2020[38]	79 (NR)	55.5 (12.7)	NR	NR	NR	NR	Mindray Z6	0.81 (0.22)	RAVLT ROCFT	Memory function
Jiang et al, 2017[39]	357 (65.0)	57.2 (9.3)	25.3 (3.3)	132.2 (16.6)	83.4 (9.3)	NR	Sequoia scanner	0.8 (0.2)	MoCA	Global cognition
Kemp et al, 2016[40]	8114 (56.3)	51.2 (8.8)	NR	NR	NR	Depression severity: 8.0 (7.8)	Toshiba (Aplio XG)	0.8 (0.2)	TMT-B	Executive function
Komulainen et al, 2007[41]	91 (100)	63.8 (3.2)	27.6 (4.4)	NR	NR	Zung self-report 20-item scale: 36.4 (5.5)	Carotid ultrasonography	1.02 (0.26)	MMSE Word Recall Test Stroop test and Letter-Digit Substitution Test	Global cognition Memory Cognitive Speed
Lim et al, 2016[42]	463 (43.2)	MP: 63.0 (6.1) NP: 64.2 (6.4)	MP: 25.0 (4.1) NP: 24.6 (3.5)	NR	NR	NR	High-resolution B-mode ultrasound	MP: 0.8 (0.5–1.8) NP: 0.7 (0.5–1.8)	MMSE Digit Span-Forward, Colour Trails Test Rey Auditory Verbal Learning Test, Story Memory and Recall BNT Brief Visuospatial Memory Test-Revised Digit Span- Backward, Block Design, Colour Trails Test 2 and Categorical Verbal Fluency (Animal Naming)	Global cognition Attention Verbal memory Language Visuospatial ability Executive function
Masley et al, 2014[43]	536 (27.4)	48.0 (7.5)	27.4 (4.7)	117.7 (15.3)	75.7 (10.4)	NR	High-resolution B-mode ultrasound	0.7 (0.1)	Index score Verbal memory and visual memory components Symbol Digit Coding Stroop Test, Continuous Performance Test Finger Tapping Test, Stroop Test	Global cognition Memory Executive function Attention Motor speed

(*Continued*)

Table 1. Continued

	Subjects characteristics						Exposure		Outcome	
References	n, female (%)	Age	BMI	SBP	DBP	Depressives (%)	IMT device	IMT average	Cognitive measurement	Cognitive construct
Matsumuto et al, 2018[25]	176 (55.7)	CI: 67.7 (12.3) Non-CI: 64.6 (9.6)		CI: 125.4 (20.9) Non-CI: 119.9 (16.1)	CI: 23.8 (2.8) Non-CI: 23.4 (3.4)	NR	Xario SSA-660A	CI: 2.0 (1.0) Non-CI: 1.7 (0.6)	MMSE, Hasegawa Dementia Scale-revised Logical Memory IA and IIA of the WMS-R Clock-drawing Test	Global cognition Immediate and delayed recall Visuo-constructional function, executive function and planning ability
Muela et al, 2018[44]	211 (54.8)	NoHTA: 52.2 (13.9) HTA 1: 52.1 (13.0) HTA 2: 51.3 (10.1)		NoHTA: 121.9 (8.3) HTA 1: 135.0 (13.5) HTA 2: 147.5 (26.1)	NoHTA:26.7 (4.2) HTA 1: 28.5 (4.6) HTA 2: 30.1 (4.6)	NR	Wall Track System, Medical Systems Arnhem)	NoHTA: 0.7 (0.1) HTA 1: 0.8 (0.1) HTA 2:0.8 (0.1)	MMSE, MoCA BNT RAVLT REY, Clock Drawing Test Semantic Verbal Fluency animal category, Phonological Verbal Fluency Forward and Backward Digit Span Tess, Trail Making Test, and Digit Symbols Substitution Test	Global cognition Language Memory Visuospatial abilities Attention and executive functions
Muller et al, 2007[45]	396 (0.0)	N-CVD: 54.5 (10.3) S-CVD: 66.8 (8.1) P-CVD: 67.7 (8.8)	N-CVD: 25.9 (0.3) S-CVD: 26.5 (0.3) P-CVD: 27.3 (0.5)	N-CVD: 134.2 (1.3) S-CVD: 145.5 (1.7) P-CVD: 140.2 (2.5)	NR	NR	Acuson Aspen	N-CVD: 0.77 (0.01) S-CVD: 0.89 (0.01) P-CVD: 0.89 (0.02)	MMSE, Rey auditory verbal learning test, and door test Digit span, TMT-A TMT-B, Word fluency test Dutch adult reading test	Memory Processing/speed Executive function
Roberts et al, 2013[46]	278 (54.3)	49.0–51.0	NR	NR	NR	NR	High-resolution B-mode ultrasound	NR	IQ test Moray House Tests 57 & 58, the English and Arithmetic tests and the Mill Hill and Raven's Progressive Matrices	IQ Language Arithmetic
Rogne et al, 2013[47]	1577 (47.3)	57 (52–61)	25.6 (3.2)	138.0 (18.0)	NR	NR	High- resolution B-mode ultrasonography	0.78 (0.69–0.89)	Digit Symbol Test Finger tapping test 12-word test parts 1 and 2 test (modification of the CVL test) MMSE	Executive function Motor speed Verbal episodic memory Global cognition
Romero et al, 2009[48]	1971 (53.0)	58.0 (10.0)	NR	126.0 (18.0)	NR	NR	Doppler spectral analyzer (Model SSH-140A)	NR	Wechsler Memory Scale Logical Memory, Paragraph A subtest, Immediate and Delayed Recall Halstead Reitan TMT (A and B) BNT, WAIS Similarities subtest, HVOT	Verbal memory Executive function Non-verbal memory
Schwerdtfeger et al, 2015[49]	124 (49.0)	37.5 (7.9)	23.8 (4.0)	NR	NR	NR	High-resolution B-mode ultrasound	0.5 (0.1)	Mainz Coping Inventory	Cognitive avoidance

(*Continued*)

Table 1. Continued

	Subjects characteristics						Exposure		Outcome	
References	n, female (%)	Age	BMI	SBP	DBP	Depressives (%)	IMT device	IMT average	Cognitive measurement	Cognitive construct
Singh-Manoux et al, 2008[50]	3896 (27.9)	H-SES-M: 62.3 (5.6) H-SES-W: 59.8 (5.5) I-SES-M: 60.0 (5.8) I-SES-W: 60.1 (5.9) L-SES-M: 60.8 (6.5) L-SES-W: 62.0 (5.7)	H-SES-M: 26.2 (3.7) H-SES-W: 25.6 (5.1) I-SES-M: 26.5 (3.8) I-SES-W: 26.4 (5.3) L-SES-M: 26.5 (4.2) L-SES-W: 27.6 (4.9)	H-SES-M: 127.9 (15.5) H-SES-W: 122.8 (17.7) I-SES-M: 127.2 (15.2) I-SES-W: 124.7 (16.9) L-SES-M: 124.5 (14.7) L-SES-W: 126.5 (17.3)	H-SES-M: 74.2 (10.3) H-SES-W: 71.9 (10.3) I-SES-M: 74.3 (10.1) I-SES-W: 72.6 (10.4) L-SES-M: 72.2 (10.1) L-SES-W: 72.6 (10.6)	NR	Aloka 5500	H-SES-M: 0.8 (0.2) H-SES-W: 0.8 (0.1) I-SES-M: 0.8 (0.2) I-SES-W: 0.8 (0.1) L-SES-M: 0.8 (0.2) L-SES-W: 0.8 (0.1)	20-word Free Recall Test Alice Heim 4-I Mill Hill Vocabulary Test “S” words and “animal” words MMSE	Short term verbal memory Inductive reasoning Verbal meaning and Encompasses Phonetic and Semantic fluency Global cognition
Smith et al, 2011[51]	124 (63.7)	52.3 (9.6)	32.8 (3.8)	138.3 (8.4)	86.1 (6.5)	8%	High- resolution B-mode ultrasonography	0.70 (0.14)	TMT (A and B), Stroop Test, Verbal Paired Associates test, COW-Association Test, Digit Span Test, Animal Naming Ruff 2 & 7 Test, Digit Symbol Substitution Test	Executive Function Psychomotor Speed
Suemoto et al, 2015[52]	8208 (55.9)	49.6 (7.3)	26.6 (4.5)	NR	NR	4.0%	Toshiba ultrasound machine	0.7 (0.2)	CERAD Delayed Word Recall test Category Fluency Test TMT-B	Verbal learning and recent memory Language and executive function Executive function, speed of processing, and attention
Wang et al, 2016[53]	3227 (43.4)	57.9 (10.9)	24.9 (3.3)	130.8 (19.9)	82.6 (11.0)	NR	Philips iU-22 ultra- sound system	NR	MMSE	Global cognition

(*Continued*)

Table 1. Continued

	Subjects characteristics						Exposure		Outcome	
References	n, female (%)	Age	BMI	SBP	DBP	Depressives (%)	IMT device	IMT average	Cognitive measurement	Cognitive construct
Wendell et al, 2009[15]	538 (60.2)	54.9 (14.0)	26.3 (4.5)	NR	NR	CES-D: 6.6 (9.6)	Ultramark 9 HDI	0.5 (0.1)	Blessed Information-Memory-Concentration (I-M-C) Test, MMSE Digits Forward, Digits Backward CVL learning slope CVL immediate, short-delay and long-delay free recall BVRT, RCFT immediate and long-delay recall TMT (A and B) Letter Fluency Category Fluency BNT RCFT copy Card Rotations Test	Attention and concentration Verbal learning Memory Nonverbal memory Attention, perceptuo-motor speed, visuomotor scanning, and mental flexibility Phonemic fluency Semantic fluency Language Visuospatial constructional ability Visuospatial function
Wendell et al, 2016[54]	1712 (55.1)	46.9 (9.3)	29.4 (7.4)	119.5 (17.2)	NR	CES-D: 14.0 (10.8)	Acuson CV 70	0.7 (0.1)	MMSE Benton Visual Retention Test CVL Animal fluency Brief Test of Attention Digit Span subtest of the Wechsler Adult Intelligence Scale-Revised TMT (A and B)	Global cognition Visuospatial memory Verbal learning and memory Language and semantic association fluency Auditory divided attention Attention and working memory Attention, visual scanning, psychomotor speed, and mental flexibility
Yue et al, 2016[55]	1826 (35.2)	63.2 (11.9)	NR	CInt: 147.2 (22.4) CImp: 149.0 (22.7)	CInt: 85.5 (12.5) CImp: 84.0 (13.6)	NR	High-resolution B-mode ultrasonography	1.4 (0.7)	MMSE	Global cognition
Zhong et al, 2011[56]	2794 (54.0)	49.0 (9.8)	NR	NR	NR	NR	Biosound AU4	0.65 (0.15)	TMT (A and B) Grooved Pegboard Test MMSE	Executive, attention and psychomotor function Executive, and psychomotor function General cognitive function

(*Continued*)

Table 1. Continued

References	Subjects characteristics						Exposure		Outcome	
	n, female (%)	Age	BMI	SBP	DBP	Depressive s (%)	IMT device	IMT average	Cognitive measurement	Cognitive construct
Zhong et al, 2012[22]	1651 (59.2)	66.8 (NR)	30.1 (5.9)	NR	NR	NR	Biosound AU4	0.86 (0.21)	MMSE TMT (A and B) Digit Symbol Substitution Test AVLT Verbal Fluency Test (VFT)	Executive function, attention and speed Psychomotor speed and sustained attention Memory Spontaneous production of words

ADAS-cog indicates Alzheimer Disease Assessment Scale-cognitive subscale; AVLT, Rey Auditory Verbal Learning Test; BNT, Boston naming test; BVMT-R, Brief Visual Memory Test–Revised; COWAT, Controlled Oral Word Association Test; CVLT, California Verbal Learning Test; HVOT, Hooper Visual Organization Test; M, men; MMSE, Mini-Mental State Examination; MoCA, Montreal cognitive assessment; NR, not reported; RAVLT, Osterrieth Auditory Verbal Learning Test; ROCFT, Rey Osterrieth Complex Figure Test; TMT, Trail Making Test; W, women; WAIS, Wechsler Adult Intelligence Scale; and WMS-R, Wechsler Memory Scale Revised.

