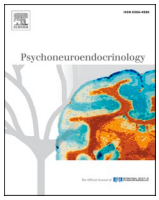
Psychoneuroendocrinology 152 (2023) 106100

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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



Allostatic load and depressive symptoms in older adults: An analysis of 12-year panel data

Cesar de Oliveira [a,1], Wael Sabbah [b,2], Eduardo Bernabé [c,*,3]

[a] Department of Epidemiology & Public Health, University College London, Torrington Place, London W1CE 6BT, United Kingdom
[b] Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, Bessemer Road, London SE5 9RS, United Kingdom
[c] Faculty of Medicine and Dentistry, Queen Mary University of London, Turner Street, London E1 2AD, United Kingdom

ARTICLE INFO

Keywords:
Depression
Depressive disorders
Allostasis
Biomarkers
Metabolism
Cohort studies

ABSTRACT

Background: Whether changes in allostatic load (AL) and depressive symptoms relate over time has not been yet fully explored. This study evaluated the association between AL and depressive symptoms over 12 years among community-dwelling older adults.

Methods: Panel data from 8291 participants in the English Longitudinal Study of Ageing were analysed. Depressive symptoms were assessed with the 8-item Centre for Epidemiologic Studies Depression Scale (CES-D). The AL score was derived from nine metabolic, cardiovascular and immune biomarkers. The association between AL and depressive symptoms was modelled in a linear hybrid model adjusting for time-invariant (sex, ethnicity) and time-variant confounders (age, marital status, education, wealth, physical activity, smoking status, alcohol intake, limitations in daily living, comorbidities).

Results: The mean AL score was 3.1 (SD: 2.1), 3.5 (2.3), 3.2 (2.3) and 3.3 (2.5) whereas the mean CES-D score was 1.4 (SD: 1.8), 1.2 (1.8), 1.2 (1.8) and 1.2 (1.7) in waves 2, 4, 6 and 8, respectively. In the adjusted model, the between-person differences (coefficient: 0.02, 95% CI: 0.01, 0.04) but not the within-individual differences (0.01; 95% CI: −0.01, 0.03) in the AL score were associated with CES-D score. The between-person coefficient indicates that participants with greater AL scores also had slightly higher CES-D scores. The within-person coefficient indicates that changes in the AL score were not associated with changes in the CES-D score.

Conclusion: AL was associated with depressive symptoms. However, most of the association was driven by differences in AL between individuals rather than changes in AL over time.

1. Introduction

Depression is a leading cause of disease burden globally and is associated with significant disability, mortality and high healthcare costs (GBD, 2019 Mental Disorders Collaborators, 2022). It affects 3.8% of the worldwide population (equivalent to 280 million prevalent cases), with higher prevalence among middle-age adults (5.0%) and older adults (5.7%) (GBD, 2019 Mental Disorders Collaborators, 2022). Depressive symptoms have been connected with physiological dysregulation across the neuroendocrine, metabolic, cardiovascular and immune systems, all of which are also involved in the stress response (Lupien et al., 2009; McEwen, 2000, 2003). Alostatic load (AL) is the accumulated wear and tear on the body as a result of its attempt to maintain homeostasis (McEwen, 2000, 2003). The prolonged exposure to stressful experiences elicits physiological responses to cope with such stressors, straining the nervous, metabolic, cardiovascular and immune systems, and predisposing individuals to accelerated aging and chronic diseases (Fava et al., 2019; Lupien et al., 2009). AL is generally measured via a composite index of indicators of cumulative strain on several organs and tissues, primarily biomarkers associated with the neuroendocrine, cardiovascular, immune and metabolic systems (Carbone et al., 2022). Several studies have shown that AL predicts increased morbidity and mortality (Guidi et al., 2021; Parker et al., 2022). There is also evidence of a positive association between poorer socioeconomic

