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 mediators 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
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 impairment9 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 stiffness11-13 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 Handbook26 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. 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 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. 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. 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. The proportion of the total variation across studies because of heterogeneity was assessed using the I² statistic, whose values were not important (0% to <30%), moderate (≥30% to <50%), substantial (≥50% to <75%), or considerable (≥75% to 100%). Moreover, the corresponding P values were also considered. 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.
| References            | Subjects characteristics | Exposure | Outcome |
|-----------------------|--------------------------|----------|---------|
|                        | n, female (%) | Age | BMI | SBP | DBP | Depressive (%) | IMT device | IMT average | Cognitive measurement | Cognitive construct |
| Al Hazzouri et al, 2015 | 2618 (57.1) | 45.3 (3.6) | NR | NR | NR | 16.2% | GE-Logiq-700 | 0.8 (0.1) | Rey AVL, Digit Symbol Substation, Stroop Interference | Delayed verbal memory, Processing speed, Executive function |
| Arntzen et al, 2012 | 4371 (51.5) | M: 58.6 (9.3) | W: 59.5 (9.9) | M: 143.1 (19.2) | W: 142.4 (22.9) | NR | M: 2.1% | W: 5.5% | High-resolution B-mode ultrasonography | 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 | 181 (45.9) | MCI: 77.5 (4.6) | C: 75.3 (5.2) | NR | NR | MCI: 18.1% | C: 4.0% | Philips HD 11 | MMSE | Global cognitive |
| Cohen-Manheim et al, 2016 | 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 | 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 | 561 (58) | 57.8 (11.9) | NR | NR | NR | 10% | Terson Smart 3300 NexGen | NR | MoCA | Global cognition |

(Continued)
| References                        | n, female (%) | Age       | BMI       | SBP       | DBP       | Depressive s (%) | IMT device       | IMT average       | Cognitive measurement                                      | Cognitive construct                                      |
|----------------------------------|---------------|-----------|-----------|-----------|-----------|------------------|------------------|------------------|-----------------------------------------------------------|-----------------------------------------------------------|
| Feinkohl et al, 201332          | 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 Bagra 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, 201433           | 251 (46.0)    | 78.0 (6.4)| 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, 201834          | 1166 (60.0)   | 70.0 (9.0)| 28.0 (5.0)| 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 Trail test, Visual–motor Integration BNT, Animal Naming, Phonetic fluency test | Episodic memory Executive function Processing speed Semantic memory |
| Gatto et al, 200935             | 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 |
| Geijseraers et al, 201646       | 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 |
| References                     | Subjects characteristics | Exposure | Outcome |
|-------------------------------|--------------------------|----------|---------|
| Haley et al, 2007            | 109 (43.0)               | NR       | NR      |
|                              | 69.2 (7.43)              | NR       | NR      |
|                              | NR                       | NR       | NR      |
|                              | NR                       | NR       | NR      |
|                              | NR                       | NR       | NR      |
|                              | High-resolution B-mode ultrasonography | 0.88 (0.13) |         |
|                              | Mindray Z6               | 0.81 (0.22) | RAVLT   |
|                              |                           |          | ROCFT   |
| Imran et al, 2020            | 79 (NR)                  | NR       | NR      |
|                              | 55.5 (12.7)              | NR       | NR      |
|                              | NR                       | NR       | NR      |
|                              | NR                       | NR       | NR      |
|                              | Mindray Z6               | 0.81 (0.22) | RAVLT   |
|                              |                           |          | ROCFT   |
| Jiang et al, 2017            | 357 (65.0)               | NR       | NR      |
|                              | 57.2 (9.3)               | NR       | NR      |
|                              | 25.3 (3.3)               | NR       | NR      |
|                              | 132.2 (16.6)             | NR       | NR      |
|                              | 83.4 (9.3)               | NR       | NR      |
|                              | Sequoia scanner          | 0.8 (0.2) | MoCA    |
| Kemp et al, 2016             | 8114 (56.3)              | NR       | NR      |
|                              | 51.2 (8.8)               | NR       | NR      |
|                              | NR                       | NR       | NR      |
|                              | Depression severity: 8.0 (78) | Toshiba (Aplio XG) | TMT-B   |
| Komulainen et al, 2007       | 91 (100)                 | NR       | NR      |
|                              | 63.8 (3.2)               | NR       | NR      |
|                              | 27.6 (4.4)               | NR       | NR      |
|                              | Zung self-report 20-item scale: 36.4 (5.5) | 1.02 (0.26) | MMSE   |
|                              | Carotid ultrasonography |          | Word Recall Test |
|                              |                           |          | Stroop test and Letter-Digit Substitution Test |
| Lim et al, 2016              | 463 (43.2)               | NR       | NR      |
|                              | MP: 63.0 (6.1)           | NR       | NR      |
|                              | NP: 64.2 (6.4)           | NR       | NR      |
|                              | MP: 25.0 (4.1)           | NR       | NR      |
|                              | NP: 24.6 (3.5)           | NR       | NR      |
|                              | MMSE, Digit Span-Forward, Colour Trails 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) | 0.7 (0.1) | Global cognition |
| Masley et al, 2014           | 536 (27.4)               | NR       | NR      |
|                              | 48.0 (7.5)               | NR       | NR      |
|                              | 27.4 (4.7)               | NR       | NR      |
|                              | 117.7 (15.3)             | NR       | NR      |
|                              | 75.7 (10.4)              | NR       | 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 |