(global test of cognition or domain-specific assessments). Random effect meta-regressions were calculated based on sample characteristics: percentage of women, mean age, BMI, and baseline IMT values. Finally, publication bias was estimated using Egger's test.[64] All the statistical analyses were performed using STATA 15 (StataCorp) software.

RESULTS

Systematic Review

The literature search retrieved 6879 studies, of which 19 cross-sectional and 15 longitudinal studies were included in this systematic review and meta-analysis[15,22–25,28–56] (Figure S1). The studies included a total of 50 779 participants aged 45.3 to 78.0 years. Table 1 and Table S1 summarize the characteristics of included studies. Table S2 summarizes the covariates used in the analyses of the included studies.

Risk of Bias Assessment

Cross-sectional studies scored between 5 and 11 points, and longitudinal studies scored between 8 and 12 points. The 4 criteria in which most articles lacked information were sample size justification, power description, variance, and outcome blinding of the assessors to the participants' exposure status (Table S3).

Meta-Analysis

The pooled ES for the unadjusted cross-sectional association between carotid IMT and cognitive function was small for global cognition (−0.25 [95% CI, −0.36 to −0.14]; Q: 134.40; I^2: 89.6%), for executive function (−0.18 [95% CI, −0.29 to −0.07]; Q: 37.15; 81.2%), for memory (−0.14 [95% CI, −0.25 to −0.04]; Q: 151.33; 90.1%), and for attention (−0.12 [95% CI, −0.29 to 0.04]; Q: 54.16; 87.1%). Considering the adjusted cross-sectional data, the pooled ES was small for global cognition (−0.15 [95% CI, −0.24 to −0.07]; Q: 78.08; I^2: 82.1%), for executive function (−0.12 [95% CI, −0.21 to −0.03]; Q: 27.04; 74.1%), for memory (−0.09 [95% CI, −0.15 to −0.03]; Q: 33.88; I^2: 55.7%), and for attention (−0.13 [95% CI, −0.26 to 0.01]; Q: 32.46; 78.4%) (Figures 1 and 2).

Additionally, for the longitudinal associations, the pooled ES for the unadjusted longitudinal association between IMT and cognitive function was small for global cognition (−0.21 [95% CI, −0.38 to −0.04]; Q: 16.37; I^2: 81.7%), for executive function (−0.14 [95% CI, −0.29 to 0.01]; Q: 50.25; I^2: 90.0%), for memory (−0.15 [95% CI, −0.30 to 0.00]; Q: 255.80; I^2: 96.5%), and for attention (−0.23 [95% CI, −0.62 to 0.17]; Q: 215.95; 98.6%). Considering the adjusted longitudinal data, the pooled ES was small for global cognition (−0.09 [95% CI, −0.20 to 0.02]; Q: 7.30; I^2: 58.9%), for executive function (−0.04 [95% CI, −0.12 to 0.04]; Q: 12.78;

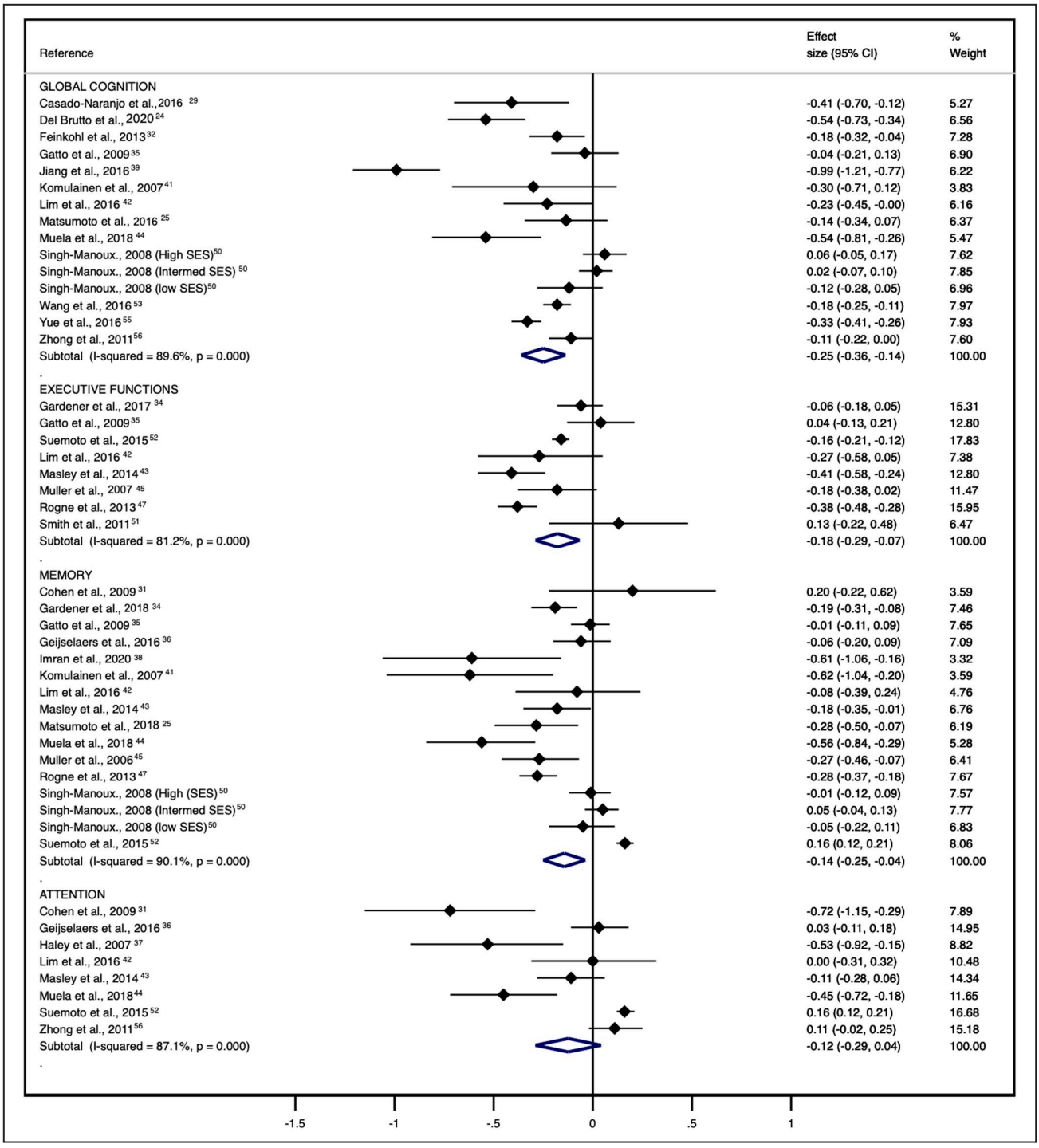

Figure 1. Forest plot for the unadjusted cross-sectional association between intima media thickness and cognitive function domains.
SES indicates socioeconomic status.

I^2: 60.9%), for memory (–0.00 [95% CI, –0.05 to 0.04]; Q: 23.32; I^2: 61.4%); and for attention (–0.04 [95% CI, –0.09 to 0.01]; Q: 3.81; 21.3%) (Figures 3 and 4).

The *Z* scores and corresponding *P* values against the hypothesis that IMT has no effect on cognitive function are reported in Table S4.

Sensitivity Analysis

Sensitivity analyses were performed excluding all the studies 1 at a time from the pooled estimates to evaluate whether any particular study modified the original summary estimate. The sensitivity analyses for the cross-sectional estimates showed that the adjusted

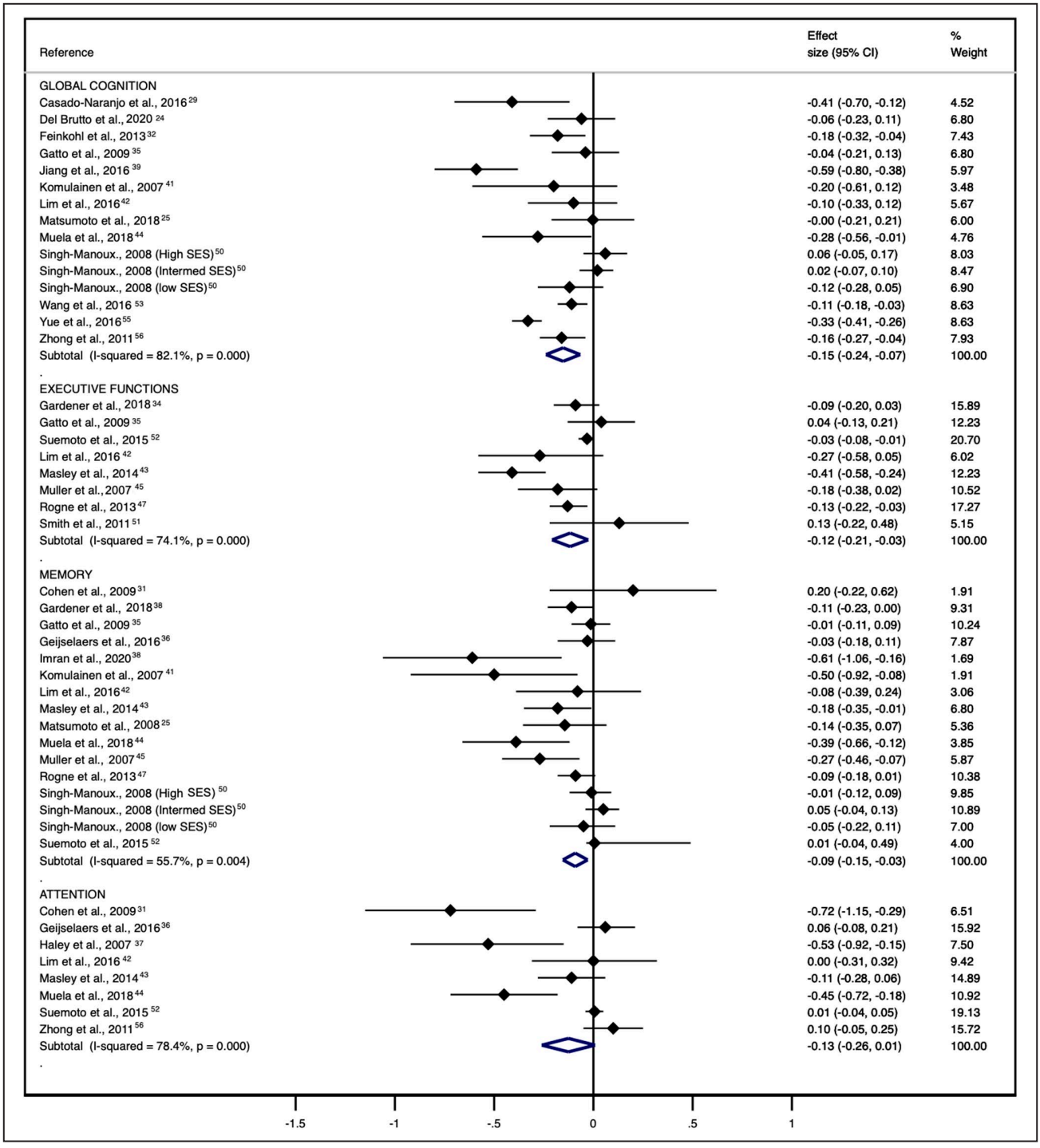

Figure 2. Forest plot for the adjusted cross-sectional association between intima media thickness and cognitive function domains.
SES indicates socioeconomic status.

association between IMT and attention became significant after excluding the studies performed by Geijselaers et al and Zhong et al.

The sensitivity analyses for the longitudinal estimates showed that the unadjusted association between IMT and cognitive function became significant after excluding the studies performed by (1) Cohen-Manheim et al, Del Brutto et al, and Feinkohl et al, for global cognition; (2) Gardener et al, and Romero et al, for executive functions; and (3) Gardener et al, Romero et al, Wendell et al, and Zhong et al, for memory (Tables S5–S8).

