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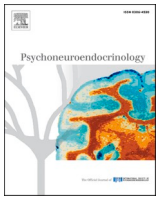

Review

The association between allostatic load and cognitive function: A systematic and meta-analytic review

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ABSTRACT

Previous research suggests that high allostatic load (AL), a biological indicator of physiological dysregulation due to chronic stress, is associated with poor cognitive functioning. To date, no studies have systematically reviewed the literature to evaluate the strength and consistency of this relationship. The objective of this study was to conduct a systematic and meta-analytic review of studies that have investigated the association between AL and performance on standardized cognitive tests among adults aged 18 years and older. A total of 18 studies were retained for review. Meta-analyses revealed a significant cross-sectional association between higher AL and poor global cognition ($r = -0.08$, $p < 0.001$) and executive function ($r = -0.07$, $p = 0.02$), but not memory ($r = -0.07$, $p = 0.10$). Due to variation in statistical methods used, longitudinal meta-analyses were not performed. Qualitative review of the literature suggests that AL algorithm, physiological systems and individual biomarkers included in the AL index, and sample age may be key moderators of the AL-cognition relationship. Although the magnitude of reported associations is small, findings support AL as a robust indicator of cognitive function among adults. Study limitations and future directions are discussed.

1. Introduction

With an aging population on the rise (Statistics Canada, 2016), there is an urgent need to delineate the biological processes that contribute to cognitive changes throughout the lifespan. Epidemiological research has demonstrated an association between dysfunction across a number of physiological parameters and poor cognitive functioning (Fiocco et al., 2019). Namely, markers of neuroendocrine function (e.g., cortisol), cardiovascular function (e.g., blood pressure), metabolic function (e.g., body composition, glucose levels, lipid profiles), and immune function (e.g., systemic inflammation) have been independently identified as biological contributors to cognitive decline (Ancelin et al., 2014; Fiocco et al., 2006; Gimeno et al., 2008; Novak and Hajjar, 2010; Steenbergen and Colzato, 2017; Yaffe et al., 2003, 2004). It is also known, however, that these biological parameters are dynamically interrelated (McEwen, 2003). As such, a measure of physiological dysregulation which integrates multiple biological systems may be a more robust predictor of cognitive function than individual risk factors considered in isolation (Seeman et al., 1997).

The allostatic load model (McEwen and Stellar, 1993) is a unifying framework that integrates multiple biological parameters from neuroendocrine, immune, metabolic, and cardiovascular systems. The model posits that allostasis, the process by which physiological stability is maintained by altering biological parameters of the internal milieu to meet environmental demands, can lead to physiological dysregulation over time. Namely, chronic or consistent intermittent activation of the neuroendocrine and immune system (i.e. primary mediators) may eventually lead to dysregulation of metabolic, and cardiovascular systems (i.e., secondary mediators). The chronic activation and imbalance of these interconnected regulatory systems ultimately results in allostatic load (AL), or the biological 'wear and tear' of the organism (McEwen, 2006; McEwen and Seeman, 1999).

AL has been identified as an antecedent to the development of significant health consequences, also known as tertiary outcomes, including impairments in cognitive functioning (Juster et al., 2010). Indeed, epidemiological studies have shown that higher AL is associated with poor cognitive functioning (Booth et al., 2015; Karlamangla et al., 2014; Seplaki et al., 2005) and an increased likelihood of cognitive decline (Karlamangla et al., 2002; Oi and Haas, 2019; Seeman et al., 2001). A number of study parameters, however, remain inconsistent across such studies. For example, the number of individual biomarkers included to calculate AL can range from as little as five (Schmitz et al., 2018) to as many as 21 (Karlamangla et al., 2002). Further, some studies fail to include primary (i.e., neuroendocrine; e.g., Crook et al., 2018; Oi

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and Haas, 2019) or secondary (i.e., cardiovascular, metabolic, immune) interconnected systems (Karlamangla et al., 2002; Seeman et al., 2001) in calculating AL. Of note, early studies investigating the association between AL and health outcomes in the MacArthur Studies of Successful Aging did not include immune system biomarkers within the AL framework (Seeman et al., 1997, 2001). Finally, algorithms used to calculate AL index may vary between studies, deviating from the traditional count-based method (Booth et al., 2015; Narbutas et al., 2019).

Given the variable measurement of AL, the strength and consistency of the relationship between AL and cognitive function remains elusive. It is also important to note that AL may be differentially associated with cognitive function depending on the cognitive domain assessed. Currently, there are no published meta-analyses that assess the overall effect size of the association between AL and cognitive performance across cognitive domains, which is important in order to determine the relevance of AL as a proxy measure of cognitive health and trajectory with age. Indeed, downstream clinical implications of understanding the association between AL and cognitive function may be important in order to detect sub-clinical thresholds of interactive physiological systems for individuals at risk of developing pathological changes in cognitive function such as dementia. Substantial research suggests that changes in cognitive function with age are highly heterogeneous, with some older adults maintaining cognitive abilities, some exhibiting minor declines, and others showing major, clinically significant decline (Barnes et al., 2007; Yaffe et al., 2009). From a prevention, detection, and treatment standpoint, elucidating a biological signature that predicts differential cognitive trajectories with age is imperative.

The objective of this review was to synthesize the extant literature on the association between AL and cognitive functioning in cognitively intact adults. Specifically, a systematic review and meta-analysis was conducted using cross-sectional and longitudinal cohort studies to investigate the relationship between AL and cognitive performance on standardized tests measuring memory, executive function, and global cognition.

2. Methods

2.1. Search strategy

Search engines included PubMed, MedLine, HealthStar, CINAHL, PsycINFO, and Scopus. Search terms included allosta* AND (cogniti* OR executive function OR attention OR memory OR processing speed OR verbal fluency OR neuropsychological test). A manual search of reference lists from review papers and articles included in the final review were also conducted. Three independent reviewers assessed papers for inclusion at three assessment phases: assessment of title, assessment of abstract, and assessment of full paper.

2.2. Selection criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. Although no restrictions were stipulated based on publication date, the search was limited to papers written in English. Studies were included if they examined the association between AL and cognitive function at baseline and/or predicted change in cognitive function over time among cognitively intact, community-dwelling adults. Studies were included if they indexed AL using biomarkers from at least two of the four regulatory systems (i.e., neuroendocrine, cardiovascular, immune, and metabolic). Studies were retained if cognitive function was measured using performance on standardized neuropsychological tests, with no restrictions placed on the cognitive domain assessed. Only cross-sectional and longitudinal studies were selected; randomized control trials, intervention studies, experimental studies and case-control studies that compared patients to control participants were excluded. Studies were also excluded if they assessed cognitive function exclusively via self-report measures or a clinical diagnosis of impairment. Moreover, studies were discarded if they examined animals, children, or adolescents younger than 18 years of age, but were retained if participants were 18 years or older. Finally, studies investigating patient populations with distinguishable deficits in cognitive function (i.e., dementia, MCI, Parkinson's disease) or neuropsychiatric disorders (i.e., schizophrenia, bipolar disorder) were excluded.

Based on PRISMA guidelines, a total of 23,182 papers were extracted. After removing duplicates, 17,833 papers were retained, of which 18 studies were included in the systematic review and 12 articles in the meta-analysis. See Fig. 1 for the PRISMA flow diagram.

2.3. Data extraction and analysis

Data was extracted from articles by three independent reviewers. Due to substantial variation in statistical methods used to investigate the association between AL and cognitive function overtime (e.g., regression residual models, growth curve models, latent change score models), meta-analyses of longitudinal studies were not conducted. As such, only cross-sectional studies were included in the meta-analytic models.