* Correspondence to: Faculty of Medicine and Dentistry, Queen Mary University of London, London E1 2AD, United Kingdom.
E-mail addresses: c.oliveira@ucl.ac.uk (C. de Oliveira), wael.sabbah@kcl.ac.uk (W. Sabbah), e.bernabe@qmul.ac.uk (E. Bernabé).
[1] https://orcid.org/0000-0002-4099-4762
[2] https://orcid.org/0000-0002-6339-9480
[3] https://orcid.org/0000-0002-1858-3713

https://doi.org/10.1016/j.psyneuen.2023.106100
Received 1 February 2023; Received in revised form 8 March 2023; Accepted 23 March 2023
Available online 24 March 2023
0306-4530/© 2023 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

circumstances and greater AL (Johnson et al., 2017). Thus, AL is valuable both as a risk factor for chronic conditions and in understanding the dynamics of the ageing process (Shiels et al., 2019; Shiels et al., 2017).

Multiple pieces of evidence support a plausible link between AL and depressive symptoms. Older adults affected by physical conditions, including obesity, diabetes, cardiovascular disease, sleep problems and cognitive impairment, are at greater risk of depression (Blazer and Hybels, 2005; Köhler et al., 2018). In addition, poor socioeconomic circumstances, negative life events, increased perceived stress and lack of social support are psychosocial factors associated with late-life depression (Fiske et al., 2009; Wu et al., 2022; Yang et al., 2015). Therefore, it is argued that sustained exposure to stress may result in dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS); and the ensuing dysregulation of primary stress mediators (i.e., cortisol and dehydroepiandrosterone sulfate in the HPA axis and epinephrine and norepinephrine in the SNS) and secondary outcomes (i.e., inflammatory and cardiometabolic biomarkers) may be associated with depression (Lupien et al., 2009; McEwen, 2003). Other studies have shown that many biological measures commonly included in the AL index, such as high blood pressure, high triglycerides, low high-density lipoprotein cholesterol, high C-reactive protein and high glycated haemoglobin, are worse in individuals with depression (Köhler et al., 2018). Despite all this evidence, it is surprising that only few longitudinal studies have evaluated the AL-depression relationship among older adults (Goldman et al., 2006; Juster et al., 2011; Kobrosly et al., 2014; McClain et al., 2022). Studies with shorter follow-ups (up to 5 years) have reported an association between baseline AL scores and changes in depressive symptoms scores (Goldman et al., 2006; Kobrosly et al., 2014; McClain et al., 2022). However, a 6-year longitudinal study found no association after accounting for demographic factors (Juster et al., 2011). Research has not yet fully explored how AL and depressive symptoms relate over time. A recent study among US adults, aged 30–64-years, found that those in the high AL trajectory (determined from 3 assessments over 9 years) had higher depressive symptoms scores than those in the low AL trajectory (Beydoun et al., 2023). In addition, a history of depression interacted with AL to predict cognitive decline over 9 years in older middle-aged adults (Perlman et al., 2022). Importantly, the association of change in AL with change in depressive symptoms has not been tested. Understanding how AL relates to depression in older adults is important, as it could help in the diagnosis and treatment of depression and physiological dysregulation, enabling more individualised and effective treatment. Therefore, this study investigated the association between AL and depressive symptoms over a 12-year period among community dwelling older English adults.

2. Methods

2.1. Study population

This research used data from the English Longitudinal Study of Ageing (ELSA), an ongoing panel study of a representative sample of adults aged 50 + years living in private households in England (Steptoe et al., 2013). The initial sample for ELSA (n = 11,391) was drawn from households previously participating in the nationally representative Health Survey for England (HSE) between 1998 and 2001. Starting in 2002–2003, there have been nine ELSA waves to collect data from interviews every two years and from health examinations every four years. The ELSA sample was refreshed using new HSE participants in waves 3, 4, 6, 7 and 9. Ethical approval for all the ELSA waves was granted by the National Research and Ethics Committee (MREC/01/2/91). Written informed consent was obtained from all participants.