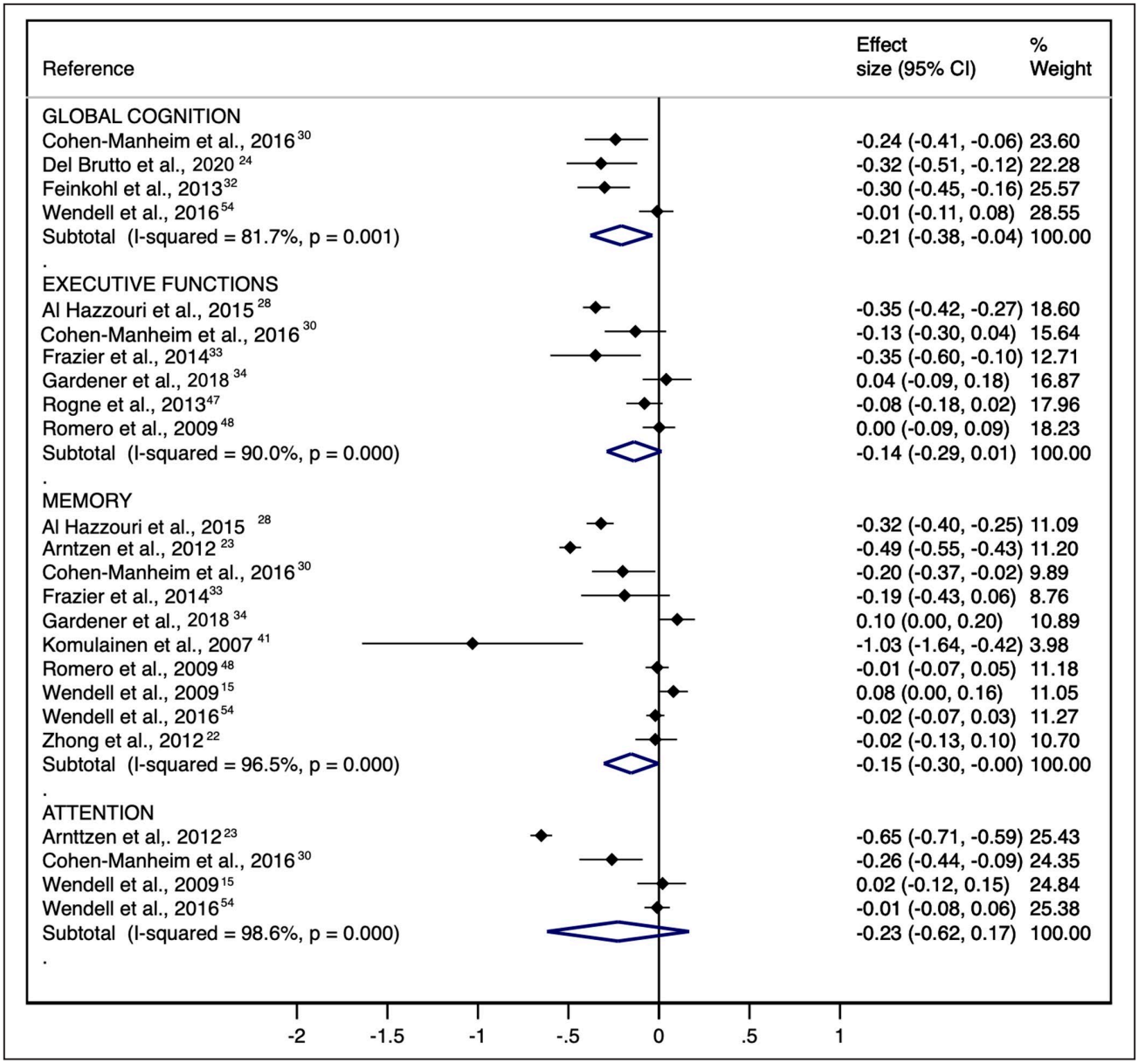

Figure 3. Forest plot for the unadjusted longitudinal association between intima media thickness and cognitive function domains.
SES indicates socioeconomic status.

Meta-Regressions and Subgroup Analyses

Meta-regressions showed that none of the considered variables (ie, % females, age, BMI, and baseline IMT values) influenced the relationship between IMT and cognitive function for the cross-sectional or longitudinal models (Table S9). Additionally, when considering the procedure characteristics, the ESs for the subgroup analyses were similar to the pooled ESs when (1) automated and not specified measurements of IMT were used for cross-sectional studies reporting on global cognition and memory; (2) bilateral carotid artery measurement was used for cross-sectional and longitudinal studies reporting on global cognition, executive functions, and memory; (3) >7 frequency of the ultrasound was used for cross-sectional studies reporting on global cognition, memory, and attention; and (4) domain-specific assessments to measure cognitive function were used for cross-sectional studies reporting on global cognition and memory (Table S10).

Publication Bias

As evaluated by Egger's test and funnel plot asymmetry, publication bias was found for (1) global cognition in the unadjusted longitudinal analysis; (2) memory in the unadjusted and adjusted cross-sectional analyses;

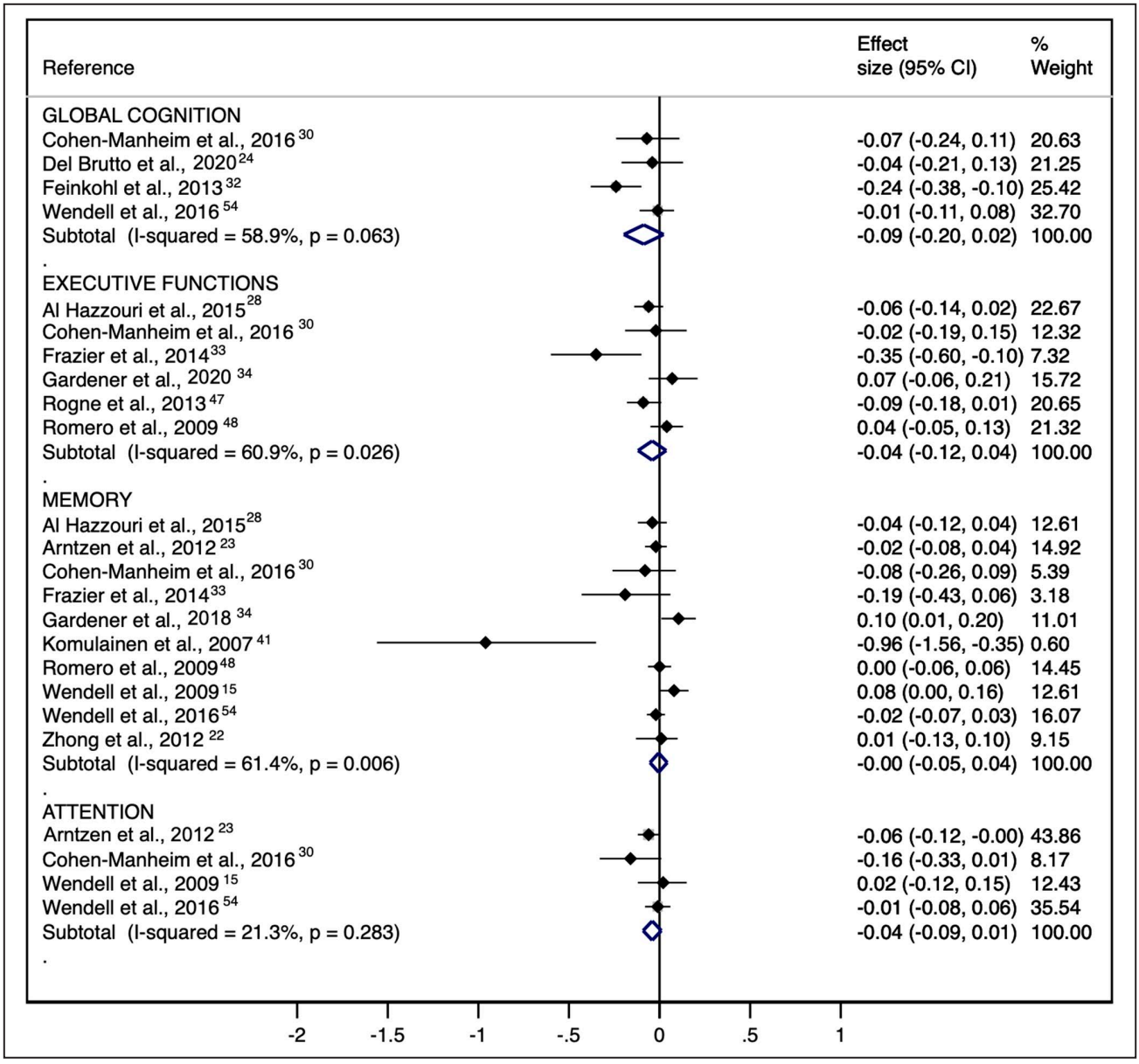

Figure 4. Forest plot for the adjusted longitudinal association between intima media thickness and cognitive function domains.

and (3) attention in the unadjusted cross-sectional analysis (Table S11 and Figures S2–S9).

DISCUSSION

The purpose of this meta-analysis was to identify associations between IMT and cognitive function in cross-sectional and longitudinal studies. Our data support a small negative association between IMT and cognitive function in cross-sectional studies, especially for global cognition, executive functions, and memory. The association between IMT and cognition lost significance in the longitudinal studies and after controlling for covariates in cross-sectional studies. Finally, our data suggest that demographic (age and sex), clinical (BMI and baseline IMT values), and procedure characteristics do not influence the strength of this association.

Data from cross-sectional studies suggest an association between IMT and cognition, indicating that cognition is reduced in people with increased IMT. The association was not significant when ESs of longitudinal studies were pooled; therefore, the pooled results did not support that IMT level predicted cognitive performance over time. This asymptomatic carotid atherosclerosis could be the image of the arterial remodeling that occurs during the natural process of vascular aging.[65] In addition, several covariates could negatively impact vascular aging, including age, sex,

diabetes, hypertension, and patient education, resulting in atherosclerosis as a maladaptive process of vascular remodeling.[66]

Significant heterogeneity was observed in the pooled analyses and explored by subgroup analyses and meta-regressions based on demographic, clinical, and procedure characteristics. Although sex, age, and BMI have been proposed to be factors affecting IMT, the results of the meta-regressions do not suggest that the relationship between IMT and cognitive functions could be influenced by these factors.[67] In addition, the different effects of hemodynamic and biochemical changes on the left and right IMT could be sources of heterogeneity; data from the subgroup analyses suggest that the bilateral IMT measurement is the most reported and reproducible method when assessing the relationship between IMT and cognitive functions.[68] The influence of other procedure characteristics including the method used to measure IMT (automated or manual methods) and cognitive functions (domain-specific assessment or global test of cognition), and the mHz applied could not be confirmed because of the lack of studies to draw conclusions.[69]

Different mechanisms have been proposed to explain the effect of IMT on cognitive function. Blood support to neural cells could be compromised as a result of 2 interrelated events: (1) the thickening of the arterial wall, which could reduce the vessel lumen and produce chronic cerebral hypoperfusion; and (2) the promotion of endothelial dysfunction by the increased wall stress.[70] Additionally, the increased wall stress has been related to an increased risk of plaque fissuring,[71] increasing the subsequent risk of neural ischemia. Atherosclerosis and embolization of the vascular microcirculation and subsequent chronic inflammation[65,72] have been suggested to precipitate cerebral small vessel disease.[73] Furthermore, the local thickening of the arterial wall could produce a microturbulent flow, reducing the supply of blood and nutrients and leading to neuronal dysfunction and cell death.

The results of this systematic review and meta-analysis should be cautiously considered, as some limitations should be mentioned. In addition to the specific limitations of the meta-analysis design, other sources of bias could be that (1) we did not use the original data but the data as reported by the studies to estimate the pooled ES; (2) substantial heterogeneity was found when pooled ESs were estimated, and diverse methods and tools were used to measure cognitive function across the included studies; (3) publication bias was found in some of the analyses; (4) language restrictions may have limited the number of included studies; and (5) our data might be limited by the use of 3 databases, and additional studies may have been found by checking other databases.