Comprehensive Meta-Analysis (CMA) software version 3.0 was used to conduct all analyses. Pearson's r correlation coefficient was chosen, with a negative coefficient indicating that higher AL was associated with poorer cognitive functioning, and data was extracted from fully adjusted models. When r was not reported, the p value was used to estimate the correlation coefficient. In deriving effect sizes and confidence intervals, random-effects models were used, and all effect sizes were first converted to Fisher's Z and then to r. The threshold for statistical significance was set at p-value less than 0.05 for the meta-analytic models in order to remain consistent with the studies retained for analyses. Publication bias was examined using funnel plots, Egger's test of the intercept (Egger et al., 1997), and by calculating fail-safe N (i.e., the number of studies that would need to be added to the meta-analysis for a p-value less than 0.05 to reach statistical insignificance). To examine the effects of each result on the overall findings, outcomes were analyzed having deleted each study from the model once (i.e., the one-study-removed method). Cumulative meta-analysis, ranked by year, was used to examine the accumulation of evidence over time. Heterogeneity was examined using Q and any p-value less than 0.10 was considered statistically significant. Previous models (Higgins et al., 2003) have shown that Cochran's Q is relatively poor at detecting true heterogeneity; hence, a more liberal threshold for detecting heterogeneity was used. Inconsistency was examined using I^2 and the following grades were applied: <25 % (very low), 25–<50 % (low), 50–<75 % (moderate), and ≥ 75 % (large; Higgins et al., 2003). Separate meta-analyses were performed for global cognition, memory, and executive function. Given the small number of studies identified, meta-regressions were not performed.

3. Results

3.1. Study characteristics

Of the papers that were retrieved, the majority of study findings (79 %) stem from secondary analyses of large cohort data, including the MacArthur Studies of Successful Aging, Midlife in the United States (MIDUS), the Third National Health and Nutrition Examination Survey (NHANES III), the Health and Retirement Study (HRS), the Whitehall II Study, the Multiethnic Study of Atherosclerosis (MESA), the Lothian Birth Cohort 1936 Study (LBC1936), the Rotterdam Study, and Taiwan's Social Environment and Biomarkers of Aging Study (SEBAS). While a majority of these studies focused on older adult participants who were cognitively intact, a select few included younger adults (e.g. MIDUS, NHANES III) and one study focused exclusively on younger adults 21–40 years of age (Ottino-González et al., 2019).

Calculation of the AL index was based on a range of biomarkers, from

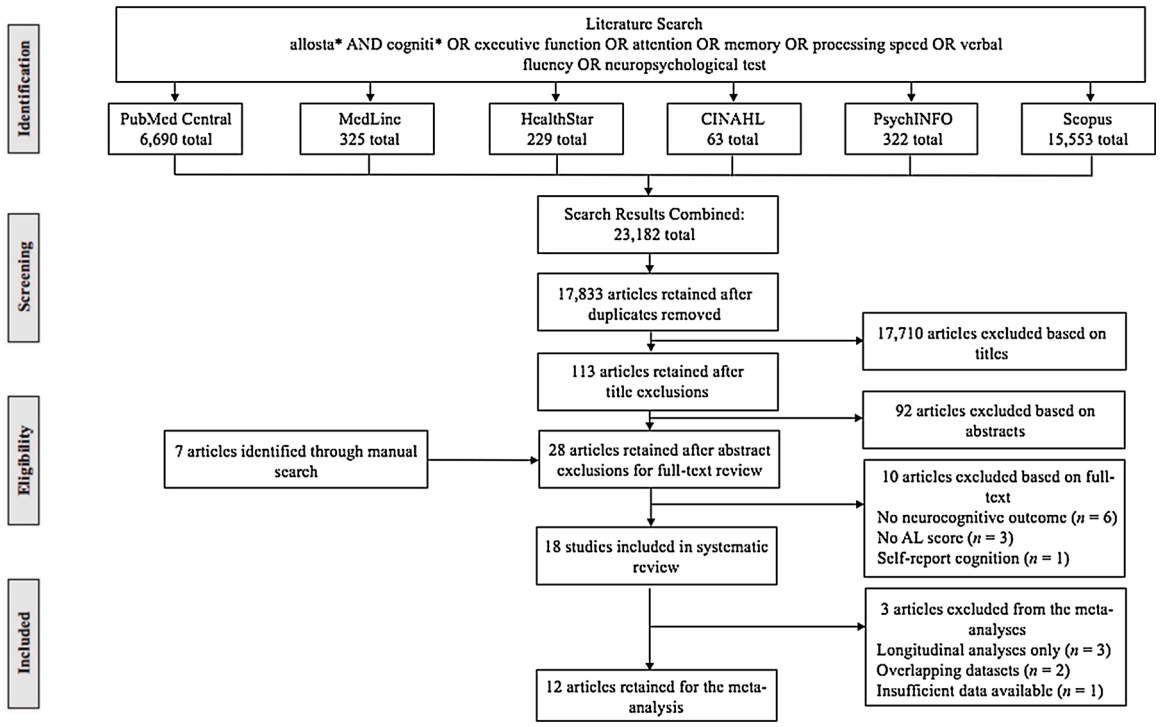

Fig. 1. PRISMA flowchart of the procedure used in article selection for the current study.

as few as five biomarkers to as many as 21 biomarkers. The most commonly included biomarker was systolic blood pressure, followed by HbA1c, triglycerides, waist-to-hip ratio, diastolic blood pressure, and cortisol. See Fig. 2 for the frequency of biomarkers included in AL indices across all studies. With the exception of research stemming from the MacArthur Studies, all AL indices included biomarkers of immune function. Analyses stemming from NHANES III, LBC1936, MESA, HRS, the Whitehall II Study, and the Rotterdam Study failed to include biomarkers of neuroendocrine function in calculating the AL index. Eleven (61 %) studies employed the traditional count-based calculation, originally devised by Seeman et al. (1997). The most frequently employed count-based algorithm was the quartile-count; however, studies also employed a decile-count algorithm, or a clinical cut-off score count-based algorithm. Four studies used the sum of individual biomarker z-scores, three studies used factor analysis in creating the AL index, one study used the canonical correlation method, and five studies included a combination of algorithms in their analyses. Due to small sample size, subsequent meta-analyses were unable to assess for effect modification based on AL index measurement.

