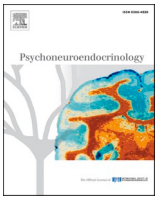
Psychoneuroendocrinology 146 (2022) 105922

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen



Depression interacts with allostatic load to predict cognitive decline in middle age

George Perlman [a,b,c], Hugo Cogo-Moreira [d], Che-Yuan Wu [a,b], Nathan Herrmann [a,e], Walter Swardfager [a,b,c,*]

[a] Hurvitz Brain Sciences Program, Sunnybrook Research Institute, 2075 Bayview Avenue, Toronto M4N 3M5, Canada
[b] Department of Pharmacology & Toxicology, University of Toronto, 1 King's College Circle, Toronto M5S 1A8, Canada
[c] Sleep and Cardiopulmonary Program, University Health Network – Toronto Rehabilitation Institute, 347 Rumsey Road, Toronto M4G 2V6, Canada
[d] Department of Education, ICT and Learning, Østfold University College, P.O.Box 700, NO-1757, Halden, Norway
[e] Department of Psychiatry, University of Toronto, 250 College Street, Toronto M5T 1R8, Canada

ARTICLE INFO

Keywords:
Allostatic load
Depression
Cognition
Executive function
Stress

ABSTRACT

Background: Allostatic load (AL) indicates the cumulative impact of stress on homeostatic mechanisms. Depression and AL have been associated with cognitive deficits, but it is unclear if they do so independently.
Methods: Using data from middle-aged participants in the observational longitudinal Midlife in the United States (MIDUS) study (n = 704, 57.5 % female, 63.8 ± 10.6 years old in 2014), we assessed whether the effect of prior depression (Composite International Diagnostic Interview Short-Form in 1995) on cognitive decline between 2004 and 2013 (composite Z-scores derived from the Brief Test of Adult Cognition by Telephone and the Stop & Go Switch Task) was moderated by AL Z-scores in 2004 (calculated from biomarkers in blood, urine, and electrocardiography).
Results: A significant depression × AL interaction predicted a decline in a composite cognitive score (β = −0.066, SE=0.029, p = 0.024) and executive function (β = −0.068, SE=0.025, p = 0.007). Depression predicted a decline in composite cognition among those with AL Z-scores above − 0.055. AL subdomains of inflammation and lipid metabolism showed evidence of moderation.
Conclusion: Middle-aged adults with depression who had higher allostatic load were at greater risk of cognitive decline. Future studies should evaluate whether the interaction predicts incident dementia, and whether interventions targeting depression or elevated AL in people who have both can attenuate cognitive decline.

1. Introduction

Depression is associated with changes in cognitive performance which often persist in people whose mood has improved (Perini et al., 2019). Depression incidence and severity also predict accelerated age-related cognitive decline in older adults (Formánek et al., 2020; Verdelho et al., 2013).

Chronic stress is a major risk factor for depression, and it can lead to chronic activation of the stress response and manifold physiological dysregulations spanning metabolic, cardiovascular, inflammatory, neuroendocrine, and autonomic systems. The term allostatic load (AL) was coined in 1993 to describe cumulative "wear and tear" on these systems that results from the efforts of an organism to adapt to changes in its environment (McEwen and Stellar, 1993). Many studies have observed cross-sectional and longitudinal associations between AL and incident morbidity (Guidi et al., 2021) and mortality (Parker et al., 2022).

The many components of AL individually or in aggregate have been associated with cognitive impairment or decline (Empana et al., 2021; Forte et al., 2019; Gardner et al., 2019; Knight et al., 2020; Morrens et al., 2022; van der Flier et al., 2018). A recent meta-analysis found that AL was associated with poorer performance in global cognition and executive function cross-sectionally, and suggested a decline in global cognition longitudinally, though there were insufficient studies to power the latter comparison (D'Amico et al., 2020). Many studies investigating the link between AL and cognition or cognitive decline did not assess depression (Booth et al., 2015; de Robert, 2018; Karlamangla et al., 2014; Kobrosly et al., 2012; Rigney, 2010), while others excluded

* Corresponding author at: Hurvitz Brain Sciences Program, Sunnybrook Research Institute, 2075 Bayview Avenue, Toronto M4N 3M5, Canada.
E-mail address: w.swardfager@utoronto.ca (W. Swardfager).

https://doi.org/10.1016/j.psyneuen.2022.105922
Received 11 June 2022; Received in revised form 6 September 2022; Accepted 7 September 2022
Available online 12 September 2022

participants with depression (Narbutas et al., 2019; Ottino-González et al., 2019). Longitudinal studies spanning the midlife period have been few (Goldman et al., 2006; Oi and Haas, 2019), and still fewer have examined depression and AL together (Schmitz et al., 2018), leaving questions about the nature of their combined effects on cognition.

While the early literature conceptualized AL in the context of depression (McEwen, 2003), and the two may be linked by chronic stress as a common risk factor (Finlay, Roth et al., 2022; Finlay, Rudd et al., 2022), there is limited evidence to suggest that AL is specific to depression. Preliminary meta-analytic evidence has indicated that AL may be elevated in psychotic disorders but not necessarily in depression (Finlay et al., 2021); therefore, it may be useful to examine the effects of AL in people with and without depression, and to consider the possibility of both independent and interactive effects. Here we aim to disentangle the effects of AL and depression on cognitive decline via moderation analysis using data from a longitudinal observational study of middle-aged adults. It is hypothesized that an interaction effect will be present such that AL and depression together will be associated with greater cognitive decline in later midlife.

2. Methods

2.1. Data source

The study is a retrospective analysis of the Midlife in the United States (MIDUS) Study. The MIDUS study was initiated in 1995 to "investigate the role of behavioral, psychological, and social factors in accounting for age-related variations in health and well-being in a national sample of Americans." (Brim et al., 1995).

MIDUS participants were recruited by dialling random phone numbers and completed a phone interview in the first wave in 1995. In the second wave (2004–09; MIDUS 2), a battery of cognitive tests was administered by telephone in addition to the original interview. A subset of participants who were deemed healthy enough to travel were recruited to one of three testing centers for the MIDUS 2 Biomarker study. Participants' blood, urine, and electrocardiography measures were taken over two days as well as a series of questionnaires assessing psychosocial phenomena. The third wave of MIDUS (2013–14; MIDUS 3) repeated the original interview series as well as the battery of cognitive assessments by telephone. Participants of MIDUS were included in this study if they completed the depression assessment tool in wave 1 and the biomarker and cognition studies in wave 2.

2.2. Depression

A past-year diagnosis of depression at Wave 1 was assessed using the Composite International Diagnostic Interview short-form (CIDI-SF), an abridged version of the tool developed by the World Health Organization (WHO) to diagnose DSM-III-R psychiatric disorders (Kessler et al., 1998). Diagnosis of a depressive episode required a two-week period with at least one of the two cardinal symptoms of depression, depressed affect (feeling sad, blue, or depressed) and anhedonia (loss of interest in most things), for most of the day or more, and almost every day or more frequently. In addition to one of the cardinal symptoms, depression diagnosis was contingent upon at least four other symptoms at the same frequency, including the other cardinal symptom and unusually high levels of: fatigue; change in appetite; insomnia; difficulty concentrating; feeling down on oneself, no good, or worthless; and thoughts about death (Kessler et al., 1998). Depression was used in models as a binary variable.

2.3. Allostatic load

Allostatic load scores were calculated based on the method of Karlamangla and colleagues (Karlamangla et al., 2014). Briefly, 24 biomarkers derived from blood, urine, body measurements and electrocardiography spanning 7 physiological domains were included. The 7 domains were cardiovascular (systolic blood pressure [SBP], diastolic blood pressure [DBP], and heart rate), glucose metabolism (glycated hemoglobin [HbA1c], fasting blood glucose, and homeostatic model assessment for insulin resistance [HOMA-IR]), lipid metabolism/body composition (body mass index [BMI], waist-hip ratio [WHR], high-density lipoprotein [HDL], low-density lipoprotein [LDL], and triglycerides), inflammation (C-reactive protein [CRP], interleukin-6 [IL-6], fibrinogen, sE-selectin, and sICAM-1), hypothalamic-pituitary-adrenal [HPA] axis (dehydroepiandrosterone sulfate [DHEA-S], and urine cortisol), sympathetic nervous system (SNS) (urine adrenaline and noradrenaline), and parasympathetic nervous system (PNS) (electrocardiography metrics standard deviation of R-R interval [SDRR], root mean square successive differences [RMSSD], low frequency power and high frequency power). A score for each of the 7 domains was computed and effects of individual AL domains were explored.