In conclusion, the pooled analysis of cross-sectional studies suggests a negative association between IMT and global cognition, executive functions, and memory. The association between IMT and cognition lost significance in longitudinal studies and when controlling for covariates in cross-sectional studies. Finally, age, sex, BMI, and baseline IMT values do not seem to modify the strength of this association. The results of this systematic review and meta-analysis do not support a strong association between IMT and longitudinal change in cognitive function, and future work is needed to address this association with the onset of cognitive impairment.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S11
Figures S1–S9

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Table S1. Characteristics of the IMT Measurement Procedures of the Studies Included in the Systematic Review and Meta-Analysis on the Association Between Cognition Parameters and IMT.

References	Manual/automated	Common carotid	mHz	Uni o bilateral	Mean or maximal	Global test of cognition or Domain specific assessments
Al Hazzouri et al., 2015[28]	Manual	Yes	13	Bilateral	Maximal IMT of the near and far wall of the CCA	Global test of cognition
Arntzen et al., 2012[23]	Automated	Yes	7.5	Right	Far and near wall of the CCA and the far wall of the bulb. Included plaque	Domain specific assessments
Casado-Naranjo et al., 2016[29]	NE	Yes	3-12	Bilateral	CCA at 1.5 cm proximal to the flow divider	Domain specific assessments
Cohen-Manheim et al., 2016[30]	Automated	Yes	7.5	Left	far wall of the left CCA, 1 cm proximal to the carotid bulb	Global test of cognition
Cohen et al., 2009[31]	Manual	Yes	7-17	Bilateral	CCA, bifurcation, and internal carotid artery, in three views (lateral, anterior, and posterior oblique) Included plaque	Global test of cognition
Del Brutto et al., 2020[24]	NE	Yes	4-15	Bilateral	Near wall and far wall of the: 1) segment extending from 1-2cm proximal to the tip of the flow divider into the CCA; (2) carotid bifurcation beginning at the tip of the flow divider and extending 1cm proximal to the flow divider tip; and (3) proximal 1cm of the internal carotid artery	Domain specific assessments
Feinkohl et al., 2013[32]	NE	Yes	NE	Bilateral (use of the higher value)	CCA, 1 to 2 cm below the bifurcation Free of plaque	Domain specific assessments
Frazier et al., 2014[33]	Automated	Yes	NE	Bilateral	Far wall far wall of the right and left distal CCA, a 1 cm length, just distal to the carotid artery bulb	Domain specific assessments
Gardener et al., 2018[34]	Automated	Yes	9-13	Bilateral	Near and far walls of the common carotid artery, bifurcation, and internal carotid artery Free of plaque	Domain specific assessments
Gatto et al., 2009[35]	Automated	Yes	NE	Right	Distal CCA far wall along a 1-cm length just distal to the carotid artery bulb.	Global test of cognition
Geijselaers et al., 2016[36]	NE	Yes	7.5	Left	Left CCA, 1 cm proximal to the carotid bulb. Free of plaque	Global test of cognition
Haley et al., 2007[37]	Automated	Yes	7.5	Left	Far wall of the left CCA, 1 cm proximal to the carotid bulb	Global test of cognition
Imran et al., 2020[38]	Manual	Yes	10	Bilateral	Near-and the far-wall of the distal part of CCA, on the 1-cm long segment from the carotid bulb	Domain specific assessments
Jiang et al., 2017[39]	Automated	Yes	NE	Bilateral	Far wall of the CCA, the 1 cm segment proximal to the bifurcation	Domain specific assessments
Kemp et al., 2016[40]	Automated	Yes	7.5	Bilateral	Outer wall, 1 cm in length from 1 cm below carotid bifurcation	Domain specific assessments
Komulainen et al., 2007[41]	Automated	NE	10	Bilateral	Far wall of the left and right bifurcation	Domain specific assessments
Lim et al., 2016[42]	NE	Yes	10.5	Bilateral	The CCA was scanned in anterior, posterior and lateral at 1cm proximal to the carotid bulb Free of plaque	Global test of cognition
Masley et al., 2014[43]	NE	Yes	5-10	Bilateral	Far wall of the right and left distal 1 cm of the CCA	Global test of cognition
Matsumuto et al., 2018[25]	NE	Yes	NE	Bilateral	The maximum value among the bilateral common and internal carotid artery in the far arterial walls	Domain specific assessments
Muela et al., 2018[44]	Automated	Yes	7.5	Left	Left CCA, 1 cm below the bifurcation at the site of the distal Free of plaque	Domain specific assessments
Muller et al., 2007[4]	NE	Yes	7.5	Bilateral	left and right distal CCA	Domain specific assessments
Roberts et al., 2013[46]	NE	Yes	7	Bilateral	Three locations in the common and internal carotid arteries	Global test of cognition
Rogne et al., 2013[47]	Semi-automated	Yes	7.5-12	Right	1cm segments of the far and near wall of the CCA, and in the most proximal 1cm segment of the bulb. Included plaque	Domain specific assessments
Romero et al., 2009[48]	NE	Yes	7.5	Bilateral	Near and far walls of CCA, carotid bulb and ICA	Global test of cognition
Schwerdtfeger et al., 2015[49]	Automated	NE	5-13	Bilateral	1 cm from carotid bifurcation from the far wall of the arteria carotid at a length of 1 cm	Domain specific assessments
Singh-Manoux et al., 2008[50]	NE	Yes	7.5	Bilateral	Right and left CCA, thickest part 1 cm proximal to the bifurcation	Domain specific assessments
Smith et al., 2011[51]	Automated	Yes	10	Bilateral	Far wall of the left and right CCA	Global test of cognition
Suemoto et al., 2015[52]	NE	Yes	7.5	Bilateral	Left and right CCA, within an area of 1 cm in length, 1 cm below the carotid bifurcation	Domain specific assessments
Wang et al., 2016[53]	Manual	Yes	5-12	Bilateral	Far wall of the CCA proximal to the bifurcation, along a plaque-free segment of 1cm	Domain specific assessments
Wendell et al., 2009[15]	NE	Yes	5-10	Right	1.5 cm proximal to the carotid bifurcation, of the far arterial wall of the right CCA	Domain specific assessments
Wendell et al., 2016[54]	NE	Yes	NE	Left	Far all of the left CCA, 1.5 cm proximal to the carotid bifurcation was identified. Free of plaque	Domain specific assessments
Yue et al., 2016[55]	NE	Yes	7.5	Bilateral	Near and far walls of the right and left CCA Included plaque	Domain specific assessments
Zhong et al., 2011[56]	NE	Yes	7.5	Bilateral	Left and right sides of the near and far walls of the CCA, the bifurcation and the internal carotid artery Included plaque	Domain specific assessments
Zhong et al., 2012[22]	NE	Yes	7.5	Bilateral	Left and right sides of the near and far walls of the CCA, the bifurcation and the internal carotid artery Included plaque	Domain specific assessments

Table S2. List of covariates used in the analyses of the included studies.

References	Unadjusted	Adjusted
Al Hazzouri et al., 2015[38]	None.	Age, sex, race, and education, smoking, physical activity, elevated depressive symptoms, body mass index, type 2 diabetes mellitus, hypertension, cystatin C–based estimated glomerular filtration rate and antihypertensive medication use.
Arntzen et al., 2012[23]	None.	Sex, age and education, physical activity, smoking, systolic blood pressure, total cholesterol, HDL cholesterol, body mass index, diabetes, coronary heart disease and depression.
Casado-Naranjo et al., 2016[29]	Education, smoking, hypertension, folate, B12, creatinine and others as covariates.	Education, smoking, hypertension, folate, B12, creatinine and others as covariates.
Cohen-Manheim et al., 2016[30]	Sex.	Sex, age, education, childhood socioeconomic status (ICBS-based), adult socioeconomic status (ICBS-based), and cigarette pack–years, BMI, plasma cholesterol, fasting plasma glucose, and systolic and diastolic blood pressure measured at ages 28–32.
Cohen et al., 2009[31]	None.	None.
Del Brutto et al., 2020[24]	None.	Demographics, cardiovascular risk factors, severe edentulism, and symptoms of depression
Feinkohl et al., 2013[32]	Age and sex.	baseline vascular risk factors (total cholesterol, brachial blood pressure, cigarette smoking.
Frazier et al., 2014[33]	Age at baseline, sex, education, CDR score, and hypertension.	Age at baseline, sex, education, CDR score, and hypertension, cerebrovascular risk factors (LDL, diabetes) and WHR.
Gardener et al., 2018[34]	Age at neuropsychological examination, education (y), time from baseline to ultrasound, and time from ultrasound to neuropsychological examination.	Age at neuropsychological examination, education (y), time from baseline to ultrasound, time from ultrasound to neuropsychological examination, sex, race/ethnicity, medicaid/no insurance status, physical activity, alcohol use, smoking, body mass index, diabetes mellitus, hypercholesterolemia, and hypertension, and brain MRI markers (WMHV, brain volume, and SBI)
Gatto et al., 2009[35]	Age, gender, race/ethnicity, education, income, CES-D score, Hcy, SBP, LDL-C, smoking status.	Age, gender, race/ethnicity, education, income, CES-D score, Hcy, SBP, LDL-C, smoking status.
Geijselaers et al., 2016[36]	Age, sex, and educational level.	Age, sex, educational level, body mass index, total/high density lipoprotein-cholesterol ratio, triglycerides, use of lipid-modifying medication, hypertension, presence of type 2 diabetes, estimated glomerular filtration rate, smoking behaviour, alcohol consumption, history of cardiovascular disease(s) and presence of a current depression.
Haley et al., 2007[37]	Age, education, sex, cardiovascular risk factors, and current systolic blood pressure.	Age, education, sex, cardiovascular risk factors, and current systolic blood pressure.
Imran et al., 2020[38]	None.	None.
Jiang et al., 2017[39]	None.	Age, gender, and education level, duration of DM, and hypertension
Komulainen et al., 2007[41]	None.	Age, education, depression, diabetes, LDL cholesterol, systolic blood pressure, cardiovascular disease (coronary heart disease, cardiac insufficiency), hormone replacement therapy at the time of IMT measures, physical activity, alcohol consumption and smoking.
Lim et al., 2016[42]	None.	Age, gender, education, hypertension, diabetes, dyslipidemia, smoking, body mass index, and APOE 4 status.
Masley et al., 2014[43]	None.	None.
Matsumuto et al., 2018[25]	None.	Sex, age and years of education, body mass index, Brinkman index, systolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, hemoglobin A1c, uric acid, bone density, and grade of deep and subcortical white matter hyperintensity.
Muela et al., 2018[44]	None.	All independent variables with P<.01 in the bivariate analysis.
Muller et al., 2007[45]	Age and education.	Age and education.
Rogne et al., 2013[47]	None.	Cardiovascular risk factors and other factors known to influence cognition.
Romero et al., 2009[48]	Age and sex.	Age, sex, time to MRI/Neuropsychological testing, diabetes, smoking, hypertension treatment, systolic blood pressure and cardiovascular disease.
Singh-Manoux et al., 2008[50]	Age and sex.	Age and sex.
Smith et al., 2011[51]	Background characteristics, CVRF, and intima medial thickness.	Background characteristics, CVRF, and intima medial thickness.
Suemoto et al., 2015[52]	None.	Age, sex, race, marital status, education, income, hypertension, diabetes, coronary artery disease, heart failure, smoking, alcohol use, physical activity, body mass index, depression, and thyroid function status.

