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A systematic review of existing peripheral biomarkers of cognitive aging: Is there enough evidence for biomarker proxies in behavioral modification interventions?
An initiative in association with the nutrition, exercise and lifestyle team of the Canadian Consortium on Neurodegeneration in Aging

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ABSTRACT

Peripheral biomarkers have shown significant value in predicting brain health and may serve as a useful proxy measurement in the assessment of evidence-based lifestyle behavior modification programs, including physical activity and nutrition programs, that aim to maintain cognitive function in late life. The aim of this systematic review was to elucidate which peripheral biomarkers are robustly associated with cognitive function among relatively healthy non-demented older adults. Following the standards for systematic reviews (PICO, PRIMSA), and employing MEDLINE and Scopus search engines, 222 articles were included in the review. Based on the review of biomarker proxies of cognitive health, it is recommended that a comprehensive biomarker panel, or *biomarker signature*, be developed as a clinical end point for behavior modification trials aimed at enhancing cognitive function in late life. The biomarker signature should take a multisystemic approach, including lipid, immune/inflammatory, and metabolic biomarkers in the biological signature index of cognitive health.

1. Introduction

Population aging has prompted intense interest in the identification of predictive factors associated with cognitive function in late life. The investigation of biomarkers, defined as cellular, biochemical or molecular variations that are measured in human tissue, cells or fluids, have shown significant value in predicting brain health. Biomarkers in cerebral spinal fluid (Fagan et al., 2007) and neuroimaging studies (Risacher & Saykin, 2013) have shown promise in predicting cognitive change in late life and conversion from mild cognitive impairment (MCI) to Alzheimer's Disease (AD); however, measurement of these biomarkers is invasive and impractical from a clinical standpoint. With the continuous development of new technologies, there has been a rise in non-invasive biomarker measurements, providing a potentially more robust approach for early identification of neuronal changes that precede cognitive deterioration and pathology. In addition to using non-invasive biomarker measurements as a diagnostic tool, peripheral biomarkers may provide a proxy measurement for clinical trials and prevention strategies that aim to prevent or slow cognitive aging. Prevention strategies of interest include evidence-based lifestyle behavior modifications, including promotion of physical activity and a healthy diet.

Engaging in physical activity has been shown to reduce the risk of cognitive impairment and dementia in elderly people, with a dose-response relationship (Laurin et al., 2001). In particular, physical activity has been found to enhance executive function processes, including planning, working memory, attentional control and inhibition (Bherer et al., 2013; Colcombe & Kramer, 2003; Smith et al., 2010). The impact of physical activity on cognitive function has been supported by cross-sectional, longitudinal and randomized controlled trials (RCTs). A

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number of studies support the importance of aerobic training to enhance cognitive function (Smiley-Oyen et al., 2008), while other studies suggest that combined aerobic and resistance training may provide optimal result (Marzolini et al., 2013). Still some studies suggest that the type of physical activity, whether it be aerobic or resistance training (Helmes & Harris, 2017; Young et al., 2015), or the intensity of the exercise program (Sanders et al., 2019), is of little consequence. Nevertheless, physical activity has been found to enhance brain volume (Colcombe et al., 2006; Erickson et al., 2007), including volume of the hippocampus (Erickson et al., 2011), an integral brain region for learning and memory and a central structure involved in AD pathology.

The importance of nutrient intake and diet on the brain has increasingly become a focal point for research in the past few years (Parrott & Greenwood, 2007). Adherence to a Western traditional diet high in red meat, refined carbohydrates, saturated fat, and processed foods associates with poor cognitive function; while a prudent dietary pattern high in fruits, vegetables, fish, nuts and seeds, associates with enhanced cognitive performance (Wengreen et al., 2013). The Mediterranean diet, which is aligned with the prudent dietary pattern, is associated with better cognitive function (Bajerska, Wozniewicz et al., 2014; Martinez-Lapiscina et al., 2013; Ye et al., 2013), decreased risk for MCI and dementia (Galbete et al., 2015; Morris et al., 2015; Psaltopoulou et al., 2013; Scarmeas et al., 2006a,b; Trichopoulou et al., 2015), and reduced risk of progressing from MCI to AD (Singh et al., 2014). It is also suggested that adherence to the Mediterranean diet is associated with less brain atrophy (Mosconi et al., 2014).

Identification of peripheral biomarkers associated with cognitive function and changes in cognitive capacity is important as they may help elucidate underlying mechanisms mediating the effects of behavioral modification on cognitive well-being. Specifically, blood biomarker signatures may serve as clinical indicators for evidence-based interventions targeting lifestyle behavior to help maintain cognition in late life. However, before biomarkers can be applied as clinical indicators, we must first determine which biomarkers are robustly associated with cognitive function and trajectory of cognitive function over time. Therefore, this review will focus on specific classes of peripheral blood biomarkers that are associated with cognitive aging, and that may serve as biological signatures to assess the efficacy of future evidence-based lifestyle interventions involving changes to physical activity and dietary intake. More specifically, this review will focus on the association between premorbid dysregulation in peripheral blood biomarkers and cognitive function in non-demented older adults.

2. Methods

Search engines included MEDLINE and Scopus. The specified date range was between January 1995 and January 2018. No language restrictions were specified. Search terms included, (biomarker* OR "biological marker" OR serum OR blood OR plasma OR circulating) AND (cogniti* OR "executive function" OR attention OR memory OR "processing speed" or "verbal fluency" OR "neuropsychological test") AND (inflammat* OR lipid OR glucose OR insulin OR vitamin OR mineral) AND (age* OR aging OR "older adult" OR senior OR elderly OR "65 and over" OR "80 and over" OR "oldest old" OR 65 + OR "85 an over" OR 85+), and NOT (patient OR Alzheimer's OR Parkinson's OR bipolar OR schizophrenia OR autism OR diabetes OR anorexia OR post-mortem OR "post mortem" OR Lupus OR HIV OR congenital OR traumatic brain injury OR cancer OR Prader-Willi) NOT (randomized OR intervention OR "drug administration" OR "drug effects" OR "cell proliferation" OR DNA OR methylation) NOT ("young adult*" OR child* OR prenatal OR neonatal OR animal* OR rat OR mouse). Additional filters in Scopus allowed for the exclusion of subject areas including biochemistry, molecular biology, mathematics, pharmacology, dentistry, engineering and business. A total of 1654 articles were retrieved. See Fig. 1 for the PRISMA flow diagram.

Three independent reviewers assessed inclusion of papers at three phases: assessment of title, assessment of abstract and assessment of full paper. At each phase, reviewers identified papers that merited review based on inclusion/exclusion criteria. Any discrepancies were discussed and resolved. Following the PICO approach, studies were included if they attempted to correlate biomarkers and cognitive function at baseline and/or predict cognitive trajectory among healthy community-dwelling older adults. Only longitudinal and cross-sectional studies were selected; randomized control trials, intervention studies, experimental studies (e.g., drug administration) and case-control studies that focused on comparing patient with control participants were eliminated. Studies were discarded if they focused on steroid hormones. Studies were discarded if they focused on animals, young adults, adolescents, or children, but were retained if they included participants 65+ in the study sample and reported a minimum mean age of 60 at baseline for cross-sectional associations, or at follow-up for longitudinal analyses. Papers were discarded if they focused on patient populations (i.e., persons with dementia or MCI), as biomarker levels may not reflect premorbid dysregulation in these study cohorts. Finally, papers were discarded if they focused on post-surgery cognitive function and if "impairment" was solely based on clinician diagnosis with no estimate of cognitive performance (e.g., simple presentation of odds ratio for impairment without providing detail on how impairment was defined based on cognitive performance on standardized tests). Additional papers were identified from review papers that were not found in the original search. A total of 222 articles were included in the systematic review. See Fig. 1 for PRISMA flow diagram.

3. Results

Given the breadth of data arising from the systematic search, evidence for peripheral biomarkers of cognitive function that may be modified by lifestyle programs such as diet and physical activity are presented using five biomarker categories that were devised by the authors following review of the literature: lipids and fatty acids, inflammation and immune, hormones and related metabolic markers, micronutrients and vitamin proxies, and other.

3.1. Lipids and fatty acids as biomarkers of cognitive function

Lipids are hydrophobic molecules that play a crucial role in cell structure and numerous physiological functions. Among them, total cholesterol (TC), high- and low-density lipoprotein (HDL and LDL) cholesterol, and triglycerides (TG) have received extensive attention related to cognitive function. Fatty acids (FA), namely long-chain polyunsaturated fatty acids (LCPUFA), have also recently received attention in the field of cognitive aging due to their neuroprotective properties (Denis et al., 2015).

Systematic review of the literature identified 52 papers that examined the association between lipids, or fatty acids, and cognitive function in late life (Table 1). Findings from cross-sectional studies (n = 32) investigating the association between cholesterol and related lipid constituents have been relatively mixed (Atzmon et al., 2002; Crichton et al., 2014; Katsumata et al., 2013; Lee et al., 2010; Leritz et al., 2016; Levin, 2014; Manzato et al., 2003; Parthasarathy et al., 2017; van Exel et al., 2002; Yaffe et al., 2002; Yin et al., 2012), with approximately half of the retrieved studies reporting null findings (Aleman et al., 2005; Chiu et al., 2012; Fischer et al., 2006; Formiga et al., 2012; Huang et al., 2009; Lai et al., 2011; Miralbell et al., 2012; Ortega et al., 2002; Takayanagi et al., 2015; Zhang et al., 2016). Although relatively small sample sizes may explain null findings (Miralbell et al., 2012), sample composition, including age (Wendell et al., 2016) and gender (Luo et al., 2013), may further muddle true associations. In the Chinese Longitudinal Healthy Longevity Survey (CLHLS, participant age range from 65 to 112 years), Lv et al. (2016) reported that higher TC, LDL and HDL associated with lower risk of cognitive impairment (measured by performance on the mini-mental

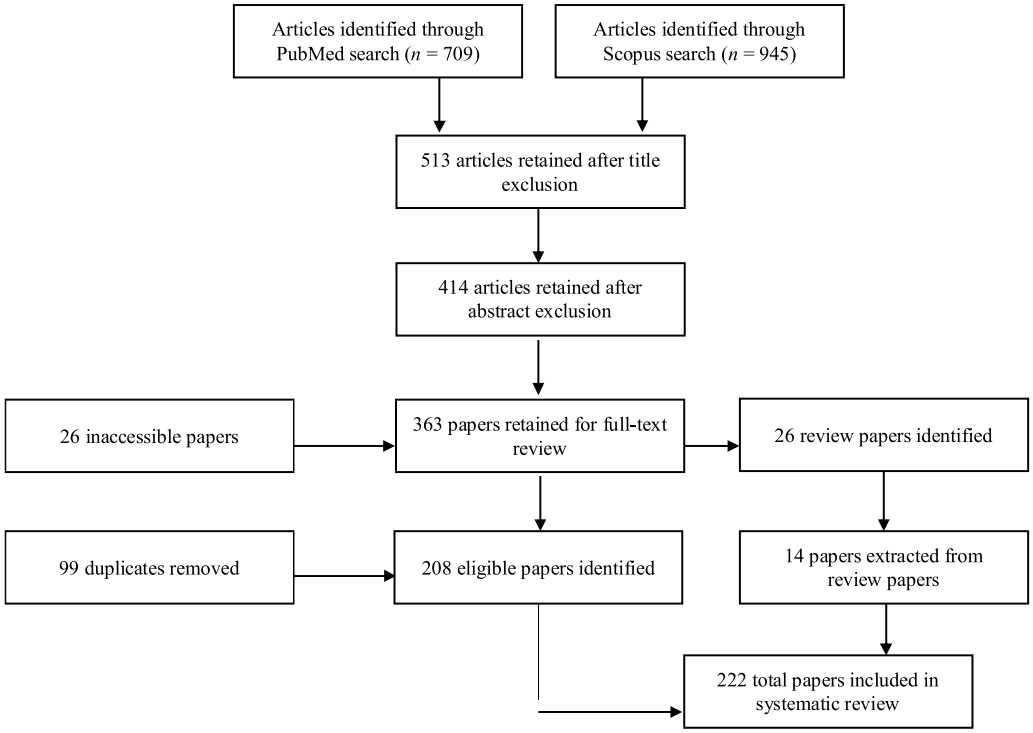

Fig. 1. PRISMA flow diagram.

state examination) among the oldest-old (80 + years), but not in the younger subgroup. In a cross sectional analysis of 190 older adults, a quadratic relationship between TC and age on cognitive function was observed such that persons 70+ year old performed better on a memory test at high and low levels of TC compared with mid-range TC; whereas persons younger than 70 years old performed worse at high and low levels (Wendell et al., 2014). Furthermore, the association between high HDL and better cognitive function may be more robust in women than men (Chanti-Ketterl et al., 2015; Lv et al., 2016). It is also important to recognize that lipids do not work in isolation to affect cognitive processes and should be considered with, or in light of, other biological systems. In a study by Cheng et al. (2014), the association between lipid level and cognitive function was dependent on homocysteine level, a marker of inflammation and proxy of vitamin B12 status. More specifically, in 1889 older adult men and women, the association between lipids (i.e., TC and LDL) and cognitive function was reported as non-linear (inverted U) at low homocysteine levels, linear at moderate homocysteine levels, and null at high homocysteine levels (Cheng et al., 2014).

Among the longitudinal studies (n = 20) that met inclusion criteria, the majority of prospective studies report a positive association between total cholesterol and global cognitive function, such that higher baseline TC is associated with preserved performance over time (Ancelin et al., 2014; Karlamangla et al., 2004; Otsuka et al., 2014; Perrig et al., 1997; Taniguchi et al., 2014; van den Kommer et al., 2009; van den Kommer et al., 2012; Wendell et al., 2014). Although null (Ammann et al., 2013; Katsumata et al., 2012; Mielke et al., 2008; Viscogliosi et al., 2016) and negative associations between cholesterol and cognition have been reported (van den Kommer et al., 2012), time of sampling matters (Solomon et al., 2009; van Vliet et al., 2009). While high serum cholesterol measured in midlife significantly predicts later cognitive function and decline, this relationship disappears or reverses when lipid levels are measured in late life (Solomon et al., 2009). For example, in the Baltimore Longitudinal Study of Aging, higher TC was found to associate with poorer global cognitive performance in middle-aged and older adults, but with better performance in the oldest old (Wendell et al., 2014). Accordingly, it seems important to establish age-adjusted criteria when measuring cholesterol as a biomarker of cognitive health in older adults.

The relationship between lipids and cognitive function may be further complicated by sex (Reynolds et al., 2010) and genetic polymorphisms, particularly the apolipoprotein E gene (*APOE*) (de Frias et al., 2007; Mooijaart et al., 2007; Yasuno et al., 2012). For instance, in a cross sectional study of adults aged 85 years and older, it was found that high TC and LDL- cholesterol were associated with better memory scores for non-carriers of the epsilon 4 (ε4) allele of the *APOE* gene, but not for ε4 *APOE* carriers (West et al., 2008); further, in a 3-year prospective study of older adults, it was found that higher HDL at baseline associated with higher composite cognitive performance at follow-up only in ε4 non-carriers (Yasuno et al., 2012). Notably, *APOE* encodes a cholesterol transporter (ApoE) associated with amyloid plaque deposition in non-demented elderly persons aged 72–96 years of age (Hughes et al., 2014).

Significantly fewer studies with the current inclusion criteria were found for FAs (n = 9). Polyunsaturated fatty acids (PUFAs), especially the omega-3 fatty acids like eicosapentaenoic acid (EPA), docosahexaenonic acid (DHA) and α-linolenic acid (ALA), are highly concentrated in nervous tissues and implicated in the amelioration of various neuropathological mechanisms (Snowden et al., 2017). Although null findings have been reported (Ammann et al., 2013; Chiu et al., 2012; Ortega et al., 2002), higher levels of PUFA's in the blood has been found to be associated with better cognitive function, especially executive functioning (Bowman et al., 2013; D'Ascoli et al., 2016; Manzato et al., 2003; Tan et al., 2012; Zamroziewicz et al., 2015). These studies are in line with results from the Framingham Heart Study, suggesting that higher plasma DHA levels at baseline (top quartile) was associated with a 47% decreased risk of dementia onset at follow-up (Schaefer et al., 2006). However, additional research is required to understand sex differences in this protective relationship. In a 5.9-year retrospective cohort of women from the Women's Health Initiative Study of Cognitive Aging, baseline DHA and EPA was significantly associated with baseline cognitive function, including fine motor speed, verbal knowledge and fluency; however, no associations were found between FAs and change in cognitive performance over time (Ammann et al., 2013). Elucidating

Table 1
Systematic Review Results for Lipids and Fatty Acids.

Study	Sample Size Mean Age Gender %female Cohort/ Location	Study design (CS/ L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect modifiers*	Adjusted Model Results
Cross-Sectional Studies						
Parthasarathy et al., 2017	*N* = 251 78 yrs 46% female *VIB Study, U.S.A.*	CS	Lipids: TG (fasting serum, measurement not specified)	Memory (Word List Learning Test of Memory Assessment Scale); EF (DRS - Perseveration, DS, COWAT)	Age; Sex; Education; Clinical dementia rating; CVD risk factors; DTI fractional anisotropy; LDL	Higher TG associated with lower EF only
D'Ascoli et al., 2016	*N* = 768 69 yrs 51% female *KIHD Risk Factor Study, Finland*	CS	FA: PUFAs (EFA DHA, DPA) (fasting serum measured using gas chromatography)	Global cognition (MMSE); Memory (Selective Reminding Test); Motor Speed (TMT-A); VF (VFT); Visual Memory (VRT)	Age; Sex; Education; Year testing; BMI; Smoking; Diabetes; Ischemia; Coping; Leisure-time; PA; Nutrient intakes	Higher PUFA associated with better motor speed and VF
Leritz et al., 2016	*N* = 120 68 yrs 62% female *U.S.A.*	CS	Lipids: LDL, HDL, TG (fasting serum, measurement not specified)	Memory (LM, CVLT, BNT); EF (DS, Stroop, TMT); VF (COWAT)	Age; Education; Medication; APOE	Higher TG and lower LDL independently associated with poorer memory only; HDL: ns
Lv et al., 2016	*N* = 2000 86 yrs 47% female *CLHLS, China*	CS	Lipids: TC, LDL, HDL, TG (fasting plasma, measured using Automatic Biochemistry Analyzer)	Global cognition (MMSE)	Age; Sex; Education; Marital status; Residence; Smoking; Alcohol; Central obesity; Sleep; Anemia; HTN; Diabetes; CKD *Effect modifiers*: Sex, Age	Increase in each lipid associated with better MMSE; Higher HDL associated with better MMSE in females only; In oldest-old (80 +) high TC, LDL and HDL associated with better MMSE; Not observed in younger subgroup
Wendell et al., 2016	*N* = 190 66 yrs 47% female *U.S.A.*	CS	Lipids: TC, HDL, LDL (fasting blood, measured enzymatically)	Memory (LM, VRT); EF (TMT, DS); Visuospatial (BD, Judgment of Line Orientation); Manual Speed (GPT)	Sex; Education; SBP; Glucose; Alcohol; Smoking; Depression; Medication *Effect modifiers*: Age	LM, VRT, TMT-B: 70 + year older adults performed best at high and low levels of TC (u-shape); < 70 yrs adults performed worse at high and low TC (inverted u-shape)
Zhang et al., 2016	*N* = 60 64 yrs 57% female *BABRI Study, China*	CS	Lipids: TC, LDL, HDL, TG (fasting and measurement not specified)	Global cognition (MMSE); Memory (AVLT, ROCF); EF (TMT-B, Stroop); Processing speed; (TMT-A, SDMT); Visuospatial (ROCF Copy, CDT); Language (VFT-Category, BNT)	Age; Sex; Education	ns
Chanti-Ketterl et al., 2015	*N* = 141 69 yrs 47% female *Czech Republic*	CS	Lipids: TC, LDL, HDL, TG (fasting serum, measurement not specified)	Memory (ROCF-R, AVLT, FCSRT); Visuospatial (ROCFT-C); EF (COWAT, DS); WM (BDS); Language (BNT); Composite (all measures combined)	Age; Sex; Education; Depression; APOE *Effect modifiers*: Sex, APOE	Higher TC associate with better composite; Higher HDL associated with better WM and composite; LDL: ns; *In females*: lower TG associated with better visuospatial skills; higher HDL associated with better composite and WM; *In males*: higher TC associated with better WM; *APOE status*: High TG associated with visuospatial skills in APOE(-) only; higher HDL associated with better cognitive composite in APOE(-) only
Liu et al., 2015	*N* = 2012 71 yrs 58% female *China*	CS	Lipids: HDL, TG (fasting plasma, measurement not specified)	Global cognition (MMSE)	Age; Sex; Education; Marital status, Smoking; Alcohol, PA, BMI, Family history of dementia; medication *Effect modifier*: Age	*Age:* Low HDL (vs high HDL) associated with lower MMSE in persons 80 + but not in persons < 80 yrs

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Table 1 (*continued*)

Study	Sample Size Mean Age Gender %female Cohort/ Location	Study design (CS/ L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect modifiers*	Adjusted Model Results
Takayanagi et al., 2015	*N* = 112 61 yrs 0% female *Baltimore ECA Follow-Up Study, U.S.A.*	CS	Lipids: TC, HDL (fasting serum, measurement not specified)	Verbal memory (RVLT immediate and delayed)	Age; Education; Psychiatric disorder	ns
Zamroziewicz et al., 2015	*N* = 40 69 yrs 73% female *U.S.A.*	CS	FA: PUFA (fasting plasma measured using gas chromatography)	EF (D-KEFS, TMT)	Age; Sex; Education; Income; BMI; Depression; PFC gray matter	Marginal association between high PUFA level and better EF
Cheng et al., 2014	*N* = 1889 73 yrs 46% female *China*	CS	Lipids: TC, LDL, HDL, TG (fasting serum measured using Roche Diagnostic kits and a Hitachi Automatic Biochemistry Analyzer 9700)	Composite (CSI-D, CERAD, Word List Recall, IU Story Recall, Animal Fluency test, BNT, Stick Design IU Token Test)	Age; Sex; Education; Smoking; BMI; CVD *Effect Modifier*: Hcy	Association between TC or LDL and cognitive composite is *dependent* on Hcy level: Inverted U at low Hcy level, linear association in mid-Hcy, no association at high Hcy; HDL, TG: ns
Crichton et al., 2014	*N* = 540 71 yrs 59% female *Maine-Syracuse Study, U.S.A.*	CS	Lipids: TC, LDL, HDL, TG (fasting blood measured using standard assay methods)	Global cognition (MMSE); Global Composite (Visual-Spatial Memory, Organization, Verbal and WM, Scanning and Tracking, Abstract Reasoning)	Age; Sex; Education; Race; BMI; Smoking; Alcohol; SBP; Diabetes	Higher HDL associated with better global composite, WM, and MMSE; TC, LDL, TG: ns
Levin et al., 2014	*N* = 1290 64 yrs 61% female *Northern Manhattan Study, U.S.A.*	CS	Lipids (part of MS analysis): HDL, TG (fasting blood, measurement not specified)	Memory (Immediate and Delayed Verbal Memory); EF (Color TMT-B, Animal Fluency, Digit Ordering, Odd Man Out, Fluency); Language (BNT, PPVT); Visual/Motor (Color TMT-A; GPT)	Age; Sex; Education; Race; Smoking; Alcohol; Risk factor treatment variables	High lipids combined (HDL and TG) associated with better Language composite only
Katsumata et al., 2013	*N* = 193 85 yrs 74% female *KOCOA Project, Japan*	CS	Lipids: TC, LDL, HDL, TC:HDL, LDL:HDL, TG:HDL (fasting blood measured using standard laboratory protocol)	Global cognition (Japanese MMSE); Memory (SPMT); Language (VFT)	Age; Sex; Education; Medication; CVD; HTN; Diabetes; Smoking; Alcohol	Higher LDL and lower TG:HDL ratio associated with better memory; Other lipid: ns
Luo et al., 2013	*N* = 767 94 yrs 67% female *PLAD, China*	CS	Lipids: HDL, LDL, TG (fasting plasma, measurement not specified)	Global cognition (MMSE)	Age; Sex; Education; Smoking; Alcohol; PA *Effect modifier*: Sex	MMSE < = 17 associated with higher TG in males only; HDL, LDL: ns
Chiu et al., 2012	*N* = 132 68 yrs 73% female *Taiwan*	CS	FA: ALA, EPA, DHA, and DPA (fasting plasma measured using gas chromatography of methyl esters)	Cognitive composite (WAIS-II Vocabulary, WMS-III Word List, WAIS-III BD, Attention, Psychomotor Speed, Sematic VF)	Age; Sex	ns
Formiga et al., 2012	*N* = 321 85 yrs 61% female *Octabaix Study, U.S.A.*	CS	Lipids: TC, HDL, LDL (fasting serum measuring using direct enzymatic colorimetric method)	Global cognition (MMSE)	Sex; Education	ns

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Table 1 (*continued*)