For each biomarker, participants in the top quartile of the sample distribution were assigned a score of 1 ("high") while those in the bottom 3 quartiles were given a score of 0 ("low"). Six biomarkers for which low values indicate potential pathophysiology (DHEA-S, HDL, and the 4 PNS markers) were coded inversely, where the bottom quartile was assigned a score of 1. High-low splits for WHR, HDL, and DHEA-S were stratified by sex a priori as these are known to differ significantly between men and women. AL scores for each physiological domain were calculated as the mean of its composite biomarker high/low scores. Each participant's domain scores were then summed for a total AL score, on a scale of 0–7. Finally, AL scores were Z-transformed for analysis. Z-scores for each AL domain were also created for use in exploratory analyses.

We considered a person taking a drug that returns the level of a given biomarker to the normal range to be considered as high risk for that biomarker, using the Multum Lexicon to categorize medications; specifically, individuals taking antihyperlipidemic drugs (category #19) were considered high risk for LDL; those taking beta-blockers (category #47) were considered high risk for heart rate; those taking diabetes medications (category #99) for fasting glucose, HbA1c, and HOMA-IR; those taking angiotensin-converting enzyme (ACE) inhibitors (#42), angiotensin receptor blockers (ARBs) (#958), or calcium channel blockers (#1313) for SBP; and those taking NSAIDs (#1602) for IL-6. For each study participant, we created medication-adjusted Z-scores for overall AL and for each AL subdomain. These medication-adjusted AL Z-scores were used in the analyses.

2.4. Cognition

The Brief Test of Adult Cognition by Telephone (BTACT) was administered by telephone in waves 2 and 3 of MIDUS. The BTACT comprises the Rey Auditory-Verbal Learning test, in which the interviewer reads a list of 15 words and the participant lists as many as they can in two trials, one immediately and one after the other cognitive exams (Lezak, 1983); the Digits Backward test of working memory, where the interviewer reads a list of numbers and the participant is asked to repeat them in reverse order; the Category Fluency test of verbal ability, speed, and executive functioning, in which participants are asked to list as many things belonging to a certain category (e.g., fruits) as possible within one minute; the Stop & Go Switch Task of reaction time, attention, and executive function, in which participants respond to the interviewer saying the words "Green" and "Red" with "Go" and "Stop", respectively, as fast as possible; the Number Series test of fluid intelligence and reasoning, where participants are asked to identify patterns in a short sequence of numbers and predict what the next number would be; and the Backwards Counting test of processing speed, in which participants are asked to count backwards from 100 aloud as fast as possible. Because exploratory and confirmatory factor analyses in MIDUS 2 revealed a two-correlated-factor structure of the BTACT comprising episodic memory and executive function (Lachman et al., 2014), domain-specific composite Z-scores were calculated for the

two factors as sums of Z-scores on individual tests. Immediate and delayed recall from the Rey Auditory-Verbal Learning test were included in the episodic memory factor while all other tests were included in the executive function score. A composite cognition score was calculated as the mean of the executive function and episodic memory scores as the primary outcome while the two component scores were examined in separate models as exploratory outcomes.

2.5. Statistical analyses

Changes in composite cognition, executive function, and episodic memory between waves 2 and 3 were examined and described via paired samples t-tests. Moderation analysis was conducted in Mplus software version 8.5 (Muthén and Muthén, 2017). AL as a moderator was tested in a regression model with an interaction term between depression and AL. The coefficients were standardized by dividing the regression coefficients by the standard deviation of the outcome variable and, for continuous predictors, by additionally normalizing by the standard deviation of said predictor. The effect of AL on composite cognition was assessed in linear regression analyses stratified by wave 1 depression status using the R package "ggeffects" (Lüdecke, 2018). Cognitive subdomains were explored in similar models. To retain participants missing cognitive data in wave 3 in the main analyses, full information maximum likelihood (FIML) estimation was employed. FIML findings were compared to the same moderation analyses conducted in models that omitted participants with missing outcome values. To determine the ranges of Z-scores over which moderation effects were observed, Johnson-Neyman interval analysis was conducted using PROCESS macro in R (Hayes, 2022). Plots were created in R with "ggplot2", and "interactions", and "lme4" packages (Wickham, 2016; Long, 2019).

All models predicted cognition in wave 3 but controlled for the previous cognitive score in wave 2 such that model outcomes can be considered to indicate a decline in cognition over ~9 years from wave 2 to wave 3; although the model parameters are estimated in terms of wave 3 cognition scores. Model 1 was adjusted for wave 2 cognition but not adjusted for other covariates; model 2 was further adjusted for demographic characteristics (sex, age, race, education level, and household income); model 3 was further adjusted for diagnoses of heart disease, hypertension, diabetes, TIA/stroke, and circulation problems, use of antidepressant medications, exercise, and smoking at wave 2. Outcomes from all 3 models are presented in Table 2 to indicate potential effects of covariates. Because Johnson-Neyman analyses could not be run with participants missing outcome values, parameters discussed further in the Results section refer to model 2 under listwise deletion unless otherwise stated for consistency in presentation.

With a sample size of 704, the current analysis was powered at 80 % to detect an effect size of 0.022 at a two-tailed α probability of 0.05, controlling for 6 covariates a priori. F^2 effect sizes were calculated using G*Power software (Faul et al., 2009).

We performed some sensitivity analyses. Because the CIDI-SF identifies participants with a depressive episode within the past year, it provides a limited snapshot into depression history and may have resulted in misclassification of some participants with depression earlier or later in their lives. We explored this limitation by including CIDI-SF from waves 2 and 3 as covariates in sensitivity analyses. Sensitivity analyses were run in men and women separately to assess whether the effects were consistent between the sexes. Because the calculation of AL scores has sometimes included adjustment for medication use and sometimes not, we also examined the relationship between AL and cognition in models where AL Z-scores were computed without adjustment for medications. The results of these models are presented in supplementary materials.

3. Results

3.1. Study population

After excluding participants missing values for baseline depression, biomarker data to generate medication-adjusted AL Z-scores, and cognitive scores at wave 2, 815 participants were included in FIML analysis (Fig. S1; Table 1). Of these, 115 had a past-year depressive episode at wave 1. The group with a past-year depressive episode at wave 1 had significantly more women, higher depression rates at waves 2 and 3, and higher BMI, smoking rate, and antidepressant use at wave 2,

Table 1
Participant demographics.

	No depression (Wave 1) (N = 700)	Depression (Wave 1) (N = 115)	P-value
Sex (female)	378 (54.0%)	81 (70.4%)	**0.0014**
Age (Wave 3) (years)	65.3 (11.8)	62.7 (10.0)	**0.013**
Have attended college	540 (77.1%)	83 (72.2%)	0.30
Race			
White	653 (93.4%)	106 (92.2%)	0.40
Black	19 (2.72 %)	2 (1.74 %)	
Indigenous	8 (1.14 %)	1 (0.87 %)	
Asian	3 (0.43 %)	0 (0 %)	
Other	16 (2.29 %)	6 (5.22 %)	
Depression (Wave 2)	53 (7.57 %)	40 (34.8 %)	**< 0.001**
Depression (Wave 3)	45 (7.09 %)	32 (31.4 %)	**< 0.001**
BMI (Wave 2) (kg/m^2)	28.9 (5.73)	30.3 (6.37)	**0.020**
Wave 2 Executive function (z-score)	0.263 (0.836)	0.153 (0.897)	0.22
Wave 3 Executive function (z-score)	-0.0486 (0.674)	-0.117 (0.671)	0.35
Wave 2 Episodic memory (z-score)	0.103 (0.909)	0.219 (0.785)	0.16
Wave 3 Episodic memory (z-score)	0.0550 (0.987)	-0.0165 (0.863)	0.46
Wave 2 Cognition composite (z-score)	0.183 (0.715)	0.186 (0.693)	0.97
Wave 3 Cognition composite (z-score)	0.00263 (0.689)	-0.0637 (0.626)	0.34
Allostatic load (z-score)	-0.0288 (0.982)	0.175 (1.10)	0.063
Household income (1000 USD)	81.4 (63.0)	61.2 (50.8)	< 0.001
Exercise (Metabolic minutes/week)	1350 (1950)	1480 (2580)	0.61
Smoking (Wave 2)	63 (9.00 %)	24 (20.9 %)	**< 0.001**
Heart disease (Wave 2)	76 (10.9 %)	9 (7.83 %)	0.41
Hypertension (Wave 2)	233 (33.3 %)	43 (37.4 %)	0.45
Diabetes (Wave 2)	71 (10.1 %)	11 (9.57 %)	0.98
TIA/stroke history (Wave 2)	23 (3.29 %)	5 (4.35 %)	0.76
Circulation problems (Wave 2)	42 (6.00 %)	9 (7.83 %)	0.59
Antidepressant use (Wave 2)	99 (14.1 %)	42 (36.5 %)	**< 0.001**
Antihyperlipidemic drug use (Wave 2)	229 (32.7 %)	43 (37.4 %)	0.38
Beta-blocker use (Wave 2)	99 (14.1 %)	14 (12.2 %)	0.67
Diabetes medication (Wave 2)	61 (8.71 %)	12 (10.4 %)	0.67
ACE inhibitor use (Wave 2)	58 (8.29 %)	12 (10.4 %)	0.56
ARB use (Wave 2)	60 (8.57 %)	14 (12.2 %)	0.28
Calcium channel blocker use (Wave 2)	52 (7.43 %)	4 (3.48 %)	0.18
NSAID use (Wave 2)	349 (49.9 %)	59 (51.3 %)	0.85

Demographics and other characteristics were summarized using means and standard deviations for continuous variables and count (%) for categorical variables. Differences between groups with and without depression at wave 1 assessed by independent samples t-test for continuous and by $\chi 2$ test for categorical measures. BMI: Body-mass index; TIA: Transient ischemic attack; ACE: Angiotensin-converting enzyme; ARB: Angiotensin-receptor blocker; NSAID: Non-steroidal anti-inflammatory drug.

as well as lower age and annual household income (Table 1). With regards to AL biomarkers, those with a past-year depressive episode at wave 1 had lower systolic and diastolic blood pressure as well as urine adrenaline levels than those without; they also had higher heart rate, BMI, CRP, and sICAM-1 (Table S1). 607 non-depressed and 98 depressed individuals had complete cognitive data and they were included in the analyses under listwise deletion.