For this research, we pooled together data from waves 2 (2004–05), 4 (2008–09), 6 (2012–13) and 8 (2015–16) where information on AL biomarkers and depression were collected. In wave 8, about half of ELSA participants were invited to health examinations (recruited purposively to prioritise those who have consistently taken part in health examinations during previous waves). There were 10,024 participants with data on AL and depressive symptoms in one or more of the selected waves. Of them, 1773 were excluded due to missing data on covariates. The study sample included 8291 participants (82.7%), of whom 1010 had complete data on 4 waves, 1564 on 3 waves, 2886 on 2 waves and 2831 on 1 wave.

2.2. Study variables

The outcome was depressive symptoms, which was assessed using the 8-item Centre for Epidemiologic Studies Depression Scale (CES-D), a self-reported instrument to identify risk of depression among older adults (Kohout et al., 1993). Its validity and reliability are comparable to the full 20-item CES-D (O'Halloran et al., 2014; Steffick, 2000). Participants reported whether they had experienced each of eight negative affect symptoms or somatic complaints in the previous week using a yes/no response format (Turvey et al., 1999). The total CES-D score ranged from 0 to 8, with higher scores indicative of more depressive symptoms. The Cronbach's alpha in this sample was 0.78.

The exposure was an AL summary measure including nine biomarkers from the cardiovascular system (systolic and diastolic blood pressure); metabolic system (high- and low-density lipoprotein [HDL and LDL] cholesterol, triglycerides and glycated haemoglobin and waist circumference) and immune/inflammatory system (fibrinogen and C-reactive protein). All (continuous) biomarkers were dichotomised based on international clinical cut-offs (normal versus risk group) and the number of biomarkers in which the participant fell in the risk group were counted to create the AL score (Carbone et al., 2022). The score varied between 0 and 9, with higher scores indicative of higher multisystem dysfunction. To account for current medication use, participants were assigned to the corresponding risk group if they used blood pressure lowering medication (systolic and diastolic blood pressure), anticoagulants (fibrinogen), lipid lowering medication (triglycerides, HDL and LDL cholesterol), diabetes medication (glycated haemoglobin) and diabetic, cholesterol and blood pressure lowering medication (CRP) (Read and Grundy, 2014; van Deurzen and Vanhoutte, 2019). The AL score was not calculated for participants missing information on 5 + biomarkers. Participants missing information on 1–4 biomarkers (n = 649) were included in the analysis by rescaling their AL score to match the scale range from 0 to 9 (number of biomarkers in the risk group X 9/number of available biomarkers) (de Oliveira et al., 2021). This same rescaling procedure was implemented with the wave 8 data because information on waist circumference was not collected (de Oliveira et al., 2021). The clinical cut-offs and counts for all biomarkers in every wave are shown in the Appendix.

Demographic factors (sex, age, ethnicity and marital status), socioeconomic measures (education and wealth), behaviours (smoking status, physical activity and alcohol intake), disability and number of comorbidities were considered as confounders of the association between AL and depressive symptoms and included in the analysis. All covariates but sex and ethnicity were treated as time-variant. Education was indicated by the highest qualification earned and categorised as low (below O-level), middle (O-level), or high (A-level or above). Total household wealth was determined from savings and investments, value of any property or business assets and net of debt (excluding pension assets). Wealth is the most accurate indicator of long-term socioeconomic conditions in ELSA (Banks et al., 2008). Wealth quintiles were determined from the distribution of values for all participants. For smoking status, participants reported whether they ever smoked and/or were currently smoking. Those who replied affirmatively to both questions were classified as current smokers, those who replied affirmatively to the first question only were classified as former smokers, and those two replied negatively to both questions were classified as never smokers. Participants reported the amount of physical activity involved in their job (if they were working) and the amount of mild, moderate or

vigorous physical activity in everyday life using 4 questions. Responses were combined to create a binary indicator of physical activity (sedentary versus active). Alcohol consumption in the previous 12 months was reported using 8 response options and classified as daily, frequently (1–2 weekly or more often) or rarely (1–2 monthly or less often). Disability was indicated by the number of instrumental activities of daily living (IADL: getting around in a strange place using a map, cooking, buying groceries, making a phone call, taking medications, doing house chores, and managing money) that participants reported as being limited. Finally, the number of comorbidities was determined from a list of 7 self-reported physician-diagnosed chronic conditions including rheumatoid arthritis, cancer, chronic lung disease, heart failure, ischemic heart disease, Parkinson's disease and stroke.