Study	Sample Size Mean Age Gender %female Cohort/ Location	Study design (CS/ L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect modifiers*	Adjusted Model Results
Miralbell et al., 2012	*N* = 86 60 yrs 59% female *Barcelona-AsIA Study, U.S.A.*	CS	Lipids: Lipoprotein(a) (fasting serum measured using nephelometry with a Delta Nephelometer Analyzer)	Global cognition (MMSE); Premorbid Intelligence (WAIS-III Vocabulary); EF (Stroop, DS); VF (COWAT); Attention (WAIS III Symbol Search, DSST, DS); Memory (WMS-III Word List and Visual Reproduction); Visual Reconstruction; (WMS-III Visual Reproduction Copy); Visuomotor Speed (GPT)	Age; Sex; Education	ns
Tan et al., 2012	*N* = 1575 67 yrs 54% female *Framingham Offspring Study, U.S.A.*	CS	FA: DHA, EPA (fasting plasma measured using gas chromatography)	Memory (LM); EF (TMT-B); Visuospatial (VRT Delayed); Abstract Reasoning (Similarities)	Age; Sex; Education; BMI; PA; Diabetes; SBP; Smoking; Strial fibrillation; CVD; APOE; Hcy; TC; Time	Higher DHA and DHA + EPA associated with better memory, EF, and abstract thinking
Yasuno et al., 2012	*N* = 1395 74 yrs 59% female *Tone Project, Japan*	CS	Lipids: TC, LDL, HDL, TG (fasting plasma measured using standard enzymatic methods on routine automated chemistry systems)	Attention (Japanese version of set dependent activity); Language (Category Cued Recall test); Language (Category Fluency Test); Reasoning (WAIS-R Similarities); Composite (all measures)	Age; Sex; Education; Depression; CVD; Diabetes; Hyperlipidemia; HTN *Effect modifier*: APOE	*APOE status:* Among APOE e4 (-) only, higher HDL associated with better performance on all tasks; higher LDL associated with higher composite cognition; TG, TC: ns
Yin et al., 2012	*N* = 836 95 yrs 72% female *CLHLS, China*	CS	Lipids: TC, HDL, LDL, TG (fasting plasma measured using commercially available diagnostic kits)	Global cognition (MMSE)	Age; Sex; Education; Race; Smoking; Alcohol; Leisure; SBP	Higher TG associated with better global cognition; TC, HDL, LDL: ns
Lai et al., 2011	*N* = 145 68 yrs 53% female *Taiwan*	CS	Lipids: TC, HDL, LDL (fasting blood, measurement not specified)	Global cognition (Screening Instrument)	Age; Sex; Smoking; Drinking; HTN; Diabetes	ns
Lee et al., 2010	*N* = 2944 72 yrs 70% female *GDMCI Study, Korea*	CS	Lipids: HDL, TG (fasting blood, measurement not specified)	Global cognition (MMSE)	Age; Sex; Education	Higher TG and lower HDL associated with cognitive impairment (MMSE < 18/30)
Huang et al., 2009	*N* = 709 94 yrs 68% female *PLAD, China*	CS	Lipids: TC, LDL, HDL, TG (fasting blood measured using standard laboratory techniques)	Global cognition (MMSE)	Age; BMI; Smoking; Alcohol; Tea intake; Exercise; FPG; BP; Sleep	ns
West et al., 2008	*N* = 185 88 yrs 45% female *U.S.A.*	CS	Lipids: TC, LDL, HDL (fasting and measurement not specified)	Memory composite (Word Recall, Savings); EF composite (TMT); Attention composite (Diamond and Letter Cancellation); Language composite (Animal Fluency, Shipley Vocabulary Test; BNT)	Age; Sex; Education; Medication; APOE *Effect modifiers*: APOE	Higher TC associated with better memory; *APOE status:* Among APOE e4(-) only, higher TC and LDL associated with better memory

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Table 1 (*continued*)

Study	Sample Size Mean Age Gender %female Cohort/ Location	Study design (CS/ L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect modifiers*	Adjusted Model Results
Fischer et al., 2006	*N* = 606 76 yrs 59% female *VITA Study, Austria*	CS	Lipids: TC, HDL, LDL, TG (fasting not specified, measured using Hitcachi 917 analyser) Lipoprotein(a) (measured using BN II Nephelometer)	Global cognition (MMSE)	None	ns
Aleman et al., 2005	*N* = 400 60 yrs 0% female *The Netherlands*	CS	Lipids: TC (fasting serum measured using automatic enzyme procedure)	Global cognition (MMSE); STM (DS); Psychomotor Speed (DSST); Verbal LTM (RAVLT); Visual Memory (Doors Test); EF (TMT); Verbal Intelligence (Dutch NART)	Age; Education	ns
Manzato et al., 2003	*N* = 191 77 yrs 57% female *ProVA Study, Italy*	CS	Lipids: TC, HDL, LDL, TG; FA: MUFA, PUFA, SFA (fasting not specified, measured using gas chromatography)	Global cognition (MMSE)	Age; Education; DBP	Higher LDL and PUFA, and lower MUFA associated with better global cognition (MMSE= > 28); TC, HDL, TG, SFA: ns
Atzmon et al., 2002	*N* = 139 98 yrs 74% female *Ashkenazi Jews in U.S.A.*	CS	Lipids: LDL, HDL, TG, Apo A-I (fasting and measurement not specified)	Global cognition (MMSE)	Sex; LDL; HDL; TG	Higher HDL associated with better global cognition; LDL, TG, APOA-I: ns
Ortega et al., 2002	*N* = 120 71 yrs. 72% female *Spain*	CS	Lipids: Cholesterol; FA: PUFA; (fasting serum, measurement not specified)	Global cognition (SPMSQ)	None	ns
Van Exel et al., 2002	*N* =561 85 yrs 67% female *Leiden 85+ Study*	CS	Lipids: TC, LDL, HDL, TG (fasting serum lipids measured using Hitachi 747 and 911)	Global cognition (MMSE)	Sex; Education; CVD	Low HDL strata associated with poorer global cognition; Low HDL increased odds of cognitive impairment (MMSE < = 18); TG, LDL, TC: ns
Yaffe et al., 2002	*N* = 1037 71 yrs 100% female *Heart Estrogen /Progestin Replacement Study, U.S.A.*	CS	Lipids: LDL, HDL, TG, lipoprotein(a) (fasting serum measured using immunochemically with a sandwich ELISA)	Global cognition (3MS)	Age; Education; Diabetes; Health status; CABG; HRT; Aspirin use	Highest quartiles of LDL, TC and lipoprotein (a) independently associated with poorer 3MS; TG, HDL: ns
Longitudinal Studies						
Viscogliosi et al., 2016	*N* = 104 80 yrs 44% female *Italy*	L, 11.2 months	Lipids: HDL, TG (fasting plasma, measurement not specified)	Global cognition (CDT)	None	ns

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Table 1 (*continued*)

Study	Sample Size Mean Age Gender %female Cohort/ Location	Study design (CS/ L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect modifiers*	Adjusted Model Results
Ancelin et al., 2014	*N* = 6855 74 yrs 60% female *Three-City Study, France*	L, 7 yrs	Lipids: TC, LDL, HDL, TG (fasting serum measured using routine enzymatic methods)	Memory (BVRT); VF (Isaacs Set Test); Psychomotor Speed, Task Switching (TMT-A&B)	Age; Education; Study Center; Baseline cognition; Marital status; BMI; Medication; Mobility; HTN; Diabetes; Depression; APOE4, APOA5, CETP; *Effect modifier*: Sex	*In females:* High LDL and HDL associated with greater decline in psychomotor speed; Low LDL and TG associated with greater decline in task switching; *In males*: upper quartile TC associated with greater decline in VF; Upper and lowest TC and LDL quartile associated with greater decline in psychomotor speed; Lowest HDL associated with increased decline in psychomotor speed; high TC and low HDL associated with greater decline in task switching
Otsuka et al., 2014	*N* = 430 67 yrs 46% female *NILS-LSA, Japan*	L, 10 yrs	Lipids: TC, HDL, TG; FA: EPA, DHA (fasting serum measured using gas-liquid chromatography)	Global cognition (MMSE)	Age; Sex; Education; Baseline MMSE; Alcohol; Smoking, CVD; Diabetes	Higher TG and DHA associated with better global cognition
Taniguchi et al., 2014	*N* = 682 75 yrs 60% female *Japan*	L, 2.7 yrs	Lipids: TC, HDL, TG (non-fasting blood measured using standard procedures)	Global cognition (MMSE)	Age; Sex; Education; Living arrangement; Outings; Alcohol; Smoking; Medical history; Height; Weight; Gait speed; Self-rated health; Functional capacity; Depression	Low TC and HDL tertile associated with greater cognitive decline
Wendell et al., 2014	*N* = 1601 54 yrs 49% female *Baltimore Longitudinal Study of Aging, U.S.A.*	L, 6.4 yrs	Lipids: TC (fasting blood measured enzymatically)	Global cognition (MMSE, BIMCT); Verbal Memory (CVLT); Visual Memory (BVRT); Attention (DS); EF (TMT-A&B); VF (Letter and Semantic Fluency); Language (BNT); Visuospatial (CRT)	Age; Sex; Race; Education; SBP; BMI; CVD; Lipid-lowering medication; Smoking; Alcohol; Depression	Higher TC association with poorer global cognition in middle and old age, but better cognitive performance in the oldest old; Lower TC associated with accelerated decline in visual memory
Ammann et al., 2013	*N* = 2157 Age range 65-84 yrs 100% female *WHISCA, U.S.A.*	L, 5.9 yrs	FA: DHA, EPA (fasting not specified, RBCs analyzed using gas chromatography)	Memory (BVRT, CVLT); Motor Speed (FTT); Spatial Ability (CRT); WM (Primary Mental Abilities Vocabulary Test); VF (COWAT); WM (DS)	Age	ns
Bowman et al., 2013	*N* = 86 86 yrs 53% female *OBAS, U.S.A.*	L, 4 yrs	FA: PUFA (fasting plasma measured using gas chromatography)	Global cognition (MMSE); Memory (WMS-R LM delayed); EF (TMT-B)	Age; Sex; Education; APOE; HTN; Depression	Higher PUFA associated with less EF decline only
Yasuno et al., 2012	*N* = 622 73 yrs 57% female *Tone Project, Japan*	L, 3 yrs	Lipids: TC, HDL, LDL, TG (fasting plasma measured using standard enzymatic methods)	Memory (Category Cued Recall Test); Language (Category Fluency Test); Attention (set-dependent activity); Reasoning (WAIS-R-Similarities)	Age; Sex; Education; Depression; Smoking; CVD; Diabetes; Hyperlipidemia; HTN *Effect modifier*: APOE	*APOE status:* Among APOE e4(-) only, higher HDL associated with better composite cognition at baseline and follow-up

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Table 1 (*continued*)

Study	Sample Size Mean Age Gender %female Cohort/ Location	Study design (CS/ L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect modifiers*	Adjusted Model Results
Katsumata et al., 2012	*N* = 148 85 yrs 74% female *KOCOA Project, Japan*	L, 2 yrs	Lipids: TG, HDL (fasting blood, measurement not specified)	Global cognition (MMSE); Memory (SPMT); EF (Verbal Fluency Initial Letter)	Age; Sex; Education	ns
Van den Kommer et al., 2012	*N* = 1030 75 yrs 53% female *LASA, The Netherlands*	L, 6 yrs	Lipids: HDL, LDL, TG Inflammation: CRP, ACT, IL-6 (non-fasting serum, lipids measured using enzymatic colorimetric tests; serum, inflammatory markers measured using ELISA)	Global cognition (MMSE); Memory (AVLT); Information Processing (ACT-15)	Age; Sex; Education; BMI; *Effect modifier*: lipid-by-inflammation interaction	High HDL associated with better immediate recall at baseline but not over time; High LDL associated with poorer MMSE and information processing at baseline and associated with greater decline in information processing over time; LDL and TG effects amplified by high ACT and CRP
Formiga et al., 2011	*N* = 62 94 yrs 79% female *NonaSantfeliu Study, Spain*	L, 3 yrs	Lipids: HDL (fasting serum measured using direct enzymatic colorimetric method)	Global cognition (MMSE)	None	Higher (versus lower) HDL associated with better global cognition
Reynolds et al., 2010	*N* = 819 64 yrs 60% female *SASTA, Sweden*	L, 10 yrs	Lipids: TC, HDL, TG; ApoA1, ApoB, ApoB:ApoA1 ratio (fasting not specified, serum cholesterol and TG measured using calorimetric enzymatic assay; apoA1 and apoB measured using radioimmunoassay and immune-turbidimetric tests)	Memory composite (DS, TPM, Names and Faces Task); Verbal composite (Information Subtest, Analogies, Synonyms); Spatial composite (BD, Figure Logic, CRT); Perceptual Speed composite (SDMT, Figure Identification)	Fasting status; Smoking; Alcohol; Medication; BMI; MAP; *Effect modifier*: Sex	*In females:* High HDL associated with maintenance of verbal composite and faster decline in perceptual speed after age 65; Higher apoB and ApoB:ApoA1 ratio predicted faster rates of verbal decline; Lower TG associated with better verbal ability, spatial ability, perceptual speed, memory, and general cognition; *In males*: Higher apoB associated with better perceptual speed and general cognition but steeper rates of decline before age 65; Higher TC associated with better perceptual speed but faster decline before 65 yrs
Van Vliet et al., 2010	*N* = 599 85 yrs 66% female *Leiden 85+ Study, The Netherlands*	L, 5 yrs	Lipids: TC, HDL (non-fasting serum measured using fulyl automated Hitachi 747 and Hitachi 911 system)	Global cognition (MMSE)	Sex; MMSE at 87 yrs	Decline in MMSE from age 85 to 87 associated with decline in TC and HDL from age 87 to 90; Changes in TC and HDL from age 85 to 87 did not associate with MMSE decline from age 87 to 90
Solomon et al., 2009	*N* = 1382 Age range 47-51 yrs 63% female *CAIDE Study, Finland*	L, 21 yrs	Lipids: TC (fasting and measurement not specified)	Global cognition (MMSE); Memory (Word Recall); VF (Category and Letter Fluency); EF (DSST, PPB, Stroop)	Age; Sex; Education; Medication; APOE; MI; Stroke; Diabetes; BMI; SBP	High TC in midlife associated with poorer memory and VF in late-life; No significant relationship between late-life TC and cognition; Decrease in TC from midlife to late-life associated with poorer memory and psychomotor speed in late-life
Van den Kommer et al., 2009	*N* = 3107 76 yrs 51% female *LASA, The Netherlands*	L, 6 yrs	Lipids: TC (non-fasting blood measured using gas chromatography-flame ionization detection)	Global cognition (MMSE); Memory (AVLT); Processing Speed (ACT-15)	Age; Sex Education; ApoE; CVD; Diabetes; Medication; Depression; Alcohol; Smoking	High baseline TC associated less decline in global cognition and processing speed

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Table 1 (*continued*)

Study	Sample Size Mean Age Gender %female Cohort/ Location	Study design (CS/ L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect modifiers*	Adjusted Model Results
Mielke et al., 2008	*N* = 436 74 yrs 100% female *WHAS-II, U.S.A.*	L, 9 yrs	Lipids: TC, HDL, LDL (non-fasting plasma measured using standard enzymatic techniques)	Global cognition (MMSE); Memory (HVLT-R); EF (TMT, PPB)	Age; Education; Race; Medication; CVD; Creatinine; Depression;	Higher HDL associated with better EF (PPB only) at baseline but not over time
De Frias et al., 2007	*N*=524 67 yrs 51% female *Betula Study, Sweden*	L, 10 yrs	Lipids: TC, TG (fasting and measurement not specified)	Episodic Memory (Word list, Face Recognition, Noun-verb Recognition Task); Semantic Memory (Choice Synonym Test; VF (VFT); Visuospatial (BD)	Age; Sex; CVD *Effect modifiers*: APOE	Overall: Higher TG predicted greater decline in vocabulary only; *APOE status:* Among APOE e4(+) only, higher TC predicted greater decline in recognition
Mooijaart et al., 2007	*N*=546 85 yrs 67% female *Leiden 85+ Study, The Netherlands*	L, 5 yrs	Lipids: apoE (non-fasting blood measured using ELISA)	Global cognition (MMSE); Episodic Memory (12 Picture Learning Test); Attention (Stroop); Processing Speed (LDCT)	Sex; Education; HTN; Diabetes; BMI; TG, HDL, LDL; APOE *Effect modifiers*: APOE	Higher baseline apoE associated poorer global cognition at baseline and follow up; *APOE status*: Among e3/e3 carriers only, higher apoE associated with worse performance of memory, attention, and processing speed (n = 436)
Karlamangla et al., 2004	*N* = 267 74 yrs 58% female *MacArthur Study of Successful Aging, U.S.A.*	L, 2.3 yrs	Lipids: non-HDL (non-fasting serum measured using the direct homogenous method)	Global cognition (SPMSQ)	Sex; Race; Baseline cholesterol; CVD; Weight	Higher non-HDL associated with better global cognition
Perrig et al., 1997	*N*= 442 75 yrs. 71% female *Basle Interdisciplinary Study on Aging, Switzerland*	L, 22 yrs	Lipids: TC (fasting plasma, measurement not specified)	Memory (C-GFT, WAIS-R Vocabulary)	Age; Sex; Education; Ferritin; SBP	Higher TC associated with better recognition performance only

Note: Studies are listed according to design (cross-sectional, longitudinal), followed by publication years, followed by alphabetical order; 3MS = Modified Mini Mental State Exam; ACT-15 = Alphabet Coding Task-15; ALA = Alpha Linolenic Acid; APOE = Apolipoprotein E gene; ApoE = apolipoprotein; AsIA = Asymptomatic Intracranial Atherosclerosis; AVLT = Auditory Verbal Learning Test; BABRI = Beijing; Aging Brain Rejuvenation Initiative; BD = Block Design; BDS = Blessed Dementia Scale; BIMCT = Blessed Information-Memory; Concentration Test; BMI = Body Mass Index; BNT = Boston Naming Test; BP = Blood Pressure; BVRT = Benton Visual Retention Test; CABG = Coronary Artery Bypass Grafting; CAIDE = Cardiovascular Risk Factors, Aging, and Dementia; CDT = Clock Drawing Test; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; C-GFT = Computerunterstutzer Gedachtnis; Funktions-Test; CKD = Chronic Kidney Disease; CLHLS = Chinese Longitudinal Healthy Longevity Survey; COWAT = Controlled; Oral Word Association Task; CRT = Card Rotations Test; CS = Cross-sectional; CSI-D = Community Screening Instrument for Dementia; CVD = Cardiovascular Disease; CVLT = California Verbal Learning Test; DBP = Diastolic Blood Pressure; DHA = Docosahexaenoic Acid; D-KEFS = Delis-Kaplan Executive Function System; DPA = Docosapentaenoic Acid; DRS = Dementia Rating Scale; DS = Digit Span; DSST = Digit Symbol Substitution Test; DTI = Diffusion Tensor Imaging; ECA = Epidemiologic Catchment Area; EF = Executive Function; EFA = Eicosapentaenoic Acid; ELISA = Enzyme-linked Immunosorbent Assay; FA = Fatty Acids; FCSRT = Free and Cued Selective Reminding Test; FPG = Fasting Plasma Glucose; FTT = Finger Tapping Test; GDMCI = Gwangju Dementia and Mild Cognitive Impairment; GPT = Grooved Pegboard Test; Hcy = Homocysteine; HDL = High-density Lipoprotein; HRT = Hormone Replacement Therapy; HTN = Hypertension; HVLT-R = Hopkin's Verbal Learning Test-Revised; KIHD = Kuopio Ischaemic Heart Disease; KOCOA = Keys to Optimal Cognitive Aging; L = Longitudinal; LASA = Longitudinal Aging Study Amsterdam; LDCT = Letter-digit Coding Test; LDL = Low-density Lipoprotein; LM = Logical Memory; LTM = Long-term Memory; MAP = Mean Arterial Pressure; MI = Myocardial Infarction; MMSE = Mini-mental State Examination; MS = Metabolic Syndrome; MUFA = Monounsaturated Fatty Acids; NART = National Adult Reading Test; NILS-LSA = National Institute for Longevity Sciences – Longitudinal Study of Aging; OBAS = Oregon Brain Aging Study; PA = Physical Activity; PFC = Prefrontal Cortex; PLAD = Project of Longevity and Aging in Dujiangyan; PPB = Purdue Pegboard Test; PPVT = Peabody Picture Vocabulary Test; ProVA = Progetto Veneto Anziani; PUFA = Polyunsaturated Fatty Acids; RBC = Red Blood Cell; ROCF = Rey-Osterrieth Complex Figure; RVLT = Rey Verbal Learning Test; SASTA = Swedish Adoption/Twin Study of Aging; SBP = Systolic Blood Pressure; SDMT = Symbol Digit Modalities Test; SFA = Saturated Fatty Acids; SPMSQ = Short Portable Mental Status Questionnaire; SPMT = Scenery Picture Memory Test; STM = Short-term Memory; TC = Total Cholesterol; TG = Triglycerides; TMT-A = Trail Making Test-Part A; TMT-B = Trail Making Test-Part B; TPM = Thurstone's Picture Memory; VF = Verbal fluency; VFT = Verbal Fluency Test; VIB = Vasculature, Ischemia, and Behaviour; VITA = Vienna Transdanube Aging; VRT = Visual Reproduction Test; WAIS-III = Wechsler Adult Intelligence Scale-Third Edition; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WHAS-II = Women's Health and Aging Study-II; WHISCA = Women's Health Initiative Study of Cognitive Aging; WM = Working Memory; WMS-III = Wechler Memory Scale-Third Edition; WMS-R = Wechsler Memory Scale-Revised.

Table 2
Systematic Review Results for Inflammatory and Immune markers.

Study	Sample Size Mean Age Gender %female Cohort/ Location	Study design (CS/ L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect modifiers*	Adjusted Model Results
Cross-Sectional Studies						
Gao et al., 2016	*N* = 139 66 yrs 86% female *SLSA, Singapore*	CS	sIL-2Ra, BCA-1, IP-10, sgp130, CTACK, 6CKine, sTNFR1, sTNFR2, TNF-a, IL-6 (fasting not specified, blood measured using ELISA)	Global cognition (MMSE, MoCA)	Age; Sex; Education; CVD; Leisure-time activities	Higher sIL-2Ra and sgp130 associated with lower MoCA score; higher sgp130 and sTNFR2 associated with lower MMSE score; High tertile sTNFR2 increase odds of impairment (MMSE ≤ 23)
Watanabe et al., 2016	*N* = 454 70 yrs 53% female *PROST, Japan*	CS	hsCRP (non-fasting serum measured using latex nephelometry assay with an automatic analyzer)	Global cognition (MMSE)	Age; Sex; BMI; Stroke; CVD; HTN; Diabetes; APOE	Higher hsCRP quartile associated with greater risk of MMSE score below 23
Tegeler et al., 2016	*N* = 1312 68 yrs 50% female *Berlin Aging Study II, Germany*	CS	CRP, IL-6, IL-10 (fasting blood, CRP measured using turbidimetric assay; serum ILs measured using highly sensitive Cytometric Bead Array flex kit)	Verbal Memory (Word List Learning); EF, Processing Speed (Phonetic and Category Fluency, DSST)	Age; Sex; Education; Depression; Cholesterol; Insulin resistance; Fat mass intake; Smoking; SBP; Medication; CVD	Higher IL-6, IL-10 and CRP each associated with poorer EF and processing speed only
Dzierzewski et al., 2015	*N* = 135 73 yrs 0% female *U.S.A.*	CS	CRP, TNFα, IL-6, and sICAM-1 (fasting plasma, CRP levels measured using high sensitivity ELISA; TNFα and IL-6 measured using Quantikine High Sensitivity ELISAs; sICAM-1 measured using regular sensitivity sICAM-1 ELISA)	Global cognition (MMSE)	Age; Education; Race; Depression; Pain; Comorbidity; BMI; Sleep; *Effect Modifier*: Sleep	Higher sICAM-1 associated with higher scores on MMSE; Both CRP and sICAM-1 interacted with sleep duration. *Sleep:* Inflammatory markers associated with global cognition in "normal" sleepers, but not "short" sleepers
Bettcher et al., 2014	*N* = 151 72 yrs 57% female *U.S.A.*	CS	IL-6 (fasting plasma measured using Quantikine ELISA kit from R&D systems)	Processing Speed (Animal Matching, Word Rhyming, Word Judgment, Word Pronunciation)	Age; Sex; HTN; Smoking; BMI; Hcy	Higher IL-6 associated with poorer information processing speed; the association is no longer significant when model is adjusted for Hcy
Windham et al., 2014	*N* = 3437 61 yrs 66% female *GENOA Study, U.S.A.*	CS	hsCRP, IL-6, sTNFR1, sTNFR2 (fasting, serum CRP measured using immunoturbidometric assay; plasma IL-6, sTNFR1, and sTNFR2 measured using multiplex assay)	Global cognition (MMSE); Memory (RAVLT, WAIS-III Incidental Learning Task); EF (TMT-B); Processing speed (WAIS-R DSST, TMT-A); Language (FAS & Animal Naming Task)	Age; Sex; Education	Higher sTNFR2 associated with poorer cognition across all domains; Higher sTNFR1 associated with poorer processing speed, EF; Higher hsCRP associated with lower processing speed; Higher IL-6 associated with poorer EF
Arfanakis et al., 2013	*N* = 95 85 yrs 73% female *Rush Memory and Aging Project, U.S.A.*	CS	CRP, TNFα (fasting not specified, plasma CRP and TNFα measured using highly sensitive multiplexed sandwich ELISA arrays)	Memory (CERAD Word List, LM); VF (BNT, Extended Range Vocabulary, NART, VFT); Working Memory (DS, Digit Ordering); Perceptual Speed (SDMT, Stroop, Number Comparison); Visuospatial (Judgment of Line Orientation, RSPM)	Age; Sex; Education; Clinical variables with significant associations with inflammation (detailed variables not provided)	Combined inflammatory biomarkers negatively associated with visuospatial performance only
Hildreth et al., 2013	*N* = 103 69 yrs 52% female *U.S.A.*	CS	IL-6, TNF-a (fasting serum measuring using ELISA)	EF (Stroop); Working Memory (LNS, Grammatical Reasoning Test, Luria Word Learning test); Processing Speed (SDMT, TMT-A&B)	Age; Education; WAIS-II Similarities, Short-Form 36-General Health; Test administrator	Increase in TNF-a associated with poorer performance on LNS only

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Table 2 (*continued*)