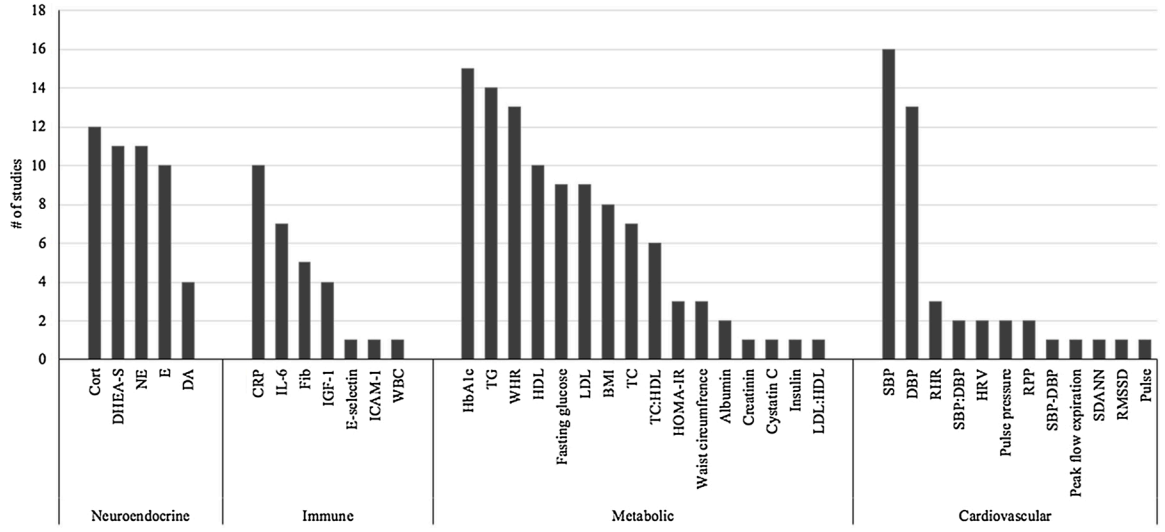

Fig. 2. Frequency of biomarkers included in AL scores across all 18 studies retained for the systematic review.
BMI: Body mass index; Cort: Cortisol; CRP: C-reactive protein; DA: Dopamine; DBP: Diastolic blood pressure; DHEA-S: Dehydroepiandrosterone sulfate; E: Epinephrine; HbA1c: Glycated hemoglobin; HDL: High-density lipoprotein; HOMA-IR: Homeostatic model of insulin resistance; HRV: Heart rate variability; IGF-1: Insulin-like growth factor-1; ICAM-1: ICAM-1: Intercellular adhesion molecule-1; IL-6: Interleukin-6; LDL: Low-density lipoprotein; NE: Norepinephrine; RHR: Resting heart rate; RMSSD: root mean square of successive differences between normal heartbeats; RPP: Resting pulse pressure; SBP: Systolic blood pressure; SDANN: standard deviation of average heart beat-to-beat intervals; TC: Total cholesterol; TG: Triglycerides; WBC: White blood cell; WHR: Waist-to-hip ratio

3.2. Cross-sectional studies

3.2.1. Review of cross-sectional studies

Systematic review of the literature identified 11 cross-sectional studies examining the relationship between AL and cognitive performance. An additional three longitudinal studies reported baseline associations between AL and cognition. See Table 1.

Of the 12 studies that examined the association between AL and global cognitive function, only one study reported a null association (Rigney, 2010). Of note, this study included a relatively small sample size ($n = 44$), which yielded a wide confidence interval, calling into question the reliability of study findings.

With memory performance as the outcome variable, three of the five studies reported the expected inverse association between AL and memory performance (de Robert, 2018; Karlamangla et al., 2014; Seeman et al., 1997). However, two of the five studies reported a null association (Booth et al., 2015; Wong, 2012). Of interest, two studies with contrasting findings were both based on secondary analyses of the MIDUS cohort. Wong (2012) reported no significant association between AL and episodic memory; whereas Karlamangla et al. (2014) reported a small ($r = -0.065$) albeit significant association. With slight variations in the number of included biomarkers, both studies used the count-based algorithm to calculate AL index. However, a notable difference between these two studies was the inclusion of covariates in the statistical model. While Wong (2012) included common covariates of cognitive function, namely age, sex, and education, Karlamangla et al. (2014) further controlled for ethnicity, parental education, and primary language. The second study to report a null association between AL and memory was that by Booth et al. (2015), whereby AL was calculated using a confirmatory bifactor model, which partitions out variance of general cognitive ability in factors representing specific cognitive domains.

Cross-sectional studies that examined the association between AL and executive function provided mixed results, likely due to the relative complexity in outcome measurement. Executive function comprises a diverse set of cognitive processes such as working memory, visual processing, and inhibition. Significant associations were reported for executive function composite scores (Karlamangla et al., 2014; Wong, 2012), however, some studies that included multiple individual measurements of executive function revealed mixed results. For example, Kobrosly et al. (2012) reported a significant association between AL and working memory in adults aged 20–59 years but failed to find a significant association between AL and visuomotor speed or perceptual motor speed. Furthermore, Ottino-González et al. (2019) reported a significant inverse association between AL and inhibitory control among participants aged 21–40 years, but further reported that the negative association between AL and performance on tasks of cognitive flexibility and working memory was limited to overweight participants.

3.2.2. Meta-analysis of cross-sectional studies

Of the 11 studies that examined the cross-sectional association between AL and global cognition, eight studies were included in the meta-analysis, yielding a total of 18,561 participants. Two studies were excluded (Booth et al., 2015; Seplaki et al., 2006) to avoid duplicate publication bias and one study (Wong, 2012) was excluded as sufficient statistics were not reported and the authors were unable to retrieve the study estimates (of note, this dissertation study also analyzed a duplicate sample). Exclusion of a duplicate sample was determined based on the earliest study publication date (exclude Seplaki et al., 2006 and retain the initial study by Seplaki et al., 2005) and sample size (exclude Booth et al., 2015 and retain Crook et al., 2018 with larger sample). Seplaki et al. (2005) included multiple AL algorithms in their analyses (see Table 1), but for the purpose of the current meta-analysis, the 16-item quartile-based count was chosen as this was the most frequently used AL algorithm across studies. Meta-analysis revealed a significant association between higher AL and poorer global cognition ($p < 0.001$). See Fig. 3.

Of the five studies that examined the cross-sectional association between AL and memory performance, four studies were included in the meta-analysis, yielding a total of 3005 participants in the model for memory. One study was excluded due to insufficient data reporting (Wong, 2012). Meta-analysis revealed that the pooled association between higher AL and poorer memory was not statistically significant ($p = 0.10$). See Fig. 3.

Finally, of the six studies that examined the association between AL and executive function, five studies were included in the meta-analysis, yielding a total of 7537 participants in the meta-analysis model for executive function. One study was excluded due to insufficient reporting of statistical data (Wong, 2012). Kobrosly et al. (2012) reported the association between AL and performance on tasks of executive function using the quartile count-based algorithm and the clinical cut-off algorithm. The quartile count-based algorithm was used for the meta-analysis to maintain consistency across studies. Although the effect size was comparable to the pooled estimate for memory, meta-analysis revealed a significant association between higher AL and poorer executive function ($p = 0.02$). See Fig. 3.

3.2.3. Publication Bias and heterogeneity

Inspection of funnel plots revealed little to no asymmetry for all cognitive outcomes. See Supplementary Fig. 1. Egger's test of the intercept was not significant for global cognition ($B_0 = -1.74$, 95 % CI = −4.02, 0.54, $p = 0.06$), memory ($B_0 = -1.09$, 95 % CI = −15.54, 13.36, $p = 0.39$), and executive function ($B_0 = 2.08$, 95 % CI = −4.20, 1.06, $p = 0.18$). Cumulative meta-analyses ranked by year showed that the association between AL and cognitive function has remained statistically significant and stable since 2016 for global cognition and since 1997 for executive function. For memory, results had remained statistically significant until 2015, at which point the association lost statistical significance. Classic fail-safe N revealed that 106 studies for global cognition and 47 studies for executive function would need to be added to each model to lose statistical significance.

Heterogeneity was statistically significant for global cognition ($Q(7) = 28.10$, $p < 0.001$), memory ($Q(3) = 12.70$, $p = 0.005$), and executive function ($Q(4) = 18.62$, $p = 0.001$). The percentage of variation across studies due to heterogeneity was moderate for global cognition ($I^2 = 74.17$), and large for memory ($I^2 = 76.38$) and executive function ($I^2 = 78.52$). Results did not change for global cognition or for executive function when a single study was deleted once from the respective model. However, within the memory domain, removal of Booth et al. (2015) revealed a significant pooled estimate for the association between AL and memory performance.

3.3. Longitudinal studies

Seven papers were identified that reported longitudinal associations between AL and change in cognitive function over time. One study reported results for AL and cognitive change among two separate cohorts (Schmitz et al., 2018), yielding a total of eight analytical cohorts reporting longitudinal associations with study lengths ranging from three to 12 years (see Table 1). All but one study exclusively examined change in global cognitive function over time. Although Seeman et al. (1997) included measures of memory and executive function in their analyses, the paper failed to report results pertaining to change in global cognition or executive function. Seven of the eight studies reported an association between higher AL and greater decline in global cognitive performance (Crook et al., 2018; Karlamangla et al., 2002; Oi and Haas, 2019; Schmitz et al., 2018; Seeman et al., 2001), with the exception of Goldman et al. (2006), who failed to find a statistically significant association in the SEBAS cohort over a 3-year period. Of note, studies reporting the strongest effect size in the association between AL and global cognition did not use the traditional count-based AL calculation. As previously mentioned, meta-analysis of longitudinal data was not possible due to substantial variations in statistical modeling.