2.3. Data analysis

All analysis were performed in Stata (StataCorp LP, College Station, TX). For descriptive purposes, AL scores and CES-D scores at every wave were compared between groups defined by each covariate, using the t-test with binary covariates and the Royston test for linear trends with ordered covariates.

The association between AL score and CES-D score was modelled in a linear hybrid model adjusted for time-invariant (sex and ethnicity) and time-variant confounders (age, marital status, education, household wealth, smoking status, physical activity, alcohol intake, IADL limitations and number of comorbidities). Hybrid models combine the advantages of fixed-effects models (analysis of within-individual changes and control for unmeasured time-invariant confounders) and random-effects models (analysis of time-invariant predictors) to handle correlated panel data with an unbalanced structure and missing observations (Firebaugh et al., 2013; Schempf Hirai and Kaufman, 2017). The effect of time-variant predictors is decomposed into (i) between-person regression coefficients (mean value across all assessments within individuals) and (ii) within-individual regression coefficients (variations around the person-specific mean) (Firebaugh et al., 2013; Twisk and de Vente, 2019). The between-person estimates represent differences in the CES-D score per unit increase in the AL score at any wave (cross-sectional associations) while the within-individual estimates represent differences in the CES-D score due to changes in the AL between two waves (longitudinal associations). A random intercept for CES-D score was included to take into account the correlated structure of the data (4 assessments at equal intervals over 12 years). Age was included as a

Table 1
Characteristics of participants at every wave.

	Wave 2		Wave 4		Wave 6		Wave 8	
	n	%	n	%	n	%	n	%
All participants	4323	100.0	5360	100.0	5248	100.0	2404	100.0
Sex								
Male	1929	44.6	2412	45.0	2338	44.6	1067	44.4
Female	2394	55.4	2948	55.0	2910	55.4	1337	55.6
Age groups[a]								
50–59 years	1473	34.1	1556	29.0	1183	22.5	329	13.7
60–69 years	1565	36.2	2116	39.5	2177	41.5	958	39.9
70–79 years	970	22.4	1263	23.6	1420	27.1	766	31.9
80 + years	315	7.3	425	7.9	468	8.9	351	14.6
Ethnicity								
White	4272	98.8	5271	98.3	5119	97.5	2361	98.2
Non-white	51	1.2	89	1.7	129	2.5	43	1.8
Marital status								
Married	3043	70.4	3712	69.3	3555	67.7	1656	68.9
Non-married	1280	29.6	1648	30.7	1693	32.3	748	31.1
Education								
High	1218	28.2	1772	33.1	1742	33.2	827	34.4
Middle	1134	26.2	1494	27.9	1524	29.0	721	30.0
Low	1971	45.6	2094	39.1	1982	37.8	856	35.6
Household wealth								
Q1 (highest)	1092	25.3	1327	24.8	1232	23.5	571	23.8
Q2	1019	23.6	1197	22.3	1196	22.8	571	23.8
Q3	895	20.7	1080	20.1	1134	21.6	539	22.4
Q4	770	17.8	986	18.4	969	18.5	431	17.9
Q5 (lowest)	547	12.7	770	14.4	717	13.7	292	12.1
Physical activity								
Active	4216	97.5	5136	95.8	5059	96.4	2309	96.0
Sedentary	107	2.5	224	4.2	189	3.6	95	4.0
Alcohol intake								
Rarely	734	17.0	988	18.4	1098	20.9	494	20.5
Frequently	1969	45.5	2367	44.2	2261	43.1	1059	44.1
Daily	1620	37.5	2005	37.4	1889	36.0	851	35.4
Smoking status								
Never	1670	38.6	2198	41.0	2010	38.3	891	37.1
Former	2080	48.1	2499	46.6	2684	51.1	1283	53.4
Current	573	13.3	663	12.4	554	10.6	230	9.6
IADL Limitations								
None	3706	85.7	4624	86.3	4506	85.9	2073	86.2
One	372	8.6	436	8.1	432	8.2	186	7.7
Two or more	245	5.7	300	5.6	310	5.9	145	6.0
Number of comorbidities								
None	2172	50.2	2892	54.0	2692	51.3	1132	47.1
One	1636	37.8	1956	36.5	2020	38.5	997	41.5
Two or more	515	11.9	512	9.6	536	10.2	275	11.4