Study	Sample Size Mean Age Gender %female Cohort/ Location	Study design (CS/ L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect modifiers*	Adjusted Model Results
Miralbell et al. (2013)	*N* = 747 66 yrs 34% female *Barcelona-AsIA Study, Spain*	CS	CRP, Resistin, PAI-I (fasting, plasma CRP measured using nephelometric method; serum resistin measured using ELISA method; fasting plasma PAI-I measured using sensitivity ELISA method)	Memory (Word List Test WMS-III); Visuospatial Skills (Visual Reproduction Test WMS-III; DSST; GPT; TMT-A); VF (Letter fluency, Semantic fluency)	Age; Sex; Education; Depression; HTN; Diabetes; Smoking; CVD risk factors	ns
Srikanth et al., 2013	*N* = 378 72 yrs 45% female *TASCOG, Tasmania*	CS	MGO (fasting serum measured using HPLC)	Verbal Memory (HVLT-R); Visual Memory (RCFT – recall); Working Memory, EF (WAIS-III DS, FAS, COWAT, Animal Category Fluency, Stroop); Processing Speed (Symbol Search, WAIS-III DSST); Attention (DS forward); Spatial Ability (RCFT –copy)	Age; Sex; Education; Mood; HTN; Diabetes; CVD; Smoking; Hypercholesterolemia; Alcohol; Stroke; Head injury; Dementia; Epilepsy; Serum creatinine, HOMA-IR; Medication	Greater MGO associated with poorer memory and EF; Association enhanced amongst stroke for EF
Bettcher et al., 2012	*N* = 141 71 yrs 57% female *U.S.A.*	CS	CRP (non-fasting serum measured using immunoturbidimetric assay)	Memory (CVLT-II)	Age; Sex; MMSE; BMI; Smoking; HTN	Detectable CRP (= > 0.1 mg/dL) performed better on delayed recall than those with non-detectable (< 0.1 mg/dL) CRP levels
Elderkin-Thompson et al., 2012	*N* = 45 69 yrs 42% female *U.S.A.*	CS	IL-6, hsCRP (fasting plasma, CRP measured using BN-II System high-sensitivity immunoassay; IL-6 measured using high sensitivity ELISA methods)	Learning and Memory (CVLT, RCFT); EF (MR, Stroop, WCST, LNS, TMT, DSST)	Age; Sex; Literacy; Global cognition; BMI; Depression	Higher levels of IL-6 associated with poorer learning and memory only; hsCRP:ns
Miralbell et al., 2012	*N* = 86 60 yrs 59% female *Barcelona-AsIA Study, Spain*	CS	CRP (fasting not specified, measured using a particle-enhanced turbidimetric immunoassay technique)	Global cognition (MMSE); Premorbid IQ (WAIS-III Vocabulary); Memory (Word List, Visual Reproduction); EF (Stroop, DS); VF (Letter and Category Fluency); Attention (WAIS III Symbol Search, Symbol Coding, DS Subtest); Visuoconstruction (WMS-III Visual Reproduction – copy); Motor Speed (GPT)	Age; Sex; Education	ns
Troller et al., 2012	*N* = 873 78 yrs 52% female *MAS, Australia*	CS	ILs:1β, -6, - 8, -10, -12p70; sVCAM-1, PAI-1, SAA, TNF-α, CRP (fasting blood, sVCAM-1, PAI-1, and SAA measured using ELISA; CRP measured using Near Infrared Particle Immunoassay rate methodology; cytokines measured using cytometric bead array)	Memory (LM Immediate and Delayed Recall); Learning (RAVLT Learning Trials and Delay Recall); Language (Animal Naming, BNT, F-A-S Test); EF, Processing Speed (DSST, TMT-A&B, GPT, BD, Stroop Interference)	Age; Sex; Education; Depression; CVD; Metabolic factors; APOE	Higher IL-6 and IL-12 associated with poorer EF/processing speed composite
Canon & Crimmins, 2011	*N* = 867 Age range 60-85 yrs 55% female *NHANES-III, U.S.A.*	CS	hsCRP (fasting not specified, measured using Behring nephelometer)	EF (WAIS-III DSST)	Age; Education; Race *Effect modifiers*: Sex	*Sex:* Higher hsCRP associated with lower EF in females but not males

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Table 2 (*continued*)

Study	Sample Size Mean Age Gender %female Cohort/ Location	Study design (CS/ L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect modifiers*	Adjusted Model Results
Lekander et al., 2011	*N* = 298 Age range 45-90 yrs 100% female *Betula Prospective Cohort Study, Sweden*	CS	IL-1β, IL-1ra, sIL-1RII, sIL-2ra, and IL-6 (fasting not specified, plasma IL-1β and sIL-1RII levels measured using Quantikine ELISA; IL-1ra, sIL-2ra, and IL-6 measured using Biosource ELISA)	Memory: Episodic, Semantic, Prospective (measures not specified)	Age; Education; BMI; Depression; Self-reported health care	Higher IL-1β associated with better semantic fluency only; Association between higher levels of IL-6 and better semantic fluency and prospective memory in persons 60 +
Wada et al., 2011	*N* = 849 68 yrs 55% female *Japan*	CS	Fibrinogen (fasting plasma measured using clotting rate assay agent)	Global cognition (MMSE)	Age; Sex; Smoking; SBP; Antihypertensive therapy; Diabetes; HDL; CRP; Maximal IMT	Increased fibrinogen associated with lower MMSE scores
Coppola et al., 2010	*N* = 112 67 yrs 61% female *Italy*	CS	Nitrotyrosine, fibrinogen (fasting plasma, nitrotyrosine measured using ELISA, fibrinogen measured using functional coagulative assay)	Global cognition (MMSE)	Age; Education; BMI; HR; SBP; DBP; RBC; WBC; TC; TG; Fibrinogen; Uric acid plasma level; ESR	Higher fibrinogen in cognitively impaired (MMSE < = 23.9) than normal (MMSE > = 24); Among cognitively impaired, higher nitrotyrosine associated with lower MMSE; association not found in cognitively normal
Marioni et al., 2010	*AAA Cohort* *N* = 2091 67 yrs 73% female *ET2DS Cohort* *N* = 1066 68 yrs 48% female *EAS Cohort* *N* = 534 74 yrs 50% female *LBC1936* *N* = 1091 70 yrs 50% female *Scotland* *Merged Sample:* *N* = 4782	CS	CRP (fasting and measurement not specified)	*AAA:* Memory (Auditory Verbal Learning Task); EF (TMT-B; DSST); Abstract Reasoning (RSPM); VF (VFT, Mill Hill Vocabulary Scale); General summary score (combined tests); *ET2DS:* Memory (Faces and Family Pictures Subtest, LM); EF (TMT, LNS, MR, DSST); VF (VFT, Crystallized measure of vocabulary); General summary score (combined tests); *EAS:* Memory (LM); EF (DSST); Abstract Reasoning (RSPM); VF (VFT, NART); General summary score (combined tests); *LBC1936:* Memory (LM); EF (DSST, LNS, MR); VF (VFT); IQ (Moray House Test No. 12); General summary score (combined tests)	Age; Sex; Vocabulary; Premorbid ability	*AAA:* Higher CRP associated with poorer general cognitive summary score and performance on DSST, abstract reasoning and VF, but not memory or TMT; *ET2DS*: Trending negative association between CRP and memory only; *EAS Cohort:* CRP negatively associated with memory only; *LBC1936:* No significant associations in fully adjusted model
Wersching et al., 2010	*N* = 447 63 years 56% female *SEARCH Study, Germany*	CS	hsCRP (non-fasting measured using highly sensitive immunonephelometric method on BNII Nephelometer)	Verbal Memory, VF, EF (composite scores, tests not specified)	Age; Sex; Education; SBP; LDL; HDL	Higher hsCRP associated with poorer EF
Luciano et al., 2009	*N* = 1053 70 yrs 50% female *LBC1936, Scotland*	CS	CRP, fibrinogen (fasting not specified, CRP measured using dry slide immuno-rate method; fibrinogen measured using automated Clauss assay)	Global cognition (Moray House Test); Memory (LM, Verbal Paired Associates, Spatial Span from WMS-III);Information Processing Speed (DSST, Symbol Search, RT, WAIS-III Inspection Time); Working Memory (DS backward, LNS); Nonverbal Reasoning (MR); EF (VFT)	Age; Sex; Global cognition; BMI; DBP; Cholesterol; Diabetes; HbA1C; Smoking	Higher levels of CRP and fibrinogen associated with slower reaction time only

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Table 2 (*continued*)

Study	Sample Size Mean Age Gender %female Cohort/ Location	Study design (CS/ L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect modifiers*	Adjusted Model Results
Baune et al., 2008	*N* = 369 72.6 years 47% female *MEMO Study, Germany*	CS	IL-1β, IL-6, IL-8, IL-10, IL-12p70, TNF-α, sIL-4R (non-fasting serum measured using cytometric bead array, with the exception of an ELISA for sIL-4R)	Global cognition (MMSE); Memory (Three Word Recall Test & Animal Word Fluency); Perceptual Speed (Stroop, LDST); Motor Function (Purdue Pegboard Test)	Age; Education; BMI; Smoking; Depression; TIA/Stroke; Diabetes; MMSE	Increased IL-8 associated with poorer memory, processing speed, and motor function; no relationship between cytokines and MMSE score; no other significant associations between cytokines and cognitive function after Bonferroni correction for multiple comparisons
Kostka et al., 2008	*N* = 270 70 yrs 60% female *Poland*	CS	Fibrinogen (fasting plasma measured using rate of clot formation by semiautomated modification of the Clauss method)	Global cognition (MMSE)	None	ns
Sweat et al., 2008	*N* = 125 62 yrs 50% female *U.S.A.*	CS	CRP (fasting plasma, measured using enzymatic immunoassay)	Memory (CVLT); Working Memory (DS backward, Visual Memory Span backward); EF (Tower of London); Attention (Attention subset of WMS-R); IQ (Shipley Vocabulary Test)	Age; Education; Medication; Diabetes *Effect modifier:* Obesity	Higher CRP associated with poorer EF; Association is strongest in obese females
Fischer et al., 2006	*N* = 606 76 yrs 59% female *VITA Study, Austria*	CS	CRP (fasting not specified, plasma, measured using Hitachi 917 analyser)	Global cognition (MMSE)	None	ns
Weuve et al., 2006	*N* = 4231 72 yrs 100% female *WHS, U.S.A.*	CS	hsCRP (fasting not specified, plasma measured using validated, high-sensitivity assay) *Note*: CRP measured 4.4-7.8 years before cognitive testing	Global cognition (TICS); Memory (EBMT); VF (Category Fluency)	Age; Education; Income; Time between blood draw and cognitive assessment; Alcohol; HTN; BMI; PA; Smoking; HRT; Lipids; Diabetes; MI	ns
Ravaglia et al., 2005	*N* = 540 73 yrs 49% female *Conselice Study, Italy*	CS	hsCRP (fasting serum measured using N-high sensitivity CRP assay with latex-enhanced immunonephelometric assay on a BN II analyzer)	Global cognition (MMSE)	Age; Sex; Education; Plasma fibrinogen; Leukocyte count; Serum ALB; BMI; Comorbid diseases; Edentulism	Higher hsCRP associated with poorer cognition
Boule et al., 2001	*N* = 2154 Age range 55-69 yrs 0% female *Caerphilly Study, Wales*	CS	Fibrinogen (fasting plasma measured using modified nephelometric method)	Global cognition (AH4); Decision Speed (CRT)	Age; Social class	ns
Longitudinal Studies						
Weinstein et al., 2017	*N* = 536 73 yrs 5% female *BIP Study, Israel*	L, 19.9 yrs	hsCRP (fasting plasma measured using chemiluminescent immunometric assay)	Memory, EF, Visuospatial Skills, Attention (NeuroTrax Mindstreams Computerized Cognitive Assessment)	Age; Sex; Education; Smoking; BMI; Diabetes; HTM; MI; Study arm; Carotid plaques	Higher baseline hsCRP associated with poor overall cognitive performance, EF, and attention, and associated with greater decline in overall cognitive performance and EF over time

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Table 2 (*continued*)

Study	Sample Size Mean Age Gender %female Cohort/ Location	Study design (CS/ L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect modifiers*	Adjusted Model Results
Bourassa & Sbarra, 2017	Subsample 1: *N* = 9066 Subsample 2: *N* = 12561 Mean age and sex not reported *ELSA, England*	L, 8 yrs	CRP (fasting not specified, plasma measured using N Latex CRP mono Immunoassay on a Behring Nephelometer II Analyzer)	Memory (Immediate and Delayed Word Recall of Ten-Word Delayed Recall Test); EF (Category Fluency Task)	Age; Sex	Higher baseline CRP associated with worse memory and EF at follow up
Matsushima et al., 2015	*N* = 64 75 yrs 73% female *Kurogawa Study, Japan*	L, 3 yrs	IL-1 β, IL-2, IL-6, sIL-2R, sIL-6R, TNF-α, hsCRP (fasting not specified, plasma measured using ELISA)	Global cognition (MMSE, FAB, CDT)	Age; Sex; Education *Effect modifiers*: Sex	*Sex*: Higher sIL-2R associated with lower MMSE at baseline in males only; no association with cognition over time
Palta et al., 2015	*N* = 336 74 yrs 100% female *WHAS-II, U.S.A.*	L, 9 yrs	IL-6, CRP (non-fasting serum measured using commercial immunosorbent assay)	Memory (HVLT-R); EF (TMT-B); Psychomotor Speed (TMT-A)	Age; Education; Race; Smoking; Alcohol; Diabetes; CVD; HTN; BMI; Depression; TMT-A in EF model only	Baseline cognitive performance did not differ across tertile of IL-6 or CRP for any cognitive domain; Individuals with higher baseline IL-6 had greater decline on psychomotor speed only during years 1 to 3; CRP: ns
Heringa et al., 2014	*N* = 363 68 yrs 48% femal *Hoorn Study, The Netherlands*	L, 4-8 yrs	Low grade inflammation (composite of hsCRP, TNF-a, IL-6, IL-8, SAA, MPO, sICAM-1) (fasting not specified, plasma measured using electrogenerated chemiluminescence technology)	Memory (DS, Corsi Block, RAVLT, RCFT, Location Learning Test); Attention/EF (TMT-B, Stroop, Briston Spatial Anticipation Test, Category and VFT); Abstract Reasoning (Advanced Progressive Matrix); Information Processing (TMT-A, Stroop); Visuoconstruction (RCFT-copy); Language (Token Test); Composite score (all tests combined)	Age; Sex; Premorbid IQ; CVD; Depression	Low-grade inflammation associated with poorer information processing and attention/EF; increase in low-grade inflammation from baseline to follow-up associated with worse attention/EF at follow-up; Individual biomarkers were not associated with cognition
Metti et al., 2014	*N* = 1323 73 yrs 53% female *Health ABC Study, U.S.A.*	L, 10 yrs	hsCRP, IL-6 (fasting serum measured using varying techniques over 10-year period)	Global cognition (3MS)	Age; Sex; Race; Education; BMI; Diabetes; APOE; Cystatin C; Medication	Baseline hsCRP or IL-6 did not associated with cognitive decline (5 points or greater decline form baseline global cognitive score); Greater variability in hsCRP levels over time associated with cognitive decline
Sanders et al., 2014	*N* = 901 76 yrs 65% female *CHS All Stars U.S.A*	L, 9 yrs	IL-6 (fasting blood, measured using ultrasensitive ELISA)	Global cognition (3MSE); EF (DSST)	Age; Sex; Race; Smoking; Race; Marital status; Chronic diseases; Weight change	Increase in IL-6 associates with greater decline in EF
Singh-Manoux et al., 2014	*N* = 5217 56 yrs 28% female *Whitehall II Study, England*	L, 10 yrs	IL-6, hsCRP (fasting serum, IL-6 measured using high-sensitivity ELISA; CRP measured using high-sensitivity immunonephelometric)	Global cognition (MMSE); Short-term Verbal Memory (test not specified); Inductive Reasoning (Alice Heim 4-1);VF (VFT)	Age; Sex; Race; Education; Smoking; Obesity; CVD; Cancer; Stroke; Diabetes; Depression	Highest tertile of IL-6 associated with poorer reasoning and VF; Highest tertile of hsCRP associated with poorer reasoning; Higher IL-6 and hsCRP associated with faster decline in reasoning and global cognition

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Table 2 (*continued*)

Study	Sample Size Mean Age Gender %female Cohort/ Location	Study design (CS/ L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect modifiers*	Adjusted Model Results
Economos et al., 2013	*N* = 1224 71 yrs 64% female *NOMAS, U.S.A.*	L, 3 yrs	IL-6, hsCRP (fasting not specified, measured using ELISA)	Global cognition (TICS-m)	Age; Sex; Education; Race; Insurance status; Depression; PA; Diabetes; Alcohol; Smoking; APOE; *Effect modifiers*: Age, Race, APOE	High IL-6 (median split) associated with greater decline in TICS-m than Low Il-6; *Age:* Association stronger in participants > 71 yrs; hsCRP: ns; Effect modification: ns
Mooijaart et al., 2013	*N*= 5653 75 yrs 52% female *PROSPER Study, The Netherlands*	L, 3.3 yrs	IL-6 (fasting not specified, plasma measured using high-sensitivity ELISA)	Global cognition (MMSE); Memory (15-PLT); EF (Stroop, LDCT); Selective Attention (Stroop); Processing Speed (LDCT)	Age; Sex; Education; Country; APOE; Test version; HTN; Diabetes; CVD; Stroke; BMI; Smoking; BP; Cholesterol	Higher IL-6 associated with poorer EF, attention, and processing speed at baseline; All tests except processing speed demonstrated higher rate of decline associated with higher IL-6
Alley et al., 2008	*N*=851 74 years 51% female *MacArthur Study of Successful Aging, U.S.A.*	L, 7 yrs	Il-6, hsCRP (fasting plasma levels measured using ELISA)	Global cognition (SPMSQ); Abstraction (Similarities Subtest of WAIS-R); Spatial Ability (GFCT); Language (BNT); Memory (Word List Recall, Spatial Recognition)	Age; Sex; Education; Race; Income; Stroke; Diabetes; Hip fracture; MI; SBP; DBP; Mortality; Practice effects; HbA1c; HDL; Waist circumference; NSAID use; Alcohol; PA; Smoking	No effects of continuous IL-6 or hsCRP on cognitive change or baseline performance; Highest tertile of IL-6 associated with increased risk of global cognitive decline
Hoth et al., 2008	*N*=78 71 yrs 39% female *U.S.A.*	L, 1 yr	hsCRP (non-fasting blood measured using a high-sensitivity assay)	Global cognition (MMSE, DRS); Memory (CVLT, Complex Figure Test, Brief Visual Memory Test); Language (BNT, Category VF) Visuospatial (Hooper Visual Organization Test, Complex Figure Test-copy, WAIS III BD); Attention, EF, Psychomotor Speed (TMT-A&B, Letter Search, COWAT, GPT, WAIS III DS, Symbol Coding)	Age; Baseline performance	High hsCRP associated with greater decline in attention-executive-psychomotor composite performance only
Komulainen et al., 2007	*N* = 97 64 yrs 100% female *North Karelia Project, Finland*	L, 12 yrs	hsCRP (fasting serum measured using commercial immunoassay using IMMULITE 2000 Analyzer)	Global cognition (MMSE); Memory (Word Recall Test); Cognitive Speed (Stroop Test, LDST)	Age; Education; Depression; HRT; Smoking; Serum cholesterols; BMI; Time of CRP measurement	Higher baseline and follow-up hsCRP associated with poorer memory only
Rafnsson et al., 2007	*N* = 452 Age range 55-74 yrs 50% female *EAS, Scotland*	L, 4 yrs	hsCRP, IL-6, ICAM-1; VCAM-1, E-selectin, and D-dimer (fasting not specified, CRP measured using high-sensitivity assay in a BN Pro-Spec nephelometer; IL-6, ICAM-1, VCAM-1, E-selectin, and D-dimer measured using high-sensitivity ELISA)	Memory (LM); Abstract Thinking (RSPM); VF (VFT); EF (DSST); Global summary score	Age; Sex; NART	IL-6 and ICAM-1 associated with baseline cognition function, with exception of memory; Increase IL-6 and ICAM-1 associated with greater decline in all cognitive measures, except memory and VF

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Table 2 (*continued*)

Study	Sample Size Mean Age Gender %female Cohort/ Location	Study design (CS/ L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect modifiers*	Adjusted Model Results
Schram et al., 2007	*Rotterdam Study:* *N* = 2433 72 yrs 58% female *Leiden 85+ Study:* *N* = 440 85 yrs 65% female *The Netherlands*	L, 4.6 yrs 5 yrs	CRP, IL-6, ACT (*Rotterdam Study*: fasting not specified, CRP measured using Rate Near Infrared Particle Immunoassay (IMMAGE); plasma IL-6 measured using ELISA technique; ACT measured using kinetic nephelometry) (*Leiden 85+ Study*: fasting not specified, CRP measured using fully automated Hitachi 747 system; unstimulated IL-6 measured using standard ELISA after an ex vivo whole blood stimulation assay; IL-6 measured using ELISA)	*Rotterdam Study*: Global cognition (MMSE); Memory (Word Fluency); EF (Stroop, LDST) *Leiden 85+ Study*: Global cognition (MMSE); Memory (12-PLT); EF (Stroop, LDST)	Age (Rotterdam Study only); Sex; Education *Leiden 85+ effect modifier*: APOE	Rotterdam: Higher CRP and IL-6 both associated with worse baseline MMSE and EF. Cognitive decline not associated with inflammatory markers. Leiden: Higher IL-6 associated with greater decline in memory and trending for global cognition; negative association between inflammatory markers and global cognition and memory was greater in APOE e4(+) carriers
van den Biggelaar et al., 2007	*N* = 267 85 yrs 63% female *Leiden 85+ Study,* *The Netherlands*	L, 5 yrs	CRP, IL-1ra, IL-1β, TNF-α, IL-6, IL-10 (fasting not specified, serum measured using standardized ex vivo danger signalling)	Global cognition (MMSE)	Sex; Education; Depression; Stroke; CVD; Diabetes; COPD; Parkinson's disease; Malignancies; Subjective well-being; Disability in daily functioning; Smoking; ALB	ns
Yaffe et al., 2007	*N* = 1724 71 yrs 59% female *SALSA,* *U.S.A.*	L, 3 yrs	CRP (fasting serum measured using Equal Diagnostics high-sensitivity CRP kit)	Global cognition (3MS); Short-term Verbal Memory (DelRec)	Age; Sex; Education; Country of birth; Depression; Stroke; MI; Smoking; Alcohol	Those with metabolic syndrome and high CRP had greater decline in 3MS score, but not DelRec score
Dik et al., 2005	*N* = 1284 75 yrs 52% female *LASA,* *The Netherlands*	L, 3 yrs	CRP, IL-6, ACT (fasting not specified, measured using ELISA developed and performed at Sanquin Research)	Global cognition (MMSE); Memory (Auditory Verbal Learning Test); Fluid IQ (RCPM); Processing Speed (Coding Task)	Age; Sex; Education	Highest ACT tertile associated with greater global decline only
Wikby et al., 2005	*NONA Longitudinal Study:* *N* = 138 90 yrs 70% female *OCTO Longitudinal Study:* *N* = 102 88 yrs 66% female *Sweden*	L, 4 yrs	IL-6 (fasting not specified, plasma measured using ELISA kit)	Global cognition (MMSE); Memory (Memory-in-Reality tests)	Age; Sex; CVD; COPD; Malignancies; Anemia; Arthritis; Diabetes; Hypothyroidism	Higher IL-6 associated with greater impairment on cognitive tasks
Teunissen et al., 2003	*N* = 92 57 yrs 43% female *MAAS,* *The Netherlands*	L, 6 yrs	IL-6, CRP, haptoglobin (fasting not specified, serum measured using commercial ELISA kits)	Episodic Memory (Word Learning Task); EF (SDMT, Stroop III)	Age; Sex; Education	Analyses similar in entire sample and in subsample of participants > = 50 years at baseline (n = 71); Increase in CRP and haptoglobin at baseline each associated with decreasing performance on Stroop and delayed recall of word list

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Table 2 (*continued*)

Study	Sample Size Mean Age Gender %female Cohort/ Location	Study design (CS/ L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect modifiers*	Adjusted Model Results
Wilson et al., 2003	*N* = 1727 78 yrs 66% female *Duke EPESE, U.S.A.*	L, 6 yrs 10 yrs	IL-6, IL-10, D-dimer, SVCAM-1, soluble L-selectin, and TGF-β (fasting not specified, d-dimer and IL-6 measured using ELISA; IL-10, SVCAM-1, and soluble L-selectin measured using quantitative solid-phase sandwich ELISA; TGF-β measured using two-antibody ELISA with biotin-streptavidin perioxidase detection)	Global cognition (SPMSQ)	Age; Sex; Education; Race; Smoking; Alcohol; BMI; Stroke; MI; HTN; Diabetes, Arthritis, Hip fracture; Cancer; Sleep; Depression; Self-rated health	D-dimer, IL-6, and SVCAM-1 positively correlated with global cognition at 6 yr follow up; D-dimer also correlated with 10 yr follow-up; D-dimer independently predicted declines in cognition at 6 yr follow-up and change in scores from 6 to 10 yr follow-up
Yaffe et al., 2003	*N* = 3031 73 yrs 51% female *Health ABC Study, U.S.A.*	L, 2 yrs	IL-6, TNFα, CRP (fasting not specified, plasma IL-6 and TNFα, serum CRP measured using duplicate using ELISA kits)	Global cognition (3MS)	Age; Sex; Education; Race; Smoking: Alcohol; BMI; Self-reported health; Depression; MI; Diabetes; HTN; Stroke; Medication	Participants in highest tertile of IL-6 or CRP performed worse on 3MS than lowest tertile at baseline and follow-up; *Additive effect:* having at least one inflammatory marker in the highest tertile associated with greater likelihood cognitive decline
Weaver et al., 2002	*N*=779 74 yrs 53% female *MacArthur Study of Successful Aging, U.S.A.*	L 2.5 yrs 7 yrs	IL-6 (fasting not specified, plasma measured using ELISA)	Summary cognitive score derived from: Memory (BNT, Delayed Recognition Span Test); Abstraction (Similarities Subtest); Visuospatial (GFCT)	Age; Race; Sex; Income; Education; Alcohol; Activity level; BMI; Cancer; Diabetes; HBA1c	IL-6 tertile predicted cognitive decline at 2.5 and 7 year follow up when cognition was dichotomoized into "low" and "high", but not when cognition was continuous