3.2. Cognitive outcomes

There was an overall decline in cognitive Z-scores among the current sample population from wave 2 to wave 3 (t = [3.62, 17.92], df = [704,706], $p < 0.001$).

In linear regression models that included an interaction term between AL and depression, there was a main effect of a past-year depression diagnosis in model 2 (adjusted for wave 2 cognition and basic demographics) but not in model 1 or model 3, which can be interpreted as an effect of depression at AL= 0. There was a main effect of AL in models adjusted for wave 2 cognition only (model 1), but not in adjusted models (Table 2). These findings were consistent between analyses under FIML and listwise deletion of participants with missing data.

3.3. Depression history and AL interaction on cognitive decline

In linear regression models there was a significant depression × AL interaction on the cognitive composite score (β = −0.066, SE=0.029, p = 0.024) at follow-up. The depression × AL interaction effect was robust between models 1, 2, and 3, and across models using listwise deletion and FIML (Table 2).

Examining the depression groups separately in stratified models, there was a significant negative effect of AL on cognition composite scores in participants with depression (β = −0.1979, SE=0.0791, p = 0.013) but not in participants without depression (β = −0.0046, SE=0.0319, p = 0.88) (Fig. 1a).

Johnson-Neyman interval analysis revealed a graded effect, where the effect of depression on cognition composite scores was negative in individuals with higher AL scores (Fig. 2a); a history of depression exerted a significant negative effect on cognition in people with AL Z-scores above − 0.055 (46.02 % of participants).

3.4. Depression history and AL interactions on cognitive subdomains

In exploratory analyses, a depression × AL interaction was observed on executive function (β = −0.068, SE=0.025, p = 0.007) but not on episodic memory (β = −0.042, SE=0.034, p = 0.21) outcomes (Table 2).

The effect of AL on executive function was significant in people with depression (β = −0.1962, SE=0.0644, p = 0.0024) but not in people without depression (β = −0.0106, SE=0.0279, p = 0.70) (Fig. 1b). AL did not predict a significant episodic memory decline in people with (β = −0.1415, SE=0.0976, p = 0.14) or without (β = 0.0119, SE=0.0362, p = 0.74) depression (Fig. 1c).

Johnson-Neyman interval analysis on individual cognitive domains revealed an effect of depression on executive function that was positive in individuals with the lowest AL scores and negative in individuals with higher AL scores (Fig. 2b). At AL Z-scores below − 1.31 (8.76 % of participants), depression had a significant positive effect on executive function, while participants with AL scores 1.17 standard deviations above the norm (12.47 % of participants) had a significant negative effect of depression history on executive function.

For episodic memory, within the observed range of moderator values, a history of depression predicted decline in those with AL Z-scores greater than − 0.37 (58.24 % of participants) (Fig. 2c).

3.5. Physiological domain-specific moderation effects

Exploratory linear regression models were conducted with Z-scores for each of the seven physiological domains assessed in the AL composite score separately. Only inflammation interacted with depression history

Table 2
Standardized regression estimates of predictors on Wave 3 cognition scores for 3 models under FIML and listwise deletion. Effects are represented as regression estimate (standard error).

	FIML	Model 1[1]	Model 2[2]	Model 3[3]	**Listwise deletion**	Model 1[1]	Model 2[2]	Model 3[3]
Cognition composite	Baseline depression	-0.029 (0.028)	**-0.054 (0.026)***	-0.041 (0.026)	Baseline depression	-0.086 (0.082)	**-0.165 (0.077)***	-0.113 (0.078)
	AL	**-0.079 (0.033)***	-0.006 (0.032)	0.027 (0.033)	AL	**-0.078 (0.033)***	-0.005 (0.032)	0.028 (0.034)
	Depression*AL interaction	-0.057 (0.031)	**-0.064 (0.029)***	**-0.060 (0.028)***	Depression*AL interaction	-0.058 (0.031)	**-0.066 (0.029)***	**-0.056 (0.028)***
Executive function	**FIML**	Model 1[1]	Model 2[2]	Model 3[3]	**Listwise deletion**	Model 1[1]	Model 2[2]	Model 3[3]
	Baseline depression	0.007 (0.024)	0.000 (0.023)	0.002 (0.023)	Baseline depression	0.020 (0.070)	0.001 (0.067)	0.014 (0.069)
	AL	**-0.084 (0.027)** ***	-0.011 (0.027)	0.016 (0.031)	AL	**-0.084 (0.027)** ***	-0.011 (0.027)	0.015 (0.031)
	Depression*AL interaction	**-0.057 (0.027)***	**-0.067 (0.025)** ***	**-0.068 (0.025)** ***	Depression*AL interaction	**-0.057 (0.027)***	**-0.068 (0.025)** ***	**-0.064 (0.026)***
Episodic memory	**FIML**	Model 1[1]	Model 2[2]	Model 3[3]	**Listwise deletion**	Model 1[1]	Model 2[2]	Model 3[3]
	Baseline depression	-0.043 (0.033)	**-0.077 (0.030)***	-0.058 (0.030)	Baseline depression	-0.127 (0.094)	**-0.230 (0.089)***	-0.166 (0.090)
	AL	**-0.078 (0.038)***	-0.014 (0.037)	0.017 (0.038)	AL	**-0.075 (0.038)***	-0.012 (0.037)	0.019 (0.039)
	Depression*AL interaction	-0.037 (0.036)	-0.040 (0.033)	-0.035 (0.032)	Depression*AL interaction	-0.038 (0.036)	-0.042 (0.034)	-0.032 (0.033)

Bold text indicates $p < 0.05$; * $p < 0.05$; ** $p < 0.01$, *** $p < 0.001$.
[1]Model 1: adjusted for corresponding cognitive Z-scores at MIDUS wave 2. Under listwise deletion, 607 non-depressed and 98 depressed participants were included for cognition composite and episodic memory analyses, while 608 non-depressed and 99 depressed participants were included for executive function.
[2]Model 2: model 1 + covariates sex, age, race, education and income. 606 non-depressed and 98 depressed participants for cognition composite and episodic memory, and 607 non-depressed and 99 depressed participants for executive function, under listwise deletion.
[3]Model 3: model 2 + covariates antidepressant use, comorbidities, exercise and smoking. 603 non-depressed and 97 depressed participants for cognition composite and episodic memory, and 604 non-depressed and 98 depressed participants for executive function, under listwise deletion.