Table 1
Characteristics of included studies.

Study	Study design (CS/L, years)	Sample size (*N*) Mean/ median age Age range Sex (% female) *Cohort, Location*	AL biomarker #	AL calculation method	System: Biomarkers	Cognitive outcome assessed (Measure)	Exclusion criteria	Covariates *Effect modifiers*	↑ AL findings
Cross-Sectional Studies									
Seplaki et al. (2005) [M]	CS	*N* = 958 Mean age = 67.7 years Age range: 54–90 years 42 % female *SEBAS, Taiwan*	16 [b]	Quartile count [a]	Immune: IL-6, IGF-1 Metabolic: TG, TC, TC:HDL, HbA1c, BMI, WHR, Fasting glucose Cardiovascular: SBP, DBP Neuroendocrine: Cort, DHEA-S, E, NE, DA	Global cognition (SPMSQ)	Not specified	Age, Sex	↓ global cognition
			10	Decile count					ns: with use of 10 biomarkers
				Sum of z-scores					
Seplaki et al. (2006)	CS	*N* = 972 Mean age: 67.7 years Age range: 50+ years 41 % female *SEBAS, Taiwan*	10	Quartile count [b] Decile count [b]	Immune: IL-6, IGF-1 Metabolic: TG, TC, TC:HDL, HbA1c, BMI, WHR, Fasting glucose Cardiovascular: SBP, DBP Neuroendocrine: Cort, DHEA-S, E, NE, DA	Global cognition (Sum of items adapted from SPMSQ, RAVLT, DS-B)	Not specified	Age, Sex	↓ global cognition
Rigney (2010) [M]	CS	*N* = 44 Mean age: 75.7 years Age range: 66–93 years 43 % female *United States*	10	Quartile count	Immune: None Metabolic: HDL, TC:HDL, HbA1c, WHR Cardiovascular: SBP, DBP Neuroendocrine: Cort, E, NE, DHEA-S	Global cognition (MMSE)	Non-English speaking, MMSE ≤ 23, Delirium, Communication deficits, Steroid use	None	ns: global cognition
Kobrosly et al. (2012) [M]	CS	*N* = 4511 Median age: 36.0 years Age range: 20–59 years 54 % female *NHANES III, United States*	10	Quartile count [a] Clinical cut-off count	Immune: WBC count Metabolic: TG, TC, HbA1c, WHR, Albumin, Creatinine Cardiovascular: SBP, DBP, RHR Neuroendocrine: None	Visuomotor speed (SRTT) Perceptual motor speed (DSST) Working memory (SDLT)	Not specified	Age, Sex, Education, Ethnicity, Computer familiarity, Alcohol, Language, Self-report energy, Stroke, Physical Activity, Income	↓ working memory ns: visuomotor speed or perceptual motor speed
Wong (2012)	CS	*N* = 1152 Mean age: 55.4 years Age range: 25–74 years	20	Quartile count	Immune: Fib, CRP, IL-6, IGF-1 Metabolic: TG, TC, HDL, LDL, HbA1c, Fasting glucose, Insulin, WHR	Global cognition (Sum of z-scores from BTACT verbal episodic memory tests and BTACT executive function tests)	Not specified	Age, Sex, Education	↓ global cognition and executive function ns: verbal episodic memory

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Table 1 (*continued*)

Study	Study design (CS/L, years)	Sample size (*N*) Mean/ median age Age range Sex (% female) *Cohort, Location*	AL biomarker #	AL calculation method	System: Biomarkers	Cognitive outcome assessed (Measure)	Exclusion criteria	Covariates *Effect modifiers*	↑ AL findings
		57 % female *MIDUS Study, United States*			Cardiovascular: SBP, DBP, Peak flow expiration Neuroendocrine: Cort, E, NE, DHEA-S, DA	Verbal episodic memory (Factor analysis of BTACT: Immediate and Delayed Word Recall from RAVLT) Executive function (Factor analysis of BTACT: DS-B, VFT, Backwards Counting, Number Series Pattern Completion)			
Karlamangla et al. (2014) [M]	CS	$N = 1076$ Median age: 57.0 years Age range: 25–74 years 57 % female *MIDUS Study, United States*	21	Quartile count	Immune: Fib, CRP, IL-6, ICAM-1, E-selectin Metabolic: TG, HDL, LDL, HbA1c, BMI, WHR, Fasting glucose, HOMA-IR Cardiovascular: SBP, RHR, RPP, HRV Neuroendocrine: Cort, DHEA-S, E, NE	Verbal episodic memory (Factor analysis of BTACT: Immediate and Delayed Word Recall from RAVLT) Executive function (Factor analysis of BTACT: DS-B, VFT, Backwards Counting, Number Series Pattern Completion, Stop and Go Switch Task)	Age < 25 or > 74, Non-English speaking, Institutionalization, No telephone, Residing outside of USA	Age, Sex, Education, Ethnicity, Parental education, Primary language *Effect modifiers*: Age, Sex	↓ verbal episodic memory and executive function ns: modification by age or sex
Booth et al. (2015) [M]	CS	$N = 658$ Mean age: 72.5 years Age range: Not specified 48 % female *LBC1936, Scotland*	10	Factor analysis	Immune: Fib, CRP, IL-6 Metabolic: TG, HDL, LDL, HbA1c, BMI Cardiovascular: SBP, DBP Neuroendocrine: None	Global cognition (Bifactor model of all tests) Processing speed (WAIS-III: DSCT, SRTT, CRTT, Symbol Search partitioned for general cognitive ability) Verbal episodic memory (WMS-III: Logical Memory Immediate	MMSE < 26	Age, Sex	↓ global cognition, processing speed, and knowledge ns: verbal episodic memory and nonverbal reasoning

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Table 1 (*continued*)

Study	Study design (CS/L, years)	Sample size (*N*) Mean/ median age Age range Sex (% female) *Cohort, Location*	AL biomarker #	AL calculation method	System: Biomarkers	Cognitive outcome assessed (Measure)	Exclusion criteria	Covariates *Effect modifiers*	↑ AL findings
						and Delayed Recall, WMS-III: Verbal Paired Associates Immediate and Delayed Recall partitioned for general cognitive ability) Knowledge (NART, WTAR, VFT partitioned for general cognitive ability) Nonverbal reasoning (WAIS-III: Matrix Reasoning, Block Design, DS-B, Letter-Number Sequencing, WMS-III Spatial Span partitioned for general cognitive ability)			
		N = 4591	8	Sum of z-scores	Immune: None	Global cognition	Race other than White, African American, Hispanic, or Asian		
Forrester (2016) [M]	CS	Mean age: 60.0 years Age range: 44–84 years 53 % female *MESA Study, United States*			Metabolic: TG, HDL, LDL, WHR, Fasting glucose Cardiovascular: SBP, DBP, Pulse pressure Neuroendocrine: None	(Sum of z-scores from CASI, DSCT, DS-F, DS-B)		Age, Sex, SES, Depression, Self-reported stress	↓ global cognition
de Robert (2018) [M]	CS	*N* = 86 Mean age: 53.5 years Age range: Not specified 56 % female *Argentina*	16	Clinical cut-off count	Immune: Fib, CRP Metabolic: TG, HDL, LDL, HbA1c, HOMA-IR, BMI, WHR Cardiovascular: SBP, RPP, HRV Neuroendocrine: Cort, DHEA-S, E, NE	Global cognition (ACE) Verbal episodic memory (ACE-Memory subscale)	CVD, Chronic diseases	Age, Sex, Education	↓ global cognition and verbal episodic memory ↑ cardiovascular markers = ↓ global cognition and verbal episodic memory ↑ immune markers = ↓ global cognition and verbal episodic memory
Narbutas et al. (2019) [M]	CS	*N* = 72 Mean age: 59.4 years	18	Sum of z-scores	Immune: CRP, IL-6 Metabolic: TG, HDL, LDL, HbA1c, WHR,	Global cognition (PACC5)	Psychiatric/ neurological condition, Psychiatric medication, Normal vision/hearing, Sleep	Age, Sex	↓ global cognition