Note: Studies are listed according to design (cross-sectional, longitudinal), followed by publication years, followed by alphabetical order; 12-PLT = 12-Picture Learning Test;15-PLT = 15-Picture Learning Test 3MS = Modified Mini Mental State Examination ; 6CKine = Chemokine Ligand 21; AAA = Aspirin for Asymptomatic Atherosclerosis ; ABC = Aging and Body Composition ; ACT = alpha1-antichymotrypsin ; ALB = Albumin; APOE = Apolipoprotein E ; AsIA = Barcelona-Asymptomatic Intracranial Atherosclerosis; BCA-1 = B Cell-attracting Chemokine 1; BD = Block Design; BIP = Bezafibrate Infarction Prevention ; BMI = Body Mass Index ; BNT = Boston Naming Test ; BP = Blood Pressure ; CDT = Clock Drawing Test ; CERAD = Consortium to; Establish a Registry for Alzheimer's Disease; CHS = Cardiovascular Health Study; COPD = Chronic Obstructive Pulmonary Disease ; COWAT = Controlled Oral Word Association Test ; CRP = C-reactive Protein ; CS = Cross-sectional; CTACK = Cutaneous T-cell-attracting Chemokine; CVD = Cardiovascular Disease ; CVLT = California Verbal Learning Test; CVLT = California Verbal Learning Test-II; DBP = Diastolic Blood Pressure ; DelRec = Delayed Word Recall Test; DRS = Dementia Rating Scale ; DS = Digit Span; DSST = Digit Symbol Substitution Test ; EAS = Edinburgh Artery Study ; EBMT = East Boston Memory Test; EF = Executive Function; ELISA = Enzyme-linked Immunosorbent Assay ; ELSA = English Longitudinal Study of Aging ; EPESE = Established Populations for Epidemiological Studies of the Elderly ; ESR = Erythrocytes Sedimentation Rate ; ET2DS = Edinburgh Type 2 Diabetes Study; FAB = Frontal Assessment Battery; GENOA = Genetic Network of Arteriopathy; GFCT = Geometric Figure Coping Test; GPT = Grooved Pegboard Test; HbA1c = Hemoglobin A1c ; Hcy = Homocysteine ; HDL = High-density Lipoprotein; HOMA-IR = Homeostatic Model Assessment of Insulin Resistance; HPLC = High Pressure Liquid Chromatography; HR = Heart Rate; HRT = Hormone Replacement Therapy; hsCRP = High sensitivity C-reactive protein; HTN = Hypertension ; HVLT-R = Hopkins Verbal Learning Test-Revised ; IL-10 = Interleukin-10 ; IL-1B = Interleukin-1B ; IL-6 = Interleukin-6 ; Il-8 = Interleukin-8 ; IMT = Intima-media Thickness ; IP-10 = Interferon Gamma-induced Protein 10; IQ = Intelligence Quotient ; L = Longitudinal; LASA = Longitudinal Aging Study Amsterdam; LBC1936 = Lothian Birth Cohort 1936 ; LDL = Low-density Lipoprotein ; LDCT = Letter-digit Coding Test ; LDST = Letter-digit Substitution Test; LM = Logical Memory; LNS = Letter Number Sequencing; MAAS = Maastricht Aging Study ; MAS = Sydney Memory and Aging Study ; MEMO = Memory and Morbidity in Augsburg Elderly ; MGO = Methylglyoxal ; MI = Myocardial Infarction ; MMSE = Mini Mental State Examination ; MPO = Myeloperoxidase; MoCA = Montreal Cognitive Assessment; MR = Matrix Reasoning; NART = National Adult Reading Test; NHANES-III = National Health and Nutrition Examination Survey-III; NOMAS = Northern Manhattan Study ; NONA = Nonagenarian; NSAID = Non-steroidal Anti-inflammatory Drug; OCTO = Octogenarian; PA = Physical Activity; PAI-1 = Plasminogen Activator Inhibitor-1; PROSPER = Prospective Study of Pravastatin in the Elderly; PROST = Project in Sado for Total Health; RAVLT = Rey Auditory Verbal Learning Test; RBC = Red Blood Cells; RCFT = Rey Complex Figure Test; RSPM = Raven's Standard Progressive Matrices; RVLT = Rey Verbal Learning Test; SAA = Serum Amyloid A; SALSA = Sacramento Area Latino Study of Aging; SBP = Systolic Blood Pressure; SDMT = Symbol Digit Modalities Test; SEARCH = Systematic Evaluation and Alternation of Risk Factors for Cognitive Health; sgp130 = Soluble Glycoprotein 130; sICAM-1 = Soluble Intercellular Adhesion Molecule-1; sIL-2Ra = Soluble Interleukin-2 Receptor Alpha; sIL-4R = Soluble Interleukin-4 Receptor; sIL-6R = Soluble Interleukin-6 Receptor; SLSA = Singapore Longitudinal Ageing Study; SPMSQ = Short Portable Mental Status Questionnaire; sTNFR1 = Soluble Tumor Necrosis Factor Receptor-1; sTNFR2 = Soluble Tumor Necrosis Factor Receptor-2; sVCAM-1 = soluble vascular cell adhesion molecule-1; TASCOG = Tasmanian Study of Cognition and Gait ;TC = Total Cholesterol; TG = Triglycerides; TIA = Transient Ischemic Attack; TICS = Telephone Interview for Cognitive Status; TICS-m = Modified Telephone Interview for Cognitive Status; TMT-A = Trail Making Test-Part A; TMT-B = Trail Making Test-Part B; TNF = Tumor Necrosis Factor; VCAM-1 = Vascular Cell Adhesion Molecule-1; VF = Verbal fluency; VFT = Verbal Fluency Test; VITA = Vienna Transdanube Aging ; CWAIS-III = Wechsler Adult Intelligence Scale-Third Edition WAIS-R = Wechsler Adult Intelligence Scale-Revised; WBC = White Blood Cells; WHAS = Women's Health and Aging Study; WHS = Women's Health Study; WMS-III = Wechsler Memory Test-Third Edition; WMS-R = Wechsler Memory Test-Revise.

the role of FAs in predicting brain health is especially important in the context of dietary interventions.

Altogether, there is evidence from cross-sectional and longitudinal studies to suggest that blood lipid levels and FAs serve as indicators of cognitive health in late life. However, conflicting results in the literature suggest that additional research is required to determine the predictive value of lipids depending on inter-individual variables including genetic variance, sex, and age (i.e. midlife vs. late life). Furthermore, given the paucity of associations with executive function and more pronounced associations with learning and memory, it is possible that the effect of lipid profile may be restricted to hippocampal-dependent cognitive functions.

3.2. Inflammatory biomarkers and cognitive function

Circulating inflammatory markers have largely been investigated for their role in cardiovascular and metabolic disorders (Hotamisligil, 2006; Libby, 2006). However, the last decade of research has shown the significance of inflammation in cognitive health in late life.

Cytokines are soluble signaling proteins produced by cells of the immune system that play a role in normal functioning of the central nervous system, including neuronal development and aging (Letiembre et al., 2007). Cytokines are divided into interleukins (IL), chemokines, lymphokines, interferons (IFN), transforming growth factors (TGF), and tumor necrosis factors (TNF) which are characterized as pro-inflammatory (e.g., IL-1, TNF-alpha, and IFN-gamma) or anti-inflammatory (e.g., IL-10 and IFN-alpha), and may even display both properties depending on the targeted cell (e.g. IL-6) (Cavaillon, 2001). In addition to cytokines, C-reactive protein (CRP), produced by the liver in response to pro-inflammatory cytokines, serves as robust indicator of systemic inflammation (Nillawar et al., 2012). There is debate as to whether inflammation is a cause, a facilitator, or an outcome of dementia (Wyss-Coray & Rogers, 2012) due to the general inconsistencies in research findings. In an attempt to understand the underlying neurocorrelates of cognitive function, high levels of CRP, IL-6 and TNF-α have been associated with decreased total brain volume in 1926 Framingham Offspring participants who were on average 60 years of age and free from neurological and cardiovascular disease (Jefferson et al., 2007). However, as this study was cross-sectional, causal inferences cannot be made.

A total of 51 studies met the current search criteria (Table 2). Cross-sectional investigation of the association between CRP, or high sensitivity CRP (hsCRP), and cognitive performance in late life suggests a relatively consistent association between high levels of CRP in the blood and poor executive functioning (Arfanakis et al., 2013; Canon & Crimmins, 2011; Luciano et al., 2009; Marioni et al., 2010; Sweat et al., 2008; Tegeler et al., 2016; Wersching et al., 2010; Windham et al., 2014). The association between CRP and other cognitive domains, including global cognitive function measured by the MMSE, is less clear (Bettcher et al., 2014; Fischer et al., 2006; Miralbell et al., 2013; Miralbell et al., 2012; Ravaglia et al., 2005; Watanabe et al., 2016; Weuve et al., 2006). Furthermore, inconstant findings do not appear to be based on whether hsCRP was employed in the analysis. Marioni et al. (2010), examined the association between CRP and cognitive function in four Scottish aging cohorts, and reported inconsistent associations between CRP and cognition, with the exception of vocabulary-based test scores. Although mixed findings are reported (Baune et al., 2008), Interleukins, especially IL-6, have also shown cross-sectional associations with cognitive function, especially executive function (Tegeler et al., 2016; Troller et al., 2012; Windham et al., 2014). Associations between IL-6 and hippocampal-dependent cognitive process have been found (Elderkin-Thompson et al., 2012), and has also been found to be modified by age. In a cross-sectional study of 49–90 year-old women, a significant interaction was observed between IL-6 and age for semantic fluency and prospective memory, suggesting that the detrimental impact of IL-6 on cognitive function increases with age (Lekander et al., 2011).

Longitudinal analyses (n = 23) have further shown a negative impact of high circulating inflammatory markers on cognitive trajectory in late life. Although null findings have been reported (Dik et al., 2005; Economos et al., 2013; Palta et al., 2015; van den Biggelaar et al., 2007), prospective studies ranging from 6 to 12-year follow-up show that high levels of circulating CRP associate with declines in global cognitive performance (Metti et al., 2014; Schram et al., 2007; Weinstein et al., 2017; Yaffe et al., 2003) memory (Komulainen et al., 2007; Singh-Manoux et al., 2014; Teunissen et al., 2003), non-verbal reasoning (Singh-Manoux et al., 2014), processing speed, and executive function (Bourassa & Sbarra, 2017; Heringa et al., 2014; Hoth et al., 2008; Marioni et al., 2009; Schram et al., 2007; Singh-Manoux et al., 2014; Teunissen et al., 2003; Weinstein et al., 2017). Prospective associations have been reported for interleukins, with IL-6 predicting declines in global cognitive function (Alley et al., 2008; Economos et al., 2013; Schram et al., 2007; Yaffe et al., 2003), memory (Elderkin-Thompson et al., 2012; Wikby et al., 2005), processing speed (Palta et al., 2015), and executive function (Mooijaart et al., 2013; Quadros & Sequeira, 2013; Rafnsson et al., 2007; Sanders et al., 2014; Schram et al., 2007; Singh-Manoux et al., 2014). In a 7-year prospective study by Alley et al. (Alley et al., 2008), the predictive value of inflammation on a range of cognitive outcomes were marginal. However, the authors reported that they observe a relationship between high levels of IL-6 and large incident declines in global cognitive function, suggesting that high levels of inflammation are associated with incident cognitive impairment (Alley et al., 2008). The statistical treatment of variables must also be considered in interpreting research findings. For example, in a study by Weaver et al. (2002), IL-6 tertile predicted low vs. high cognitive performance at 2.5 and 7-year follow-up, but failed to significantly predict trajectory of cognitive function as a continuous variable.

Together, it may be postulated that small variations in inflammatory biomarkers may not significantly affect brain health when they are considered individually. In the Hoorn Study (Heringa et al., 2014), it was found that low grade inflammation, measured by a composite of hsCRP, IL-6, TNF-a, IL-8, serum amyloid A, myeloperoxidase, and soluble intercellular adhesion molecule-1, associated with worse attention and executive function at follow-up. However, none of the individual biomarkers were associated with cognition. Potential effect modifiers in the relationship between inflammatory biomarkers and cognitive function have been suggested (Heringa et al., 2014; Matsushima et al., 2015). For example, more robust associations between inflammation and cognition have been reported in women than men (Sanders et al., 2014) and carriers of the *APOE ε4* allele (Schram et al., 2007). Further, baseline levels may be less predictive of cognitive trajectory than variability of inflammatory markers over time. For example, in a 10-year prospective study of biracial men and women, baseline CRP and IL-6 did not predict cognitive decline; rather, greater variability in hsCRP levels over time associated with global cognitive decline (Metti et al., 2014).

3.3. Metabolic markers and cognitive function

Obesity and type 2 diabetes mellitus (T2DM) are associated with impaired cognitive function (Kodl & Seaquist, 2008; Qiu et al., 2014; Sabia et al., 2009) and increased risk for AD (Ott et al., 1999; Xu et al., 2011). As such, circulating biomarkers associated with these metabolic states have been investigated for their role in neurodegeneration including glucose, insulin, and insulin-like growth factors. A total of 48 articles that met inclusion criteria examined the association between peripheral metabolic biomarkers and cognitive function in non-demented older adults (see Table 3).

Cross-sectional analyses between circulating insulin levels and cognitive function have suggested a robust inverse association (Di Bonito et al., 2007; Frazier et al., 2015; Pavlik et al., 2013; Yan-Ling et al., 2014). Analyses of 395 older adults from the Texas Alzheimer's

Table 3
Systematic Review Results for metabolic-related biomarkers.

Study	Sample Size Mean Age Gender %female *Cohort/* *Location*	Study design (CS/ L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect modifiers*	Adjusted Model Results
Cross-Sectional Study						
Martens et al., 2017	*N* = 2987 60 yrs 49% female *MAAS,* *The Netherlands*	CS	Creatinine, cystatin C (combined to assess eGFR) (fasting not specified, serum, creatinine measured using Jaffé method, cystatin C measured using particle-enhanced immunoturbidimetric assay)	Memory (VLT); EF, Processing Speed (Stroop, CST, LDST)	Age; Sex; Education; Glucose metabolism; Waist circumference; HDL; TG; Medication; Smoking; Alcohol; SBP; CVD; Depression; *Effect modifier*: Age	Tertile and continuous eGFR not associated with cognition; *Age*: High eGRF in 70 + years associated with lower cognitive performance. Association not found in < 70 years.
Perice et al., 2016	*N* = 103 97 yrs 80% female *Longevity Genes Project,* *U.S.A.*	CS	IGF-1, IGFBP-3 (fasting not specified, serum IGF-1 measured using LC-MS; IGFBP-3 measured using chemiluminescent immunometric assay)	Global cognition (MMSE)	Age; Education; Depression; Smoking; Alcohol, IGFBP-3; *Effect modifiers:* Sex	Lowest tertile IGF-1 associated with lower risk of cognitive impairment (MMSE < 25/30, or Blind MMSE < 16/22); *Sex*: Association restricted to females only
Liu et al. (2015)	*N* = 2012 71 yrs 58% female *China*	CS	Glucose (fasting serum, measurement not specified)	Global cognition (MMSE)	Age; Sex; Education; Smoking; Alcohol; BMI; Marital status; PA; Dementia; Medication	Hyperglycemia (> = 5.6 mmol/L) associated with poorer global cognition
Frazier et al., 2015	*N* = 119 73 yrs 54% female *U.S.A.*	CS	HOMA-IR [fasting insulin (μU/mL) × fasting glucose (mg/dL)]/405] (fasting blood, measurement not specified)	WM (DS backward, N-back Test, Dot Counting, Running-Letter Memory); EF (Stroop, Design Fluency Switching, Number-Letter, Flanker); Processing Speed (Abstract Matching, Distance Judgment, Length Judgment, MRT, Visual Search, Shape Judgment, Abstract Matching 2)	Age; Sex; Education; LDL; BMI; WMH; MAP	Higher HOMA-IR associated with poorer WM and EF only
Goh & Hart, 2015	*N* = 472 Age range 29-72 yrs 0% female *Singapore*	CS	IGF-1, IGFBP-3, insulin, glucose (fasting serum, IGF markers measured using immunoradiometric assay kits; insulin and glucose measured using Abbott's Axsym platform, glucose measured using the hexokinase method)	Perceptual Speed (SDMT); WM (DS)	Age; Exercise	High glucose associated with poorer perceptual speed and WM
Goh & Hart, 2014	*N* = 472 Age range 29-72 yrs 0% female *Singapore*	CS	Glucose (fasting not specified, blood measured using hexokinase method on an Abbott Architect automated platform)	Perceptual Speed (SDMT); Attention (DS)	Age; Exercise; Waist/height ratio	High glucose (> 5.6 mmol/l) associated with poorer perceptual speed only
Levin et al., 2014	*N* = 1290 64 yrs 61% female *Northern Manhattan Study,* *U.S.A.*	CS	Glucose (part of metabolic syndrome analysis) (fasting blood, measurement not specified)	Memory (List Learning); EF (Colour Trails 2, Animal Fluency, Digit Ordering, Odd Man Out, Fluency); Language (BNT, PPVT); Visuomotor Speed (Colour Trails 1; GPT)	Age; Sex; Education; Race; Smoking; Alcohol; Risk factor treatment variables	High Glucose associated with poorer visuomotor composite only
Lin et al., 2014	*N* = 94 61 yrs 58% female *U.S.A.*	CS	IGF-1 (fasting not specified, plasma measured using Human IGF-1 Quantikine ELISA)	Memory (RAVLT)	Age; Sex; Education; HRT; HTN medication; Sleep quality	ns

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Table 3 (*continued*)

Study	Sample Size Mean Age Gender %female *Cohort/* *Location*	Study design (CS/ L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect modifiers*	Adjusted Model Results
Yan-Ling et al., 2014	*N* = 661 93 yrs 67% female *PLAD,* *China*	CS	Insulin, glucose (fasting serum, glucose measured using glucose oxidase methods; insulin measured using RIA)	Global cognition (MMSE)	Age; Sex; Education; BMI; Lipids; BP; Uric acid	Hypoinsulinemia (> 15.00 mU/mL) associated with poorer cognition; Glucose: ns
Luo et al., 2013	*N* = 767 94 yrs 67% female *PLAD,* *China*	CS	Glucose (plasma fasting, measurement not specified)	Global cognition (MMSE)	Age; Sex; Education; Smoking; Alcohol; PA	ns
Pavlik et al., 2013	*N* = 198 70 yrs 33% female *Texas Alzheimer's Research and Care Consortium, U.S.A.*	CS	Insulin (fasting serum measured using multiplexed immunoassay human Multi-Analyte Pro- file)	Global cognition (MMSE); Memory (WMS-R, LM, BVRT); EF (TMT, DS); IQ (NART – errors); Verbal Fluency (COWAT, BNT)	Age; Sex; Education; BMI	Higher insulin associated with poorer performance on IQ, COWAT, LM, BVRT and DS
Miralbell et al., 2012	*N* = 86 51 yrs 59% female *Barcelona – AsIA Study,* *Spain*	CS	Resistin (fasting serum measured using ELISA)	Global cognition (MMSE); Memory (Word List, BVRT); EF (Stroop, DS); Verbal Fluency (Letter and Category Fluency); Attention (Symbol Search, Symbol Coding, DS forward); Visual Construction (Visual Reproduction - copy); Visuomotor Speed (GPT)	Age; Sex; Education	ns
Bellar et al., 2011	*N* = 28 71 yrs 78% female *U.S.A.*	CS	IGF-1 (fasting serum measured using ELISA)	Global cognition (3MS); WM (Letter Number Sequence Test); EF (TMT-A&B); Attention (Ruff's 2 and 7 test)	Age; Sex; Education	Increasing IGF-1 associated with better EF, attention and WM
Al-Delaimy et al., 2009	*N* = 1535 74 yrs 58% female *Rancho Bernardo Study,* *U.S.A.*	CS	IGF-1, IGFBP-1 (non-fasting blood measured using the Nichols Institute Diagnostics Commercial Kit)	Global cognition (MMSE); VF; EF (TMT-B)	Age; Education; Time since last meal; Estrogen use; *Effect modifier*: Sex	Higher IGF-1 tertile associated with better global and VF; Higher IGFBP-1 tertile associated with poorer global cognition only; *Sex:* Associations restricted to men
Angelini et al., 2009	*N* = 75 78 yrs 64% female *Italy*	CS	IGF-1 (fasting serum, measurement not specified)	Global cognition (MMSE, CAMCOG)	None	Higher IGF-1 associated with better global cognition
Alfaro et al., 2008	*N* = 313 77 yrs 51% female *Mataró Aging Study,* *Spain*	CS	IGF-1, IGFBP3 (fasting blood measured using commercially validated immunoassay kits)	Global cognition (MMSE)	None *Effect modifier*: Sex	Higher IGF-1 associated with better cognition in females only
Gunstad et al., 2008	*N* = 35 74 yrs 54% female *U.S.A.*	CS	Leptin (fasting serum measured using the R&D Systems Quantikine Human Leptin ELISA kit)	Global cognition (MMSE); Memory (HVLT); EF (TMTA&B, Letter-number sequencing; DSC); Verbal Fluency (BNT, Letter and Animal Fluency)	Age; Sex; Education	Higher leptin associated with poorer performance on TMT-B only

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Table 3 (*continued*)

Study	Sample Size Mean Age Gender %female *Cohort/* *Location*	Study design (CS/ L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect modifiers*	Adjusted Model Results
Rolandsson et al., 2008	*N* = 411 50 yrs 56% female *Betula Study, Sweden*	CS	Glucose (fasting serum measured using Reflotron bench-top analyzer)	Episodic Memory (Recall and Recognition); Semantic Memory (Knowledge and Fluency)	Age; Education; HTN; TC; BMI; Depression; Smoking; CVD; *Effect modifier*: Sex	Higher glucose associated with poorer episodic memory in females only
Di Bonito et al., 2007	*N* = 182 72 yrs 67% female *Italy*	CS	Glucose, insulin, HbA1c (fasting plasma, insulin measured using immunoenzymatic methods; HbA1 measuring using HPLC method; glucose measured using standard procedures)	Global cognition (MMSE)	Age; Sex; Creatinine; Folate	Higher glucose, insulin, but not HbA1c significantly associated with poorer global cognition
Fischer et al., 2006	*N* = 606 76 yrs 59% female *VITA Study, Austria*	CS	HbA1c (fasting not specified, blood measured using Roche Integra Analyser)	Global cognition (MMSE)	None	ns
Okereke et al., 2006	*N* = 376 56 yrs (blood) 65+ yrs (cognition) *Physicians' Health Study, U.S.A.*	CS	IGF-1 (free/total), IGFBP-3 (fasting not specified, assessed at midlife, measured using ELISA)	Global cognition (TICS); Memory (BNT, delayed recall of TICS 10-work list); Verbal Fluency (Category Fluency); Global score (composite all tests combined)	Age; HTN; Dyslipidemia; Smoking; Alcohol; BMI; Depression; Cancer	Lowest tertile free IGF-1 associated with lower global cognition and memory; IGFBP-3: ns
Aleman et al., 2005	*N* = 400 60 yrs 0% female *The Netherlands*	CS	Glucose (fasting serum measured using reagent-strip glucose oxidase method, GlucoTouch reflectometer)	Global cognition (MMSE); Memory (DS, RAVLT, Doors Test); EF (TMT-A&B); Psychomotor Speed (DSST);Verbal Intelligence (DART)	Age; Education	ns
Arwert et al., 2005	*N* = 24 80 yrs 43% female *LASA, The Netherlands*	CS	IGF-1 (fasting not specified, plasma measured using commercially available assays)	WM (DNMTS Task)	None	High IGF-1 (vs. Low) associated with faster RT for easy items only
MacLullich et al., 2004	*N* = 111 68 yrs 0% female *Scotland*	CS	HbA1c (fasting serum, measurement not specified)	Memory (RAVLT; LM); Visuospatial (BVRT, BVNT); Abstract Thinking (RSPM); Processing Speed (DSST); IQ (NART)	None	Higher HbA1c associated with poorer memory only
Ravaglia et al., 2003	*N* = 650 73 yrs 55% female *Conselice Study, Italy*	CS	Creatinine (fasting not specified, serum measured using Jaffé method)	Global cognition (MMSE)	Age; Sex; Education; Income; Active lifestyle; Coffee intake; Meat intake; BMI, HTN; CVD; Diabetes	Higher creatinine in participants with MMSE score of 24-25 vs. > 28
Aleman et al., 2001	*N* = 25 69 yrs 0% female *U.S.A.*	CS	IGF-1 (fasting blood measured using commercially available RIA)	Crystallized IQ composite (WAIS – Information, Vocabulary, BJLO, Brus Reading Test); Fluid IQ composite (WAIS – BD, DSST, CST); Memory (RAVLT)	Education; SHBG; Testosterone	Higher IGF-1 associated with lower fluid intelligence composite only

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Table 3 (*continued*)