Table S2. List of covariates used in the analyses of the included studies. (continue)

References	Unadjusted	Adjusted
Wang et al., 2016[53]	None.	Age, sex, education, income level, body mass index, physical exercise, systolic blood pressure, diastolic blood pressure, high-density lipoprotein cholesterol, hypertension, diabetes mellitus, dyslipidemia, smoking, and drinking
Wendell et al., 2009[15]	Age, years of education, MAP, BMI, total cholesterol, and depressive symptoms were treated as continuous covariates, and gender, race, smoking, and cardiovascular medications.	Age, years of education, MAP, BMI, total cholesterol, and depressive symptoms were treated as continuous covariates, and gender, race, smoking, and cardiovascular medications.
Wendell et al., 2016[54]	Age, sex, race, poverty status, education, substance use, depressive symptoms, systolic blood pressure, total cholesterol, body mass index, antihypertensive use, lipid-lowering medication use, cardiovascular disease, and diabetes.	Age, sex, race, poverty status, education, substance use, depressive symptoms, systolic blood pressure, total cholesterol, body mass index, antihypertensive use, lipid-lowering medication use, cardiovascular disease, and diabetes.
Yue et al., 2016[655]	None.	None.
Zhong et al., 2011[56]	Age, sex, and education	Age, sex, education, marital status, family income, hypertension, CVD, diabetes, smoking and heavy drinking status, regular exercise, SF-36 mental score, HDL cholesterol, anti-hypertensive medications and use of statins.
Zhong et al., 2012[22]	Age, sex and education	Hemoglobin A1C, SF-36 mental score, antihypertensive medications, body mass index, heavy drinking, HDL cholesterol and smoking.

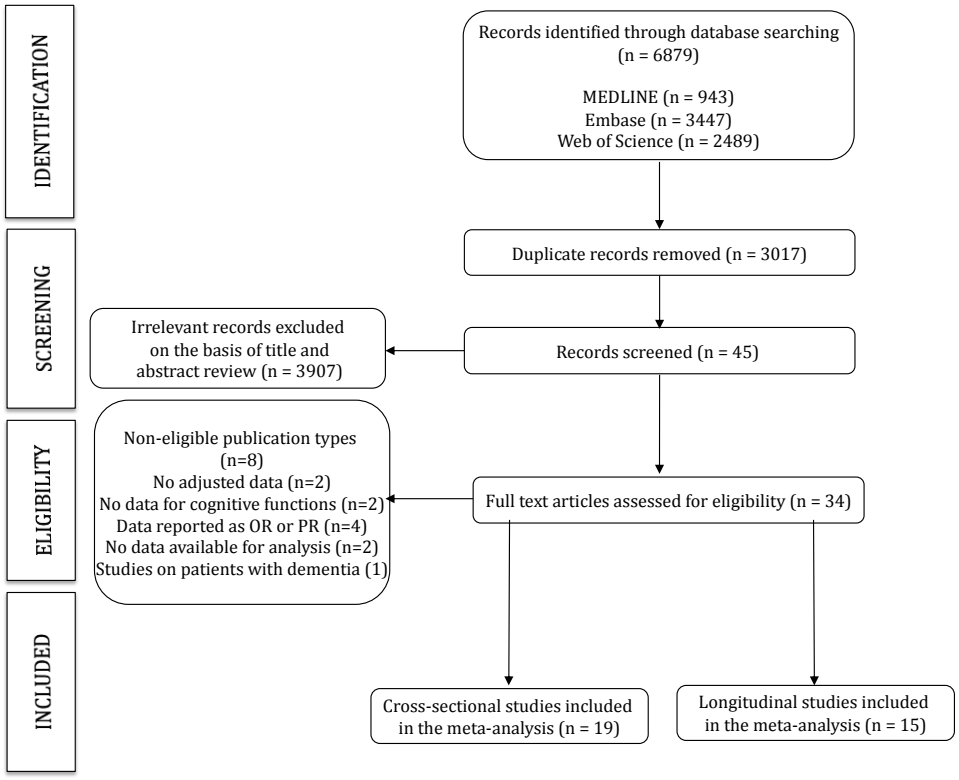

Figure S1. Preferred Reporting Items for Systematic Reviews flowchart.

Table S3. Risk of bias of cross-sectional and longitudinal included studies. Numbers representing the questions included in the The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

References	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
Al Hazzouri et al., 2015[28]	Y	Y	Y	Y	NR	Y	Y	Y	Y	Y	Y	Y	Y	Y	12
Arntzen et al., 2012[23]	Y	Y	Y	Y	NR	NR	Y	Y	Y	NR	Y	Y	Y	Y	11
Casado-Naranjo et al., 2016[29]	Y	Y	Y	Y	NR	-	-	Y	Y	-	Y	Y	-	Y	9
Cohen-Manheim et al., 2016[30]	Y	Y	Y	Y	NR	NR	Y	Y	Y	Y	Y	NR	Y	Y	11
Cohen et al., 2009[31]	Y	Y	Y	Y	NR	-	-	Y	Y	-	Y	Y	-	N	8
Del Brutto et al., 2020[24]	Y	Y	Y	Y	NR	Y	Y	Y	Y	NR	Y	Y	Y	Y	12
Feinkohl et al., 2013[32]	Y	Y	N	Y	NR	Y	Y	Y	Y	Y	Y	NR	Y	Y	11
Frazier et al., 2014[33]	Y	Y	Y	Y	NR	NR	Y	Y	Y	Y	Y	Y	Y	N	11
Gardener et al., 2018[34]	Y	Y	Y	Y	NR	Y	Y	N	Y	Y	Y	NR	Y	Y	12
Gatto et al., 2009[35]	Y	Y	N	Y	NR	-	-	Y	Y	-	Y	NR	-	Y	7
Geijselaers et al., 2016[36]	Y	Y	Y	Y	NR	-	-	Y	Y	-	Y	NR	-	Y	8
Haley et al., 2007[37]	Y	Y	Y	Y	NR	-	-	Y	Y	-	Y	NR	-	Y	8
Imran et al., 2020[38]	Y	Y	Y	Y	NR	-	-	N	Y	-	Y	NR	-	N	6
Jiang et al., 2017[39]	Y	Y	Y	Y	NR	-	-	Y	Y	-	Y	NR	-	Y	8
Kemp et al., 2016[40]	Y	Y	Y	Y	NR	-	-	Y	Y	-	Y	NR	-	N	7
Komulainen et al., 2007[41]	Y	Y	Y	Y	NR	Y	Y	N	Y	Y	Y	NR	N	Y	10
Lim et al., 2016[42]	Y	Y	NR	Y	NR	-	-	N	Y	-	Y	NR	-	Y	6
Masley et al., 2014[43]	Y	Y	NR	Y	NR	-	-	N	Y	-	Y	NR	-	N	5
Matsumuto et al., 2018[25]	Y	Y	NR	Y	NR	-	-	Y	Y	-	Y	Y	-	Y	7
Muela et al., 2018[44]	Y	Y	NR	Y	NR	NR	-	Y	Y	-	Y	Y	-	Y	8
Muller et al., 2007[4]	Y	Y	N	Y	NR	NR	-	Y	Y	-	Y	NR	-	Y	7
Roberts et al., 2013[46]	Y	Y	Y	Y	NR	Y	Y	Y	Y	Y	Y	NR	-	Y	11
Rogne et al., 2013[47]	Y	Y	Y	Y	NR	Y	Y	Y	Y	Y	Y	NR	N	Y	11
Romero et al., 2009[48]	Y	Y	Y	Y	NR	Y	Y	Y	Y	Y	Y	Y	N	Y	12
Schwerdtfeger et al., 2015[49]	Y	Y	NR	Y	NR	-	-	Y	Y	-	Y	NR	-	Y	7
Singh-Manoux et al., 2008[50]	Y	Y	N	Y	NR	-	-	Y	Y	-	Y	Y	-	Y	7
Smith et al., 2011[51]	Y	Y	Y	Y	NR	-	-	N	Y	-	Y	NR	-	Y	7
Suemoto et al., 2015[52]	Y	Y	Y	Y	NR	-	-	Y	Y	-	Y	NR	-	Y	8
Wang et al., 2016[53]	Y	Y	N	Y	NR	-	-	Y	Y	-	Y	NR	-	Y	7
Wendell et al., 2009[15]	Y	Y	NR	Y	NR	NR	Y	Y	Y	Y	Y	NR	NR	Y	9
Wendell et al., 2016[54]	Y	Y	N	Y	NR	NR	Y	Y	Y	Y	Y	NR	N	Y	8
Yue et al., 2016[55]	Y	Y	N	Y	NR	-	-	Y	Y	-	Y	NR	-	Y	7
Zhong et al., 2011[56]	Y	Y	N	Y	NR	-	-	N	Y	-	Y	NR	-	Y	6
Zhong et al., 2012[22]	Y	Y	NR	Y	NR	NR	Y	N	Y	Y	Y	NR	NR	Y	8

Y: yes; N: no; NR: not reported

Table S4: Heterogeneity, inconsistence estimations for DerSimoniand random effects methods and z scores and corresponding p-values against the hypothesis that IMT has no effect on cognitive function.

		Hypothesis values		Inconsistence	Heterogeneity	
	Q	**p**	**τ^2**	**I2**	**z**	**p**
Cross-sectional Unadjusted						
Global cognition	134.40	0.000	0.039	89.6	4.40	0.000
Executive function	37.15	0.000	0.012	81.2	3.15	0.002
Memory	151.33	0.000	0.036	90.1	2.65	0.008
Attention	54.16	0.000	0.042	87.1	1.47	0.142
Cross-sectional Adjusted						
Global cognition	78.08	0.000	0.021	82.1	3.46	0.001
Executive function	27.04	0.000	0.010	74.1	2.51	0.012
Memory	33.88	0.000	0.007	55.7	2.86	0.004
Attention	32.46	0.000	0.024	78.4	1.83	0.067
Longitudinal Unadjusted						
Global cognition	16.37	0.001	0.025	81.7	2.37	0.018
Executive function	50.25	0.000	0.031	90.0	1.78	0.075
Memory	255.80	0.000	0.052	96.5	2.00	0.046
Attention	215.95	0.000	0.157	98.6	1.13	0.259
Longitudinal Adjusted						
Global cognition	7.30	0.063	0.007	58.9	1.56	0.120
Executive function	12.78	0.026	0.005	60.9	1.03	0.305
Memory	23.32	0.006	0.003	61.4	0.20	0.843
Attention	3.81	0.283	0.000	21.3	1.57	0.116

Table S5. Sensitivity analyses by removing studies one by one from the pooled unadjusted cross-sectional analysis. The effect size and 95% interval confidence (95%IC) represents the pooled estimations after excluding from the analysis the corresponding reference.