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Table 1 (*continued*)

Study	Study design (CS/L, years)	Sample size (*N*) Mean/ median age Age range Sex (% female) *Cohort, Location*	AL biomarker #	AL calculation method	System: Biomarkers	Cognitive outcome assessed (Measure)	Exclusion criteria	Covariates *Effect modifiers*	↑ AL findings
		Age range: 50–69 years 67 % female *Belgium* *N* = 103 Mean age: 30.9 years Age range: 21–40 years			BMI, Fasting glucose Cardiovascular: SBP, RHR, Pulse pressure, SDANN, RMSSD Neuroendocrine: Cort, E, NE, DHEA-S Immune: Fib, CRP Metabolic: TG, LDL:HDL, HOMA-IR	Cognitive flexibility (Sum of z-scores from WCST, TMT)	apnea, BMI < 18 or > 29 kg/m^2, Smoking, Illicit drug use, Excessive caffeine/ alcohol intake, Diabetes, Shift work, Hypertension, Hypothyroidism, Cognitive impairment	Age, Sex, Income	↓ inhibitory control in total sample ns: cognitive flexibility or working memory in total sample
Ottino-Gonzalez et al. (2019) [M]	CS	63 % female *Spain*	7	Sum of z-scores	Cardiovascular: SBP – DBP Neuroendocrine: Cort	Inhibitory control (Stroop Test) Working memory (WAIS-III: Letter-Number Sequencing)	Age ≥ 21 or ≤ 40, BMI < 18.5 kg/m^2	*Effect Modifier:* Healthy weight vs. overweight	↓ cognitive flexibility in overweight group only ns: modification by weight for inhibitory control or working memory
Longitudinal Studies									
		N = 1189 Mean age: Not specified Age range: 70–79 years 51 % female *MacArthur Studies of Successful Aging,* *United States*		Quartile count [a] Decile count Sum of z-scores	Immune: None Metabolic: HDL, TC:HDL, HbA1c, WHR Cardiovascular: SBP, DBP Neuroendocrine: Cort, E, NE, DHEA-S	Global cognition (Sum of scores from memory, abstract reasoning, and spatial ability tests) Memory composite (Sum of scores from DSRT, Delayed Word Recall, Delayed Story Recall) Verbal memory (BNT) Abstract Reasoning (WAIS-R Similarities) Spatial ability (ADAS Geometric Copy)			↓ baseline global cognition, memory composite, spatial ability, and abstract reasoning Verbal memory: cross-sectional statistics not reported ↑ decline in memory composite and verbal memory Global cognition, abstract reasoning, spatial ability: longitudinal statistics not reported Decile count and sum of z-scores: statistics not reported
Seeman et al. (1997) [M]	L, 3 years		10				Age < 70 or > 79, ADL disability, Physical disability, Balance problems, SPMSQ < 6, Delayed recall < 3 out of 6 words	Age, Sex, Education, Ethnicity, CVD, Physical activity, Income	
Seeman et al. (2001)	L, 7 years	*N* = 1189 Mean age: Not specified	10	Quartile count [a] Decline count	Immune: None Metabolic: HDL, TC:HDL, HbA1c, WHR	Global cognition (Sum of scores from language,	Age < 70 or > 79, ADL disability, Physical disability, Balance problems, SPMSQ < 6, Delayed	Age, Sex, Education, Ethnicity, CVD, Income,	↑ decline in global cognition ↑ syndrome X markers (cardiovascular

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Table 1 (*continued*)

Study	Study design (CS/L, years)	Sample size (*N*) Mean/ median age Age range Sex (% female) *Cohort, Location*	AL biomarker #	AL calculation method	System: Biomarkers	Cognitive outcome assessed (Measure)	Exclusion criteria	Covariates *Effect modifiers*	↑ AL findings
		Age range: 70–79 years 51 % female *MacArthur Studies of Successful Aging, United States*		Sum of z-scores	Cardiovascular: SBP, DBP Neuroendocrine: Cort, DHEA-S, E, NE	abstract reasoning, spatial ability, delayed spatial recognition, delayed word recall, and delayed story recall tests) [c]	recall < 3 out of 6 words	Cancer, Broken bones	and metabolic) = ↑ change in global cognition ns: non-syndrome X markers (neuroendocrine) and cognition Decile count and sum of z-scores: statistics not reported
Karlamangla et al. (2002)	L, 7 years	*N* = 447 Mean age: 74.1 years Age range: 70–79 years 51 % female *MacArthur Studies of Successful Aging, United States*	8	Canonical correlation	Immune: None Metabolic: HbA1c, WHR Cardiovascular: SBP, DBP Neuroendocrine: Cort, DHEA-S, E, NE	Global cognition (Summary measure of BNT, DSRT, ADAS Geometric Copy, WAIS-R Similarities using canonical correlation)	ADL disability, Physical disability, Balance problems, SPMSQ < 6, Delayed recall < 3 out of 6 words	Age, Sex, Ethnicity, CVD, Physical activity, Smoking, Alcohol consumption, Psychological functioning, Baseline global cognition	↑ decline in global cognition ↑neuroendocrine markers = ↑ decline in global cognition
Goldman et al. (2006)	L, 3 years	*N* = 820 Mean age: 67.4 years Age range: 54–91 years	16	Decile count	Immune: IL-6, IGF-1 Metabolic: TG, TC, TC:HDL, HbA1c, BMI, WHR, Fasting glucose	Global cognition (Sum of items from SPMSQ, RAVLT, DS-B)	Not specified	Age, Sex, Depression, Cognitive Impairment, Smoking, # of chronic conditions, Urban/rural residence, Mobility limitations	ns: change in global cognition ↑ clinical markers (cardiovascular and metabolic) = ↑ change in cognition
Crook et al. (2018) [M]	L, 6.7 years	42 % female *SEBAS, Taiwan* *N* = 1020 Mean age: 69.5 years Age range: Not specified 50 % female *LBC1936, Scotland*	9	Sum of z-scores	Cardiovascular: SBP, DBP Neuroendocrine: Cort, DHEA-S, E, NE, DA Immune: Fib, CRP Metabolic: TG, TC:HDL, HbA1c, BMI, Albumin Cardiovascular: SBP, DBP Neuroendocrine: None	Global cognition (Factor analysis of WAIS-III: DSCT, Block Design, Symbol Search, Letter-Number Sequencing, Matrix Reasoning)	MMSE < 24, Stroke, Dementia, PD	Age, Sex, Education, # of medical conditions *Effect modifier*: APOE4 status	ns: non-clinical markers (immune and neuroendocrine) and cognition ↓ baseline global cognition for APOE4+ and APOE4- ↑ decline in global cognition for APOE4+ and APOE4- ns: modification by APOE4 status
Schmitz et al. (2018)	*Whitehall II Study:* L, 10 years	*Whitehall II Study:* *N* = 4635 Mean age: 55.2 years Age range: 45–69 years 26 % female *England*	*Whitehall II Study:* 5	*Whitehall II Study:* Factor analysis	*Whitehall II Study:* Immune: CRP Metabolic: TG, LDL, fasting glucose, waist circumference Cardiovascular: SBP:DBP Neuroendocrine: None	*Whitehall II Study:* Global cognition (Factor analysis of VFT, 20-word Free Recall Test, AH4-I)	*Whitehall II Study:* Not specified	*Whitehall II Study:* Age, Sex, Education, Ethnicity, Depression, Smoking, Physical activity	*Whitehall II Study:* ↑ decline in global cognition

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Table 1 (*continued*)