Study	Sample Size Mean Age Gender %female *Cohort/* *Location*	Study design (CS/ L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect modifiers*	Adjusted Model Results
Aleman et al., 1999	*N* = 25 69 yrs 0% female *U.S.A.*	CS	IGF-1 (fasting blood measured using commercially available RIA)	General knowledge (WAIS – Information); Vocabulary (WAIS – Vocabulary); Visuospatial (BJLO); Reading Ability (Brus Reading Test); Organization/Construction (WAIS – BD); Processing Speed (DSST); Movement Planning (CST); Memory (RAVLT)	Education	Higher IGF-1 associated with lower score on DSST and CST
Rollero et al., 1998	*N* = 22 77 yrs 32% female *Italy*	CS	IGF-1, GH (fasting plasma, IGF measured using EDTA; GH measured using vacutainers)	Global cognition (MMSE)	None	Higher IGF-1 associated with better global cognition
Paolisso et al., 1997	*N* = 49 78 yrs (*n* = 30), 102 yrs (*n* = 19) 47% female *Italy*	CS	IGF-1, IGFBP-3 (fasting not specified, plasma measured using RIA)	Global cognition (MMSE)	Age; Sex	Higher IGF-1 and IGF-1/IGFBP-3 associated with better global cognition
Longitudinal Studies						
Tumati et al., 2016	*N* = 400 60 yrs 0% female *The Netherlands*	L, 8 yrs	IGF-1 (fasting blood measured using immunometric technique on Advantage Chemiluminescience System)	Global cognition (MMSE); Memory (RAVLT, Doors Test); EF (DS, TMT); Processing Speed (DSST); Verbal Fluency (VFT)	Age; Education; Smoking; BMI; PA; Glucose; Baseline cognition	IGF-1 quintiles not associated with cognitive function at baseline; Higher IGF-1 quintile associated with poorer processing speed and global cognition at follow-up
Viscogliosi et al., 2016	*N* = 104 80 yrs 44% female *Italy*	L, 11.2 months	Glucose (fasting plasma, measurement not specified)	Global cognition (CDT)	None	ns
Taniguchi et al., 2014	*N* = 682 75 yrs 60% female *Japan*	L, 2.7 yrs	HbA1c, creatinine, ALB, glucose (non-fasting blood measured using standard procedures)	Global cognition (MMSE)	Age; Sex; Education; Study area; Living arrangement; Frequency outdoors; Alcohol; Smoking; Chronic disease; Height/Weight; Gait speed; Self-rated health; TMIG-IC; Depression	Lower ALB associated with impairment at follow-up (decline of at least 3 points on MMSE); Compared to high ALB tertile, lowest tertile increased risk of cognitive impairment at follow-up; Glucose or HbA1c: ns
Vannorsdall et al., 2014	*N* = 436 74 yrs 100% female *WHAS-II, U.S.A.*	L, 9 yrs	Uric acid (fasting and measurement not specified, serum)	T1-T3: Global cognition (MMSE); Memory (HVLT-R); EF (TMT, PPB); Attention (Brief Test of Attention); T3-T6: Pattern Comparison Test, CDT; T4-T6: DS, Verbal Fluency	Baseline uric acid; Age, Education; Race; BMI; Perceived health status; HTN; Diabetes; Stroke; Alcohol; Diuretics; baseline CRP; baseline IL-6	High uric acid associated with poor baseline attention only; not associated with cognitive change over time
Infurna, & Gerstorf, 2013	*N* = 4177 67 yrs 59% female *HRS, Germany*	L, 4 yrs	HbA1c (fasting blood, measurement not specified)	Memory (Immediate and Delayed Free-Recall)	Age; Sex; Education; *Effect modifiers*: Age	Lower HbA1c associated with less memory decline at follow-up; *Age*: lower HbA1c protective against decline in memory at follow-up in adults > = 70 at baseline
Katsumata et al., 2012	*N* = 148 85 yrs 74% female *KOCOA Project, Japan*	L, 2 yrs	HbA1c (fasting blood, measurement not specified)	Global cognition (MMSE); Memory (Scenery Picture Memory Test); EF (Verbal Fluency Initial Letter)	Age; Sex; Education	High HbA1c associated with greater decline in memory only

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Table 3 (*continued*)

Study	Sample Size Mean Age Gender %female *Cohort/* *Location*	Study design (CS/ L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect modifiers*	Adjusted Model Results
Deijen et al., 2011	*N* = 30 61 yrs 77% female *The Netherlands*	L, 4 yrs	GH, IGF-1 (fasting serum, GH measured using immunometric assay; IGF-1 measured using chemoluminiscentic assay)	Memory (Associate Learning Task); Attention (DS forward); WM (DS backward)	Baseline test score	Low IGF-1 associated with decline in WM; Higher GH associated with better memory and WM at follow-up
Euser et al., 2010	*PROPSER Cohort, Scotland, Ireland, The Netherlands:* *N* = 5019 75 yrs 52% female *Rotterdam Study, The Netherlands:* *N* = 3428 72 yrs 58% female *Merged sample:* *N* = 8447	*PROSPCohort:* L, 2.5 yrs *Rott Study:* L, 5 yrs	*PROSPER Cohort:*Glucose (fasting serum, measurement not specified) *Rotterdam Study:*Glucose, HOMA index (fasting serum, measurement not specified)	Global cognition (MMSE); Memory (12-PLT); EF (LDST, Stroop); Verbal Fluency (Word Fluency Test)	Age; Sex; Education; Study; BMI, HDL, SBP, DBP, Country, Treatment group; *Effect modifiers*: Diabetes	*Merged sample:* ns; *PROSPER Cohort:* higher FG in persons without diabetes history associated with greater rate of decline in memory only; *Rotterdam Study:* ns
Okereke et al., 2010	*N* = 1353 71 yrs 0% female *Physicians' Health Study II, U.S.A.*	L, 3.3 yrs	Insulin, C-peptide (fasting plasma, insulin measured using RAI; C-peptide measured using antiserum M1230 in an alcohol precipitation nonequilibrium assay)	Global cognition (TICS); Memory (EBMT; Delayed TICS word list); VF (Category Fluency); Summary score (all tests)	Age; HTN; Dyslipidemia; CVD; Depression; Smoking; BMI; Alcohol; PA	Higher insulin quartile associated with greater decline in global cognition andVF; Higher C-peptide quartile associated with greater decline in summary cognitive score and trend for memory and VF
Van Vliet et al., 2010	*N* = 599 85 yrs 66% female *Leiden 85+ Study, The Netherlands*	L, 5 yrs	Glucose (non-fasting serum measured using fully automated Hitachi 747 and Hitachi 911 system)	Global cognition (MMSE)	Sex; Baseline MMSE score	ns
Holden et al., 2009	*N* = 2871 74 yrs 51% female *Health ABC Study, U.S.A.*	L, 4 yrs	Leptin (fasting blood measured using Sensitive Human Leptin RIA Kit)	Global cognition (3MS)	Sex; Race; Education; Baseline cognition; HTN; MI; Diabetes; Days in hospital; BMI; Body fat	Compared to lowest tertile, highest leptin tertile associated with less cognitive decline
Okereke et al., 2009a,b	*N* = 1187 64 yrs 100% female *NHS, U.S.A.*	L, 4.4 yrs	Insulin, C-peptide (fasting plasma, insulin measured using RAI; C-peptide measured using antiserum M1230 in an alcohol precipitation nonequilibrium assay)	Global cognition (TICS); Memory (EBMT, TICS Delay Word Recall); EF (DS); Summary score (all tests)	Age; Education; Smoking; HRT; HTN; Dyslipidemia; BMI; Alcohol; PA; Anti-depressant use	Compared to reference group (LowC peptide/LowInsulin), LowC-peptide/ HighInsulin group showed greater decline in memory, more so than; HighC-peptide/ HighInsulin group; HighC-peptide/ HighInsulin showed greater decline on summary score than reference group
Okereke et al., 2008	*N* = 1187 64 years 100% female *NHS, U.S.A.*	L, 4.4 yrs	C-peptide (plasma c-peptide measured using antiserum M1230 in an alcohol precipitation non-equilibrium assay)	Global cognition (TICS); Memory (EBMT, TICS Delay Word Recall); EF (DS); Summary score (all tests)	Age; Education; Smoking; HRT; HTN; Cholesterol; BMI; PA; Anti-depressant use	Increase in C-peptide quartile associated with greater decline in global cognition, memory, and cognitive summary score

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Table 3 (*continued*)

Study	Sample Size Mean Age Gender %female *Cohort/* *Location*	Study design (CS/ L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect modifiers*	Adjusted Model Results
van Oijen et al., 2008	*N* = 1416 70 yrs 100% female *NHS, U.S.A.*	L, 4 yrs	Insulin (fasting plasma measured using RAI)	Global cognition (TICS); Memory (EBMT); VF (Category Fluency); EF (DS)	Age; Education; BMI, Smoking HTN; Cholesterol; CVD; Alcohol; PA; HRT	Higher insulin quartile associated with poorer global function, VF and EF; Higher insulin quartile associated with greater decline in global cognition, and verbal fluency
Okereke et al., 2007	*N* = 590 Age range 60-68 yrs 100% female *NHS, U.S.A.*	L, 10 yrs	IGF-1/IGFBP-3 molar ratio (fasting not specified, plasma measured using ELISA)	Global cognition (TICS); Memory (EBMT, Delayed Recall of TICS 10-word list);VF (Category Fluency); WM (DS backward)	Age; Education; HTN; Smoking; Anti-depressant use; BMI; Alcohol; IGFBP-3 in models primarily focusing on IGF-1; *Additional adjustment* for PA, updating of covariates through duration of study; Depression	Bottom quintile of molar ratio associated with worse performance on all cognitive tests, except memory; No longer significant after additional adjustments
Yaffe et al., 2007	*N* = 1724 71 yrs 59% female *SALSA, U.S.A.*	L, 3 yrs	Glucose (fasting serum, measurement not specified)	Global cognition (3MS); Short-term Verbal Memory (DelRec)	Age; Sex; Education; Birth place; Depression; Stroke; MI; Smoking; Alcohol	Higher glucose associated with poorer global cognition over time
Yaffe et al., 2004	*N* = 7027 66 yrs 100% female *U.S.A.*	L, 4 yrs	Glucose (fasting blood, measurement not specified)	Global cognition (SBT); Memory (Word List); EF (TMT); VF (Word List Fluency Test); Composite (all tests)	Age; Education; Race; Depression; Smoking; Stroke; BMI; Medication	IFG (glucose > 6.10 and < 7 nmol/L) at baseline associated with greater decline in EF and composite; IFG group had 64% higher risk of cognitive impairment
Dik et al., 2003	*N* = 1318 75 yrs 51% female *LASA, The Netherlands*	L, 3 yrs	IGF-1 (non-fasting serum measured using immunoradiometric assay)	Global cognition (MMSE);Memory (RAVLT); Fluid IQ (RCPM); Information Processing (ACT)	Age; Sex; Education; BMI; ALB; Chronic disease; Functional limitations; PA; Depression	IGF-1 quintile showed positive threshold effect for information processing at baseline and 3-year follow-up with lowest quintile associated with poorer performance
Kalmijn et al., 2000	*N* = 186 67 yrs 50% female *Rotterdam Study, The Netherlands*	L, 1.9 yrs	IGF-1, IGFBP-1, IGFBP-3 (fasting serum measured using available immunoradiometric assays)	Global cognition (MMSE)	Age; Sex; Education; BMI; Fasting insulin	Higher total IGF-1 and total IGF-1/IGFBP-3 ratio associated with less cognitive decline; Free IGF: ns

Note: Studies are listed according to design (cross-sectional, longitudinal), followed by publication years, followed by alphabetical order; 12-PLT = 12-Picture Learning Test; 3MS = Modified Mini Mental State Examination; ABC = Aging and Body Composition; ACT = Alphabet Coding Task; AH4 = Alice Heim Group Ability Test; ALB = Albumin; AsIA = Asymptomatic Intracranial Atherosclerosis; BD = Block Design; BJLO = Benton Judgment of Line Orientation; BMI = Body Mass Index; BNT = Boston Naming Test; BP = Blood Pressure; BVRT = Benton Visual Retention Test; CAMCOG = Cambridge Cognition Examination; CDT = Clock Drawing Test; COWAT = Controlled Oral Word Association Test; CRP = C-reactive Protein; CRT = Choice Reaction Time; CS = Cross-sectional; CST = Concept Shifting Task; CVD = Cardiovascular Disease; DBP = Diastolic Blood Pressure; DelRec = Delayed Word Recall Test; DNMTS = Delayed-Non-Match-To-Sample; DS = Digit Span; DSST = Digit Symbol Substitution Test; EBMT = East Boston Memory Test; EDTA = Edetate Disodium; eGFR = Estimated Lobular Filtration Rate; EF = Executive Function; ELISA = Enzyme-Linked Immunosorbent Assay; GH = Growth Hormone; GPT = Grooved Pegboard Test; HDL = High-density Lipoprotein; HOMA-IR = Homeostatic Model Assessment of Insulin Resistance; HPLC = High Performance Liquid Chromatography; HRS = Health and Retirement Study; HRT = Hormone Replacement Therapy; HTN = Hypertension; HVLT = Hopkin's Verbal Learning Test; HVLT-R = Hopkin's Verbal Learning Test-Revised; IGF-1 = Insulin-like Growth Factor-1; IGFBP-1 = Insulin-like Growth Factor Binding Protein-1; IGFBP-3 = Insulin-like Growth Factor Binding Protein-3; IL-6 = Interleukin-6; IQ = Intelligence Quotient; KOCOA = Keys to Optimal Cognitive Aging; L = Longitudinal; LASA = Longitudinal Aging Study Amsterdam; LC–MS = Liquid Chromatography Mass Spectrometry; LDL = Low-density Lipoprotein; LDST = Letter-digit Substitution Test; LM = Logical Memory; MAAS = Maastricht Aging Study; MAP = Mean Arterial Pressure; MI = Myocardial Infarction; MMSE = Mini-Mental State Examination; NART = National Adult Reading Test; NHS = Nurses' Health Study; PA = Physical Activity; PLAD = Project of Longevity and Aging in Dujiangyan; PPVT = Peabody Picture Vocabulary Test; PROSPER = Prospective Study of Pravastatin in the Elderly; RAVLT = Rey Auditory Verbal Learning Test; RCPM = Raven's Coloured Progressive Matrices; RIA = Radioimmunoassay; RSPM = Raven's Standard Progressive Matrices; SBP = Systolic Blood Pressure; SBT = Short Blessed Test; SDMT = Symbol Digit Modalities Test; SHBG = Sex Hormone Binding Globulin ; TC = Total Cholesterol; TG = Triglycerides; TICS = Telephone Interview for Cognitive Status; TMIG-IC = Tokyo Metropolitan Institute of Gerontology Index of Competence; TMT-A = Trail Making Test Part A; TMT-B = Trail Making Test Part B; VF = Verbal fluency; VFT = Verbal Fluency Test; VITA = Vienna Transdanube Aging; WAIS = Wechsler Adult Intelligence Scale; WHAS-II = Women's Health and Aging Study-II; WM = Working Memory; WMH = White Matter Hypointensity; WMS-R = Wechsler Memory Scale-Revised.

Research and Care Consortium showed an association between high insulin levels and poorer performance across multiple cognitive domains in non-demented men and women, including premorbid intelligence, verbal fluency, executive function and verbal memory (Pavlik et al., 2013). Importantly, these findings were documented in the absence of diabetes. In contrast, a study of 661 men and women with a mean age of 93 years, persons with hypoinsulinemia displayed poorer global cognitive function compared to persons with normal insulin levels (Yan-Ling et al., 2014), suggesting a U-shape association between circulating insulin level and optimal cognitive performance. A similar U-shape association with dementia risk was found in men from the Honolulu-Asia Aging Study (Peila, Rodriguez et al., 2004). Longitudinal studies further suggest a relationship between serum insulin levels and cognitive change over years (Okereke et al., 2006; Okereke et al., 2010; Okereke et al., 2008; Okereke et al., 2009a; van Oijen et al., 2008). In the Nurses' Health Study of non-diabetic women, fasting plasma insulin levels measured at baseline were associated with accelerated declines in verbal memory and global cognitive function (van Oijen et al., 2008). It is important to note, however, that blood was drawn 10 years prior to baseline cognitive testing, when many of the participants were in midlife. Similar findings were reported in older men of the Physicians' Health Study II. Specifically, in men aged 60 to 92 years, higher fasting insulin was associated with declines in verbal fluency and performance on the Telephone Interview for Cognitive Status (Okereke et al., 2010). This research group has also shown that increasing levels of C-peptide, a proxy measure of insulin synthesis, is associated with declines in verbal memory (Okereke et al., 2008; Okereke et al., 2009a) and global cognitive function in women (Okereke et al., 2010; Okereke et al., 2008).

A number of studies have reported cross-sectional and longitudinal associations between measures of blood glucose and cognitive function in late life. Cross-sectional studies have reported null findings (Aleman et al., 2005; Luo et al., 2013; Yan-Ling et al., 2014) and negative associations between glucose and cognitive function, with higher circulating glucose associated with poorer global cognition (Di Bonito et al., 2007; Liu et al., 2015), visual-motor/processing speed function (Goh & Hart, 2014, 2015; Levin et al., 2014), and memory (Rolandsson et al., 2008). Similarly, longitudinal studies have reported null effects (Euser et al., 2010; van Vliet et al., 2010; Viscogliosi et al., 2016) and a negative effect of high baseline glucose levels on declines in cognitive function (Yaffe et al., 2007). In a 4-year longitudinal study of older non-demented women (Yaffe et al., 2004), it was found that impaired fasting glucose at baseline predicted greater 4-year decline in executive function and composite cognitive function among non-diabetic women. Although blood glucose has been reported to negatively impact global cognitive trajectory among older men (Yaffe et al., 2007), some research suggests that the impacts are greater in women than men (Rolandsson et al., 2008).

Studies examining the association between glycosylated hemoglobin (HbA1c) - a marker of average blood glucose concentration over the preceding three months - and cognitive function, have consistently shown negative associations with memory performance in late life (Infurna & Gerstorf, 2013; Katsumata et al., 2012; MacLullich et al., 2004). Research suggests that the relationship between blood glucose and memory is mediated by hippocampal structure and microstructure (Kerti et al., 2013). In a study evaluating 30 non-diabetic middle-aged and older adult men and women, aged 53–89 years, participants with increased serum glucose levels not only performed more poorly on cognitive tests of learning and memory, but also presented with smaller hippocampi (Convit et al., 2003).

Insulin-like growth factor 1 (IGF-1) is a neurotrophin secreted primarily by the liver following stimulation by growth hormone (GH), whose blood concentration can be affected by insulin levels and nutrient intake. Small, cross-sectional studies have reported that high IGF-1 is associated with better global cognitive performance (Aleman et al., 2001; Aleman et al., 1999; Angelini et al., 2009; Paolisso et al., 1997; Rollero et al., 1998) and executive functioning (Arwert et al., 2005; Bellar et al., 2011) in late life. In a study of 1535 older men and women from the Rancho Bernardo Study, multivariate analyses revealed a positive dose-response effect of serum IGF-1 on global cognitive function and verbal fluency in women only (Al-Delaimy et al., 2009). This sex-specific association between IGF-1 and global cognition was also found in a sample of older men and women (80% female, mean age 97 years old) from the Longevity Genes Project (Perice et al., 2016). Additional research is needed to understand sex-specific hormonal modulators of this differential relationship.

Longitudinal analyses have reported relatively consistent but modest associations between IGF-1 and cognitive trajectory (Deijen et al., 2011; Dik et al., 2003; Okereke et al., 2007). In comparing the lowest quintile to all other IGF-1 quintiles, a threshold effect was reported in the Longitudinal Aging Study Amsterdam project such that low IGF-1 associated with poorer baseline performance and greater 3-year decline in processing speed among older adults (Dik et al., 2003). In the Rotterdam Study, higher bound IGF-1, but not free IGF-1, was associated with less cognitive decline over a 2-year follow-up (Kalmijn et al., 2000) suggesting that bioavailable IGF-1 by itself may not influence cognitive function.

Additional, less investigated, metabolic biomarkers that met the systematic search criteria included leptin, resistin (Miralbell et al., 2012), creatinine (Martens et al., 2017; Ravaglia et al., 2003), uric acid (Vannorsdall et al., 2014), and albumin (La Rue et al., 1997; Taniguchi et al., 2014). These studies collectively suggest that threshold-level disturbance in metabolic function, independent of a defined metabolic disorder, may perturb cognitive performance and trajectory of cognitive function in late life.

3.4. Micronutrient biomarkers and cognitive function

Circulating micronutrients may be key biomarkers for cognitive aging in the context of behavior modification programs targeting diet. A number of cross-sectional (n = 81) and longitudinal (n = 36) studies have been published over the last three decades on the association between blood and serum micronutrient levels and cognitive function (See Table 4).

Among the various micronutrient biomarkers investigated, a vast number of studies have focused on vitamin B status (de Lau et al., 2007; Doets et al., 2014; Feng et al., 2009; Garrod et al., 2008; Hassing et al., 1999; Hausman et al., 2011; Jannusch et al., 2017; Lewis et al., 2005; Lildballe et al., 2011; Lindeman et al., 2000; McCracken et al., 2006; Michelakos et al., 2013; Mooijaart et al., 2005; Moorthy et al., 2012; Selhub et al., 2009; Tangney et al., 2011; Tettamanti et al., 2006; Xiu et al., 2012); in particular, vitamin B12 (Bernard et al., 1998; Jelicic et al., 2001; Kang et al., 2006; Morris, 2012; Tangney et al., 2009; Wahlin et al., 1996). Although serum B12 may seem to be the most direct way to measure vitamin B12 status, employing this method has resulted in inconsistent findings, which may be attributed to the vitamin's low bioavailability for cellular uptake (Quadros & Sequeira, 2013). However, other measures of B12 status including homocysteine (Hcy), methylmalonic acid (MMA), and holotranscobalamin (holoTC), have fared better in predicting cognitive function and cognitive trajectory over time. In addition to its inflammatory properties, Hcy is a non-protein-derived amino acid that is commonly used as a marker for vitamin B status including vitamin B12 and folic acid (Jacques et al., 2001). Although Hcy levels are not found to differentiate between stages of cognitive impairment (e.g., cognitively intact vs. impaired without dementia vs. impaired with dementia) (Ravaglia et al., 2000), high levels of Hcy tend to consistently associate with poorer performance on measures of global cognition and executive function in both cross-sectional (Aleman et al., 2005; Allam et al., 2013; Budge et al., 2000; Budge et al., 2002; Cheng et al., 2010; Clarke et al., 2008; Di Bonito et al., 2007; Duthie et al., 2002; Elias et al., 2006; Elias et al., 2008; Elias et al., 2005; Feng et al., 2006; Ford et al., 2012; Hin et al.,

Table 4
Systematic Review Antioxidants, Minerals, Vitamins and Vitamin Proxy Biomarkers.

Study	Sample Size Mean Age Gender %female *Cohort/ Location*	Study design (CS/L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect Modifiers*	Adjusted Model Results
Cross-sectional Studies						
Jannusch et al., 2017	*N* = 657 67 yrs 46%female *1000BRAINS Study, Germany*	CS	B1, B6 (fasting and measurement not specified)	Episodic Memory (VG, BVRT); EF (TMT-A&B, 5-Punkte-Test, L50 + (Subtest 3), FWI); WM (CBTT, Visual Pattern, Zahlennachsprechen);Attention (AKT, TMT-A); Language (Wortschatztest, RW)	Age; Sex	Higher B1 associated with poorer visual WM and problem solving performance; B6: ns
Lee et al., 2017	*N* = 2940 72 yrs 67% female *Korean Urban Rural Elderly Cohort Study, Korea*	CS	25(OH)D (fasting serum measured using chemiluminescence immunoassay)	Global cognition (Korean MMSE)	Age; Sex; Education; Smoking; Alcohol; PA; MI; Stroke; Depression; Residential site; Season	Low 25(OH)D (< 25 nmol/L) associated with increased risk of cognitive impairment (MMSE < 22)
Annweiler et al., 2016	*N* = 2273 70 yrs 45% female *SEED Study, Singapore*	CS	25(OH)D (non-fasting serum measured using ECLIA)	Global cognition (AMT)	Age; Sex, Smoking; Alcohol; Education; Race; BMI; MAP; Glasses use; Gait disorders; Anxiodepressive disorders; HbA1c; LDL; eGFR	High 25(OH)D (> 20 ng/mL) associated with better global cognition compared with deficient and insufficient levels
Bradburn et al., 2016	*N* = 225 74 yrs 52% female *MyoAge Study, England, France, The Netherlands, Estonia, Finland*	CS	Osteocalcin (vit K proxy) (fasting plasma measured using commercial multiplex immunoassays)	Global cognition (MMSE); Memory (CANTAB Paired Associate Learning); WM (CANTAB Spatial Span); EF (CANTAB One Touch Stockings)	Age; Education; Country; *Effect modifier:* Sex	*In females*: High osteocalcin associated with global cognition and EF only; *In males*: ns
Hsu et al., 2016	*N* = 225 68 yrs 50% female *Taiwan*	CS	Hcy (fasting plasma, measurement not specified)	Global cognition (MMSE, CASI, SOB); Memory (Taiwanese Word Sequence Learning Test); EF (mWCST); Attention (DS, DSST); Language (VFT); Visuospatial (3D Block Construction Models)	Age; Sex; HTN; Education; Diabetes; Smoking; TC	Higher Hcy associated with lower global cognition, language, visuospatial skills, DSST
Lam et al., 2016	*N* = 179 66 yrs 64% female *U.S.A.*	CS	25(OH)D (fasting serum measured using commercially available enzyme-immunoassay)	Memory (RAVLT); Attention (DS)	Age; Sex; Depression; Anxiety; Stress; NART; Ionised calcium; PTH	Higher 25(OH)D associated with poorer memory only
Pettersen et al., 2016	*N* = 142 55 yrs 72% female *Canada*	CS	25(OH)D (fasting not specified, plasma measured using HPLC tandem mass spectrometry)	Memory (CANTAB-Verbal Recognition Memory-Recall); EF (VFT, DS, CANTAB-Spatial WM); Attention (DS forward)	Age; Sex; Education; BMI; Depression; PA	Supratherapeutic vit D (25(OH)D > =100nmol/L) associated with better verbal fluency than insufficient, low sufficient, and high sufficient levels
Polito et al., 2016	*N* = 903 74 yrs 51% female *InveCe.Ab Study, Italy*	CS	Hcy, folate, B12 (fasting serum measured using chemiluminescent micropartide immunoassay)	Global cognition (MMSE); Memory (BSRT, RAVLT); EF (RCPM, CDT); Attention (AM, TMT-A&B); Language (SVFT); Visuospatial (ROCF)	Age; Sex; Education; SBP; Diabetes; CVD; Stroke/ TIA; Hypercholesterolemia, MTHFR C677 T CT, MTHFR C677 T TT, APOE	Higher Hcy associated with poorer EF only; Folate, B12: ns
Brouwer-Brolsma et al., 2015	*N* = 846 73 yrs 41% female *B-PROOF Study, The Netherlands*	CS	25(OH)D (fasting serum measuring using isotope dilution-online solid phase extraction LCTMS)	Global cognition (MMSE); Memory (RAVLT); Attention, WM (DS); Processing speed (TMT-A, SDMT); Concept-shifting Interference (TMT-B); Inhibition (Stroop)	Age; Sex; BMI, Education; Alcohol; Smoking; PA; Season; Center; Depression; Creatinine	Highest 25(OH)D tertile associated better attention and WM only
Lu et al., 2015	*N* = 611 72 yrs 57% female *China*	CS	Thiamine, TDP (fasting blood measured using HPLC fluoroscopy)	Global cognition (MMSE)	None	Higher TDP associated with better global cognition; Thiamine: ns
Chei et al., 2014	*N* = 2004 85 yrs 53% female *CLHLS, China*	CS	25(OH)D (fasting plasma measured using ELISA)	Global cognition (Chinese MMSE)	Age; Sex; Education; BMI; SBP, DBP; eGFR; Smoking; Alcohol; Outdoor activities; ADL; Depression; Study site; Glucose; Glyceride; TC	Higher 25(OH)D associated with better global cognitive function and decreased odds of impairment