(Continued)
### Table 1. Continued

| Subjects characteristics | Exposure | Outcome |
|--------------------------|----------|---------|
| References               | n, female (%) | Age | BMI | SBP | DBP | Depressive s (%) | IMT device | IMT average | Cognitive measurement | Cognitive construct |
| Matsumoto et al, 2018 13 | 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 |
| Muela et al, 2018 14 | 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) | NoHTA26.7 (4.2) HTA 1:285 (4.6) HTA 2:301 (4.6) | NR | Wall Track Systems, 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 Test, Trail Making Test, and Digit Symbols Substitution Test |
| Muller et al, 2007 15 | 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 | 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 |
| Roberts et al, 2013 16 | 278 (54.3) | 49.0–51.0 | 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 |
| Rogne et al, 2013 17 | 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 | Execuive function Motor speed Verbal episodic memory Global cognition |
| Romero et al, 2009 18 | 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 |
| Schwerdtfeger et al, 2015 19 | 124 (49.0) | 37.5 (7.9) | 23.8 (4.0) | NR | NR | High-resolution B-mode ultrasound | 0.5 (0.1) | Mainz Coping Inventory | Cognitive avoidance |

(Continued)
### Table 1. Continued

| References                  | n, female (%) | Age      | BMI      | SBP      | DBP      | Depressive (%) | IMT device | IMT average | Cognitive measurement     | Cognitive construct                  |
|-----------------------------|---------------|----------|----------|----------|----------|----------------|------------|-------------|----------------------------|--------------------------------------|
| Singh-Manoux et al, 2008[^5^] | 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) | NR | Aloka 5500 | H-SES-M: 74.2 (10.3) H-SES-W: 71.9 (10.3) I-SES-M: 74.5 (10.1) I-SES-W: 72.6 (10.4) L-SES-M: 72.2 (10.1) L-SES-W: 72.6 (10.6) | NR | 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 phonetic and semantic fluency Global cognition |
| Smith et al, 2011[^1^]       | 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[^2^]     | 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[^3^]        | 3227 (43.4)   | 57.9 (10.9) | 24.9 (3.3) | 130.8 (19.9) | 82.6 (11.0) | NR | Philips iU-22 ultrasound system | NR | MMSE | Global cognition |

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Table 1. Continued

| References          | n, female (%) | Age     | BMI     | SBP     | DBP     | Depressive s (%) | IMT device       | IMT average   | Cognitive measurement                                                                 | Cognitive construct                                                                 |
|---------------------|---------------|---------|---------|---------|---------|------------------|------------------|--------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Wendell et al., 2009 | 338 (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-Q) Test, MMSE                              | Attention and concentration, Verbal learning, Memory, Nonverbal memory, Attention, perceptuomotor speed, visuomotor scanning, and mental flexibility |
| Wendell et al., 2016 | 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, Visual and semantic association fluency, Auditory divided attention, Attention and working memory, Attention, visual scanning, psychomotor speed, and mental flexibility |
| Yue et al., 2016    | 1826 (35.2)   | 63.2 (11.9) | NR      | 147.2 (22.4) | 149.0 (22.7) | CINT: 85.5 (12.5) | High-resolution B-mode ultrasonography | 1.4 (0.7)    | MMSE                                                                                   | Global cognition                                                                 |
| Zhong et al., 2011  | 2794 (54.0)   | 49.0 (9.8)  | NR      | NR      | NR      | Biosound AU4      | TMT (A and B)   | 0.65 (0.15)   | Grooved Pegboard Test, MMSE                                                             | Executive, attention and psychomotor function, Executive, and psychomotor function, General cognitive function |