Study	Study design (CS/L, years)	Sample size (*N*) Mean/ median age Age range Sex (% female) *Cohort, Location*	AL biomarker #	AL calculation method	System: Biomarkers	Cognitive outcome assessed (Measure)	Exclusion criteria	Covariates *Effect modifiers*	↑ AL findings
	Rotterdam Study:	*Rotterdam Study:*	*Rotterdam Study:*	*Rotterdam Study:*	*Rotterdam Study:*	*Rotterdam Study:*	*Rotterdam Study:*	*Rotterdam Study*	*Rotterdam Study:*
	L, 12 years	*N* = 2940 Mean age: 65.0 years Age range: 55+ years 57 % female *The Netherland*	5	Factor analysis	Immune: CRP Metabolic: TG, LDL, fasting glucose, waist circumference Cardiovascular: SBP:DBP Neuroendocrine: None	Global cognition (Factor analysis of Stroop Test, VFT, Verbal Learning Test, Purdue Pegboard Test, Letter-Digit Substitution Task)	Not specified	Age, Sex, Education, Ethnicity, Depression, Smoking, Physical activity:	↑ decline in global cognition
Oi and Haas (2019) [M]	L, 6 years	*N* = 9449 Mean age: 70.7 years Age range: 50–100 years 56 % female *HRS, United States*	9	Quartile count	Immune: CRP Metabolic: HDL, LDL, HbA1c, Waist circumference, Cystatin C Cardiovascular: SBP, DBP, Pulse Neuroendocrine: None	Global cognition (m-TICS)	Not specified	Age, Sex, Ethnicity, Childhood SES, Adulthood SES	↓ baseline global cognition ↑ decline in global cognition

Note. [a] : Where multiple, AL algorithm used in meta-analysis; [b] : Sex-specific AL score; [c] : Exact cognitive tests not specified; [M] : Study included in meta-analysis. ACE: Addenbroke's Cognitive Examination; ADAS: Alzheimer's Disease Assessment Scale; AH4-I: Alice Heim 4-I; AL: Allostatic load; APOE4: Apolipoprotein E4; BMI: Body mass index; BNT: Boston Naming Test; BTACT: Brief Test of Adult Cognition by Telephone CARDIA: Coronary Artery Risk Development in Young Adults; CASI: Cognitive Abilities Screening Test; Cort: Cortisol; CRP: C-reactive protein; CRTT: Choice Reaction Time Test; CS: Cross-sectional; CVD: Cardiovascular disease; DA: Dopamine; DBP: Diastolic blood pressure; DHEA-S: Dehydroepiandrosterone sulfate; DS-B: Digit Span-Backwards; DS-F: Digit Span-Forwards; DSCT: Digit Symbol Coding Test; DSRT: Delayed Spatial Recognition Test; DSST: Digit Symbol Substitution Test; E: Epinephrine; Fib: Fibrinogen; HbA1c: Glycated hemoglobin; HDL: High-density lipoprotein; HOMA-IR: Homeostatic model of insulin resistance; HRS: Health and Retirement Study; HRV: Heart rate variability; ICAM-1: Intercellular adhesion molecule-1; IGF-1: Insulin-like growth factor-1; IL-6: Interleukin-6; IQ: Intelligence quotient; L: Longitudinal; LBC1936: Lothian Birth Cohort 1936; LDL: Low-density lipoprotein; m-TICS: Modified Telephone Interview for Cognitive Status; MESA: Multiethnic Study of Atherosclerosis ; MIDUS: Midlife in the United States ; MMSE: Mini-mental State Examination; NART: National Adult Reading Test; NE: Norepinephrine; NHANES III: Third National Health and Nutrition Examination Survey; ns: Not significant ; PACC5: Preclinical Alzheimer Cognitive Composite score; PD: Parkinson's disease; RAVLT: Rey Auditory Verbal Learning Test; RHR: Resting heart rate; RMSSD: root mean square of successive differences between normal heartbeats; RPP: Resting pulse pressure; SBP: Systolic blood pressure; SDANN: standard deviation of average heart beat-to-beat intervals; SDLT: Serial Digit Learning Test; SEBAS: Social Environment and Biomarkers of Aging Study; SES: Socioeconomic status; SPMSQ: Short Portable Mental Status Questionnaire; SRTT: Simple Reaction Time Test; TC: Total cholesterol; TG: Triglycerides; TMT: Trail Making Test; VFT: Verbal Fluency Task; WAIS-III: Wechsler Adult Intelligence Scale III; WAIS-R: Wechsler Adult Intelligence Scale Revised; WBC: White blood cell; WCST: Wisconsin Card Sorting Task; WHR: Waist-to-hip ratio; WMS-III: Wechsler Memory Scale III; WTAR: Wechsler Test of Adult Reading.

4. Discussion

This is the first systematic review and meta-analysis to integrate and critically examine existing cross-sectional and longitudinal studies investigating the association between AL and cognitive function in adults. Casting a relatively wide net, which resulted in 17,833 papers to review, 18 papers were extracted for analysis. Among cross-sectional studies, there was sufficient data to pool results for global cognition, memory, and executive function. Meta-analyses revealed that higher AL was significantly associated with poorer global cognition and executive function, with relatively small pooled estimates below $r = 0.20$. Further, the association between AL and memory was not statistically significant. Despite differences in statistical significance, pooled effect size estimates were highly consistent between the three cross-sectional models. The difference in statistical significance between models may be due to the smaller sample size in the AL-memory model, which is more sensitive to outlier data (i.e., Booth et al., 2015). Due to the small number of papers identified for review, there was insufficient data available to conduct meta-regression analyses to examine the impact of moderator variables. Accordingly, the analyses of potential effect-modifiers in the AL-cognition relationship is limited to qualitative review.

As previously alluded to, calculation of the AL index may provide a source of variation in research outcomes. In reviewing the extracted papers, studies differed with respect to number of biomarkers, types of biomarkers, and the algorithm used to calculate the AL index. Based on systematic observation, it is plausible that the AL algorithm affected study findings as choice of algorithm may determine sensitivity of the AL index and its relationship with cognitive function. Indeed, smaller estimates were observed for studies that employed the traditional count-based AL index calculation (Seeman et al., 1997), relative to other algorithms such as a sum of the biomarker z-scores. Despite the inclusion of both count-based and sum of z-score algorithms, the seminal paper by Seeman et al. (1997) only reported results for the quartile count-based algorithm, while noting that the sum of z-scores provided a "stronger effect". A potential limitation of the traditional count-based algorithm is that individual AL scores are determined based on the variation of each biomarker within the analytical sample. This is particularly problematic if the sample is comprised of relatively healthy, high-functioning