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Table 4 (*continued*)

Study	Sample Size Mean Age Gender %female *Cohort/ Location*	Study design (CS/L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect Modifiers*	Adjusted Model Results
Annweiler et al., 2014	*N* = 110 71 yrs 56% female *GAIT Study, France*	CS	25(OH)D (fasting serum measured using RAI)	Global cognition (MMSE); Mental Flexibility (TMT-B); WM (N-back test); Inhibition (Stroop Interference Test); Motor Inhibition (Go/No-Go Task)	Age; Sex; BMI; Education; Comorbidities; Depression; MMSE score; Calcemia; eGFR	Deficient 25(OH)D (< 25 nmol/L) associated with poorer mental flexibility compared with insufficient (25-50 nmol/L) and sufficient (> 50) group
Doets et al., 2014	*N* = 2203 72 yrs 55% female *Hordaland Health Study, Norway*	CS	Folate, B12, Hcy (fasting not specified, plasma folate and B12 measured using microbiological assays; plasma Hcy measured using automated HPLC assay)	Overall cognition (summary score by factor loading of DST, BD, KOLT, COWAT, TMT-A)	Sex; Education; CVD; HTN; APOE; Creatinine; *Effect modifier:* B12 by folate	Folate: Higher folate associated with better cognitive function; B12, Hcy: ns; *Effect* of folate on cognition stronger in lower B12 levels
Milman et al., 2014	*N* = 253 97 yrs 74% female *Longevity Genes Project, U.S.A*	CS	25(OH)D (fasting not specified, serum measured using LCTMS)	Global cognition (MMSE, Blind MMSE); EF (CDT-Command); Visuospatial (CDT-Copy)	Age; Sex; Education; BMI; Smoking; Depression; HDL; Comorbidities	Insufficient 25(OH)D (< 30 ng/mL) associated with greater global cognitive impairment (MMSE < 25/30, or Blind MMSE < 16/22) and visuospatial impairment (CDT copy < 8/10)
Allam et al., 2013	*N* = 45 68 yrs 29% female *Egypt*	CS	Hcy (fasting plasma measured using EDTA)	Global cognition (MMSE, ACE)	Age; Education	Higher Hcy associated with poorer global cognition
Brouwer-Brolsma et al., 2013a	*N* = 103 75 yrs *sex not specified *SENECA Study, The The Netherlands*	CS	25(OH)D (fasting plasma measured using competitive protein-binding assay)	Global cognition (MMSE)	Age; Sex; BMI; Education; Smoking; Alcohol; PA; Center; Calcium intake	ns
Brouwer-Brolsma, van de Rest et al., 2013	*N* = 127 79 yrs 61% female *ProMuscle Study, The Netherlands*	CS	25(OH)D (fasting serum measured using mass spectrometry)	Global cognition (MMSE); Memory (Word Learning Test); Attention, WM (DS); Processing Speed (TMT-A &B, Stroop); EF (Stroop, VFT, TMT-B/A, Reaction Time Task)	Age; Sex; Education; BMI; Alcohol; Smoking; PA; Season	Higher 25(OH)D associated with better EF and processing speed
Johnson et al., 2013	*N* = 298 96 yrs 79% female *GCS, U.S.A.*	CS	Lutein, zeaxanthin, cryptoxanthin, α-carotene, β-carotene, lycopene, α-tocopherol, retinol (fasting not specified, serum measured using HPLC)	Global cognition (MMSE); Memory (FOME); Abstract Reasoning (WAIS-III Similarities Subtest); Verbal Fluency (COWAT)	Age; Sex; Education; Diabetes; HT; BMI; Smoking; Alcohol	Lutein: Higher lutein associated with better memory, verbal fluency, and abstract reasoning; Zeaxanthin: Higher zeaxanthin associated better all measures of cognition; Cryptoxanthin: Higher cryptoxanthin associated with better abstract reasoning only; β-carotene: Higher β-carotene associated with better memory, verbal fluency, and abstract reasoning; α-tocopherol: Higher α-tocopherol associated with better memory and abstract reasoning; α-carotene, lycopene, retinol: ns
Kong et al., 2013	*N* = 662 66 yrs 57% female *China*	CS	Hcy (fasting serum measured using enzyme catalysis assay)	Global cognition (MMSE, BCAT)	Age; Sex; Education	Higher Hcy associated with poorer BCAT scores only
Michelakos et al., 2013	*N* = 593 Age range 65-80 + yrs 57% female *Velestino Study, Greece*	CS	Folate, B12 (fasting blood, measurement not specified)	Global cognition (MMSE)	Age; Education; Social activity; Depression; *Effect modifier*: Sex	*In females*: Low folate associated with cognitive impairment (MMSE < 24/30); *In males*: ns; B12: ns

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Table 4 (*continued*)

Study	Sample Size Mean Age Gender %female *Cohort/ Location*	Study design (CS/L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect Modifiers*	Adjusted Model Results
Nurk et al., 2013	*N* = 2195 70-74 yrs. 55% female *Hordaland Health Study*	CS	Betaine and choline (non-fasting plasma measured using normalized liquid chromatography = tandem MS detection)	Global cognition (MMSE); Memory (Kendrick Object Learning Test); Perceptual speed and EF (m-DST); Sensorimotor speed (TMT-A); Visuospatial (m-BD);VF (COWAT)	Sex, education, APOE4, CVD, smoking, plasma folate, plasma creatinine, MMA genotype; *Effect modifier*: vitamin B12	Higher choline (> 8.4umol/l) associated with better sensorimotor speed, EF, and global cognition; Combined low choline and betaine increased risk of poor visuospatial skills; Low choline combined with low B12 increased poor global cognition; Low betaine combined with low B12 increased poor memory
Presse et al., 2013	*N* = 320 76 yrs 54% female *NuAge, Canada*	CS	Phylloquinone (vit K) (serum, measured using standardized HPLC procedures)	Verbal Memory (RL/RI-16 FCRT); Visual Memory (ROCF-recall); EF (ROCF-Copy, Stroop, Brown Peterson Test-Interference, DSST); Processing Speed (Stroop, CRT)	Age; Sex; Tester; Education; BMI; Diabetes; HTN; Depression; Smoking; Alcohol; PA; Vitamin/mineral supplements; Diet; Lipids	Higher vit K associated with better verbal memory only
Ford et al., 2012	*N* = 1778 82 yrs 0% female *HIMS, Australia*	CS	Hcy (fasting plasma measured using reverse-phase HPLC as per Araki & Sako method)	Global cognition (TICS)	Age; Education; Depression; PA; Stroke; Diabetes; CVD; HTN; Smoking; Alcohol; Head injury; Renal function; Thyroid function; Lipids; Glucose; BMI; SBP; DBP	Higher Hcy associated with increased risk of cognitive impairment (TICS ≤ 27)
Menant et al., 2012	*N* = 463 78 yrs 54% female *Memory and Ageing Study, Australia*	CS	25(OH)D (fasting not specified, serum measured using direct competitive chemiluminescent immunoassay)	Global cognition (MMSE); Attention, Processing Speed (DSMT);Visuospatial (BD); Motor Speed and Task-switching (TMT-A &B)	Age; Education	Lower 25(OH)D associated with poorer task-switching ability and visuospatial skills only
Moorthy et al., 2012	*N* = 1955 68 yrs 74% female *BPRHS & NAME Study, U.S.A.*	CS	Folate, B12, B6, Hcy (fasting not specified, plasma Hcy measured using HPLC; folate and B12 measured using Immulite chemiluminescent assay; B6 measured using tyrosine decarboxylase apoenzyme method)	Global cognition (MMSE); Memory, EF, Attention (tests not disclosed)	Age; Sex; Education; APOE; Kidney function; Diabetes; HTN	B12: Lower B12 associated with poorer global cognition; B6: Lower B6 associated with poorer global cognition, attention and EF; Folate, Hcy: ns
Xiu et al., 2012	*N* = 1412 Age range 65-97 yrs 47% female *NAHSIT, Taiwan*	CS	Hcy, B1, B2, B6, folate, B12 (fasting not specified, plasma Hcy measured using automated analyzer; additional techniques unknown)	Global cognition (SPMSQ)	Age; Sex; Education; Race; Substance abuse; PA; Home region; Financial status; Comorbidities; Energy intake; Diet; Vitamin intake	ns
Chan et al., 2011	*N* = 939 73 yrs 0% female *Os Study, Hong Kong*	CS	25(OH)D (fasting serum measured using competitive RIA)	Global cognition (CSI-D)	Age; BMI; PA; ADL; Diet; Smoking; Alcohol; Season; Chronic diseases; PTH	Ns
Hausman et al., 2011	*N* = 276 96 yrs 80% female *GCS, U.S.A.*	CS	Folate, B12 (non-fasting blood measured using Quantaphase ii B12/ folate radioassay)	Global cognition (MMSE)	None	ns
Llewellyn et al., 2011	*N* = 3325 74 yrs 55% female *NHANES III, U.S.A.*	CS	25(OH)D (fasting not specified, serum measured using RAI)	Global cognition (MMSE); Memory (MMSE, EBMT); Attention (DS)	Age; Sex; Race; Education; Season; Smoking; BMI; Alcohol; Income; Mobility; PA; Stroke; Diabetes; HTN; vit E	Sufficient vit D (> = 75 nmol/L) associated with better cognition than insufficient (25(OH)D > = 50 < 75 nmol/L), deficient (> = 25 < 50 nmol/L) and severely insufficient (< 25 nmol/L) vit D levels

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Table 4 (*continued*)

Study	Sample Size Mean Age Gender %female *Cohort/ Location*	Study design (CS/L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect Modifiers*	Adjusted Model Results
Lildballe et al., 2011	*N* = 839 75 yrs 61% female *England*	CS	B12, holoTC, MMA, Hcy (fasting not specified, serum B12 measured using ACS Centaur system; holoTC measured using RIA; MMA measured using GC-MS; Hcy measured using Abbott IMx autoanalyzer)	Global cognition (MMSE)	Age; Sex; Diabetes; CVD; Depression; Smoking; H2-antagonist treatment	Lower B12 and holoTC each associated with risk of cognitive impairment (MMSE < 22); Higher MMA and Hcy each associated with risk of cognitive impairment
Tangney et al., 2011	*N* = 121 79 yrs 51% female *CHAP, U.S.A.*	CS	B12, MMA, Hcy, MCA (non-fasting serum, B12 measured by competitive displacement immunoassay; MMA, Hcy, MCA measured using stable-isotope dilution and capillary GC-MS)	Memory (Word List Memory, LM); WM (DS, Digit Ordering); Verbal Fluency (BNT, NART-Short Form); Visuospatial (JLOSPM); Perceptual speed (SDMT, Number Comparisons);	Age; Sex; Education; Race; Smoking; Alcohol; BMI; HTN; APOE; Creatinine	Higher levels of each marker (but not vitamin B12 itself) associated with lower global cognition; Higher MMA and MCA associated with lower episodic memory; MMA negatively associated with perceptual speed; Higher MCA associated with lower semantic memory
West et al., 2011	*N* = 199 87 yrs 40% female *U.S.A.*	CS	Hcy, B12, folate (fasting serum measurement not specified)	Memory (Immediate and Delayed Recall, Recognition, Savings);EF, Language (TMT-A&B, Letter Cancellation, SVFT, Shipley Vocabulary Test, BNT)	Age; Sex; Education; Smoking; APOE; Serum B12; Serum folate	Higher Hcy associated with poorer EF/language only; B12, folate; ns
Cheng et al., 2010	*N* = 182 72 yrs 54% female *China*	CS	Hcy (fasting plasma measured using enzymatic conversion method using a Total Hcy Bichemical Assay kit by automatic biochemical analyzer)	Global cognition (BCAT)	Age; Education	High Hcy (≥ 16 μM) associated with lower BCAT
Seamans et al., 2010	*N* = 387 65 yrs 49% female *ZENITH Study, Ireland, France, Italy*	CS	25(OH)D (fasting serum measured using commercially available ELISA)	Visual Memory, WM, Attention (CANTAB)	Age; Sex; BMI; RBC-Zn status; Season; Center; *Effect modifier:* Sex	Higher 25(OH)D associated with better cognitive function; Fewer cognitive errors in third tertile of 25(OH)D compared to first tertile; *Sex*: Association stronger in females than men
Buell et al., 2009	*N* = 1080 75 yrs 76% female *NAME Study, U.S.A.*	CS	25(OH)D (fasting blood measured using Diasorin I RIA assay)	Verbal intelligence (NART); Memory (LM, Word List Learning); EF, Processing Speed (DSST, TMT, Mental Alternations, BD); Abstract Thinking (MR); Verbal Fluency (COWAT)	Age; Sex; Race; Education; BMI; Center; Kidney function; Season; PA; Alcohol; Hcy; APOE; Vitamin supplement	Higher 25(OH)D associated with better EF/processing speed, abstract thinking
Feng et al., 2009	*N* = 539 65 yrs 60% female *SLSA, Singapore*	CS	B12 (fasting blood measured using radioassay with Elecsys reagent kit)	Global cognition (MMSE); Episodic Memory (RAVLT Immediate Recall); Visual Memory (SDMT); Attention, WM (DS forward and backward); Information Processing (VRT)	Age; Sex; Education; Smoking; Alcohol; HTN; Diabetes; CVD; PA; *Effect modifier*: APOE	Higher B12 associated with better episodic memory, WM and global cognition in APOE e4(+) only
Lee et al., 2009	*N* = 3133 60 yrs 0% female *EMAS, Italy, Belgium, Poland, Sweden, England, Spain, Hungary, Estonia*	CS	25(OH)D (fasting serum measured using RAI)	Memory (CTRM); Processing Speed (DSST); Visuospatial (ROCF)	Age; Education; Depression; BMI; PA; Physical performance; Smoking; Alcohol; Center; Season; *Effect modifier*: Age decade	Higher 25(OH)D associated with better processing speed only; *Age:* Association restricted to older males
Llewellyn et al., 2009	*N* = 1766 78 yrs 60% female *Health Survey for England 2000*	CS	25(OH)D (non-fasting serum measured using DiaSorin Kit)	Global cognition (AMT)	Age; Sex; Education; Race; Season; Smoking; Alcohol; Mobility; Albumin; Psychiatric morbidity; Medical history	Lowest 25(OH)D quartile associated with increased odds of cognitive impairment (AMT score < 7/10).

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Table 4 (*continued*)

Study	Sample Size Mean Age Gender %female *Cohort/ Location*	Study design (CS/L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect Modifiers*	Adjusted Model Results
Selhub et al., 2009	*N* = 1302 60 + yrs 100% female *NHANES-III, U.S.A.*	CS	Folate, B12, MMA (fasting serum, measurement not specified)	EF (DSST)	None	B12: Low B12 (< 148 pmol/L or serum MMA > 210 nmol/L) associated with cognitive impairment (score < 34/133); Folate: High folate (> 59 nmol/L) with normal B12 associated with lower impairment; Low B12 and high folate associated with highest impairment; MMA: ns
Tassino et al., 2009	*N* = 205 71 yrs 70% female *Brazil*	CS	Hcy (fasting not specified, serum measured using chemical luminescence method)	Global cognition (MMSE)	Age; Education; Folate	Higher Hcy associated with lower MMSE score
Clarke et al., 2008	*N* = 2403 79 yrs 59% female *OHAP & Banbury, England*	CS	B12, folate, Hcy (frozen serum samples thawed; Hcy measured using fluorescence polarization immunoassay in the OHAP and by GC-MS in Banbury cohort; B12 measured using automated chemiluminescence system; folate measured using microbiological method)	Global cognition (MMSE)	Age; Sex; Smoking; Study cohort	B12, folate: Compared with highest tertile, mid and low tertile folate and low tertile of B12 associated with cognitive impairment (MMSE < 23/30); Hcy: compared with lowest Hcy, mid and high Hcy tertile associated with impairment
Elias et al., 2008	*N* = 911 62 yrs 59% female *Main-Syracuse Study, U.S.A.*	CS	Hcy (fasting plasma measured using fluorescence polarization immunoassay)	Global cognition (MMSE); Global composite (Visuospatial Memory and Organization, Scanning and Tracking, Verbal Episodic Memory and WM); WM; Similarities (standardized scores generated from HRNTB and WAIS III)	Age; Education; Sex; Race; Previous cognitive exams; CVD; B12; *Effect modifier*: APOE	APOE e4(-): no associations found; APOE(+): Higher Hcy associated with lower global cognition, global composite, Similarities, WM
Garrod et al., 2008	*N* = 1089 70 yrs 59% female *SALSA, U.S.A.*	CS	B12, holoTC (fasting plasma, B12 measured using radioligand binding assay; holoTC measured using monoclonal antibody capture followed by radioligand binding assay)	Global cognition (3MS); Memory (Word List)	Age; Sex; Education; Diabetes; Stroke; Depression; Hcy, Creatinine; *Effect modifier*: Depression	High holoTC and holoTC:B12 ratio associated with better global cognition only; B12: ns; *Depression:* Association between holoTC:B12 and cognition restricted to high Depression
Koike et al., 2008	*N* = 124 75 yrs 57% female *Japan*	CS	Hcy, folate, B12, (fasting, plasma Hcy measured using HPLC; serum folate and B12 measured using chemiluminescient immunoassay)	Global cognition (MMSE)	Age; Sex; BMI; Creatinine; Diabetes; Smoking; Alcohol	Higher Hcy associated with poorer cognition; Higher Folate and B12 each associated with better cognition
Lam et al., 2008	*N* = 1451 75 yrs 59% female *Rancho Bernardo Study, U.S.A.*	CS	Zinc, copper, iron (fasting plasma measured using rapid simultaneous assay)	Global cognition (MMSE); Memory (Buschke-Fuld Selective Reminding Test, Heaton Visual Reproduction Test); Concentration (BIMCT);Visuomotor Tracking, Attention (TMT-B);Verbal Fluency (SVFT)	Age; Education; Alcohol; Smoking; PA; Estrogen use for females; *Effect modifier*: Sex	*In females:* Higher zinc associated with higher BIMCT scores; Higher iron and copper levels associated with lower scores on Buschke test; *In men:* Inverted U relationship of iron; Low and high iron associated with poorer memory and serial 7 s; high and very low copper levels associated with worse TMT-B scores
Ravaglia et al., 2008	*N* = 666 74 yrs 53% female *Conselice Study, Italy*	CS	α-tocopherol (fasting plasma measured using reverse-phase HPLC)	Global cognition (MMSE)	Age; Sex; Education; APOE; Smoking; PA; BMI; Diet; CVD; Stroke	ns

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Table 4 (*continued*)

Study	Sample Size Mean Age Gender %female *Cohort/ Location*	Study design (CS/L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect Modifiers*	Adjusted Model Results
Akbaraly et al., 2007a	*N* = 589 74 yrs 61% female *EVA Study, France*	CS	Carotenoids: lutein, zeaxanthin, β-cryptoxanthin, lycopene, α-carotene, trans-β-carotene, cis-β-carotene, total carotenoids (fasting not specified, plasma measured using HPLC)	Global cognition (MMSE); EF (TMT-A&B, DSS); Verbal Fluency (VFT); Psychomotor Speed (FTT)	Age; Sex; Education; Smoking; Alcohol; Medication; BMI; Diabetes; HTN	Zeaxanthin: Higher zeaxanthin associated with better EF, verbal fluency, and psychomotor speed; Lycopene: Higher lycopene associated with higher scores on TMT-B and DSS; Lutein, β-cryptoxanthin, α-carotene, trans-β-carotene, cis-β-carotene, total carotenoids: ns
de Lau et al., 2007	*N* = 1033 72 yrs 52% female *RSS, The Netherlands*	CS	Folate (non-fasting plasma measured using microbiological assay)	Global cognition compound (reading Stroop, Paper-and-Pencil Memory Scanning Task, LDST, immediate/delay recall); Memory compound (immediate/delay recall); Psychomotor compound (reading Stroop, Paper-and-Pencil Memory Scanning Task, LDST)	Age; Sex; Alcohol; Smoking; Diabetes; Depression; SBP; Medication; Intima-media thickness; Vitamin intake; Creatinine; B12; Hcy	Higher folate associated with better global cognitive function, psychomotor speed, and memory
Di Bonito et al., 2007	*N* = 182 72 yrs 67% female *Italy*	CS	Hcy (fasting plasma measured using immunoenzymatic method)	Global cognition (MMSE)	Age; Sex; Creatinine; Folate	Higher Hcy associated with poorer MMSE; Odds for impaired cognition (MMSE < 24) significantly associated with increased Hcy
Dunn et al., 2007	*N* = 526 60+ yrs 100% female *Cognitive Change in Women Study, U.S.A.*	CS	α-tocopherol (non-fasting serum measured using HPLC)	Memory (Word List Learning Test, LM, Visual Reproduction subtests); Language (BNT, FAS); Visuospatial (Constructions Test, JLOSPM, Visual Target Cancellation Test); Attention (DS); EF (TMT, Visual Verbal Test)	Age; NART	Lowest α-tocopherol quartile associated with increased odds of memory impairment and impairment in 2+ cognitive domains [impairment = 2 SD below the mean for each test stratified by age and education]
Elias et al., 2006	*N* = 812 62 yrs 58% female *Maine-Syracuse Study, U.S.A.*	CS	Hcy, B6, folate (fasting plasma, Hcy measured using fluorescence polarization immunoassay; B6 measured using HPLC; folate and B12 measured using paramagnetic particle chemiluminescent immunoassay)	Global composite score (all scales); Visuospatial (VRT, MR, BD, Object Assembly, Hooper Visual Organization Test); Scanning and Tracking Composite (TMT-A&B, DSD, Search Symbol); Verbal Memory Composite (LM, HVLT); WM Composite (DS, Letter-Number Sequence, COWAT); Abstract Reasoning (Similarities)	Age; Sex; Education; Race; Prior testing; CVD; Depression; Diabetes; SBP; Smoking; Alcohol; BMI; Renal function; Coffee intake; APOE; TC, CRP; B6, B12, folate, Hcy	Hcy: Higher Hcy associated with lower composite scores, except verbal memory composite; Folate: Higher folate associated with higher global composite, similarities; B6: High B6 associated with higher scores on all composite scores except verbal memory composite
Feng et al., 2006	*N* = 451 64 yrs 60% female *SLSA, Singapore*	CS	Hcy, folate, B12 (fasting plasma Hcy determined with automated chemiluminescent enzyme immunoassay; serum folate and B12 determined by radioassay kit)	Attention, WM (DS and Spatial Span); Episodic Memory (RAVLT); Visual Memory (Visual Reproduction); EF (Design Fluency, Trails A&B); Verbal Fluency (SVFT); Processing Speed (SDMT); Visuospatial (BD)	Age; Sex; Education; Smoking; Alcohol; BMI; Cholesterol; HTN; Diabetes; CVD; Renal function; Depression; Creatinine	Higher Hcy associated with lower visuospatial skills and processing speed; Higher folate associated with better verbal fluency and memory; B12: ns
Hin et al., 2006	*N* = 1000 81 yrs 60% female *England*	CS	B12, holoTC, MMA, Hcy, folate (fasting not specified, serum B12 measured using Beckman immunoassay; holoTC measured using RAI; MMA and Hcy measured using stable isotope-dilution capillary GC-MS; folate measured using microbiological assay)	Global cognition (MMSE)	Age; Sex; Smoking	Lowest quartile for B12, holoTC, and folate associated with increased impairment (MMSE < 22/30); Highest quartile of MMA and Hcy associated with increased impairment
McCracken et al., 2006	*N* = 84 78 yrs 50% female *Cognitive Function and Ageing Study, Wales*	CS	HoloTC, B12, folate, MMA, (non-fasting blood, HoloTC measured using RAI; B12 and folate measured using immunoassay analyser; MMA quantified using in-house GC-MS method)	Global cognition (MMSE, CAMCOG)	Age; Sex; Education; Creatinine; Folate/B12/ MMA/HoloTC	Higher MMA associated with lower MMSE score, lower CAMCOG-language comprehension, COMCOG-language expression, CAMCOG-ideation, and CAMCOG-praxis; Higher folate associated with better total CAMCOG score, CAMCOG-remote memory score, CAMCOG-ideation, and CAMCOG-praxis; HoloTC, B12: ns