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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. 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 (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; I²: 89.6%), for executive function (−0.18 [95% CI, −0.29 to −0.07]; Q: 37.15; I²: 81.2%), for memory (−0.14 [95% CI, −0.25 to −0.04]; Q: 151.33; I²: 90.1%), and for attention (−0.12 [95% CI, −0.29 to 0.04]; Q: 54.16; I²: 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; I²: 82.1%), for executive function (−0.12 [95% CI, −0.21 to −0.03]; Q: 27.04; I²: 74.1%), for memory (−0.09 [95% CI, −0.15 to −0.03]; Q: 33.88; I²: 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; I²: 81.7%), for executive function (−0.14 [95% CI, −0.29 to 0.01]; Q: 50.25; I²: 90.0%), for memory (−0.15 [95% CI, −0.30 to 0.00]; Q: 255.80; I²: 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; I²: 58.9%), for executive function (−0.04 [95% CI, −0.12 to 0.04]; Q: 12.78;
$\bar{P}$: 60.9%, for memory (−0.00 [95% CI, −0.05 to 0.04]; Q: 23.32; $\bar{P}$: 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
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).
Meta-Regressions and Subgroup Analyses

Meta-regressions showed that none of the considered variables (i.e., % 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;
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 inflammation65,72 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.

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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 |
|--------------------------------|-------------------|----------------|------|-----------------|-----------------|--------------------------------------------------------|
| Alf Hasszouri et al., 2015     | Manual            | Yes            | 13   | Bilateral       | Maximal IMT of the near and far wall of the CCA         | Global test of cognition                                |
| Arnzten et al., 2021           | 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-Narbono et al., 2016    | NE                | Yes            | 3-12 | Bilateral       | CCA at 1.5 cm proximal to the flow divider               | Domain specific assessments                             |
| Cohen-Manheim et al., 2016     | 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             | 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        | 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          | NE                | Yes            | NE   | Bilateral       | CCA, 1 to 2 cm below the bifurcation Free of plaque     | Domain specific assessments                             |
| Frazier et al., 2014           | 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 Free of plaque | Domain specific assessments                             |
| Gardner et al., 2018           | 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             | Automated        | Yes            | NE   | Right           | Distal CCA far wall along a 1 cm length just distal to the carotid artery bulb. | Global test of cognition                                |
| Geijseraes et al., 2016        | 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             | 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             | Manual            | Yes            | 10   | Bilateral       | Near and 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             | Automated        | Yes            | NE   | Bilateral       | Far wall of the CCA, the 1 cm segment proximal to the bifurcation | Domain specific assessments                             |
| Kemp et al., 2016              | Automated        | Yes            | 7.5  | Bilateral       | Outer wall, 1 cm in length from 1 cm below carotid bifurcation | Domain specific assessments                             |
| Komulainen et al., 2007        | Automated        | NE             | 10   | Bilateral       | Far wall of the left and right bifurcation               | Domain specific assessments                             |
| Lim et al., 2016               | NE                | Yes            | 10.5 | Bilateral       | The CCA was scanned in anterior, posterior and lateral at 1 cm proximal to the carotid bulb Free of plaque | Domain specific assessments                             |