Global cognition			
Reference	**ES**	**LL**	**UL**
Casado-Naranjo et al., 2016	-0.241	-0.355	-0.126
Del Brutto et al., 2020	-0.228	-0.339	-0.116
Feinkohl et al., 2013	-0.256	-0.375	-0.137
Gatto et al., 2009	-0.265	-0.382	-0.149
Jiang et al., 2016	-0.193	-0.285	-0.101
Komulainen et al., 2007	-0.247	-0.361	-0.134
Lim et al., 2016	-0.251	-0.367	-0.135
Matsumoto et al., 2018	-0.258	-0.374	-0.141
Muela et al., 2018	-0.232	-0.345	-0.119
Singh-Manoux., 2008 (High SES)	-0.274	-0.387	-0.161
Singh-Manoux., 2008 (Intermed SES)	-0.272	-0.386	-0.158
Singh-Manoux., 2008 (low SES)	-0.260	-0.378	-0.142
Wang et al., 2016	-0.259	-0.388	-0.130
Yue et al., 2016	-0.244	-0.363	-0.124
Zhong et al., 2011	-0.262	-0.383	-0.114
Executive function			
Reference	**ES**	**LL**	**UL**
Gardener et al., 2018	-0.198	-0.324	-0.071
Gatto et al., 2009	-0.210	-0.325	-0.095
Suemoto et al., 2015	-0.176	-0.332	-0.019
Lim et al., 2016	-0.169	-0.287	-0.052
Masley et al., 2014	-0.145	-0.258	-0.032
Muller et al., 2007	-0.177	-0.299	-0.054
Rogne et al., 2013	-0.140	-0.244	-0.037
Smith et al., 2011	-0.199	-0.312	-0.086
Memory			
Reference	**ES**	**LL**	**UL**
Cohen et al., 2009	-0.157	-0.265	-0.048
Gardener et al., 2018	-0.140	-0.251	-0.029
Gatto et al., 2009	-0.157	-0.274	-0.040
Geijselaers et al., 2016	-0.151	-0.264	-0.038
Imran et al., 2020	-0.127	-0.234	-0.021
Komulainen et al., 2007	-0.125	-0.231	-0.019
Lim et al., 2016	-0.147	-0.257	-0.038
Masley et al., 2014	-0.142	-0.252	-0.031
Matsumoto et al., 2018	-0.134	-0.243	-0.025
Muela et al., 2018	-0.119	-0.224	-0.014
Muller et al., 2007	-0.135	-0.244	-0.026
Rogne et al., 2013	-0.128	-0.231	-0.025
Singh-Manoux., 2008 (High SES)	-0.157	-0.273	-0.041
Singh-Manoux., 2008 (Intermed SES)	-0.163	-0.282	-0.045
Singh-Manoux., 2008 (low SES)	-0.152	-0.264	-0.039
Suemoto et al,, 2015	-0.161	-0.251	-0.072
Attention			
Reference	**ES**	**LL**	**UL**
Cohen et al., 2009	-0.064	-0.217	0.089
Geijselaers et al., 2016	-0.163	-0.364	0.037
Haley et al., 2007	-0.078	-0.239	0.083
Lim et al., 2016	-0.142	-0.321	0.038
Masley et al., 2014	-0.130	-0.315	0.054
Muela et al., 2018	-0.067	-0.222	0.089
Suemoto et al., 2015	-0.186	-0.377	0.005
Zhong et al., 2011	-0.180	-0.387	0.027

ES: effect size; LL: low limit; UL: upper limit.

Table S6. Sensitivity analyses by removing studies one by one from the pooled adjusted cross-sectional analysis. The effect size and 95% interval confidence (95% IC) represents the pooled estimations after excluding from the analysis the corresponding reference.

Global cogniton			
Reference	**ES**	**LL**	**UL**
Casado-Naranjo et al., 2016	-0.140	-0.228	-0.053
Del Brutto et al., 2020	-0.160	-0.251	-0.068
Feinkohl et al., 2013	-0.151	-0.244	-0.058
Gatto et al., 2009	-0.161	-0.252	-0.070
Jiang et al., 2016	-0.123	-0.203	-0.043
Komulainen et al., 2007	-0.151	-0.239	-0.062
Lim et al., 2016	-0.156	-0.246	-0.066
Matsumoto et al., 2018	-0.162	-0.252	-0.072
Muela et al., 2018	-0.146	-0.235	-0.057
Singh-Manoux., 2008 (High SES)	-0.170	-0.257	-0.084
Singh-Manoux., 2008 (Intermed SES)	-0.168	-0.256	-0.080
Singh-Manoux., 2008 (low SES)	-0.155	-0.247	-0.064
Wang et al., 2016	-0.158	-0.257	-0.060
Yue et al., 2016	-0.130	-0.208	-0.052
Zhong et al., 2011	-0.153	-0.247	-0.059
Executive function			
Reference	**ES**	**LL**	**UL**
Gardener et al., 2018	-0.124	-0.234	-0.014
Gatto et al., 2009	-0.139	-0.241	-0.039
Kempt et al., 2016	-0.139	-0.251	-0.027
Suemoto et al., 2015	-0.107	-0.201	-0.013
Masley et al., 2014	-0.070	-0.131	0.010
Muller et al., 2007	-0.110	-0.208	-0.011
Rogne et al., 2013	-0.117	-0.229	-0.004
Smith et al., 2011	-0.131	-0.225	-0.036
Memory			
Reference	**ES**	**LL**	**UL**
Cohen et al., 2009	-0.097	-0.159	-0.034
Gardener et al., 2018	-0.092	-0.160	-0.024
Gatto et al., 2009	-0.103	-0.172	-0.034
Geijselaers et al., 2016	-0.099	-0.166	-0.031
Imran et al., 2020	-0.079	-0.137	-0.021
Komulainen et al., 2007	-0.081	-0.141	-0.021
Lim et al., 2016	-0.093	-0.158	-0.028
Masley et al., 2014	-0.085	-0.149	-0.020
Matsumoto et al., 2017	-0.089	-0.155	-0.024
Muela et al., 2018	-0.076	-0.135	-0.017
Muller et al., 2007	-0.078	-0.139	-0.016
Rogne et al., 2013	-0.095	-0.165	-0.025
Singh-Manoux., 2008 (High SES)	-0.103	-0.171	-0.034
Singh-Manoux., 2008 (Intermed SES)	-0.106	-0.168	-0.043
Singh-Manoux., 2008 (low SES)	-0.096	-0.163	-0.029
Suemoto et al., 2015	-0.096	-0.162	-0.031
Attention			
Reference	**ES**	**LL**	**UL**
Cohen et al., 2009	-0.072	-0.191	0.046
Geijselaers et al., 2016	-0.174	-0.337	-0.011
Haley et al., 2007	-0.085	-0.214	0.043
Lim et al., 2016	-0.143	-0.289	0.003
Masley et al., 2014	-0.138	-0.294	0.019
Muela et al., 2018	-0.072	-0.196	0.053
Suemoto et al., 2015	-0.184	-0.377	0.009
Zhong et al., 2011	-0.178	-0.337	-0.019

ES: effect size; LL: low limit; UL: upper limit

Table S7. Sensitivity analyses by removing studies one by one from the pooled unadjusted longitudinal analysis. The effect size and 95% interval confidence (95% IC) represents the pooled estimations after excluding from the analysis the corresponding reference.

Global cognition			
Reference	**ES**	**LL**	**UL**
Cohen-Manheim et al., 2016	-0.200	-0.424	0.023
Del Brutto et al., 2020	-0.176	-0.375	0.024
Feinkohl et al., 2013	-0.177	-0.381	0.028
Wendell et al., 2016	-0.287	-0.383	-0.190
Executive function			
Reference	**ES**	**LL**	**UL**
Alhazzouri et al., 2015	-0.068	-0.162	0.025
Cohen-Manheim e alt., 2016	-0.139	-0.314	0.035
Frazier et al., 2014	-0.106	-0.269	0.057
Gardener et al., 2018	-0.173	-0.338	-0.008
Rogne et al., 2013	-0.151	-0.340	0.038
Romero et al., 2009	-0.168	-0.336	-0.001
Memory			
Reference	**ES**	**LL**	**UL**
Alhazzouri et al., 2015	-0.134	-0.297	0.029
Arntzen et al., 2012	-0.088	-0.195	0.191
Cohen-Manheim et al., 2016	-0.149	-0.310	0.012
Frazier et al., 2014	-0.150	-0.309	0.009
Gardener et al., 2018	-0.185	-0.344	-0.025
Komulainen et al., 2007	-0.117	-0.269	0.035
Romero et al., 2009 (CCAIMT)	-0.175	-0.347	-0.003
Wendell et al., 2009	-0.183	-0.344	-0.022
Wendel et al., 2016	-0.176	-0.352	0.001
Zhong et al., 2012	-0.171	-0.335	-0.007
Attention			
Reference	**ES**	**LL**	**UL**
Arnttzen et al,. 2012	-0.067	-0.204	0.071
Cohen-Manheim et al., 2016	-0.215	-0.697	0.267
Wendell et al., 2009	-0.307	-0.779	0.165
Wendell et al., 2016	-0.299	-0.754	0.154

ES: effect size; LL: low limit; UL: upper limit

Table S8. Sensitivity analyses by removing studies one by one from the pooled adjusted longitudinal analysis. The effect size and 95% interval confidence (95% IC) represents the pooled estimations after excluding from the analysis the corresponding reference.

Global cognition			
Reference	**ES**	**LL**	**UL**
Cohen-Manheim et al., 2016	-0.093	-0.240	0.053
Del Brutto et al., 2020	-0.102	-0.248	0.044
Feinkohl et al., 2013	-0.027	-0.102	0.048
Wendell et al., 2016	-0.125	-0.255	0.004
Executive function			
Reference	**ES**	**LL**	**UL**
Alhazzouri et al., 2015	-0.040	-0.144	0.063
Cohen-Manheim et al., 2016	-0.046	-0.136	0.044
Frazier et al., 2014	-0.019	-0.080	0.041
Gardener et al., 2017	-0.061	-0.144	0.023
Rogne et al., 2013	-0.030	-0.125	0.064
Romero et al., 2009	-0.063	-0.150	0.025
Memory			
Reference	**ES**	**LL**	**UL**
Alhazzouri et al., 2015	-0.001	-0.054	0.052
Arntzen et al., 2012	-0.005	-0.061	0.052
Cohen-Manheim et al., 2016	-0.001	-0.051	0.049
Frazier et al., 2014	0.001	-0.046	0.049
Gardener et al., 2017	-0.017	-0.063	0.030
Komulainen et al., 2007	0.002	-0.035	0.039
Romero et al., 2009 (CCAIMT)	-0.008	-0.065	0.049
Wendell et al., 2009	-0.016	-0.065	0.033
Wendell et al., 2016	-0.005	-0.063	0.053
Zhong et al., 2012	-0.007	-0.060	0.045
Attention			
Reference	**ES**	**LL**	**UL**
Arnttzen et al,. 2012	-0.030	-0.112	0.052
Cohen-Manheim et al., 2016	-0.033	-0.176	0.010
Wendell et al., 2009	-0.050	-0.108	0.008
Wendell et al., 2016	-0.057	-0.128	0.014

ES: effect size; LL: low limit; UL: upper limit

Table S9. Meta-regression of IMT and cognition domains by percentage of females and mean age, BMI, and baseline IMT values of included studies.

	% female			Age			BMI			Baseline IMT	
	n	ß (95%CI)	p	n	ß (95%CI)	p	n	ß (95%CI)	p	n	ß (95%CI)	p
Global cognition												
Cross-sectional data												
Unadjusted	15	-0.007	0.225	15	-0.008	0.174	8	0.003	0.736	13	-0.136	0.552
Adjusted	15	-0.002	0.597	15	-0.006	0.083	8	0.002	0.701	13	-0.110	0.462
Longitudinal data												
Unadjusted	3	0.007	0.873	4	-0.010	0.202	3	0.002	0.973	3	-0.430	0.641
Adjusted	3	0.025	0.271	4	-0.001	0.331	3	-0.018	0.667	3	-0.628	0.259
Executive function												
Cross-sectional data												
Unadjusted	8	0.003	0.401	7	-0.001	0.895	8	0.068	0.057	7	0.458	0.721
Adjusted	8	0.003	0.277	7	-0.001	0.973	8	0.039	0.241	7	0.404	0.705
Longitudinal data												
Unadjusted	5	0.007	0.728	6	-0.001	0.878	-	-	-	5	-0.369	0.577
Adjusted	5	0.015	0.350	6	-0.002	0.486	-	-	-	5	-0.281	0.565
Memory												
Cross-sectional data												
Unadjusted	14	-0.002	0.555	15	-0.003	0.573	14	-0.043	0.147	16	-0.245	0.205
Adjusted	14	0.000	0.877	15	-0.002	0.447	14	-0.031	0.139	16	-0.161	0.192
Longitudinal data												
Unadjusted	9	-0.013	0.141	10	0.000	0.938	7	0.009	0.928	10	-0.758	0.306
Adjusted	9	-0.010	0.132	10	0.000	0.977	7	0.006	0.789	10	-0.105	0.711
Attention												
Cross-sectional data												
Unadjusted	7	-0.0003	0.982	8	-0.021	0.100	5	-0.120	0.262	7	-2.093	0.148
Adjusted	7	-0.001	0.949	8	-0.018	0.137	5	-0.0107	0.259	7	-2.028	0.172
Longitudinal data												
Unadjusted	3	0.073	0.372	4	-0.012	0.584	3	0.108	0.638	4	-1.348	0.262
Adjusted	3	0.010	0.462	4	-0.006	0.270	3	0.013	0.635	4	-0.295	0.297

NA: Not Available; BMI: body mass index; IMT: intima media thickness.