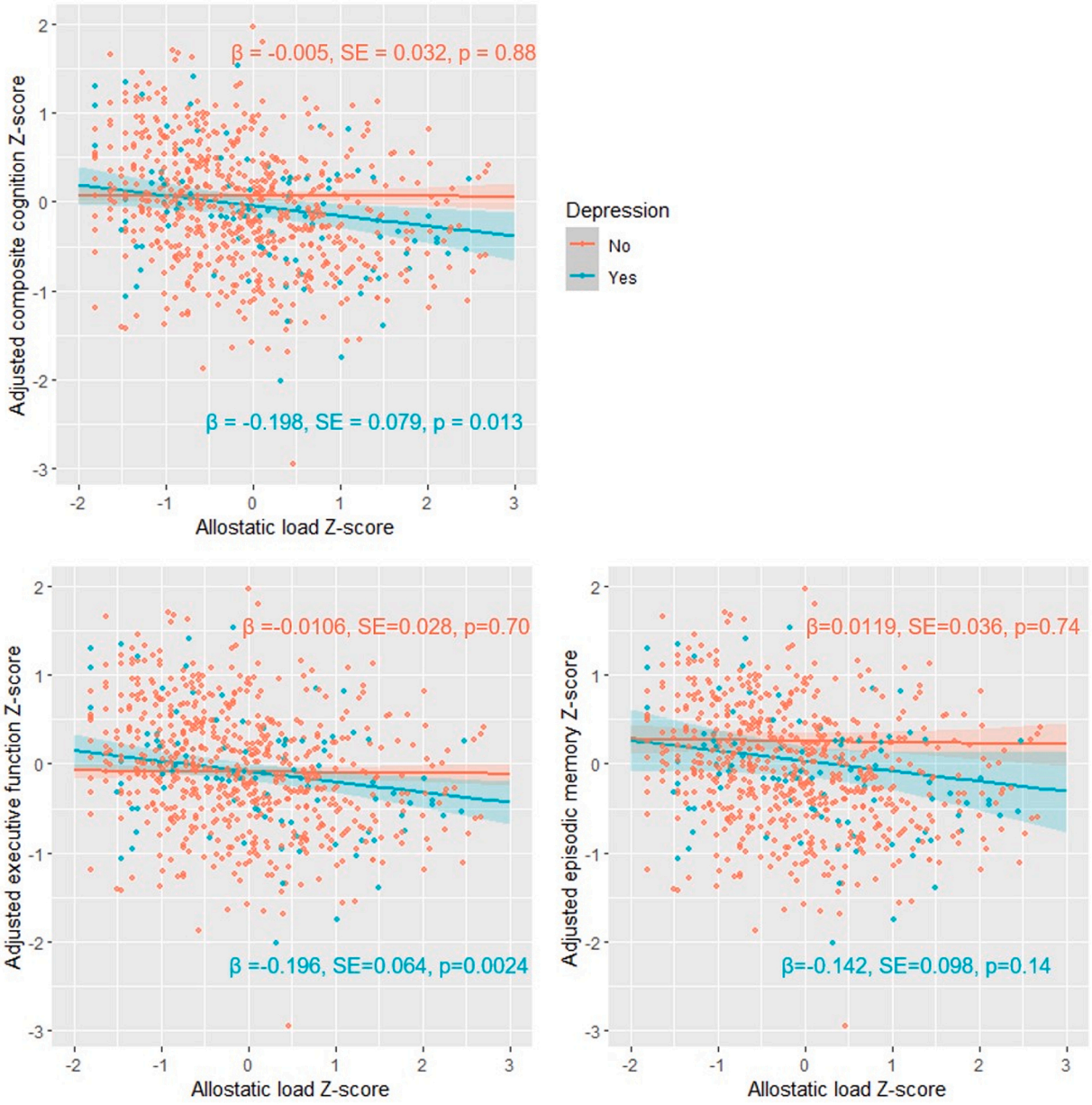


Fig. 1. Allostatic load Z-score vs. cognition by depression group. Shaded regions indicate 95 % confidence intervals. Outcomes are **a)** cognition composite scores, **b)** executive function scores, and **c)** episodic memory scores. Red: non-depressed at wave 1; blue: depressed at wave 1. Model 2 regression slopes (adjusted for cognition at wave 2, sex, age, race, education, and household income).

to predict a significant decline in composite cognition (β = −0.074, SE=0.034, p = 0.029); (Table S2).

For individual cognitive domains, lipid metabolism interacted with depression significantly to predict a decline in executive function (β = −0.085, SE=0.027, p = 0.002), while there was no significant interaction between depression and any physiological domain predicting a decline in episodic memory (Table S2).

3.6. Sensitivity analyses

When including CIDI-SF from waves 2 and 3 as covariates the results were highly consistent with those of the main analyses (Table S3).

In sensitivity analyses in men and women separately, the effect sizes for the interaction between AL and depression were consistent with those from the unstratified models, although the effect sizes for overall cognition and executive function were numerically larger among women (Table S4). These models were not powered to test significance.

In models that used AL scores unadjusted for medication use, the results were highly consistent with those of the main analyses (Table S5).

4. Discussion

Here we describe a moderation effect where a history of depression interacted with allostatic load to predict cognitive decline over 9 years in older middle-aged adults. The majority of previous studies on AL and cognition have been cross-sectional, and many did not assess depression or excluded participants with depression (D'Amico et al., 2020). To our knowledge, this is the first study to examine the interaction effect of depression and allostatic load on cognition longitudinally. In models fully adjusted for covariates, AL and depression predicted cognitive decline in middle-aged adults interactively but not independently.

The present finding may explain heterogeneity in cognitive outcomes in previous studies of depression or AL. Previously, one longitudinal

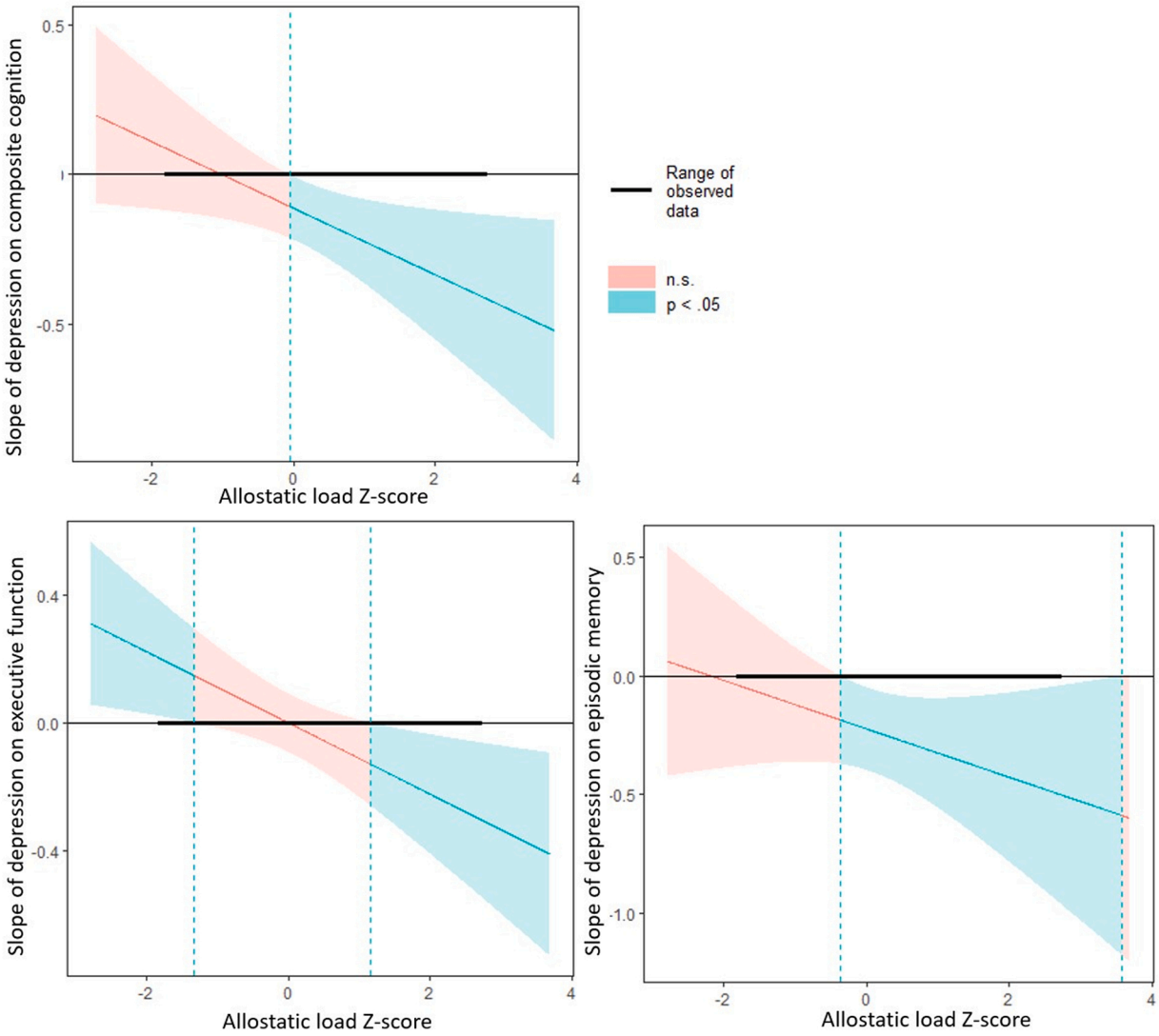


Fig. 2. Johnson-Neyman plots. Slope of depression on cognitive scores depends on AL score. Outcomes are **a)** cognition composite scores, **b)** executive function, and **c)** episodic memory. Model 2 regression slopes under listwise deletion (adjusted for executive function at wave 2, sex, age, race, education, and household income).

study from the MacArthur Study of Successful Aging found that AL predicted cognitive decline in models adjusted for depression (Karlamangla et al., 2002), but that study did not test an interaction effect. The present finding elucidates risk of cognitive decline, and it identifies a clinically relevant risk group with depression and high AL, which may be an important population group to target for preventive intervention.