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Study	Sample Size Mean Age Gender %female *Cohort/ Location*	Study design (CS/L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect Modifiers*	Adjusted Model Results
Tettamanti et al., 2006	*N* = 471 87 yrs 77% female *Monzino 80-plus Study, Italy*	CS	B12, folate (fasting serum measured using microparticle enzyme immune-assay)	Global cognition (MMSE)	Age; Sex; Education; Smoking; HTN; Diabetes; MI; Stroke; Creatinine; Folate or B12	Higher folate associated with better MMSE scores; B12: ns
Aleman et al., 2005	*N* = 400 60 yrs 0% female *The Netherlands*	CS	Hcy (fasting serum measured using fluorescence polarization immunoassay on IMx analyzer)	Global cognition (MMSE); Memory (Dutch RAVLT, Doors Test); Short Term Memory (DS); EF, Attention (TMT- A&B); Psychomotor Speed (DSST); Verbal Intelligence (DART)	Age; Education	Higher Hcy associated with lower processing capacity and speed
Elias et al., 2005	*N* = 705 65 yrs 51% female (Older adult subset) *Framingham Offspring Study, U.S.A.*	CS	Hcy (fasting plasma measured using HPLC with fluorimetric detection)	Memory (Paired Associate Learning, LM, VRT); EF (TMT); Abstract Thinking (Similarities); Visuospatial (Hooper Visual Organization Test);Verbal Fluency (BNT); Composite cognition score (all measures)	Age; Sex; Education; Folate; B6; B12	Higher Hcy associated with lower composite cognitive score, abstract thinking, memory, visuospatial and verbal fluency (Note: ns in younger subgroups, not presented here)
Lewis et al., 2005	*N* = 116 76 yrs 82% female *U.S.A.*	CS	MMA (non-fasting serum measured using capillary GC-MS)	Attention, WM (Number Recall and Sequencing); Spatial Memory, Learning (Object Memory Test, Pictorial Incident Learning); Processing Speed (Symbol Scanning, Pictorial Animal Decoding); Nonverbal Reasoning (MR); Verbal Fluency (COWAT)	Age; Sex; Education; Race; Creatinine; B12	Higher MMA associated with poor performance on nonverbal reasoning only
Schafer et al., 2005	*N* = 1140 59 yrs 66% female *Baltimore Health Study, U.S.A.*	CS	Hcy (non-fasting serum measured using fluorescence polarization immunoassay)	Memory (RAVLT, ROCF, Symbol Digit, Paired Associate Learning); EF (PPB, Stroop, TMT-B); Language (BNT, Category and Letter Fluency); Conceptual Reasoning (RCPM); Psychomotor Speed (FTT, SRT, PPB); Visuoperception (ROCF-copy, TMT-A)	Age; Sex; Education; Race; BMI; Alcohol; Smoking; TC; Stroke; CVD; HTN; Diabetes; Kidney disease; APOE	Higher Hcy associated with lower scores on all tests except BNT, Stroop, and ROCF delayed recall
Bunce et al., 2004	*N* = 167 83 yrs 80% female *Sweden*	CS	B12, folate (fasting not specified, serum measured using RAI)	Memory (Word Recall List)	Age; Sex; Education; *Effect modifier*: APOE	Low B12 associated with poorer memory in APOE e4(+) only; Folate: ns
Garcia et al., 2004	*N* = 281 73 yrs 75% female *Canada*	CS	B12, MCA, Hcy (fasting blood measured using GC-MS and HPLC)	Memory (CVLT); EF (Stroop)	Age; Sex; Education	Higher MCA associated with lower memory only; B12, Hcy: ns
Ravaglia et al., 2004	*N* = 62 73 yrs 47% female *Conselice Study, Italy*	CS	Hcy, folate, B12 (fasting, serum folate and B12 measured using immediate immuno-ECLIA analysis; plasma Hcy measured with fully automatized IMx assay)	Global Cognition (MMSE); Memory (Prose Memory Test, RVLT, Visual Memory Test, CBTT); Verbal Fluency (Phonemic Word Fluency, Sentence Construction); Visuospatial (CBTT); Logical Reasoning (RPMT); Copy (Constructional Praxis)	Age; Education; Creatinine	Higher Hcy associated with poorer MMSE scores and phonemic word fluency only; B12, Folate: ns
Miller et al., 2003	*N* = 1,789 70 yrs 58% female *SALSA, U.S.A.*	CS	Hcy (fasting plasma measured using HPLC with post-column fluorescence detection)	Global cognition (3MS); Memory (Delayed-Recall Scale); Language (Object-Naming Scale, PAS); Abstract Thinking (Verbal Conceptual-Thinking Scale); Attention (Verbal Attention-Span Scale); Visuospatial (Pattern-Recognition Scale)	Age; Sex; Education; Acculturation; RBC folate; plasma B12; Serum creatinine; Depression	Higher Hcy associated with poorer global cognition, PAS, verbal attention, and pattern recognition only
Ravaglia et al., 2003	*N* = 650 73 yrs 55% female *Conselice Study, Italy*	CS	Hcy, folate, B12, (fasting, plasma Hcy measured using fully automatized IMx assay; serum folate and B12 measured using immediate immuno-ECLIA analysis)	Global cognition (MMSE)	Age; Sex; Education; Income; Creatinine; B vitamin index; Active lifestyle; Coffee and meat intake; BMI; HTN; CVD; Diabetes	Higher Hcy associated with lower global cognition; B12, folate: ns

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Study	Sample Size Mean Age Gender %female *Cohort/ Location*	Study design (CS/L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect Modifiers*	Adjusted Model Results
Budge et al., 2002	*N* = 158 74 yrs 49% female *England*	CS	Hcy (non-fasting serum measured using Abbott-Axis Imx immunoassay)	Global cognition (MMSE, CAMCOG)	Education; Depression; DBP; BMI; Medication; Diabetes; Serum folate, B12, cystatin C; Smoking; *Effect modifier:* Age	Higher Hcy associated with lower CAMCOG score only; *Age:* Association strongest in males aged 70 +
Duthie et al., 2002	*N* = 331 Age range 66-81 yrs 50% female *Scotland*	CS	Hcy, folate, B12, (fasting plasma and erythrocyte folate and B12 measured using Simultrac Radioassay Kit; plasma Hcy measured by reverse-phase HPLC with DS30 Hcy Assay Kit and DS30 analyzer)	Global Cognition (MMSE); Memory (RAVLT); Language (NART); Abstract Thinking (RCPM); EF (DSST, BD)	Sex; Childhood IQ	Hcy: Higher Hcy associated with poorer global cognition, abstract thinking, and EF; B12: Higher B12 associated with better global cognition and language; Folate: Higher folate with better global cognition, memory, language, EF
Ortega et al., 2002	*N* = 120 71 yrs 72% female *Spain*	CS	α-tocopherol (fasting serum measured using reversed-phase HPLC)	Global Cognition (Spanish SPMSQ)	None	Lower α-tocopherol associated with worse global cognition
Prins et al., 2002	*N* = 1077 72 yrs 51% female *RSS, The Netherlands*	CS	Hcy (non-fasting measured using fluorescence polarization immunoassay using an IMx analyzer)	Global Cognition (MMSE); Memory Composite (Immediate and Delayed Recall); Psychomotor Speed Composite (Stroop, LDST, Letter Subtask of Memory Scanning Test); Global composite (z-scores of all tasks)	Age; Sex; Education; Depression; Creatinine; Alcohol; Smoking	Higher Hcy associated with lower composite psychomotor, memory and global cognitive scores; Highest Hcy quintile vs all other quintiles associated with poorer performance on all tests except MMSE, Memory Scanning Task, and immediate and delayed recall of VFT
Stewart et al., 2002	*N* = 238 65 yrs 53% female *England*	CS	Hcy, folate (non-fasting plasma Hcy measured using fluorescence polarization immunoassay on IMX analyser; serum folate measured by competitive protein binding enzyme immunoassay on Immuno 1 analyser)	Global Cgnition (MMSE); Memory (Verbal Recall and Recognition, WHO Visual Associations Test); EF (TMT-A&B); Praxis (CDT); Language (BNT); Verbal Fluency (Animal Naming)	Age; Occupation; Smoking; Alcohol; WHR; BMI; HTN; Diabetes; PA; Lipids; Fibrinogen	Highest Hcy quartile (vs. lower quartiles) associated with cognitive impairment (MMSE < 20); Folate: ns
Jelicic et al., 2001	*N* = 698 69 yrs 52% female *LASA (Wave1), The Netherlands*	CS	B12, folate (measurement and fasting not specified)	Memory (Modified 15 Words Test); Processing Speed (Coding Task)	Age; Education	Low B12 (< 210 pmol/L) associated with poorer processing speed; folate: ns
Morris et al., 2001	*N* = 1270 70 yrs 68% female *NHANES-III, U.S.A.*	CS	Hcy, folate (serum Hcy measured using the HPLC method of Araki and Sako; folate measured using standardized protocols) *fasting not specified	Memory (MMSE 3 Word Recall, Paragraph Delayed-Recall Test)	Age; Sex; Education; Race; Income; Further adjustment for serum folate and creatinine concentration based on analyses	Folate: High folate associated with better memory; Hcy: Hcy 80th percentile associated with worse memory in persons with low folate only
Budge et al., 2000	*N* = 156 74 yrs 51% female *England*	CS	Hcy, B12, folate, (non-fasting serum, Hcy and B12 measured using Abbott-Axis Imx immunoassay; folate measured using AbbottImx binding assay)	Global cognition (CAMCOG, MMSE)	Age; Sex; IQ; Depression	Higher Hcy associated with lower CAMCOG scores only; B12, folate: ns
Lindeman et al., 2000	*N* = 795 74 yrs 50% female *U.S.A.*	CS	B12, folate, vit C (fasting not specified, serum B12 and folate measured using radioassay;vit C measured using automated analysis method)	Global cognition (MMSE); Memory (FOME); EF (Colour TMT); Attention (DS)	Age; Sex; Race; Education; Depression	Lower folate associated with poorer global cognition, attention, memory and EF; B12, vit C: ns
Hassing et al., 1999	*N* = 71 92 yrs 72% female *Sweden*	CS	B12, folate (fasting not specified, serum measured using RAI)	Memory (Face Recognition Task, Immediate and Delayed Word Recall and Recognition, FOME)	Education	Folate: Normal folate (≥13nmol/L) associated with better object recall immediate and delayed word recall than participants with low folate ; B12: ns

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Study	Sample Size Mean Age Gender %female *Cohort/ Location*	Study design (CS/L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect Modifiers*	Adjusted Model Results
Perkins et al., 1999	*N* = 4809 60 + yrs 55% female *NHANES III Study, U.S.A.*	CS	Selenium, vit C, vit E, vit A, β-carotene (serum, measurement and fasting not specified)	Memory (Household Adult Questionnaire)	Age; Education; Income; CVD; Iron; Ferritin; Cholesterol; TG, HDL; Folate; Calcium	Vit E: lower vit E per unit of cholesterol associated with poorer memory; vit A, β-carotene, vit C, and selenium: ns
Bernard et al., 1998	*N* = 303 71 yrs 0.6% female *U.S.A.*	CS	B12 (serum, fasting and measurement not specified)	Global Cognition (MMSE)	Alcohol; Vitamin/mineral supplement; Income; Education	B12 deficiency (B12 < 200 pg/mL) associated with poorer global cognition; Association no longer significant if B12 deficiency broadly defined (< 300 pg/mL and MMA or HC elevated by +2 SD)
Schmidt et al., 1998	*N* = 1769 62 yrs 58% female *The Austrian Stroke Prevention Study, Austria*	CS	α-carotene, β-carotene, gamma-tocopherol, α-tocopherol, ascorbate, zeaxanthin, etinol, cyrpotoxanthin, canthaxanthin, lycopene (fasting not specified, plasma measured using reversed-phase HPLC)	Global Cognition (MDRS)	Age; Sex; Education; Monthly variations in antioxidant concentration; Smoking; TC; TG; HTN; Diabetes; CVD	Lower β-carotene and α-tocopherol each associated with poorer cognition; All other antioxidants: ns
Perrig et al., 1997	*N* = 442 75 yrs 30% female *Basle Interdisciplinary Study on Aging, Switzerland*	CS	Ascorbic acid, β-carotene, α-tocopherol, ferritin (fasting plasma, measurement not specified)	Implicit Memory, Explicit Memory, WM (C-GFT); Semantic Memory (Vocabulary Test)	Age; Sex; Education; SBP; Cholesterol	Higher ferritin associated with lower free-recall and recognition performance; Higher ascorbic acid associated with better free-recall and vocabulary;Higher α-tocopherol associated with poorer memory performance; Higher β-carotene associated with better performance on all measures except free recall
Gale et al., 1996	*N* = 921 65 + yrs 45% female *England, Scotland, Wales*	CS	Ascorbic acid (vit C) (plasma, measurement and fasting not specified)	Global cognition (Hodkinson Mental Test)	Age; Sex; BP; Cholesterol	Ns
Wahlin et al., 1996	*N* = 230 85 yrs 82% female *KADS, Sweden*	CS	B12, folate (fasting not specified, blood measured using RAI)	Episodic Memory (word list presented 2 s/word and 5 s/word; Free Recall and Recognition)	Age; MMSE	B12 normal/folate normal group performed better than B12 low/folate low and B12 normal/folate low groups on free recall only
Riggs et al., 1996	*N* = 70 66 yrs 0% female *Normative Aging Study, U.S.A.*	CS	Hcy, B12, folate, B6 (fasting plasma, Hcy measured using Araki and Sako method; B12 and folate measured using radioassay kit; B6 measured using procedure from Buhlmann Laboratories)	Memory (Word List, Active Memory, Pattern Memory); EF (DS); Verbal Fluency (SVFT, BNT, WAIS-R Vocabulary); Spatial Reasoning; Constructional Praxis	Age; Education; Cancer; Diabetes; HTN	B6: Highest quartile B6 associated with better DS only; Hcy, B12, folate: Higher Hcy quartile and lowest B12 and folate associated with poorer performance on constructional praxis
Longitudinal Studies						
Laughlin et al., 2017	*N* = 1058 75 yrs 62% female *Rancho Bernardo Study, U.S.A.*	L, 12 yrs	25(OH)D (serum, measurement and fasting not specified)	Global cognition (MMSE); Memory (Long Term Retrieval); EF (TMT-B); Verbal Fluency (SVFT)	Age; Sex; Education; Season	Baseline 25(OH)D insufficiency (< 20 ng/ml) related to poorer performance on all tests at baseline, but not related change over time
Mendonca et al., 2017	*N* = 765 85 yrs 61% female *Newcastle 85 + Study, England*	L, 5 yrs	B12, folate, Hcy (fasting plasma, folate and B12 measured using chemiluminescence; Hcy measured using immunoassay)	Global cognition (MMSE); Attention, Concentration (CDRS-SRT); Information Processing, Decision Making (CDRS-CRT); Sustained Attention (CDRS-DVT)	Sex; Education; APOE; HTN; Diabetes; CVD; Smoking; Alcohol; BMI; Depression; PA; Renal function	Hcy: Highest quartile Hcy associated with poorer global cognition at baseline. No association with change over time; Folate: Highest quartile associated with better global cognition at baseline. No association with change over time; B12: ns

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Study	Sample Size Mean Age Gender %female *Cohort/ Location*	Study design (CS/L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect Modifiers*	Adjusted Model Results
Kuzma et al., 2016	*CHS, U.S.A.:* *N* = 1291 72 yrs 68% female *LASA, The Netherlands:* *N* = 915 74 yrs 55% female	*CHS:* L, 6 yrs *LASA:* L, 13 yrs	25(OH)D (*CHS:* fasting not specified, serum measured using HPLC tandem mass spectrometry; *LASA:* fasting not specified, serum measured using competitive protein binding assay)	*CHS*: Global cognition (MMSE); Memory (BVRT); *LASA*: Global cognition (MMSE); Memory (Dutch RAVLT)	Age; Sex; Education; Income; BMI; Smoking; Alcohol; Depression; Gait; Season; Baseline memory; Time of follow-up	*CHS:* Lower baseline 25(OH)D associated with greater decline in memory, but not global cognition; *LASA:* Lower baseline 25(OH)D associated with greater decline in global cognition, but not memory
Matchar et al., 2016	*N* = 1202 80 yrs 47% female *CLHLS, China*	L, 2 yrs	25(OH)D (fasting plasma measured using ELISA)	Global cognition (MMSE)	Age; Sex; Education; Abdominal obesity; HTN; Depression; ADL; Diabetes; Smoking; Alcohol; Season; TC; Baseline cognition	Lower baseline 25(OH)D associated with greater risk of cognitive decline
Granic et al., 2015	*N* = 775 85+ yrs *sex not specified *Newcastle 85+ Study, England*	L, 3 yrs	25(OH)D (fasting serum measured using DiaSorin Radioimmune Assay kit)	Global cognition (MMSE); Attention (CDRS – SRT, CRT, DVT)	Sex; Education; Income; Smoking; Alcohol; WHR; HTN; CVD; Diabetes; Osteoporosis; Renal function; Depression; PA	At baseline, lowest and highest 25(OH)D tertile associated with increased odds of cognitive impairment and slower attention scores compared to middle group; Highest and lowest quartile of 25(OH)D associated with poorer attention at follow-up
Miller et al., 2015	*N* = 382 75 yrs 62% female *U.S.A.*	L, 5 yrs	25(OH)D (non-fasting blood measured using competitive immunoassay)	Episodic Memory Composite (Word List Learning); Semantic Memory Composite (Object Naming, PAS); EF Composite (Verbal Fluency, DS, Visual Span, List Sorting); Spatial Localization (Reproduce Spatial Relationships)	Age; Sex; Education; Race; BMI; Season; Vascular risk; APOE	No association between baseline 25(OH)D as continuous variable and cognition at baseline; Vit D deficiency (25(OH)D < 12 ng/mL) associated with lower baseline semantic memory and EF only; Higher 25(OH)D associated with slower decline in EF, episodic and semantic memory; similar findings for vitD deficiency
Bartali et al., 2014	*N* = 1185 60-70 yrs 100% female *NHS, U.S.A.*	L, 9 yrs	25(OH)D (fasting not specified, plasma measured using RAI)	Global cognition (MMSE); Memory Composite (TICS-10, EBMT); EF (SVFT, DS backward)	Age; Education; Assay batch; Time between blood draw and cognitive interview; Season	Lower baseline 25(OH)D associated with worse cognitive performance on global and category fluency scores only at 9-year follow up (but not 6-year follow up)
Perna et al., 2014	*N* = 527 74 yrs 58% female *ESTHER Study, Germany*	L, 4 yrs	25(OH)D (fasting not specified, serum measured using automated IDS-iSYS)	Global cognition (COGTEL)	Age; Sex; Education; MI; Stroke; Diabetes; Depression; Smoking; Kidney disease; PA; Season	Lower baseline 25(OH)D associated with lower COGTEL scores at baseline and greater decline over time
Schneider et al., 2014	*N* = 1642 62 yrs 60% female *ARIC Study, U.S.A.*	L, 10.6 yrs	25(OH)D (fasting not specified, serum measured using LCTMS)	Memory (DelRec); EF (DSST); Language (Word Fluency Test)	Age; Sex; Education; Income; PA; Smoking; Alcohol; BMI; Waist circumference, vit D supplements	ns
Wilson et al. 2014	*N* = 2,777 74 yrs 56% female *Health ABC Study, U.S.A.*	L, 4 yrs	25(OH)D (fasting serum measured using 2-step RAI)	Global cognition (3MS); EF (DSST)	Age; Sex; Education; Race; Testing site; Season; Kidney disease (eGFR < 60); Depression; Alcohol; Smoking; BMI; PA	Low baseline 25(OH)D (< 30 ng/mL) associated with poorer baseline global and EF; Low baseline 25(OH)D associated with greater decline in global cognition only
Hooshmand et al., 2012	*N* = 274 70 yrs 62% female *CAIDE Study, Finland*	L, 7.4, yrs	Hcy, folate, holoTC (fasting not specified, serum Hcy measured using chemiluminescent microparticle immunoassay; folate measured using chemiluminescent microparticle folate binding protein assay using Architect *i* system; holoTC measured using microparticle enzyme immunoassay using AxSym System)	Global cognition (MMSE); Memory (Immediate Word Recall); EF (Stroop); Verbal Fluency (SVFT); Psychomotor Speed (PPB, LDST)	Age; Sex; Education; SBP; BMI; Smoking; Stroke; APOE; Renal function; Baseline cognition	Higher baseline Hcy associated with greater decline in global cognition, memory, and verbal fluency; Higher baseline holoTC associated with better global cognition, EF, and psychomotor speed at follow-up; Folate: ns

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Study	Sample Size Mean Age Gender %female *Cohort/ Location*	Study design (CS/L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect Modifiers*	Adjusted Model Results
Morris et al., 2012	*N* = 549 75 yrs 62% female *FHS, U.S.A.*	L, 8 yrs	B12 (non-fasting blood measured using microbial assay)	Global cognition (MMSE)	Age; Sex; Education; BMI; Alcohol; *Effect modifier*: Folate	Lower baseline B12 quintiles (< 257 pmol/L) associated with greater MMSE decline; *Effect* of low B12 greater in persons with high folate level
Slinin et al., 2012	*N* = 6257 77 yrs 100% female *SOF, U.S.A.*	L, 4 yrs	25(OH)D (fasting serum measured using mass spectrometry)	Global cognition (MMSE); EF (TMT-B)	Age; Education; Clinic site; Season; Self-report health; Walking; ADL; BMI; HTN; Diabetes; Depression; Baseline cognition; vit D supplements	Lower baseline 25(OH)D associated with greater global cognitive decline only
Brown et al., 2011	*N* = 499 74 yrs 56% female *MacArthur Study of Successful Aging, U.S.A.*	L, 7 yrs	Hcy, B12, folate (non-fasting plasma, Hcy measured using HPLC; folate measured using microbial assay; B12 measured using radioassay method; B6 measured using tyrosine decarboxylase method)	Composite cognitive score (Confrontation Naming, Delayed Verbal Memory Task, Delayed Recognition Span Test, Copy Geometric Figures, Similarities Subtest)	Age; Sex; Education; Race; *Effect modifier*: APOE	Hcy: Higher baseline Hcy associated with worse baseline cognitive score, but not change over time; B12, folate: ns; no effect modification found
Llewellyn et al., 2010	*N* = 858 74 yrs 57% female *InCHIANTI Study, Italy*	L, 5.2 yrs	25(OH)D (fasting serum measured using RAI)	Global cognition (MMSE); EF (TMT-A&B)	Age; Sex; Education; Season; BMI; Mobility; Diabetes; Stroke; HTN; Smoking; Alcohol; Depression; Energy intake; vit E supplement; Baseline cognition	deficient baseline 25(OH)D (< 25 nmol/L) associated with declines in MMSE and Trails B
van den Kommer et al., 2010	*N* = 1257 75 yrs 52% female *LASA, The Netherlands*	L, 6 yrs	Hcy (non-fasting blood measured using Abbott IMx analyzer)	General cognition (MMSE); Memory (AVLT); Processing Speed (Coding Task); Fluid Intelligence (RCPM)	Age; Sex; Education; HTN; B12; Creatinine; HDL; *Effect modifiers*: IL-6, CRP, ACT	Higher baseline Hcy associated with faster decline in processing speed and fluid intelligence. Impact of higher Hcy on immediate recall, retention, and information processing was greater in high levels of IL-6, CRP, and middle ACT tertile, respectively; Effect of higher Hcy on information processing greater in middle ACT tertile, and lower and middle CRP tertile
Tangney et al., 2009	*N* = 516 80 yrs 60% female *CHAP, U.S.A.*	L, 6 yrs	B12, MMA, Hcy, cystathionine, MCA (non-fasting serum, B12 measured using automated competitive displacement immunoassay; MMA, Hcy, crystathlonine, MCA measured using stable-isotope solution and capillary GC-MS)	Global cognition (MMSE); Memory (EBMT);Processing Speed (SDMT); Cognitive Composition (average of all tests)	Age; Sex; Race; Education; Cognitive activities; Smoking; Alcohol; Fat intake; Dietary vitamin & fish intake; Creatinine; *Effect modifier*: Sex	Higher baseline B12 associated with slower rates of decline in cognitive composite; Higher baseline MMA associated with faster rates of decline in cognitive composite; Sex: stronger association among men; Hcy, MCA, crystathionine: ns
Kang et al., 2008	*N* = 858 65 yrs 100% female *NHS, U.S.A.*	L, 4 yrs	β-cryptoxanthin, α-tocopherol (70% fasting plasma, measured using HPLC)	Global cognition (TICS)	Age at blood draw; Age at interview; Education; Diabetes; HTN; Cholesterol; Age of menopause; HRT; BMI; Smoking; PA; Alcohol; Antidepressant and aspirin use	ns
Kim et al. 2008	*N* = 607 72 yrs 57% female *Korea*	L, 2.4 yrs	B12, folate, Hcy (fasting plasma, B12 and folate measured using immunoassay; Hcy measured using HPLC)	Global cognition (Korean MMSE)	WHODAS-II; Vascular risk; APOE	Lower baseline quintile folate and higher quintile Hcy associated with greater cognitive decline
Akbaraly et al., 2007a,b	*N* = 702 65 yrs 62% female *EVA Study, France*	L, 9yrs	Selenium (fasting serum measured using electrothermal atomic absorption spectronomy)	Global cognition (MMSE); EF (TMT-B, DSS), Psychomotor Speed (FTT) *test performance dichotomoized by percentile	Age; Sex; Education; Baseline selenium; Diabetes; Dyslipidemia, HTN, CVD	Greater 9-year decrease in selenium associated with greater 9-year decline on MMSE, DSS, and FTT; 2-year decline in selenium not associated with change in cognition