Table S10. Subgroup analyses of the association between IMT and cognition domains by IMT and cognition measurement procedure characteristics of included studies. n represents number of studies included in each subgroup analysis; bold font indicates effects size similar to the reported in the main analyses and italics indicates effect size opposite to the reported in the main analyses.

	Manual/automated			mHz			Lateraly			Cognition method		
Global cognition	**Type**	**ES (95%CI)**	**n**	**Classification**	**ES (95%CI)**	**n**	**Place**	**ES (95%CI)**	**n**	**Classification**	**ES (95%CI)**	**n**
Cross-sectional data												
Unadjusted	Manual	-0.18 (-0.25; 0.11)	1	Range	**-0.17 (-0.32; -0.02)**	**6**	Bilateral	**-0.26 (-0.38; -0.13)**	**12**	Domain specific assessments	**-0.27 (-0.39; -0.15)**	**13**
	Automated	**-0.26 (-0.49; -0.02)**	**7**	>7	**-0.28 (-0.42; -0.14)**	**5**	Right	-0.04 (-0.21; 0.13)	1	Global test of cognition	-0.12 (-0.30; 0.06)	2
	Not specified	**-0.26 (-0.38; -0.15)**	**7**	Not specified	-0.33 (-0.70; 0.04)	4	Left	-0.54 (-0.82; -0.27)	1			
							Not specified	-0.18 (-0.32; -0.04)	1			
Adjusted	Manual	-0.11 (-0.19; -0.03)	1	Range	*-0.06 (-0.15; 0.03)*	*6*	Bilateral	**-0.15 (-0.25; -0.05)**	**12**	Domain specific assessments	**-0.17 (-0.26; -0.07)**	**13**
	Automated	*-0.14 (-0.29; 0.01)*	*7*	>7	**-0.23 (-0.34; -0.04)**	**5**	Right	-0.04 (-0.21; 0.13)	1	Global test of cognition	-0.06 (-0.20; 0.07)	2
	Not specified	**-0.18 (-0.28; -0.07)**	**7**	Not specified	-0.20 (-0.43; 0.03)	4	Left	-0.28 (-0.56; -0.01)	1			
							Not specified	-0.18 (-0.32; -0.04)	1			
Longitudinal data												
Unadjusted	Manual	-0.24 (-0.41; -0.06)	1	Range	-0.28 (-0.41; -0.15)	1	Bilateral	-0.28 (-0.41; -0.15)	1	Domain specific assessments	-0.20 (-0.42; 0.02)	3
	Automated	-	-	>7	-	-	Right	-	-	Global test of cognition	-0.24 (-0.41; -0.06)	1
	Not specified	-0.20 (-0.42; 0.02)	3	Not specified	-0.15 (-0.43; 0.13)	2	Left	-0.01 (-0.10; 0.09)	1			
							Not specified	-0.30 (-0.45; -0.16)	1			
Adjusted	Manual	-0.07 (-0.24; 0.10)	1	Range	-0.05 (-0.18; 0.07)	2	Bilateral	-0.05 (-0.18; 0.07)	2	Domain specific assessments	-0.09 (-0.24; 0.05)	3
	Automated	-	-	>7	-	-	Right	-	-	Global test of cognition	-0.07 (-0.24; 0.10)	1
	Not specified	-0.09 (-0.24; 0.05)	3	Not specified	-0.12 (-0.34; 0.11)	2	Left	-0.01 (-0.20; 0.02)	1			
							Not specified	-0.24 (-0.38; -0.10)	1			
	Manual/automated			**mHz**			**Lateraly**			**Cognition method**		
Executive functions	**Type**	**ES (95%CI)**	**n**	**Classification**	**ES (95%CI)**	**n**	**Place**	**ES (95%CI)**	**n**	**Classification**	**ES (95%CI)**	**n**
Cross-sectional data												
Unadjusted	Manual	-	-	Range	-0.28 (-0.51; -0.05)	3	Bilateral	**-0.17 (-0.28; -0.07)**	**6**	Domain specific assessments	-0.20 (-0.33; -0.07)	4
	Automated	-0.09 (-0.33; 0.14)	4	>7	0.16 (-0.21; -0.12)	4	Right	-0.18 (-0.59; 0.24)	2	Global test of cognition	-0.14 (-0.41; 0.14)	4
	Not specified	-0.24 (-0.37; -0.11)	4	Not specified	0.04 (-0.13; 0.21)	1	Left	-	-			
							Not specified	-	-			
Adjusted	Manual	-	-	Range	-0.20 (-0.36; -0.04)	3	Bilateral	**-0.15 (-0.28; -0.02)**	**6**	Domain specific assessments	-0.08 (-0.15; -0.02)	4
	Automated	-0.07 (-0.16; 0.02)	4	>7	-0.08 (-0.20; 0.04)	4	Right	-0.06 (-0.22; 0.10)	2	Global test of cognition	-0.14 (-0.41; 0.14)	4
	Not specified	-0.21 (-0.42; 0.00)	4	Not specified	0.04 (-0.13; 0.21)	1	Left	-	-			
							Not specified	-	-			
Longitudinal data												
Unadjusted	Manual	-0.35 (-0.42; -0.27)	2	Range	-0.05 (-0.14; 0.04)	3	Bilateral	**-0.15 (-0.34; 0.04)**	**5**	Domain specific assessments	-0.16 (-0.41; 0.09)	3
	Automated	-0.08 (-0.18; 0.02)	3	>7	-0.35 (-0.42; -0.28)	1	Right	-0.08 (-0.18; 0.02)	1	Global test of cognition	-0.10 (-0.16; 0.07)	3
	Not specified	0.00 (-0.09; 0.09)	1	Not specified	-0.15 (-0.50; 0.19)	2	Left	-	-			
							Not specified	-	-			
Adjusted	Manual	-0.05 (-0.13; 0.02)	2	Range	-0.02 (-0.12; 0.08)	3	Bilateral	**-0.03 (-0.12; 0.06)**	**5**	Domain specific assessments	-0.02 (-0.08; 0.05)	3
	Automated	-0.10 (-0.28; 0.09)	3	>7	-0.06 (-0.14; 0.02)	1	Right	-0.09 (-0.19; 0.01)	1	Global test of cognition	-0.10 (-0.18; 0.09)	3
	Not specified	0.04 (-0.05; 0.13)	1	Not specified	-0.14 (-0.52; 0.24)	2	Left	-	-			
							Not specified	-	-			

Table S10. Subgroup analyses of the association between IMT and cognition domains by IMT and cognition measurement procedure characteristics of included studies. (continued) n represents number of studies included in each subgroup analysis; bold font indicates effects size similar to the reported in the main analysis and italics indicated effect size opposite to the reported in the main analysis.

	Manual/automated			mHz			Lateraly			Cognition method		
Memory	**Type**	**ES (95%CI)**	**n**	**Classification**	**ES (95%CI)**	**n**	**Place**	**ES (95%CI)**	**n**	**Classification**	**ES (95%CI)**	**n**
Cross-sectional data												
Unadjusted	Manual	-0.61 (-1.06; -0.16)	1	Range	*-0.11 (-0.23; 0.01)*	*6*	Bilateral	**-0.13 (-0.26; -0.01)**	**11**	Domain specific assessments	**-0.19 (-0.34; -0.05)**	**11**
	Automated	**-0.14 (-0.26; -0.02)**	**9**	>7	*-0.21 (-0.43; 0.02)*	*8*	Right	-0.15 (-0.41; 0.11)	2	Global test of cognition	-0.05 (-0.13; 0.02)	5
	Not specified	**-0.11 (-0.30; -0.08)**	**6**	Not specified	-0.13 (-0.40; 0.13)	2	Left	-0.16 (-0.54; 0.23)	3			
							Not specified	-	-			
Adjusted	Manual	-0.61 (-1.06; -0.16)	1	Range	*-0.05 (-0.12; 0.01)*	*6*	Bilateral	**-0.11 (-0.19; -0.02)**	**11**	Domain specific assessments	**-0.12 (-0.20; -0.03)**	**11**
	Automated	*-0.06 (-0.13; 0.01)*	*9*	>7	**-0.19 (-0.34; -0.03)**	**8**	Right	-0.05 (-0.13; 0.02)	2	Global test of cognition	-0.04 (-0.12; 0.03)	5
	Not specified	**-0.12 (-0.20; -0.04)**	**6**	Not specified	-0.04 (-0.15; 0.07)	2	Left	-0.10 (-0.39; 0.19)	3			
							Not specified	-	-			
Longitudinal data												
Unadjusted	Manual	-0.29 (-0.39; -0.18)	2	Range	0.02 (-0.12; 0.15)	3	Bilateral	**-0.14 (-0.30; 0.01)**	**7**	Domain specific assessments	**-0.18 (-0.43; 0.06)**	**6**
	Automated	-0.34 (-0.75; 0.07)	4	*>7*	*-0.29 (-0.53; -0.05)*	*5*	Right	-0.21 (-0.76; 0.35)	2	Global test of cognition	-0.14 (-0.31; 0.04)	4
	Not specified	0.00 (-0.04; 0.05)	4	No specified	-0.06 (-0.20; 0.08)	2	Left	-0.02 (-0.07; 0.03)	1			
							Not specified	-	-			
Adjusted	Manual	-0.05 (-0.12; 0.03)	2	Range	-0.06 (-0.02; 0.14)	3	Bilateral	**-0.03 (-0.11; 0.05)**	**7**	Domain specific assessments	**0.00 (-0.08; 0.08)**	**6**
	Automated	-0.08 (-0.25; 0.10)	4	>7	**-0.02 (-0.09; 0.04)**	**5**	Right	-0.03 (-0.07; 0.12)	2	Global test of cognition	-0.02 (-0.06; 0.03)	4
	Not specified	-0.01 (-0.03; 0.05)	4	Not specified	-0.06 (-0.20; 0.08)	2	Left	-0.02 (-0.07; 0.03)	1			
							Not specified	-	-			

	Manual/automated			mHz			Lateraly			Cognition method		
Attention	**Type**	**ES (95%CI)**	**n**	**Classification**	**ES (95%CI)**	**n**	**Place**	**ES (95%CI)**	**n**	**Classification**	**ES (95%CI)**	**n**
Cross-sectional data												
Unadjusted	Manual	-	-	Range	-0.11 (-0.28; 0.06)	1	Bilateral	0.07 (-0.06; 0.19)	4	Domain specific assessments	0.01 (-0.16; 0.18)	4
	Automated	-0.41 (-0.70; -0.11)	4	>7	**-0.13 (-0.31; 0.05)**	**7**	Right	-	-	Global test of cognition	-0.30 (-0.60; 0.00)	4
	Not specified	0.07 (-0.05; 0.18)	4	Not specified	-	-	Left	-0.39 (-0.76; -0.01)	4			
							Not specified	-	-	Domain specific assessments	-0.03 (-0.16; 0.11)	4
Adjusted	Manual	-	-	Range	-0.11 (-0.28; 0.06)	1	Bilateral	0.01 (-0.05; 0.06)	4	Global test of cognition	-0.30 (-0.60; 0.00)	4
	Automated	-0.41 (-0.70; -0.11)	4	>7	**-0.14 (-0.29; 0.02)**	**7**	Right	-0.38 (-0.78; 0.01)	4			
	Not specified	0.01 (-0.05; 0.07)	4	Not specified			Left	-	-			
							Not specified	-	-			
Longitudinal data												
Unadjusted	Manual	-0.26 (-0.43; -0.08)	1	Range	-0.11 (-0.39; 0.16)	2	Bilateral	-0.26 (-0.44; -0.09)	1	Domain specific assessments	-0.22 (-0.60; 0.27)	3
	Automated	-0.65 (-0.71; -0.59)	1	>7	-0.65 (-0.71; -0.59)	1	Right	-0.32 (-0.97; 0.34)	2	Global test of cognition	-0.26 (-0.44; -0.09)	1
	Not specified	-0.00 (-0.07; 0.06)	2	No specified	-0.01 (-0.08; 0.06)	1	Left	-0.01 (-0.08; 0.06)	1			
							Not specified	-	-	Domain specific assessments	-0.03 (-0.08; 0.01)	3
Adjusted	Manual	-0.16 (-0.33; 0.01)	1	Range	-0.08 (-0.22; 0.05)	2	Bilateral	-0.16 (-0.33; 0.01)	1	Global test of cognition	0.16 (-0.33; 0.01)	1
	Automated	-0.06 (-0.12; 0.00)	1	>7	-0.06 (-0.12; 0.00)	1	Right	-0.04 (-0.11; 0.02)	2			
	Not specified	0.00 (-0.07; 0.06)	2	Not specified	-0.01 (-0.08; 0.06)	1	Left	-0.01 (-0.08; 0.06)	1			
							Not specified	-	-			

ES: Effect size; CI: Confidence Interval.