A previous finding from the Rotterdam and Whitehall II longitudinal studies found a significant mediation effect of scores on the Center for Epidemiological Studies-Depression scale on the association between a cardiometabolic risk score measured previously, and subsequent cognitive decline (Schmitz et al., 2018). The present findings do not preclude that effect; however, they suggest caution using mediation analysis. The detection of an interaction between depression and AL suggests that mediation effects involving depression and tenets of the AL should be estimated carefully in models that take into account both mediation and moderation effects (VanderWeele, 2016), lest they be subject to exposure-mediator confounding.

In this study, depression predicted cognitive decline in participants with AL greater than 0.055 standard deviations below the norm, identifying a point at which individuals were at risk. It has been proposed that up to a point the neuroendocrine response to stress (HPA axis) is adaptive, after which it is unable to maintain allostasis and the immune system and possibly other metabolic/vascular processes are engaged, adversely affecting brain function (Guidi et al., 2021; Arnaldo et al., 2022). The results suggest that AL may be a useful construct to identify summary risk of later cognitive decline among those with depression.

In exploratory analyses, there was a significant interaction between AL and depression predicting executive decline, which was moderated primarily by lipid metabolism/body composition. We were not able to examine mechanisms; however, future studies might consider the implications of these risk factors on the microvasculature and the cerebral white matter, and/or a decline in blood flow to frontal brain regions, both of which are involved in executive function. Cerebral small vessel disease observed as white matter hyperintensities among other markers on magnetic resonance imaging (MRI) (Wardlaw et al., 2013) has been associated with executive dysfunction in late-life depression (Park et al., 2018), and future studies might explore neuroanatomical mediators of the metabolic indices identified in people with depression.

The interaction between depression and AL was non-significant for episodic memory loss (Fig. 1c, Table 1). This may be consistent with meta-analytic findings that showed an association between AL and executive function but not memory (D'Amico et al., 2020). High variances in memory scores among depression groups, their relatively small sample size, and lower test-retest reliability of the memory component of the BTACT (Lachman et al., 2014) may have contributed. The meta-analysis of D'Amico and colleagues found significant

heterogeneity, although possible differences in rates of major depressive disorder (MDD) between the included studies were not explored as a potential contributor. Attempts might be made to replicate the interaction effects described here in further studies.

We did not find evidence of moderation via the HPA axis or autonomic domains of AL. The reason for this is unclear; however, fluctuations of these systems due to circadian and other factors such as psychosocial stressors may be larger than those of metabolic, vascular, and immune markers and thus more representative of physiological state than trait. Participation in the MIDUS biomarker study required travel and an overnight stay at one of three national centres with collection of urine, followed by a 6:30 am wakeup the following day before blood collection and HRV measurement. The distance of travel, disruption to the circadian rhythm, and sleep quality under those circumstances may have varied significantly between participants resulting in variations in autonomic and neuroendocrine markers.

It has been suggested that variations in the levels of neuroendocrine markers may translate into long-term consequences when the neuroendocrine response is chronically activated and eventually dysregulated (Arnaldo et al., 2022), which may not have been reflected in interindividual differences in the HPA axis and autonomic point measures used. DHEA-S is considered to be a biomarker of acute stress (Dutheil et al., 2021), and urine catecholamine levels fluctuate with both acute and chronic stress (Akerstedt et al., 1983; Hawk et al., 2000). An example of a more stable indicator of HPA axis dysregulation is the level of methylation of the glucocorticoid receptor gene, which is increased with parental stress and early-life adversity in humans (Turecki and Meaney, 2016).

In adjusted models, AL had no effect on cognition in the absence of depression (Table 2), which suggests that the preventive utility of agents targeting tenets of AL might be examined or tested specifically in MDD. Few studies have investigated the preventive efficacies of treatments for hyperlipidemia, hypertension, and inflammation on long-term cognitive decline in people with depression. Treatments for type 2 diabetes mellitus have generated mixed results on protecting against cognitive decline (Guo et al., 2014; Wu et al., 2020). In populations unselected for MDD, the use of antidiabetic drugs, including metformin, intranasal insulin, thiazolidinediones, incretin mimetics, and dipeptidyl peptidase IV inhibitors, has been linked to slower cognitive decline compared to non-users in older adults with diabetes (Wu et al., 2020; Michailidis et al., 2022). Medications used to treat hypertension may also attenuate cognitive decline (Gupta et al., 2020; Peters et al., 2020). Evidence for a protective role of statins has been mixed (Zeki Al Hazzouri et al., 2022; Zhen Zhou et al., 2021).

In this study, inflammation interacted particularly with depression history to predict a significant decline in composite cognition. In MDD, inflammation has garnered interest as a potential mediator of the depression-cognition relationship, and a mediation effect has been found in the current study population (Zainal and Newman, 2022). Evidence for protective effects of most NSAIDs against the rate of cognitive decline and incidence of mild cognitive impairment (MCI) has been mixed (Côté et al., 2012; Imbimbo et al., 2010; Rivers-Auty et al., 2020). The antibiotic minocycline, known to counteract microglial activation (Nettis, 2021), is currently under investigation as a depression treatment and it may be more effective in people with high baseline CRP levels (Nettis et al., 2021); however, there is minimal evidence for its efficacy on cognition in healthy or depressed populations. In one study of escitalopram for geriatric depression, adjunctive treatment with memantine blocked inflammation-associated decline in executive function over six months (Van Dyk et al., 2020). The antioxidant N-acetylcysteine may not benefit depressive symptoms (Kishi et al., 2020); however, some studies suggest cognitive benefits in healthy adults or in those with AD (Bradlow et al., 2022; Skvarc et al., 2017), pointing to the need to examine cognitive benefits in MDD. Similarly, lithium has been proposed to prevent cognitive decline in AD and related disorders (Foster and Gallicchio, 2018) and 2 years low-dose lithium slowed cognitive decline vs. placebo in people with MCI (Forlenza et al., 2019).

While studies have found that antidepressants in people with depression improve aspects of cognition in the short term (Rosenblat et al., 2016; Prado et al., 2018), few longer-term studies have examined their impact on cognitive decline. One study found that long-term treatment with a selective serotonin reuptake inhibitor (SSRI) predicted delayed progression to Alzheimer's disease in elderly patients with MCI (Bartels et al., 2018); however, another study assessing elderly adults with depressive symptoms found greater cognitive decline over 6 years in antidepressant users compared to non-users (Saczynski et al., 2015). Overall, the evidence may be inconclusive since observational studies comparing antidepressant use vs. non-use are often subject to confounding by indication, whereas trials are often too brief to observe longer-term changes in cognitive trajectories. A meta-analysis of 5 studies found that the multi-modal SSRI vortioxetine improved performance on the digit symbol substitution test over 8 weeks (McIntyre et al., 2016), and longer studies might be warranted to determine effects on long-term cognitive decline. Given the current finding that depression and AL predict cognitive decline together but not independently, successful treatment of either pathology may be preventive; however, additional prospective studies that adjust for confounders are needed to confirm this.

4.1. Limitations

Consensus has yet to be reached on the implications of different ways of modeling AL; however, we followed precedents consistent with previous literature (Juster et al., 2010; Juster and Lupien, 2012; Duong et al., 2017; McLoughlin et al., 2020). One challenge is the confounding influence of medications. For example, an individual with diagnosed hypertension who is taking antihypertensive drugs may have systolic and diastolic blood pressure scores within a healthy range. The accrued toll of the participant's pathophysiology may thus be masked using an agent that changes the level of the biomarker. While we considered the presence of the treatment to indicate intrinsic homeostatic stress, other methods have been suggested, including adjusting for medication use as covariates in analyses, and adjusting biomarker levels for expected changes due to medication use (Duong et al., 2017; McLoughlin et al., 2020). A sensitivity analysis conducted in the current study suggested consistency between the methods.

Some aspects of the MIDUS study design constrain its demographics and thereby limit its generalizability. While random-digit dialing is a widely used method for random sampling in large populations, it has been suggested to select for participants with higher socioeconomic status than the general population, including those with higher levels of education and increased access to medical care (Glasser and Metzger, 1972; Olson et al., 1992). The biomarker study further required participants to be in sufficient health to travel, so participants who were most severely affected by cumulative AL may not have been represented in the sample. Additionally, 93 % of participants in the current study population (recruited in 1995–96) were white, which is above the prevalence of 75–80 % estimated in the 1990 and 2000 United States censuses (US Census Bureau, 2001). Roughly 12 % of the US population in 1990 and 2000 was Black, compared to 2.6 % of the current cohort (Table 1). While the second wave of the MIDUS study added a community-based oversample of Black participants, the current analysis was only possible in participants recruited in wave 1. Replication analyses in non-white populations and in those outside the United States are needed.