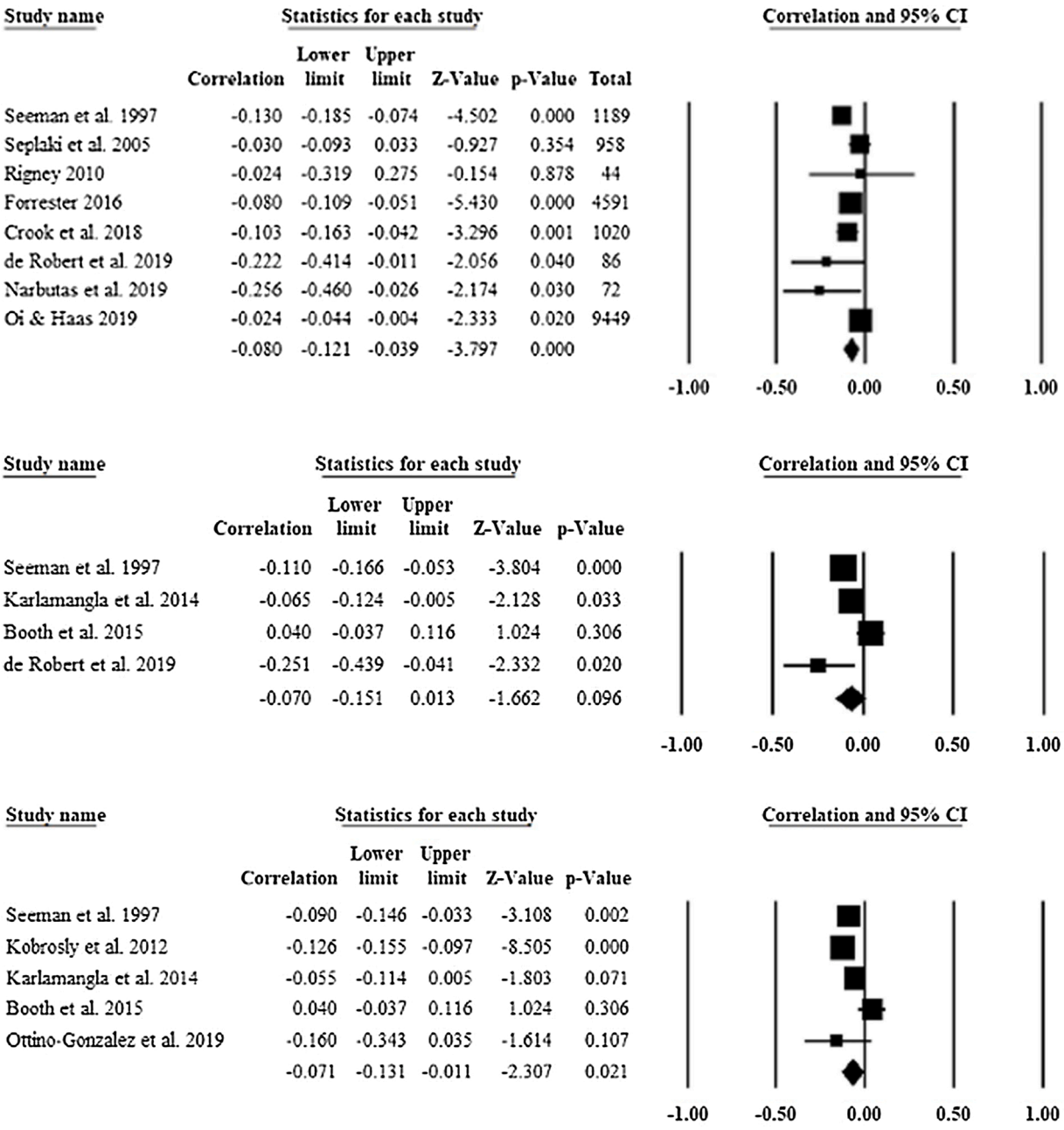

Fig. 3. Forest plots for random effects meta-analysis of cross-sectional studies showing results for global cognition (top), memory (middle), and executive function (bottom) as outcome measures.

individuals, which may not represent the population at large. To highlight this point, using a decile-based cut-off score, Goldman et al. (2006) did not find an association between AL and change in global cognition. It may be argued that decile cut points may be less sensitive than quartile cut points as an early warning threshold for subsequent cognitive decline in a healthy sample, thus reducing the power to detect an association between AL and cognition. For this reason, the use of clinical cut-off scores may provide more meaningful AL indices. However, with only two studies employing clinical cut off scores to derive total AL, this assertion is purely speculative. Furthermore, biomarkers commonly included in the AL index, such as cortisol, do not have known clinical thresholds. Another limitation of the traditional count-based model is that it assumes equal impact across biomarkers and across systems, downplaying the intricate interconnection between biological systems. Algorithms such as sum of z-scores may correct for this assumption by allowing the weight of each biomarker to vary depending on its deviation from the sample's mean (Juster et al., 2010). More sophisticated methods such as canonical correlations (i.e., weighting AL components to find the optimal linear combination between AL and cognitive function) or data-driven factor-analytic approaches may also be beneficial to consider. It is worth noting, however, that traditional factor analytic methods have been postulated to be too simplistic an approach to best represent the AL construct as a measure of accumulated dysregulation due to chronic stress (Crook and Booth, 2017). Indeed, the process underlying dysregulation across multiple physiological systems is not reflected by a single latent factor, and the assumption of independence of the observed biomarker variables is likely violated given that individual biomarkers are dynamically interrelated. It is unclear, however, if and how factor-analytic approaches differ in their predictive value of cognitive function as only two studies employed factor analyses in deriving AL (Booth et al., 2015; Schmitz et al., 2018). Nonetheless, the appropriateness of factor analytic methods for deriving AL should be

considered in future studies.

Along a similar vein, the number of interconnected systems included in the AL index varied between studies, with some studies omitting immune system function and others not including neuroendocrine markers. This is not surprising given that the body of work examining the association between AL and cognition largely stems from secondary analyses of pre-existing cohort data, whereby the primary objective was not to provide a robust measure of AL. Acknowledging the challenge associated with collecting reliable neuroendocrine bio-analytes due to diurnal rhythms, dysregulation of the neuroendocrine system resulting from overactivation of the hypothalamic-pituitary-adrenal axis may be especially relevant in predicting episodic memory function (Lupien et al., 1998). Of note, among the limited studies that investigated the association between AL and memory, Booth et al. (2015) was the one study to report null findings with respect to AL and memory performance and was also the only study to omit neuroendocrine biomarkers in calculating the AL index. Indeed, the pooled association between AL and memory performance became significant when Booth et al. (2015) was removed from the meta-analytic model. However, in dividing AL into clinical (i.e., cardiovascular and metabolic) and non-clinical (i.e., immune and neuroendocrine) clusters, Goldman et al. (2006) found that higher scores on the clinical cluster, but not the non-clinical cluster, associated with greater global cognitive decline. It may be argued that secondary mediators (i.e., cardiovascular and metabolic systems) provide greater predictive value in estimating global cognitive trajectory as dysregulation of these systems extend from the wear and tear of primary mediators (i.e., neuroendocrine and immune systems) and may reflect more extensive wear and tear of the organism. This postulation is supported by Seeman et al. (2001), who reported that the association between AL and change in global cognitive function was stronger for secondary mediators ($b = .61$) relative to the entire AL index ($b = .58$) and primary mediators ($b = .46$). It is possible that the predictive value of the full AL index was minimized by including primary mediators, which in itself did not associate with global cognitive change. It may also be postulated, however, that neuroendocrine markers are most important to include when assessing memory performance due to the deleterious effect of stress hormones on hippocampal function (Lupien et al., 1998). As such, it remains unclear whether all four systems are necessary to include in the AL index when investigating the impact of AL on cognitive function, and whether the differential weight of each system varies depending on time-course and cognitive domain.

In addition to AL estimation methods, variations in the cognitive tests employed and the calculation techniques used for deriving cognitive performance scores may constitute important sources of heterogeneity in the meta-analysis. With respect to cognitive tests used, global cognitive screening tools such as the Mini-Mental State Examination, the Short Portable Mental Status Questionnaire, and the modified Telephone Interview for Cognitive Status may result in less variability within a cognitively healthy sample due to ceiling effects, thus compromising sensitivity of the analytical model and underestimating the association between AL and global cognitive function (Franco-Marina et al., 2010). In order to assess global cognitive function in individuals without cognitive impairment, aggregation of multiple standardized cognitive test scores from various cognitive domains may be advantageous as it may better reflect a range in global cognitive performance in healthy adults.

With respect to calculation techniques, computation of scores pertaining to global cognition varied substantially between studies. Some studies derived scores based on a single cognitive test such as the mTICS (e.g., Oi and Haas, 2019), while other studies calculated a global composite score (e.g., Seeman et al., 1997; Goldman et al., 2006) or employed dimension reduction techniques to derive a factor analytic score (e.g., Crook et al., 2018; Karlamangla et al., 2014) based on test performance across multiple cognitive domains. Consequently, variations in cognitive score calculations may contribute to the observed heterogeneity in the current study. Of note, Booth et al. (2015) used a confirmatory bifactor model, which partitions out variance of general cognitive ability in factors representing specific cognitive domains. Although a significant association was reported for global cognition, Booth et al. (2015) was the only study to report a null association between AL and measures of memory and executive function. Together, variations in the cognitive testing battery and calculation techniques may significantly contribute to heterogeneity in the data and undermine the ability to make direct comparisons between studies.