Table S11. Meta-bias for the association between IMT and cognitive function domains.

	Coeficient	p
Cross-sectional Unadjusted		
Global cognition	-2.193	0.224
Executive function	-0.023	0.988
Memory	0.188	0.002
Attention	-3.491	0.002
Cross-sectional Adjusted		
Global cognition	-0.104	0.695
Executive function	-0.135	0.200
Memory	-1.868	0.018
Attention	-1.917	0.086
Longitudinal Unadjusted		
Global cognition	-6.497	0.087
Executive function	1.743	0.692
Memory	0.945	0.826
Attention	-0.648	0.584
Longitudinal Adjusted		
Global cognition	-2.102	0.602
Executive function	-1.479	0.512
Memory	1.992	0.103
Attention	-0.057	0.937

Figure S2. Funnel plot for comparison-specific cross-sectional pooled effect sizes for global cognition.

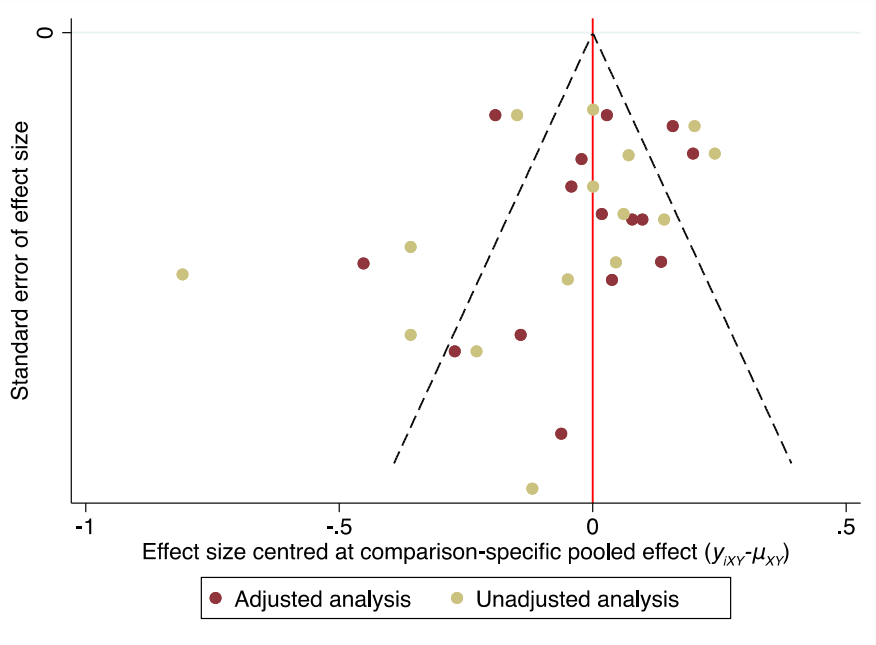

Figure S3. Funnel plot for comparison-specific cross-sectional pooled effect sizes for executive functions.

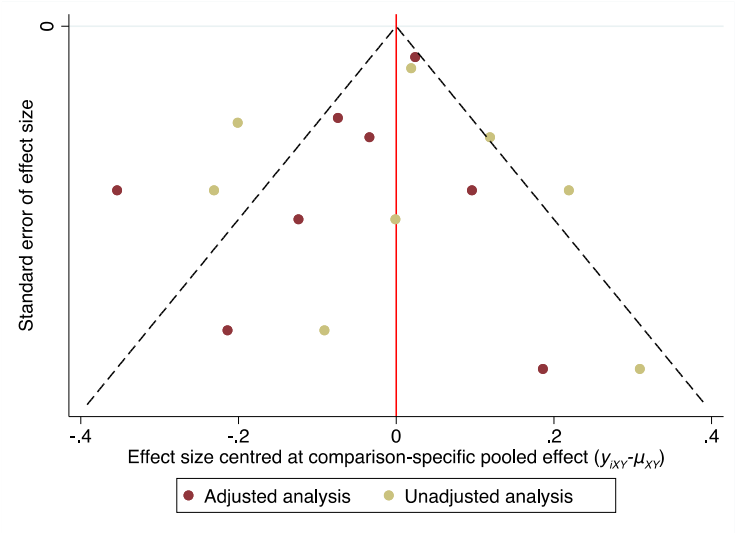

Figure S4. Funnel plot for comparison-specific cross-sectional pooled effect sizes for memory.

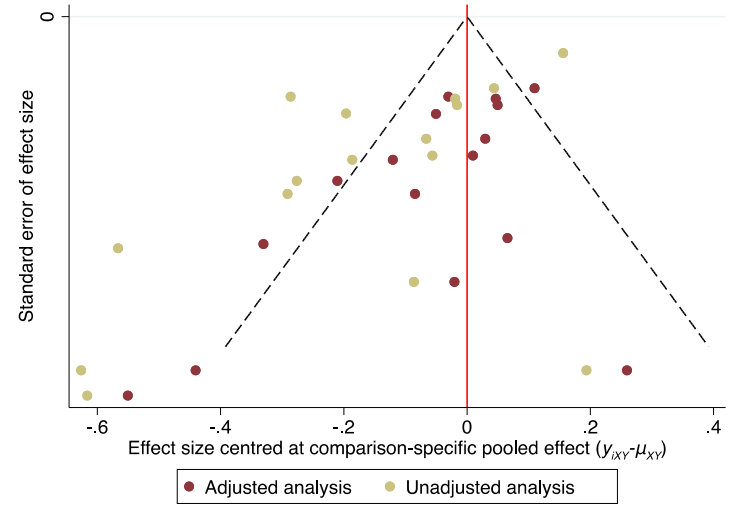

Figure S5. Funnel plot for comparison-specific cross-sectional pooled effect sizes for attention.

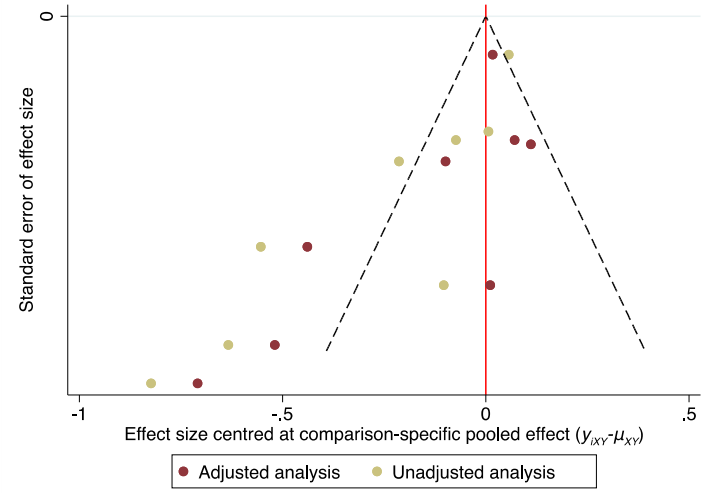

Figure S6. Funnel plot for comparison-specific longitudinal pooled effect sizes for global cognition.

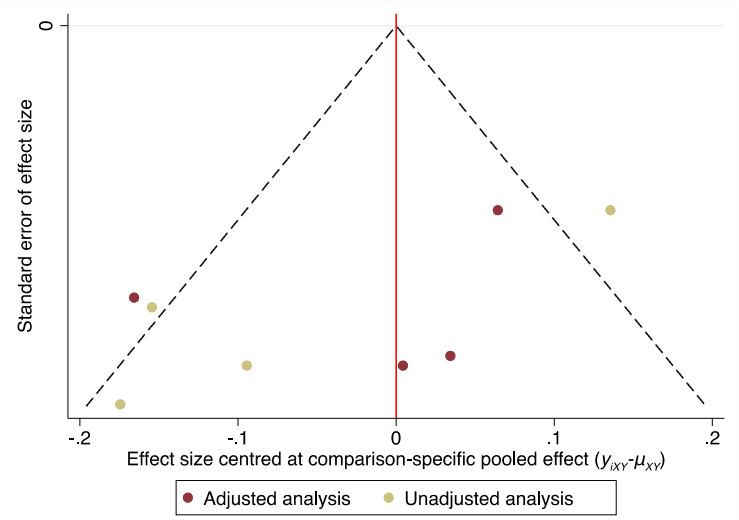

Figure S7. Funnel plot for comparison-specific longitudinal pooled effect sizes for executive functions.

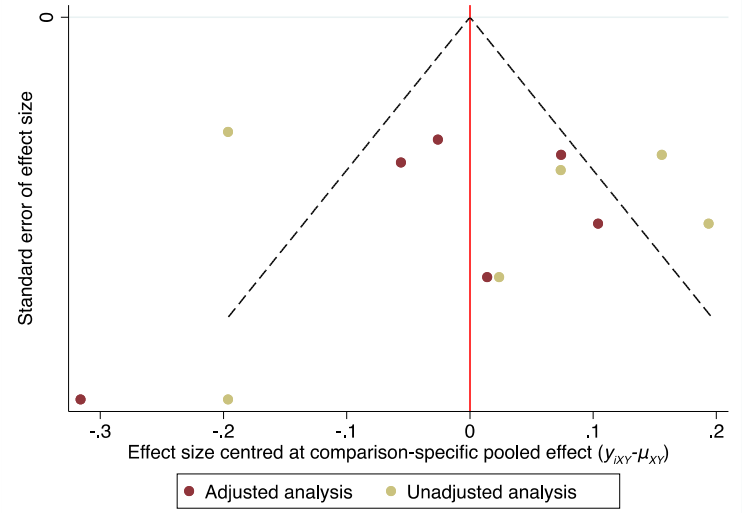

Figure S8. Funnel plot for comparison-specific longitudinal pooled effect sizes for memory.

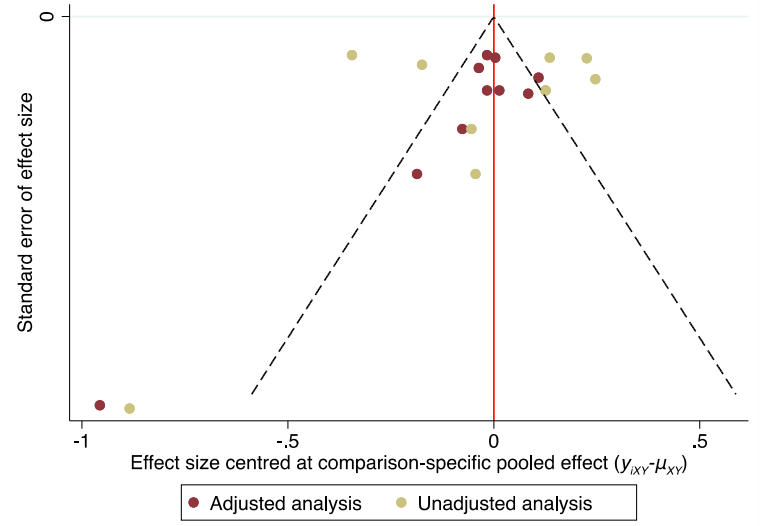

Figure S9. Funnel plot for comparison-specific longitudinal pooled effect sizes for attention.