The sample included only 97 participants with recent depression at baseline, providing limited power to detect interactive and independent effects on cognitive decline. Numerically, interaction effects between depression and AL on cognition were larger in women; however, the sample was underpowered to detect effects in either men or women separately, or to test a formal interaction with sex. The use of the CIDI-SF

to identify a depressive episode within the past year may have resulted in misclassification of some participants with a history of depression, and a 1-year history at a mean participant age of 46 provided a limited snapshot into depression history. In supplementary moderation models that included CIDI-SF from waves 2 and 3 as covariates, minimal differences were seen in the effects of baseline depression, AL, and their interaction, compared to the main analyses. Further studies should examine whether chronicity, state or trait features, or qualitative features of depression interact with AL to predict cognitive decline.

4.2. Conclusion

Depression was a predictor of cognitive decline in late middle age specifically among those who developed high AL, and AL was associated with cognitive decline specifically among people with evidence of depression. Markers of inflammation, lipid metabolism, and body composition may be particularly useful in predicting the likelihood of cognitive decline in older adults with depression. Future studies should examine whether the confluence of AL and depression is a risk factor for dementia and whether the domains identified might serve as targets for intervention. Neuroimaging and neurodegenerative fluid biomarker studies may be warranted to identify relevant substrates.

Funding

The authors gratefully acknowledge support from the Heart and Stroke Foundation Centre for Stroke Recovery, the Canadian Institutes of Health Research [PJT-159711], the Natural Sciences and Engineering Research Council of Canada [RGPIN-2017-06962], the National Institute of Diabetes and Digestive and Kidney Diseases Diabetic Complications Consortium (DiaComp, DK076169)[16GRU3711], and the University of Toronto Centre for Collaborative Drug Research [Catalyst Grant]. The work was made possible in part by funding from the Canada Research Chairs Program. The funders were not involved at any stage of the study.

CRediT authorship contribution statement

George Perlman: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing – original draft and revision. **Hugo Cogo-Moreira**: Conceptualization; Methodology; Writing - revision. **Che-Yuan Wu**: Methodology; Formal analysis; Interpretation; Writing – revision. **Nathan Herrmann**: Methodology; Interpretation; Writing – revision. **Walter Swardfager**: Conceptualization; Funding acquisition; Methodology; Supervision; Writing – original draft and revision.

Acknowledgements

We would like to thank Elaine Cornell and Russell Tracy from the Tracy lab as well as Barry Radler for email correspondence.

Conflicts of interest

All authors declare no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2022.105922.

References

Akerstedt, T., Gillberg, M., Hjemdahl, P., Sigurdson, K., Gustavsson, I., Daleskog, M., Pollare, T., 1983. Comparison of urinary and plasma catecholamine responses to mental stress. Acta Physiol. Scand. 117 (1), 19–26. https://doi.org/10.1111/j.1748-1716.1983.tb07174.x.

Arnaldo, I., Corcoran, A.W., Friston, K.J., Ramstead, M.J.D., 2022. Stress and its sequelae: an active inference account of the etiological pathway from allostatic overload to depression. Neurosci. Biobehav. Rev. 135, 104590 https://doi.org/10.1016/j.neubiorev.2022.104590.

Bartels, C., Wagner, M., Wolfsgruber, S., Ehrenreich, H., Schneider, A., 2018. Impact of SSRI therapy on risk of conversion from mild cognitive impairment to Alzheimer's dementia in individuals with previous depression. Am. J. Psychiatry 175 (3), 232–241. https://doi.org/10.1176/appi.ajp.2017.17040404.

Booth, T., Royle, N.A., Corley, J., Gow, A.J., Valdés Hernández, M., del, C., Muñoz Maniega, S., Ritchie, S.J., Bastin, M.E., Starr, J.M., Wardlaw, J.M., Deary, I.J., 2015. Association of allostatic load with brain structure and cognitive ability in later life. Neurobiol. Aging 36 (3), 1390–1399. https://doi.org/10.1016/j.neurobiolaging.2014.12.020.

Bradlow, R.C.J., Berk, M., Kalivas, P.W., Back, S.E., Kanaan, R.A., 2022. The potential of N-Acetyl-L-cysteine (NAC) in the treatment of psychiatric disorders. CNS Drugs 36 (5), 451–482. https://doi.org/10.1007/s40263-022-00907-3.

Brim, O.G., Baltes, P.B., Bumpass, L.L., Cleary, P.D. , 1995. *MIDUS* - Midlife in the United States, A National Longitudinal Study of Health and Well-being. ⟨http://midus.wisc.edu/scopeofstudy.php⟩.

Census Bureau, U.S., 2001. Population by race and hispanic or latino origin for the United States: 1990 and 2000. Census Gov. https://www.census.gov/data/tables/2000/dec/phc-t-01.html.

Côté, S., Carmichael, P.-H., Verreault, R., Lindsay, J., Lefebvre, J., Laurin, D., 2012. Nonsteroidal anti-inflammatory drug use and the risk of cognitive impairment and Alzheimer's disease. Alzheimer's Dement. 8 (3), 219–226. https://doi.org/10.1016/j.jalz.2011.03.012.

D'Amico, D., Amestoy, M.E., Fiocco, A.J., 2020. The association between allostatic load and cognitive function: a systematic and meta-analytic review. Psychoneuroendocrinology 121, 104849. https://doi.org/10.1016/j.psyneuen.2020.104849.

Duong, M.T., Bingham, B.A., Aldana, P.C., Chung, S.T., Sumner, A.E., 2017. Variation in the calculation of allostatic load score: 21 examples from NHANES. J. Racial Ethn. Health Disparities 4 (3), 455–461. https://doi.org/10.1007/s40615-016-0246-8.

Dutheil, F., de Saint Vincent, S., Pereira, B., Schmidt, J., Moustafa, F., Charkhabi, M., Bouillon-Minois, J.-B., Clinchamps, M., 2021. DHEA as a biomarker of stress: a systematic review and meta-analysis. Front. Psychiatry. https://doi.org/10.3389/fpsyt.2021.688367.

Empana, J.-P., Boutouyrie, P., Lemogne, C., Jouven, X., van Sloten, T.T., 2021. Microvascular contribution to late-onset depression: mechanisms, current evidence, association with other brain diseases, and therapeutic perspectives. Biol. Psychiatry 90 (4), 214–225. https://doi.org/10.1016/j.biopsych.2021.04.012.

Faul, F., Erdfelder, E., Buchner, A., Lang, A.-G., 2009. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav. Res. Methods 41 (4), 1149–1160. https://doi.org/10.3758/BRM.41.4.1149.

Finlay, S., Rudd, D., McDermott, B., Sarnyai, Z., 2021. Allostatic load in psychiatry—systematic review and meta-analysis. Psychoneuroendocrinology 131, 105555. https://doi.org/10.1016/j.psyneuen.2021.105555.

Finlay, S., Rudd, D., McDermott, B., Sarnyai, Z., 2022. Allostatic load and systemic comorbidities in psychiatric disorders. Psychoneuroendocrinology 140, 105726. https://doi.org/10.1016/j.psyneuen.2022.105726.

Finlay, S., Roth, C., Zimsen, T., Bridson, T.L., Sarnyai, Z., McDermott, B., 2022. Adverse childhood experiences and allostatic load: a systematic review. Neurosci. Biobehav. Rev. 136, 104605 https://doi.org/10.1016/j.neubiorev.2022.104605.

Forlenza, O.V., Radanovic, M., Talib, L.L., Gattaz, W.F., 2019. Clinical and biological effects of long-term lithium treatment in older adults with amnestic mild cognitive impairment: randomised clinical trial. Br. J. Psychiatry 215 (5), 668–674. https://doi.org/10.1192/bjp.2019.76.

Formánek, T., Csajbók, Z., Wolfová, K., Kučera, M., Tom, S., Aarsland, D., Cermakova, P., 2020. Trajectories of depressive symptoms and associated patterns of cognitive decline. Sci. Rep. 10 (1), 20888. https://doi.org/10.1038/s41598-020-77866-6.

Forte, G., Favieri, F., Casagrande, M., 2019. Heart rate variability and cognitive function: a systematic review. Front. Neurosci. https://doi.org/10.3389/fnins.2019.00710.

Foster, J., Gallicchio, V., 2018. Proposed prophylactic use of lithium to improve cognitive decline and mental health in disorders such as Alzheimer's disease and depression. Madr. J. Clin. Res. 2 (1), 46–52. https://doi.org/10.18689/mjcr-1000108.

Gardner, M., Lightman, S., Kuh, D., Comijs, H., Deeg, D., Gallacher, J., Geoffroy, M.-C., Kivimaki, M., Kumari, M., Power, C., Hardy, R., Richards, M., Ben-Shlomo, Y., 2019. Dysregulation of the hypothalamic pituitary adrenal (HPA) axis and cognitive capability at older ages: individual participant meta-analysis of five cohorts. Sci. Rep. 9 (1), 4555. https://doi.org/10.1038/s41598-019-40566-x.