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Study	Sample Size Mean Age Gender %female *Cohort/ Location*	Study design (CS/L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect Modifiers*	Adjusted Model Results
Clarke et al., 2007	*N* = 691 76 yrs 60% female *OHAP, England*	L, 10 yrs	holoTC, Hcy, MMA, B12, folate (non-fasting serum, holoTC measured using ELISA, Hcy measured using fluorescence polarization immunoassay, MMA measured using GC-MS, competitive protein binding assay on automated chemiluminescence system, folate measured using microbiological method)	Global cognition (MMSE)	Sex; Education; Smoking; CVD; SBP; APOE; Other vitamin markers	Higher baseline holoTC, lower tHcy and MMA associated with slower rates of cognitive decline; Folate, B12: ns
Hu et al., 2006	*N* = 455 74 yrs 59% female *MacArthur Study of Successful Aging U.S.A.*	L, 7 yrs	β-carotene (fasting not specified, serum measured using isocratic liquid chromatography)	Global cognition (SPMSQ)	Age; Sex; Race; Education, Income; CRP; IL-6; Cholesterol; BMI; Smoking; Alcohol; Baseline SPMSQ *Effect modifier:* APOE	Lower baseline β-carotene associated with greater cognitive decline in APOE e4(+) only
Kang et al., 2006	*N* = 391 63 yrs 100% female *NHS, U.S.A.*	L, 4 yrs	B12, folate (70% plasma fasting measured using a radioassay kit)	Global cognition (TICS); Memory (EBMT); VFT; EF (DS)	Age; Education; Assay batch; Time between blood draw and cognitive interview; Diabetes; BP; Cholesterol; HRT; Age menopause; menopause; BMI; Smoking; Alcohol; PA; Medication; Mental health and energy-fatigue index, vitE usage	ns
Kado et al., 2005	*N* = 499 74 yrs 54% female *MacArthur Study of Successful Aging, U.S.A.*	L, 7 yrs	Hcy, folate, B12, and B6 (non-fasting plasma, Hcy measured using HPLC with fluorimetric detection; plasma folate measured using 96-well plate microbial assay; plasma B12 measured using radioassay method; B6 measured using tyrosine decarboxylase method)	Summary cognition score: Language (Confrontation Naming); Verbal Memory (Delayed Recall); Spatial Memory (Delayed Recognition Span Test); Visuospatial (Geometric Figure Copying); Conceptualization and Abstract Concept Formation (Similarities Subtest)	Age; Sex	Higher baseline Hcy, lower folate, and lower B6 associated with poorer baseline summary cognition; Higher quartile of Hcy and lower quartile of folate and B6 associated with increased risk of cognitive decline; B12: ns
Mooijaart et al., 2005	*N* = 559 85+ yrs 66% female *Leiden 85+ Study, The Netherlands*	L, 4 yrs	Hcy, B12, folate (fasting not specified, serum Hcy levels measured using fluorescence polarization immunoassay on an IMx Analyzer; B12 and folate measured using Dual Count Solid Phase No Boil Assay)	Global cognition (MMSE); Memory (12-word Learning Test); Attention (Stroop); Processing Speed (LDCT)	Sex; Education	Hcy: Higher baseline Hcy associated with poorer baseline global cognition and memory, but better attention; No association with cognitive change; Folate: Higher folate associated with better baseline global cognition; no association with cognitive change; B12: ns
Nurk et al., 2005	*N* = 2,189 Age range 65-67 yrs 55% female *Hordaland Homocysteine Study, Sweden*	L, 6 yrs	Hcy, folate, B12 (non-fasting plasma, Hcy measured using fully automated HPLC; folate and B12 measured using microbiological assays)	Global cognition (KOLT)	Sex; Education; APOE; CVD; HTN; Smoking; Depression; Coffee intake; MTHFR; Vitamin supplements	Hcy: Highest baseline quintile Hcy and at follow-up associated with increased risk of memory deficit at follow-up; Same pattern trending for folate; B12: ns
Tucker et al., 2005	*N* = 321 67 yrs 0% female *Veterans Affairs Normative Aging Study, U.S.A.*	L, 3 yrs	Hcy, B12, folate, and B6 (fasting plasma, Hcy measured using adapted Araki and Sako method; folate and B12 measured using commerical radioassay kit form Bio-Rad; PLP (B6) measured using tyrosine decarboxylase)	Global cognition (MMSE); Memory (Word List); WM (DS backward); Verbal Fluency; Constructional Praxis (Spatial Copying)	Age; Education; Smoking; Alcohol; BMI; Diabetes; SBP; Baseline cognition; Creatinine	Hcy: High baseline Hcy associated with decline in memory and constructional praxis; Folate: High baseline folate associated with maintenance of constructional praxis; B12, B6: ns

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Table 4 (*continued*)

Study	Sample Size Mean Age Gender %female *Cohort/ Location*	Study design (CS/L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect Modifiers*	Adjusted Model Results
Garcia et al., 2004	*N* = 180 73 yrs 72% female *Canada*	L, 2.3 yrs	Hcy (fasting not specified, serum measured using capillary GC-MS and HPLC)	Global cognition (MDRS, MMSE); Memory (CVLT); EF (Stroop)	Age; Education; B12; Folate; Diabetes; HTN	Increasing Hcy over time associated with decline in EF over time; Decreasing Hcy overtime not associate with EF change
Luchsinger et al., 2004	*N* = 679 76 yrs 71% female *WHICAP, U.S.A.*	L 3,206 person-yrs	Hcy (fasting plasma measured using HPLC with fluorescence detection)	Memory (Selective Reminding Test); Verbal Fluency, Language (BNT, COWAT, Boston Diagnostic Aphasia Evaluation); Abstract Reasoning (Similarities Subtest, Nonverbal Identities/Oddities Subtest of MDRS); Visuospatial (Rosen Drawing Test, matching version of BVRT)	Age; Sex; Education; APOE	ns
Dufouil et al., 2003	*N* = 1241 67 yrs 58% female *EVA Study, France*	L, 4 yrs	Hcy (fasting plasma measured using HPLC with fluorimetric detection)	Global cognition (MMSE); EF (TMT-B); Processing Speed (DSST, FTT)	Age; Sex; Education; BMI; Alcohol; Smoking; HTN; Hypercholesterolemia; Glycemic status; CVD; Folate and B12 concentrations; Baseline cognition	Higher baseline Hcy quartile associated with poorer baseline global cognition, and processing speed only. Hcy ≥ 15 μmol/L associated with greater declines in global cognition and processing speed only
Eussen et al., 2002	*N* = 586 Age range 70-75 yrs 55% female *SENECA Study, The Netherlands*	L, 5 yrs	B12, folate (fasting plasma measured using radioassay kits)	Global cognition (MMSE)	None	ns
McCaddon et al., 2001	*N* = 32 79 yrs 68% female *Wales*	L, 5 yrs	Hcy (fasting serum measured using HPLC)	Global cognition (MMSE, ADAS-Cog)	Age; Sex; Education; HTN; Smoking; Creatinine	Higher baseline Hcy predicted greater rate of cognitive decline (MMSE only); Higher baseline Hcy associated with poorer word recall, constructional praxis (complex figures), and orientation at 5-year follow-up (ADAS-Cog)
Berr et al., 2000	*N* = 1166 65 yrs 59% female *EVA Study, France*	L 4 yrs	TBARS, selenium, carotenoids, alpha-tocopherol (fasting plasma, TBARS measured using fluotometry, carotenoid measured using spectrophotometric assay, alpha-tocopherol measured using HPLC, selenium measured using EAAS)	Global cognition (MMSE)	Age; Sex; Education; Depression; Alcohol; Smoking; BMI; TC; TG; Baseline MMSE; *Effect modifiers*: sex, age, TBARS by antioxidants	Higher baseline TBARS associated with greater global decline – effect greater for older persons and men; f-tocopherol: ns; Risk of decline in high TBARS greater in persons with low selenium, carotenoids, and alpha-tocopherol
Kalmijn et al., 1999	*N* = 702 68 yrs 60% female *RSS, The Netherlands*	L, 2.7 yrs	Hcy (non-fasting serum measured using high-pressure liquid chromatography of Araki and Sako)	Global cognition (MMSE)	Age; Sex; Education; Baseline cognition; Alcohol; Smoking; HTN; Stroke; Atherosclerosis	Lowest and highest Hcy tertile associated with greater decline in global cognition; Association between per unit increase in Hcy and cognitive impairment over time
Berr et al., 1998	*N* = 1389 65 yrs 59% female *EVA Study, France*	L, 4 yrs	Carotenoids, α-tocopherol, selenium (fasting plasma, carotenoids measured with spectrophotometer; α-tocopherol RBC measured with HPLC assay and spectrophotometric detector; selenium measured using electrothermal atomic absorption spectometry)	Global cognition (MMSE); Memory (AVLT); Attention (TMT-B); Psychomotor Speed (DSST);	Age; Education; Smoking; Alcohol; CVD	Carotenoids: Low carotenoid associated with greater risk of poorer performance on TMT-B and DSS; α-tocopherol, selenium: ns

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Table 4 (*continued*)

Study	Sample Size Mean Age Gender %female *Cohort/ Location*	Study design (CS/L, yrs)	Biomarker (Reported measure technique)	Cognition Outcomes (Measure)	Model Covariates *Effect Modifiers*	Adjusted Model Results
La Rue et al., 1997	*N* = 137 77 yrs 51% female *New Mexico Aging Process Study, U.S.A.*	L, 6 yrs	Riboflavin, thiamine, folate, ascorbate acid (fasting plasma ascorbate measured using automated colorimetric procedure; riboflavin and thiamine measured using automated method; plasma and erythrocyte folate measured using a radioassay kit)	Abstract Thinking (Shipley-Hartford Intelligence Test Abstraction scale); Memory (LM, Visual Reproduction, ROCFT)	Age	Thiamine, riboflavin, folate at 6-year follow-up negatively correlated with Shipley-Hartford Abstraction test; Plasma ascorbate at 6-year follow-up positively correlated with Rey-Osterreith Copy test

Note: Studies are listed according to design (cross-sectional, longitudinal), followed by publication years, followed by alphabetical order; 25(OH)D = 25-hydroxyvitamin D; 3MS = Modified Mini Mental Status Exam; ABC = Aging and Body Composition; ACE = Addenbrooke's Cognitive Examination; ADAS-Cog = Cognitive Component of Alzheimer's Disease Assessment Scale; ADL = Activities of Daily Living; AKT = Atters-Konzentrations Test; AMT = Abbreviated Mental Test; ANART = American National Adult Reading Test; APOE = Apolipoprotein E ; ARIC = Atherosclerosis Risk in Communities ; B-PROOF = B-Vitamins for the Prevention of Osteoporotic Fractures; B1 = Vitamin B1; B12 = Vitamin B12; B2 = Vitamin B2; B6 = Vitamin B6; BCAT = Basic Cognitive; Aptitude Test ; BD = Block Design; BIMCT = Blessed Information-Memory-Concentration Test; BMI = Body Mass Index; BNT = Boston Naming Test; BPRHS = Boston Puerto Rican Health Study; BSRT = Babcock Story Recall Test; BVRT = Benton Visual Retention Test; C-GFT = Computerunterstutzer Gedachtnis Funktions-Test ; CAIDE = Cardiovascular Risk Factors, Aging and Dementia; CAMCOG = Cambridge Mental Disorders of the Elderly Examination; CANTAB = Cognition Neuropsychological Test Automated Battery ; CASI = Cognitive Abilities Screening Instrument; CBTT = Corsi Block Tapping Test; CDRS = Cognitive Drug Research System; CDT = Clock Drawing Test; CHAP = Chicago Health and Aging Project ; CHS = Cardiovascular Health Study ; CLHLS = Chinese Longitudinal Healthy Longevity Survey ; COGTEL = Cognitive Telephone Screening Instrument ; COWAT = Controlled Oral World Associations Test; CRP = C-reactive Protein; CRT = Choice Reaction Time; CS = Cross-sectional; CSI-D =; Community Screening Instrument for Dementia; CTRM = Camden Topographical Recognition Memory Test; CVD = Cardiovascular Disease; CVT = Choice Vigilance Task; DART = Dutch Adult Reading Test; DBP = Diastolic Blood Pressure; DelRec = Delayed Word Recall Test ; DRS = Dementia Rating Scale; DS = Digit Span; DSMT = Digit Symbol Matching Test; DSST = Digit Symbol Substitutions Test ; EAAS = Electrothermal Atomic Absorption Spectronomy ; EBMT = East Boston Memory Test; ECLIA =; Electrochemiluminescence Immunoassay; EDTA = Ethylenediaminetetraacetic Acid; EF = Executive Function; eGFR = Estimated Glomerular Filtration Rate; EGRAC = Erythrocyte Glutathione Reductase Activity Coefficient; ELISA = enzyme-linked immunosorbent assay; EMAS = European Male Ageing Study; ESTHER = Epidemiologische Studie zu Chancen der Verhütung; Früherkennung und optimierten THerapie chronischerERkrankungen in der älteren Bevölkerung; ETKAC = Erythrocyte transketolase activation coefficient; EVA = Etude du Vieillissement Arteriel; FCRT = Free and Cued Recall Task; FHS = Framingham Heart Study; FOME = Fuld Object Memory Evaluation; FTT = Finger Tapping Test ; FWI = Farb-Wort Interferenztest; GAIT = Gait and Alzheimer Interactions Tracking ; GC–MS = Gas Chromatography-Mass Spectrometry; GCS = Georgia Centenarian Study; GPT = Grooved Pegboard Test; HbA1c = Glycosylated haemoglobin; Hcy = Homocysteine ; HDL = High-density Lipoprotein; HIMS = Health in Men Study; holoTC = Holotranscobalamin; HPLC = High Performance Liquid Chromatography; HRNTB = Halstead Reitan Neuropsychological Test Battery; HRT = Hormone Replacement Therapy; HTN = Typertension; HVLT = Hopkins Verbal Learning Test; InCHIANTI = Invecchaire in Chianti; InveCe.Ab = Invecchiamento Cerebrale ad Abbiategrasso; JLOSPM =; Judgment of Line Orientation and Standard Progressive Matrices; KADS = Kungsholmen Aging and Dementia Study; KOLT = Kendrick Object Learning Test; L = Longitudinal; L50+ = Leistungsprüfungssystem 50+; LASA = Longitudinal Aging Study Amsterdam; LCTMS = Liquid Chromatography Tandem Mass Spectrometry; LDCT = Letter-digit Coding Test; LDL = Low-density Lipoprotein; LDST = Letter-digit Substitution Test; LM = Logical Memory; MAP = Mean Arterial Pressure; MCA = Methylcitric Acid ; MDRS = Mattis Dementia Rating Scale; MI = Myocardial Infarction ; MMA = Methylmalonic Acid;MMSE = Mini-Mental State Examination; MR = Matrix Reasoning; MRT = Mental Rotation Test; MTHFR = Methylenetetrahydrofolate reductase; mWCST = Modified Wisconsin Card Sort Task; NAHSIT = Elderly Nutrition and Health Survey in Taiwan; NAME = Nutrition, Aging Memory in Elders ; NART = National Adult Reading Test; NHANES-III = National Health and Nutrition Examination Survey-III; NHS = Nurses' Health Study; NuAge = Quebec Longitudinal Study on Nutrition and Successful Aging; OHAP = Oxford Healthy Aging Project; PA = Physical Activity; PAS = Picture Association Task; PLP = Plasma Pyridoxal Phosphate; PPB = Purdue Peg Board; PPVT = Peabody Picture Vocabulary Test; PTH = Parathyroid Hormone; RAI = Radioimmunoassay; RAVLT = Rey Auditory Verbal Learning Test; RBC-Zn = Erythrocyte Zinc Concentration; RCPM = Raven's Coloured Progressive Matrices; ROCF = Rey-Osterrieth Complex Figure; RSS = Rotterdam Scan Study; RW = Regensburger Wortflüssigkeitstest; SALSA = Sacramento Area Latino Study on Aging ; SBP = Systolic Blood Pressure; SDMT = Symbol Digit Modalities Test; SEED = Singapore Epidemiology of Eye Diseases ; SENECA = Survey in Europe on Nutrition and the Elderly; SLSA = Singapore Longitudinal Ageing Study; SOB = Sum of Box; SOF = Study of Osteoporotic Fractures; SPMSQ = Short Portable Mental Status Questionnaire; SRT = Simple Reaction Time; SVFT = Semantic Verbal Fluency Test; TBARS = Thiomarbituric acid reactive substances; TC = Total Cholesterol; TDP = Thiamine Diphosphate; TG = Triglycerides; TIA = Transient Ischemic Attack; TICS = Telephone Interview for Cognitive Status; TMT-A = Trail Making Test Part A; TMT-B = Trail Making Test Part B; TPM = Thurstone's Picture Memory; VFT = Verbal Fluency Test; VG = Verbaler Gedächtnistesl vitA = Vitamin A; vitC = Vitamin C; vitE = Vitamin E; vitK = Vitamin K; VLT = Verbal Learning Test; VRT = Visual Reproductions Test; WAIS-III = Wechsler Adult Intelligence Scale-Third Edition; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WHICAP = Washington; Heights-Inwood Columbia Aging Project ; WHODAS-II = World Health Organization Disability Assessment Schedule-II; WHR = Wait-Hip Ratio; WM = Working Memory; ZENITH = Zinc Effects in Nutrient/Nutrient Interactions and Trends in Health and Ageing.

2006; Hsu et al., 2016; Koike et al., 2008; Kong et al., 2013; Lildballe et al., 2011; Miller et al., 2003; Morris et al., 2001; Polito et al., 2016; Prins et al., 2002; Ravaglia et al., 2003; Ravaglia et al., 2004; Riggs et al., 1996; Schafer et al., 2005; Stewart et al., 2002; Tangney et al., 2011; Tassino et al., 2009; West et al., 2011) and longitudinal analyses (Brown et al., 2011; Clarke et al., 2007; Clarke et al., 2008; Dufouil et al., 2003; Garcia et al., 2004; Hooshmand et al., 2012; Kado et al., 2005; Kalmijn et al., 1999; Kim et al., 2008; McCaddon et al., 2001; Mendonca et al., 2017; Nurk et al., 2005; Tucker et al., 2005; van den Kommer et al., 2010). Importantly, changes in Hcy over time are also associated with changes in cognitive function. In a prospective study of healthy community-dwelling older adults, increases in Hcy over 2.3 years significantly correlated with rate of decline in executive function (Garcia et al., 2004). This dynamic characteristic Hcy and its impact on cognitive wellbeing suggests that fasting Hcy may serve as a robust biomarker of cognitive function in the context of behavior modification programs, especially programs that include diet modification. Furthermore, Hcy has been found to interact with markers of inflammation in determining cognitive decline in late-life (van den Kommer et al., 2010). Effect modification in the relationship between peripheral

vitamin B and cognitive function among healthy older adults has also been reported. For example, the effect of circulating B12 on cognition is reportedly stronger among APOE e4 carriers than non-carriers (Bunce et al., 2004; Feng et al., 2009).

In the last decade, there has been an increase in research examining the association between 25-hydroxyvitamin D (25(OH)D, vitamin D) status and cognitive function in late life. Among the cross-sectional and longitudinal studies published, a relatively consistent association has been reported between higher serum 25(OH)D and better cognitive function, especially executive function and global cognitive function (Annweiler et al., 2014; Annweiler et al., 2016; Brouwer-Brolsma et al., 2015; Brouwer-Brolsma et al., 2013a; Brouwer-Brolsma et al., 2013b; Buell et al., 2009; Chei et al., 2014; Lam et al., 2016; Lee et al., 2009; Lee et al., 2017; Llewellyn et al., 2011; Llewellyn et al., 2009; Menant et al., 2012; Milman et al., 2014; Pettersen, 2016; Seamans et al., 2010). Of the two studies that reported null findings, one study failed to report the sex of the sample (Brouwer-Brolsma et al., 2013a) and the other conducted the analyses in an exclusively male sample (Chan et al., 2011). In the European Male Aging Study cohort, including over 3000 men between the ages 40–79 years, it was found that the association between 25(OH)D and executive function was limited to older men (Lee et al., 2009). Accordingly, additional studies are required to elucidate potential sex differences in the association between 25(OH)D and cognitive function.

Longitudinal associations between vitamin D and cognitive outcomes tend to be more robust in studies with shorter follow-up periods than those with longer follow-up periods (Bartali et al., 2014; Granic et al., 2015; Kuzma et al., 2016; Laughlin et al., 2017; Llewellyn et al., 2010; Matchar et al., 2016; Perna et al., 2014; Schneider et al., 2014; Slinin et al., 2012; Wilson et al., 2014). In a longitudinal study of 382 older adults, Miller et al. (Miller et al., 2015) noted the importance of statistical treatment of the predictor variable. Specifically, no association was found between 25(OH)D and cognitive outcomes at baseline when vitamin D was treated as a continuous variable; however, categorizing participants as vitamin D deficient (< 12 ng/mL) versus non-deficient resulted in a significant association between vitamin D deficiency (i.e. low vitamin D) and poorer cognition. However, both continuous and categorical vitamin levels predicted cognitive trajectory over five years. The presentation of both continuous and categorical data is important as it provides an understanding of potential threshold effects depending on time of cognitive assessment.

Among the various antioxidant nutrients examined, α-tocopherol (vitamin E) has been found to associate cross-sectionally with global cognitive function (Akbaraly et al., 2007a,b; Ortega et al., 2002; Schmidt et al., 1998) and memory (Dunn et al., 2007; Perrig et al., 1997), with no evidence in predicting cognitive trajectory (Berr et al., 1998; Kang & Grodstein, 2008). Carotenoids, including β-carotene, lutein, lycopene, and zeaxanthin have shown to associate with measures of executive function, both cross-sectionally (Akbaraly et al., 2007a,b; Johnson et al., 2013) and longitudinally (Berr et al., 1998; Hu et al., 2006), with lower carotenoid levels at baseline associated with risk of poor executive at follow-up. In a 9-year longitudinal examination of the association between selenium and cognitive function in the EVA Study, 2-year change in plasma selenium did not associate with cognitive change; however, greater 9-year decrease in selenium associated with a greater 9-year decline in global cognition and executive function (Akbaraly et al., 2007a,b). This study not only addresses the importance of treating blood biomarkers as dynamic, but also highlights the complexities associated with the timing of exposure assessments.

3.5. Other biomarkers associated with cognition in late life

A total of two studies met criteria for the systematic review with biomarkers that did not fall within any of the aforementioned categories: brain derived neurotrophic factor (BDNF) and amyloid beta, both of which are implicated in the pathophysiology of dementia and Alzheimer's disease (Lu et al., 2014). In a cross-sectional study of 1389 older adults aged 57 to 79 (51% female) from the Dose-Response to Exercise Training Study, lower levels of plasma BDNF were associated with poorer performance on tasks of global cognitive function, memory, and verbal fluency in women only after controlling for age, education, depression, glucose metabolism, smoking and alcohol consumption and medication use (Komulainen et al., 2008). As part of the Nurses' Health Study, Okereke et al. (2009b) found that higher Aβ-40: Aβ-42 ratio at baseline and increasing Aβ-40: Aβ-42 ratio over 10 years in 481 women (mean age 63 years at baseline) predicted greater decline in global cognitive function. Although further research is needed to determine the stability of peripheral Aβ measurement, BDNF has shown promise as a modifiable circulating biomarker (Dinoff et al., 2016; Heyman et al., 2012).

3.6. Relevance to lifestyle behaviours: beyond the systematic review

Circulatory biomarkers may serve as a relatively non-invasive, low cost and time-efficient tool to assess the effectiveness of physical activity and/or diet regimens for brain health. Including biological analytes as an outcome measure in RCTs may further elucidate biological mechanisms that underlie the efficacy of lifestyle programs on fostering cognitive health. The present systematic review suggests relatively consistent associations between cognitive function in non-demented older adults and markers of inflammation, metabolic function, and Hcy. Importantly the relationship between these biomarkers may impose interacting effects on cognitive function, and may further be modified by other factors including sex, age, and genetic polymorphisms.

Stemming from the cardiovascular literature, over three decades of research suggest that physical activity may affect the immune system. According to a systematic review of 42 articles published between 1975 and 2004, cross-sectional and longitudinal designs demonstrate long-term anti-inflammatory effects in response to physical activity (Kasapis & Thompson, 2005). RCTs have also demonstrated improvements in circulating lipid levels (e.g., Pattyn et al., 2013) and metabolic markers (e.g. Davidson et al., 2009; Irwin et al., 2009; Sigal et al., 2007; Verrusio et al., 2016) in response to physical activity. However, the majority of trials have commonly been conducted in patient populations, including persons with diabetes, obesity, or cancer. Further, few studies have examined the interaction among biomarkers in response to physical activity programs. For example, a RCT involving post-menopausal Japanese women showed that improvement in inflammation was partially explained by changes in HDL cholesterol (Nishida et al., 2015). As the current systematic review highlights the importance of examining interconnected systems when evaluating biomarkers of cognitive health, it will be important to examine how metabolic and inflammatory markers interact in response to physical activity programs that target cognitive health in late life.

Similar to physical activity regimens, changes in diet and nutrient intake have been shown to influence circulating biomarkers that are associated with poor cognitive function (Roman et al., 2008). The PREDIMED study, a parallel group, multicenter, randomized trial in 7447 high cardiovascular risk older men and women, showed that adherence to a Mediterranean diet was associated with a lower dietary inflammatory index (DII), composed of interleukins (IL-1B, IL-4, IL-6, IL-10), TNF-alpha, and CRP (Garcia-Arellano et al., 2015). Again, a majority these studies have focused on patient populations including persons with cardiovascular disease, diabetes, and metabolic disorder.

Altogether, it is suggested that circulating biomarkers that are predictive of brain health may be modifiable through lifestyle behaviors. However, there is limited knowledge regarding the interrelationship between lifestyle factors and peripheral biomarkers, and the mediating role of biomarkers in the effect of lifestyle behavior on brain health. Accordingly, more research is needed to understand the interaction or aggregate role of multiple lifestyle behaviors on cognitive health and related circulatory biomarkers. For example, research shows

that nutrient intake and physical activity have an interactive effect on cognitive functions and cognitive trajectory over time. In a prospective longitudinal study of older men and women, high sodium intake in combination with a sedentary lifestyle associated with faster decline in global cognitive functions over 4 years (Fiocco et al., 2012). However, little is known about the interactive effect of physical activity and diet on circulating peripheral biomarkers associated with cognition.

3.7. The optimal strategy for development of a biomarker proxy of cognitive health

One important limitation to the existing literature is that studies often tend to take a simple approach by assessing individual biological systems and individual system biomarkers in isolation, without considering a multisystemic effect on cognitive function. Further, as suggested by the systematic review, biomarkers may have differential associations based on sex, race and genetic polymorphisms. It is also important to note that changes in assay development have occurred between 1995 and 2018. Continued modification and improvements in assay techniques may further result in differential outcomes; however, upon reviewing the reported measurement techniques across studies (displayed in tables), this was not consistently observed in the present review.

Although interleukin inflammatory markers, insulin, and Hcy show relatively consistent promise as biomarker proxies of cognitive health, it is recommended that a comprehensive biomarker panel, or *biomarker signature*, be developed as a clinical end point for behavior modification trials aimed at enhancing cognitive function in late life. The biomarker signature should take a multisystemic approach, for instance, including lipid, immune/inflammatory, and metabolic biomarkers in the biological signature index of cognitive health. The use of new modeling approaches such as machine learning may further add to our understanding of the complex and multifactorial biological underpinnings of cognitive trajectory in late life. Based on this review, threshold levels of dysfunction may be more sensitive predictor variables than continuous levels of peripheral biomarkers. Follow-up assessment of a panel of biomarkers in conjunction with cognitive performance in randomized trials would allow for the creation of mediation models that can be used to evaluate the direct and indirect effect of exercise and/or diet on cognitive health. This type of analysis is a critical step in developing cost- and time-efficient behavior modification programs to improve cognitive wellbeing in late life.

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