Although meta-analyses were not conducted with longitudinal studies, results from individual studies suggest a relatively robust association between AL and global cognitive trajectory over time. It may be postulated that length of follow-up may contribute to the strength of the association between AL and change in cognition, with longer follow-up since baseline reflecting longer periods of interconnected systemic wear and tear (Beckie, 2012). Indeed, the AL model fundamentally proposes that the physiological burden and health consequences of chronic stress accumulates over time throughout the lifespan, which may be difficult to capture using cross-sectional models or short-term follow-up assessments. Indeed, the only longitudinal study that failed to find a relationship between AL and change in global cognitive function was Goldman et al. (2006), whereby the length of follow-up at three years was substantially lower than other longitudinal studies with follow-up times of six to 12 years. Although cross-sectional and longitudinal effect sizes could not be directly compared, it is hypothesized that the pooled effect size of the association between AL and cognitive change would be larger than cross-sectional associations of AL and cognitive function. Indeed, higher AL at baseline reflects the current wear and tear on interconnected physiological systems, which may weakly associate with current cognitive function; however, accumulation of physiological dysregulation over time leads to the final stage of AL progression, referred to as allostatic overload, evidenced by tertiary outcomes such as cognitive impairment (Juster et al., 2010). However, the Whitehall II study (Schmitz et al., 2018), which had a longer follow-up time compared to other studies at 10 years, was composed of mostly males (74 %), underscoring the importance of investigating potential effect-modifiers of the AL-cognition relationship.

Although meta-regression analyses to examine the impact of moderator variables was not possible due to an insufficient sample size, effect modification of sex and age may be important to consider. While Karlamangla et al. (2014) failed to find effect-modification by sex in the MIDUS cohort, additional research is needed to elucidate sex and gender differences in the association between AL and cognitive function, especially given the increased risk of dementia among females (Laws et al., 2016), and known sex-based modifications in the relationship between individual biomarkers and cognitive function (Fiocco et al., 2019). In light of reported sex difference in biomarker levels (Lew et al., 2017; Larsson et al., 2009), it may also be important to derive sex-based AL scores. Only one of the retrieved studies (Seplaki et al., 2006), however, derived AL scores taking into consideration sex differences in biomarker levels by defining biomarker cut points separately by sex.

In addition to sex, age may also be considered an important effect modifier in the association between AL and cognitive function, especially considering that variability in cognitive performance is lower among younger adults relative to older adults (Rowe and Kahn, 1997). For example, the lack of association between AL and components of executive function (i.e., working memory and cognitive flexibility) in the study by Ottino-González et al. (2019) may be due to the restricted age range of younger participants (i.e., 21–40 years). Notably, this association was significant among the subsample of overweight participants. As increased weight has been found to associate with increased epigenetic age (Nevalainen et al., 2017), it is possible that this subsample of overweight participants physiologically represented an older adult group. Moreover, although Karlamangla et al. (2014) failed to find an effect modification by age in the MIDUS sample, executive function was assessed using a composite measure of executive function, which may not be as sensitive to the effects of age. Importantly, including a

larger age range of participants or conducting purposeful stratification by age (e.g., younger adults, middle-aged adults, older adults) may provide greater insight in the association between AL and domains of cognition due to higher variability in physiological markers and cognitive performance with increasing age (Crimmins et al., 2003; Geronimus et al., 2006). It may also be postulated that sub-domains of executive functioning may be differentially associated with AL (Ottino-González et al., 2019), highlighting the need for additional research to systematically examine the relationship between AL and multiple sub-domains of cognition.

While findings generated from this meta-analysis and systematic review contribute to the literature examining the association between AL and cognitive function, this study is not without limitations. First, a small number of studies were identified in the systematic literature search and the meta-analyses, which may have over- or underestimated true effect sizes and inflated estimates of heterogeneity among cross-sectional studies. As such, meta-analyses should be replicated as more studies accumulate in the literature. Studies also differed with respect to model adjustments and did not present unadjusted model estimates for the exploration of effect modification. In light of these study limitations, results must be interpreted with caution. Additionally, the variation in statistical methods used to examine associations between AL and cognitive function over time precluded longitudinal meta-analyses from being conducted. This highlights the need for methodological consistency across studies in order to directly compare findings and to determine a true effect size.

Of note, metabolic syndrome (MetS), an index of cardiometabolic risk factors that parallel the cardiovascular and metabolic biomarkers included in AL formulation, was not explicitly included in the search strategy as the study objective was to investigate the traditional AL construct incorporating biomarkers from all four physiological systems. In order to retain as many papers as possible, articles that omitted biomarkers from an entire physiological system were not excluded, provided that at least two out of the four systems were represented in the data. This decision was made due the acknowledgment that most studies use pre-existing cohort data whereby the primary objective was not to assess AL. The systematic search resulted in 25 papers that examined the association between MetS and cognitive function. After full review of the articles, however, none of the studies were eligible for inclusion due to the presentation of MetS as a binary variable (i.e., MetS = yes/MetS = no), insufficient reporting of results, and the target population (i.e., clinical samples with cognitive impairments).

A final limitation of the current study is that estimates are derived from observational studies, precluding the ability to establish causality in the relationship between AL and cognitive function. Indeed, other health concerns associated with high AL have been found to cluster with poor cognitive health such as cardiovascular and metabolic diseases (Lai et al., 2020). Poor cognitive performance may also affect factors that propagate higher AL as poor cognitive health has been identified as a contributing factor to increased chronic stress (Osmanovic-Thunström et al., 2015).

Before the clinical utility of AL to detect sub-clinical states of cognitive impairment can be determined, additional investigation is required. In particular, the notable absence of a gold standard representation of AL severely limits inter-study comparisons. For example, although data-driven models have been proposed (Wiley et al., 2016), debate remains with respect to the utility of factor analytic models to represent the AL construct (Crook and Booth, 2017). Clearly, research is needed to identify the optimal AL algorithm and biological indicator/systems that are sensitive to cognitive change across multiple domains. It is also important to measure change in AL over time concurrently with cognitive function. Indeed, AL is not static (McEwen and Stellar, 1993) and thus dynamic changes in AL may provide greater insight into cognitive fluctuations over time. Moreover, all but one longitudinal study assessed global cognition only, highlighting the need for future research to investigate the relationship between AL and change in multiple domains of cognition. Further, a larger number of studies are needed to expand on the current findings in order to quantitatively assess moderators of the AL-cognition relationship such as sociodemographic factors. While ethnicity was controlled for in some of the reported studies, health disparities across race and social groups need to be explored. Indeed, a combination of biopsychosocial and genetic factors are likely to modify the biological processes that contribute to differences in health outcomes (Szanton et al., 2005). Thus, future research is encouraged to assess a diverse set of factors that moderate the association between AL and cognitive function. Cross-collaboration between multidisciplinary research groups is important to help move this endeavor forward.

5. Conclusion

Despite the limitations, this study provides a critical stepping-stone in synthesizing the current literature on the relationship between AL and cognition. Given the projected increase in cognitive loss as the population ages, it is important to understand the biological mechanisms that underlie changes in cognition in order to design effective prevention strategies and treatment options. With further investigation, the AL framework may hold promise in identifying critical periods for intervention and may be positioned as a biological endpoint for interventions aimed at maintaining cognitive health.

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Author Contributions

DD conceptualized the study design; DD, MA, and AJF reviewed papers; DD conducted statistical analyses; DD wrote the manuscript under the supervision of AJF; and DD, MA, and AFJ had responsibility for the final content.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2020.104849.

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