| Masley et al., 2014            | NE                | Yes            | 5-10 | Bilateral       | Far wall of the right and left distal 1 cm of the CCA    | Global test of cognition                                |
| Matsumoto et al., 2018         | NE                | Yes            | NE   | Bilateral       | The maximum value among the bilateral common and internal carotid artery in the far arterial walls | Domain specific assessments                             |
| Muella et al., 2018            | 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., 2014            | NE                | Yes            | 7.5  | Bilateral       | Left and right distal CCA                               | Domain specific assessments                             |
| Roberts et al., 2013           | NE                | Yes            | 7    | Bilateral       | Three locations in the common and internal carotid arteries | Global test of cognition                                |
| Rogne et al., 2013             | Semi-automated   | Yes            | 7.5:12| Right          | 1 cm segments of the far and near wall of the CCA, and in the most proximal 1 cm segment of the bulb. Included plaque | Domain specific assessments                             |
| Romero et al., 2009            | NE                | Yes            | 7.5  | Bilateral       | Near and far walls of CCA, carotid bulb and ICA          | Global test of cognition                                |
| Schwedtfeger et al., 2015      | Automated        | NE             | 5-13 | Bilateral       | 1 cm from carotid bifurcation from the far wall of the artesia carotid at a length of 1 cm | Domain specific assessments                             |
| Singh Manoux et al., 2006      | Automated        | Yes            | 7.5  | Right           | Left and left CCA, thickest part 1 cm proximal to the bifurcation | Domain specific assessments                             |
| Smith et al., 2011             | Automated        | Yes            | 10   | Bilateral       | Far wall of the left and right CCA                      | Global test of cognition                                |
| Suemoto et al., 2015           | NE                | Yes            | 7.5  | Bilateral       | Left and right CCA, within an area 1 cm in length, 1 cm below the carotid bifurcation | Domain specific assessments                             |
| Wang et al., 2016              | Manual            | Yes            | 5-12 | Bilateral       | Far wall of the CCA proximal to the bifurcation, along a plaque-free segment of 1 cm | Domain specific assessments                             |
| Wendell et al., 2009           | 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           | 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., 2018               | NE                | Yes            | 7.5  | Bilateral       | Near and far walls of the right and left CCA Included plaque | Domain specific assessments                             |
| Zhong et al., 2011             | 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             | 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                             |
| References | Unadjusted | Adjusted |
|------------|------------|----------|
| Al Hazzouri et al., 2015 | 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. |
| Arentsen et al., 2012 | 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 | Education, smoking, hypertension, folate, B12, creatinine and others as covariates. | Education, smoking, hypertension, folate, B12, creatinine and others as covariates. |
| Cohen-Manhein et al., 2016 | 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., 2020 | None. | Demographics, cardiovascular risk factors, severe edentulism, and symptoms of depression. |
| Del Brutto et al., 2019 | Age and sex. | None. |
| Geijselaers et al., 2016 | 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 | 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 SBV). |
| Gatto et al., 2009 | 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. |
| Geijserlaers et al., 2016 | 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 | Age, education, sex, cardiovascular risk factors, and current systolic blood pressure. | Age, education, sex, cardiovascular risk factors, and current systolic blood pressure. |
| Imam et al., 2020 | None. | None. |
| Jiang et al., 2017 | None. | Age, gender, and education level, duration of DM, and hypertension. |