Glasser, G.J., Metzger, G.D., 1972. Random-digit dialing as a method of telephone sampling. J. Mark. Res. 9 (1), 59–64. https://doi.org/10.2307/3149607.

Goldman, N., Turra, C.M., Glei, D.A., Lin, Y.-H., Weinstein, M., 2006. Physiological dysregulation and changes in health in an older population. Exp. Gerontol. 41 (9), 862–870. https://doi.org/10.1016/j.exger.2006.06.050.

Guidi, J., Lucente, M., Sonino, N., Fava, G.A., 2021. Allostatic load and its impact on health: a systematic review. Psychother. Psychosom. 90 (1), 11–27. https://doi.org/10.1159/000510696.

Guo, M., Mi, J., Jiang, Q.-M., Xu, J.-M., Tang, Y.-Y., Tian, G., Wang, B., 2014. Metformin may produce antidepressant effects through improvement of cognitive function among depressed patients with diabetes mellitus. Clin. Exp. Pharmacol. Physiol. 41 (9), 650–656. https://doi.org/10.1111/1440-1681.12265.

Gupta, A., Perdomo, S., Billinger, S., Beddhu, S., Burns, J., Gronseth, G., 2020. Treatment of hypertension reduces cognitive decline in older adults: a systematic review and

meta-analysis. BMJ Open 10 (11), e038971. https://doi.org/10.1136/bmjopen-2020-038971.
Hawk, L.W., Dougall, A.L., Ursano, R.J., Baum, A., 2000. Urinary catecholamines and cortisol in recent-onset posttraumatic stress disorder after motor vehicle accidents. Psychosom. Med. 62 (3), 423–434. https://doi.org/10.1097/00006842-200005000-00016.
Hayes, A.F. , 2022. Introduction to Mediation, Moderation, and Conditional Process Analysis: Third Edition: A Regression-Based Approach. https://www.guilford.com/books/Introduction-to-Mediation-Moderation-and-Conditional-Process-Analysis/Andrew-Hayes/9781462549030.
Imbimbo, B., Solfrizzi, V., Panza, F., 2010. Are NSAIDs useful to treat Alzheimer's disease or mild cognitive impairment? Front. Aging Neurosci. https://doi.org/10.3389/fnagi.2010.00019.
Juster, R.-P., Lupien, S., 2012. A sex- and gender-based analysis of allostatic load and physical complaints. Gend. Med. 9 (6), 511–523. https://doi.org/10.1016/j.genm.2012.10.008.
Juster, R.-P., McEwen, B.S., Lupien, S.J., 2010. Allostatic load biomarkers of chronic stress and impact on health and cognition. Neurosci. Biobehav. Rev. 35 (1), 2–16. https://doi.org/10.1016/j.neubiorev.2009.10.002.
Karlamangla, A.S., Singer, B.H., McEwen, B.S., Rowe, J.W., Seeman, T.E., 2002. Allostatic load as a predictor of functional decline. MacArthur studies of successful aging. J. Clin. Epidemiol. 55 (7), 696–710. https://doi.org/10.1016/s0895-4356(02)00399-2.
Karlamangla, A.S., Miller-Martinez, D., Lachman, M.E., Tun, P.A., Koretz, B.K., Seeman, T.E., 2014. Biological correlates of adult cognition: midlife in the United States (MIDUS. Neurobiol. Aging 35 (2), 387–394. https://doi.org/10.1016/j.neurobiolaging.2013.07.028.
Kessler, R.C., Andrews, G., Mroczek, D., Ustun, B., Wittchen, H.-U., 1998. The world health organization composite international diagnostic interview short-form (CIDI-SF. Int. J. Methods Psychiatr. Res. 7 (4), 171–185. https://doi.org/10.1002/mpr.47.
Kishi, T., Miyake, N., Okuya, M., Sakuma, K., Iwata, N., 2020. N-acetylcysteine as an adjunctive treatment for bipolar depression and major depressive disorder: A systematic review and meta-analysis of double-blind, randomized placebo-controlled trials. Psychopharmacology 237 (11), 3481–3487. https://doi.org/10.1007/s00213-020-05629-2.
Knight, E.L., Giuliano, R.J., Shank, S.W., Clarke, M.M., Almeida, D.M., 2020. Parasympathetic and sympathetic nervous systems interactively predict change in cognitive functioning in midlife adults. Psychophysiology 57 (10), e13622. https://doi.org/10.1111/psyp.13622.
Kobrosly, R.W., Seplaki, C.L., Jones, C.M., van Wijngaarden, E., 2012. Physiologic dysfunction scores and cognitive function test performance in U.S. adults. Psychosom. Med. 74 (1), 81–88. https://doi.org/10.1097/PSY.0b013e3182385b1e.
Lachman, M.E., Agrigoroaei, S., Tun, P.A., Weaver, S.L., 2014. Monitoring cognitive functioning: psychometric properties of the brief test of adult cognition by telephone. Assessment 21 (4), 404–417. https://doi.org/10.1177/1073191113508807.
Lezak, M.D., 1983. Neuropsychological. Assessment, second ed. Oxford University Press.
Long, J. , 2019. interactions: Comprehensive, User-Friendly Toolkit for Probing Interactions. R Package Version 1.1.0. https://cran.r-project.org/web/packages/interactions/citation.html.
Lüdecke, D., 2018. ggeffects: tidy data frames of marginal effects from regression models. J. Open Source Softw. 3 (26), 772. https://doi.org/10.21105/joss.00772.
McEwen, B.S., 2003. Mood disorders and allostatic load. Biol. Psychiatry 54 (3), 200–207. https://doi.org/10.1016/S0006-3223(03)00177-X.
McEwen, B.S., Stellar, E., 1993. Stress and the individual. Mechanisms leading to disease. Arch. Intern. Med. 153 (18), 2093–2101.
McIntyre, R., Harrison, J., Loft, H., Jacobson, W., Olsen, C., 2016. The effects of vortioxetine on cognitive function in patients with major depressive disorder: a meta-analysis of three randomized controlled trials. Int. J. Neuropsychopharmacol. 19 (10), pyw055. https://doi.org/10.1093/ijnp/pyw055.
McLoughlin, S., Kenny, R.A., McCrory, C., 2020. Does the choice of Allostatic Load scoring algorithm matter for predicting age-related health outcomes. Psychoneuroendocrinology 120, 104789. https://doi.org/10.1016/j.psyneuen.2020.104789.
Michailidis, M., Tata, D.A., Moraitou, D., Kavvadas, D., Karachrysafi, S., Papamitsou, T., Vareltzis, P., Papaliagkas, V., 2022. Antidiabetic drugs in the treatment of Alzheimer's disease. Int. J. Mol. Sci. 23 (9), 4641. https://doi.org/10.3390/ijms23094641.
Morrens, M., Overloop, C., Coppens, V., Loots, E., Van Den Noortgate, M., Vandenameele, S., Leboyer, M., De Picker, L., 2022. The relationship between immune and cognitive dysfunction in mood and psychotic disorder: a systematic review and a meta-analysis. Mol. Psychiatry 1–10. https://doi.org/10.1038/s41380-022-01582-y.
Muthén, L.K., Muthén, B.O. , 2017. Mplus User's Guide. Eighth Edition. *Muthén & Muthén*. ⟨https://www.statmodel.com/ugexcerpts.shtml⟩.
Narbutas, J., Egroo, M.V., Chylinski, D., González, P.V., Jimenez, C.G., Besson, G., Ghaemmaghami, P., Hammad, G., Muto, V., Schmidt, C., Luxen, A., Salmon, E., Maquet, P., Bastin, C., Vandewalle, G., Collette, F., 2019. Cognitive efficiency in late midlife is linked to lifestyle characteristics and allostatic load. Aging 11 (17), 7169–7186. https://doi.org/10.18632/aging.102243.
Nettis, M.A., 2021. Minocycline in major depressive disorder: and overview with considerations on treatment-resistance and comparisons with other psychiatric disorders. Brain Behav. Immun. Health 17, 100335. https://doi.org/10.1016/j.bbih.2021.100335.
Nettis, M.A., Lombardo, G., Hastings, C., Zajkowska, Z., Mariani, N., Nikkheslat, N., Worrell, C., Enache, D., McLaughlin, A., Kose, M., Sforzini, L., Bogdanova, A., Cleare, A., Young, A.H., Pariante, C.M., Mondelli, V., 2021. Augmentation therapy with minocycline in treatment-resistant depression patients with low-grade peripheral inflammation: results from a double-blind randomised clinical trial. Neuropsychopharmacology 46 (5), 939–948. https://doi.org/10.1038/s41386-020-00948-6.
Oi, K., Haas, S., 2019. Cardiometabolic risk and cognitive decline: the role of socioeconomic status in childhood and adulthood. J. Health Soc. Behav. 60 (3), 326–343. https://doi.org/10.1177/0022146519867924.
Olson, S.H., Kelsey, J.L., Pearson, T.A., Levin, B., 1992. Evaluation of random digit dialing as a method of control selection in case-control studies. Am. J. Epidemiol. 135 (2), 210–222. https://doi.org/10.1093/oxfordjournals.aje.a116273.
Ottino-González, J., Jurado, M.A., García-García, I., Caldú, X., Prats-Soteras, X., Tor, E., Sender-Palacios, M.J., Garolera, M., 2019. Allostatic load and executive functions in overweight adults. Psychoneuroendocrinology 106, 165–170. https://doi.org/10.1016/j.psyneuen.2019.04.009.
Park, J.H., Lee, S.B., Lee, J.J., Yoon, J.C., Han, J.W., Kim, T.H., Jeong, H.-G., Newhouse, P.A., Taylor, W.D., Kim, J.H., Woo, J.I., Kim, K.W., 2018. Depression plays a moderating role in the cognitive decline associated with changes of brain white matter hyperintensities. J. Clin. Psychiatry 79 (5), 4199. https://doi.org/10.4088/JCP.17m11763.
Parker, H.W., Abreu, A.M., Sullivan, M.C., Vadiveloo, M.K., 2022. Allostatic load and mortality: a systematic review and meta-analysis. Am. J. Prev. Med. https://doi.org/10.1016/j.amepre.2022.02.003.
Perini, G., Cotta Ramusino, M., Sinforiani, E., Bernini, S., Petrachi, R., Costa, A., 2019. Cognitive impairment in depression: recent advances and novel treatments. Neuropsychiatr. Dis. Treat. 15, 1249–1258. https://doi.org/10.2147/NDT.S199746.
Peters, R., Yasar, S., Anderson, C.S., Andrews, S., Antikainen, R., Arima, H., Beckett, N., Beer, J.C., Bertens, A.S., Booth, A., van Boxtel, M., Brayne, C., Brodaty, H., Carlson, M.C., Chalmers, J., Corrada, M., DeKosky, S., Derby, C., Dixon, R.A., Anstey, K.J., 2020. Investigation of antihypertensive class, dementia, and cognitive decline. Neurology 94 (3), e267–e281 https://doi.org/10.1212/WNL.0000000000008732.
Prado, C.E., Watt, S., Crowe, S.F., 2018. A meta-analysis of the effects of antidepressants on cognitive functioning in depressed and non-depressed samples. Neuropsychol. Rev. 28 (1), 32–72. https://doi.org/10.1007/s11065-018-9369-5.
Rigney, T., 2010. Allostatic load and delirium in the hospitalized older adult. Nurs. Res. 59 (5), 322–330. https://doi.org/10.1097/NNR.0b013e3181ec156b.
Rivers-Auty, J., Mather, A.E., Peters, R., Lawrence, C.B., Brough, D., Alzheimer's Disease Neuroimaging Initiative, 2020. Anti-inflammatories in Alzheimer's disease—potential therapy or spurious correlate? Brain Commun. 2 (2) https://doi.org/10.1093/braincomms/fcaa109.
de Robert, S.C.C., 2018. Impact of allostatic load on cognitive level, memory and left ventricular mass. Argent. J. Cardiol. 87, 1.
Rosenblat, J.D., Kakar, R., McIntyre, R.S., 2016. The cognitive effects of antidepressants in major depressive disorder: a systematic review and meta-analysis of randomized clinical trials. Int. J. Neuropsychopharmacol. 19 (2), pyv082. https://doi.org/10.1093/ijnp/pyv082.
Saczynski, J.S., Rosen, A.B., McCammon, R.J., Zivin, K., Andrade, S.E., Langa, K.M., Vijan, S., Pirraglia, P.A., Briesacher, B.A., 2015. Antidepressant use and cognitive decline: the health and retirement study. Am. J. Med. 128 (7), 739–746. https://doi.org/10.1016/j.amjmed.2015.01.007.
Schmitz, N., Deschênes, S.S., Burns, R.J., Danna, S.M., Franco, O.H., Ikram, M.A., Kivimäki, M., Singh-Manoux, A., Tiemeier, H., 2018. Cardiometabolic dysregulation and cognitive decline: potential role of depressive symptoms. Br. J. Psychiatry. J. Ment. Sci. 212 (2), 96–102. https://doi.org/10.1192/bjp.2017.26.
Skvarc, D.R., Dean, O.M., Byrne, L.K., Gray, L., Lane, S., Lewis, M., Fernandes, B.S., Berk, M., Marriott, A., 2017. The effect of N-acetylcysteine (NAC) on human cognition – a systematic review. Neurosci. Biobehav. Rev. 78, 44–56. https://doi.org/10.1016/j.neubiorev.2017.04.013.
Turecki, G., Meaney, M.J., 2016. Effects of the social environment and stress on glucocorticoid receptor gene methylation: a systematic review. Biol. Psychiatry 79 (2), 87–96. https://doi.org/10.1016/j.biopsych.2014.11.022.
van der Flier, W.M., Skoog, I., Schneider, J.A., Pantoni, L., Mok, V., Chen, C.L.H., Scheltens, P., 2018. Vascular cognitive impairment. Nat. Rev. Dis. Prim. 4 (1), 1–16. https://doi.org/10.1038/nrdp.2018.3.
Van Dyk, K., Siddarth, P., Rossetti, M., Ercoli, L.M., Milillo, M.M., Lavretsky, H., 2020. Memantine can protect against inflammation-based cognitive decline in geriatric depression. Brain, Behav., Immun. - Health 9, 100167. https://doi.org/10.1016/j.bbih.2020.100167.
VanderWeele, T.J., 2016. Mediation analysis: a practitioner's guide. Annu. Rev. Public Health 37, 17–32. https://doi.org/10.1146/annurev-publhealth-032315-021402.
Verdelho, A., Madureira, S., Moleiro, C., Ferro, J.M., O'Brien, J.T., Poggesi, A., Pantoni, L., Fazekas, F., Scheltens, P., Waldemar, G., Wallin, A., Erkinjuntti, T., Inzitari, D., Study, on behalf of the L, 2013. Depressive symptoms predict cognitive decline and dementia in older people independently of cerebral white matter changes: the LADIS study. J. Neurol., Neurosurg. Psychiatry 84 (11), 1250–1254. https://doi.org/10.1136/jnnp-2012-304191.
Wardlaw, J.M., Smith, E.E., Biessels, G.J., Cordonnier, C., Fazekas, F., Frayne, R., Lindley, R.I., O'Brien, J.T., Barkhof, F., Benavente, O.R., Black, S.E., Brayne, C., Breteler, M., Chabriat, H., DeCarli, C., de Leeuw, F.-E., Doubal, F., Duering, M., Fox, N.C., Dichgans, M., 2013. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol. 12 (8), 822–838. https://doi.org/10.1016/S1474-4422(13)70124-8.
Wickham, H., 2016. ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag, New York https://cran.r-project.org/web/packages/ggplot2/citation.html.