| Komulainen et al., 2007 | 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 | None. | Age, gender, education, hypertension, diabetes, dyslipidemia, smoking, body mass index, and APOE 4 status. |
| Masley et al., 2014 | None. | None. |
| Matsumoto et al., 2018 | 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 hypointensity. |
| Muela et al., 2018 | None. | All independent variables with P<.01 in the bivariate analyses. |
| Muller et al., 2007 | Age and education. | Age and education. |
| Rogne et al., 2013 | None. | Cardiovascular risk factors and other factors known to influence cognition. |
| Romero et al., 2009 | 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 | Age and sex. | Age and sex. |
| Smith et al., 2017 | Background characteristics, CVRF, and intima medial thickness. | Background characteristics, CVRF, and intima medial thickness. |
| Suemoto et al., 2015 | 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   | 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 | 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 | 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    | None.                                           | None.                                                                     |
| Zhong et al., 2011  | 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  | 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 Hazouri et al., 2015 | Y | Y | Y | Y | NR | Y | Y | Y | Y | Y | Y | Y | Y | 12  |
| Amten et al., 2021 | Y | Y | Y | Y | NR | Y | Y | Y | NR | Y | Y | Y | Y | Y | 11  |
| Casado-Naranjo et al., 2016 | Y | Y | Y | Y | NR | - | - | Y | Y | - | Y | Y | - | Y | 9   |
| Cohen-Manheim et al., 2016 | Y | Y | Y | Y | NR | Y | Y | Y | Y | NR | Y | Y | Y | Y | 11  |
| Cohen et al., 2009 | Y | Y | Y | Y | Y | NR | - | - | Y | Y | - | Y | Y | - | N | 8   |
| Del Brutto et al., 2020 | Y | Y | Y | Y | NR | Y | Y | Y | Y | Y | NR | Y | Y | Y | 12  |
| Feinkohl et al., 2013 | Y | Y | N | Y | NR | Y | Y | Y | Y | Y | NR | Y | Y | Y | 11  |
| Frazier et al., 2014 | Y | Y | Y | Y | NR | Y | Y | Y | Y | Y | Y | Y | Y | N | 11  |
| Gardener et al., 2018 | Y | Y | Y | Y | NR | - | - | Y | Y | Y | NR | Y | Y | Y | 12  |
| Gatto et al., 2009 | Y | Y | N | Y | NR | - | - | Y | Y | - | Y | Y | N | Y | 7   |
| Geijselaers et al., 2016 | Y | Y | Y | Y | NR | - | - | Y | Y | - | Y | NR | Y | Y | 8   |
| Haley et al., 2007 | Y | Y | Y | Y | NR | - | - | Y | Y | - | Y | NR | Y | N | 8   |
| Imran et al., 2020 | Y | Y | Y | Y | NR | - | - | N | Y | - | Y | NR | - | N | 6   |
| Jiang et al., 2017 | Y | Y | Y | Y | NR | - | - | Y | Y | - | Y | NR | - | Y | 8   |
| Kemp et al., 2016 | Y | Y | Y | Y | NR | - | - | Y | Y | - | Y | NR | - | N | 7   |
| Komulainen et al., 2007 | Y | Y | Y | Y | NR | Y | Y | N | Y | Y | Y | NR | Y | N | 10  |
| Lim et al., 2016 | Y | Y | NR | Y | NR | - | - | N | Y | - | Y | NR | Y | Y | 6   |
| Masley et al., 2014 | Y | Y | NR | Y | NR | - | - | N | Y | - | Y | NR | - | N | 5   |
| Matsumoto et al., 2018 | Y | Y | NR | Y | NR | Y | Y | Y | Y | Y | Y | - | Y | 7   |
| Mueta et al., 2018 | Y | Y | NR | Y | NR | - | - | Y | Y | - | Y | NR | Y | Y | 8   |
| Muller et al., 2007 | Y | Y | N | Y | NR | NR | - | - | Y | Y | - | Y | NR | Y | 7   |
| Roberts et al., 2016 | Y | Y | Y | Y | NR | Y | Y | Y | Y | Y | Y | NR | - | Y | 11  |
| Rogne et al., 2013 | Y | Y | Y | Y | NR | Y | Y | Y | Y | Y | Y | Y | Y | N | 11  |
| Romero et al., 2009 | Y | Y | Y | Y | NR | Y | Y | Y | Y | Y | Y | Y | Y | N | 12  |
| Schwerdtfeger et al., 2015 | Y | Y | NR | Y | NR | - | - | Y | Y | - | Y | NR | - | Y | 7   |
| Singh-Manoux et al., 2008 | Y | Y | N | Y | NR | - | - | Y | Y | - | Y | Y | - | Y | 7   |
| Smith et al., 2011 | Y | Y | Y | Y | NR | - | - | N | Y | - | Y | NR | - | Y | 7   |
| Suzuki et al., 2015 | Y | Y | Y | Y | NR | - | - | Y | Y | - | Y | NR | - | Y | 8   |
| Wang et al., 2016 | Y | Y | N | Y | NR | - | - | N | Y | - | Y | NR | - | Y | 7   |
| Wendell et al., 2009 | Y | Y | NR | Y | NR | Y | Y | Y | Y | Y | NR | Y | N | 9   |
| Wendell et al., 2016 | Y | Y | N | Y | NR | Y | Y | Y | Y | Y | NR | N | Y | 8   |
| Yue et al., 2016 | Y | Y | Y | Y | NR | - | - | Y | Y | - | Y | NR | - | Y | 7   |
| Zhong et al., 2011 | Y | Y | N | Y | NR | - | - | Y | Y | - | Y | NR | - | Y | 6   |
| Zhong et al., 2012 | Y | Y | NR | Y | NR | Y | Y | Y | Y | Y | Y | NR | N | Y | 8   |

Y: yes; N: no; NR: not reported
Table S4: Heterogeneity, inconsistence estimations for DerSimonian 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             | τ²            | 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.

| Reference               | ES   | LL   | UL   |
|-------------------------|------|------|------|
| Global cognition        |      |      |      |
| Casado-Naranjo et al., 2016 | -0.241 | -0.355 | -0.126 |
| Del Brutto et al., 2020   | -0.228 | -0.339 | -0.116 |
| Feinhol 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        |      |      |      |
| 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                    |      |      |      |
| 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 |
| Geijsehaers 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                 |      |      |      |
| Cohen et al., 2009        | -0.064 | -0.217 | 0.089 |
| Geijsehaers 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.

| 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           | -0.136 | -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 |

| Reference | ES    | LL    | UL    |
|-----------|-------|-------|-------|
| Gardner 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 |

| Reference | ES    | LL    | UL    |
|-----------|-------|-------|-------|
| Cohen et al., 2009 | -0.097 | -0.159 | -0.034 |
| Gardner et al., 2018 | -0.092 | -0.160 | -0.024 |
| Gatto et al., 2009    | -0.103 | -0.172 | -0.034 |
| Geijseelaers 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 |

| Reference | ES    | LL    | UL    |
|-----------|-------|-------|-------|
| Cohen et al., 2009 | -0.072 | -0.191 | 0.046 |
| Geijseelaers 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 et al., 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     |
| AMRTZEN 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 |
| WENDELL et al., 2016 | -0.176 | -0.352 | 0.001 |
| ZHONG et al., 2012 | -0.171 | -0.335 | -0.007 |
| ATTENTION | Reference | ES     | LL     | UL     |
| AMRTZEN 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 |
| AMRTZEN 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 |

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        | β (95% CI) | p    | n        | β (95% CI) | p    | n        | β (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.

| Global cognition | Manual/automated | mHz | Laterally | Cognition method |
|------------------|------------------|-----|-----------|------------------|
|                  | Type             | n   | Place     | ES (95% CI)      |
| Cross-sectional data | Manual          | -1.18 (-0.25; 0.11) | 1 | Range | -0.17 (-0.32; -0.02) |
| Adjusted         | Automated       | -0.26 (-0.49; -0.02) | 7 | >7 | -0.28 (-0.42; -0.14) |
|                  | Not specified   | -0.26 (-0.38; -0.15) | 7 | Not specified | -0.33 (-0.70; 0.04) |
|                  | Manual          | -0.11 (-0.19; -0.03) | 1 | Range | -0.06 (-0.15; 0.03) |
|                  | Automated       | -0.14 (-0.29; 0.01) | 7 | >7 | -0.23 (-0.34; -0.04) |
|                  | Not specified   | -0.18 (-0.28; -0.07) | 7 | Not specified | -0.20 (-0.43; 0.03) |
| Longitudinal data | Manual          | -0.24 (-0.41; -0.06) | 1 | Range | -0.28 (-0.41; -0.15) |
| Adjusted         | Automated       | -0.20 (-0.42; 0.02) | 3 | Not specified | -0.15 (-0.43; 0.13) |
|                  | Not specified   | -0.09 (-0.24; 0.05) | 3 | Not specified | -0.12 (-0.34; 0.11) |
| Executive functions | Manual          | -0.35 (-0.42; -0.27) | 2 | Range | -0.05 (-0.14; 0.04) |
|                  | Automated       | -0.08 (-0.18; 0.02) | 3 | >7 | -0.35 (-0.42; -0.28) |
|                  | Not specified   | 0.00 (-0.09; 0.09) | 1 | Not specified | -0.15 (-0.50; 0.19) |
|                  | Manual          | -0.05 (-0.13; 0.02) | 2 | Range | -0.02 (-0.12; 0.08) |
|                  | Automated       | -0.10 (-0.28; 0.09) | 3 | >7 | -0.06 (-0.14; 0.02) |
|                  | Not specified   | 0.04 (-0.05; 0.13) | 1 | Not specified | -0.14 (-0.52; 0.24) |
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.

| Memory | Type | Manual/automated | n | Classification | mHz | n | Place | Laterality | ES (95% CI) | 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 | - | - | - |
| | 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 | - | - | - |
| 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 | - | - | - |
| | 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 | - | - | - |

ES: Effect size; CI: Confidence Interval.
Table S11. Meta-bias for the association between IMT and cognitive function domains.

|                              | Coefficient | p    |
|------------------------------|-------------|------|
| **Cross-sectional Unadjusted** |             |      |
| Global cognition             | -2.193      | 0.224|
| Executive function           | -0.023      | 0.968|
| 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.