Wu, C.-Y., Ouk, M., Wong, Y.Y., Anita, N., Edwards, J.D., Yang, P., Shah, B.R., Kapral, M., Herrmann, N., Lanctot, K.L., Macintosh, B.J., Rabin, J.S., Black, S.E., Swardfager, W., 2020. Relationships between oral hypoglycemic drugs and memory decline in people with type 2 diabetes: a stratified longitudinal observational study. Alzheimer's Dement. 16 (S6), e041312 https://doi.org/10.1002/alz.041312.

Zainal, N.H., Newman, M.G., 2022. Inflammation mediates depression and generalized anxiety symptoms predicting executive function impairment after 18 years. J. Affect. Disord. 296, 465–475. https://doi.org/10.1016/j.jad.2021.08.077.

Zeki Al Hazzouri, A., Jawadekar, N., Grasset, L., Kaiser, P., Kezios, K., Calonico, S., Glymour, M., Hirsch, C., Arnold, A.M., Varadhan, R., Odden, M.C., 2022. Statins and cognitive decline in the cardiovascular health study: a comparison of different analytical approaches. J. Gerontol.: Ser. A 77 (5), 994–1001. https://doi.org/10.1093/gerona/glab220.

Zhen Zhou, P., Joanne Ryan, P., Michael, E., Ernst, P., Sophia Zoungas, M., Andrew, M., Tonkin, P., Robyn, L., Woods, P., John, J., McNeil, M., Christopher, M., Reid, P., Andrea, J., Curtis, P., Rory Wolfe, P., Jo Wrigglesworth, Bs, Raj, C., Shah, M.D., Elsdon Storey, M., Anne Murray, M.D., Suzanne, G., Orchard, P., Mark, R., Nelson, M., Group, A.I., 2021. Effect of statin therapy on cognitive decline and incident dementia in older adults. J. Am. Coll. Cardiol. https://doi.org/10.1016/j.jacc.2021.04.075.