IADL: instrumental activities of daily living
[a] These groups were chosen for presentation purposes only

random effect to account for individual variation in the rate of change in CES-D score. The Stata's *xthybrid* suite was used (Schunck and Perales, 2017).

The influence of our methodological choices on the findings was checked in three sensitivity analysis (SA). The first SA checked the influence of imputing the AL score by including only participants with full AL data. The second SA checked the influence of rescaling the AL score for wave 8 by excluding waist circumference (which was not available in wave 8) from the calculation of the AL score. The third SA checked the influence of including AL data from wave 8 (when half of participants were invited to the health examination) by reducing the panel data from 12 to 8 years (waves 2, 4 and 6).

3. Results

We analysed 17,335 data points in 8291 adults (4323, 5360, 5248 and 2404 in waves 2, 4, 6 and 8, respectively), with an average of 2.1 data points per participant (range: 1–4). Participants in the study sample were more likely to be younger, White, married, more educated, wealthier and healthier (including having lower AL and CES-D scores) than those excluded for missing data. The study sample is described by wave in Table 1. The mean AL score was 3.1 (SD: 2.1, range: 0–9), 3.5 (SD: 2.3), 3.2 (SD: 2.3) and 3.3 (SD: 2.5) whereas the mean CES-D score was 1.4 (SD: 1.8, range: 0–8), 1.2 (SD: 1.8), 1.2 (SD: 1.8) and 1.2 (SD: 1.7) in waves 2, 4, 6 and 8, respectively.

At every wave, monotonic upward trends in the AL score (Table 2)

Table 2
Cross-sectional associations between covariates and AL score.

		Wave 2		Wave 4		Wave 6		Wave 8	
		Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Sex									
	Male	3.0	(2.0)	3.5	(2.2)	3.3	(2.3)	3.4	(2.5)
	Female	3.2	(2.1)	3.5	(2.4)	3.2	(2.3)	3.2	(2.5)
	P value[a]	*0.002*		*0.634*		*0.556*		*0.107*	
Age groups									
	50–59 years	2.8	(2.0)	2.8	(2.2)	2.5	(2.1)	2.4	(2.2)
	60–69 years	3.1	(2.1)	3.5	(2.3)	3.1	(2.3)	3.0	(2.4)
	70–79 years	3.7	(2.0)	4.1	(2.3)	3.8	(2.3)	3.7	(2.5)
	80 + years	3.2	(1.9)	4.2	(2.1)	4.1	(2.3)	3.9	(2.5)
	P value for trend[a]	*< 0.001*		*< 0.001*		*< 0.001*		*< 0.001*	
Ethnicity									
	White	3.1	(2.1)	3.5	(2.3)	3.2	(2.3)	3.3	(2.5)
	Non-white	3.1	(1.7)	3.6	(2.2)	3.4	(2.1)	3.2	(2.3)
	P value	*0.858*		*0.758*		*0.470*		*0.879*	
Marital status									
	Married	3.1	(2.1)	3.3	(2.3)	3.2	(2.3)	3.2	(2.4)
	Non-married	3.3	(2.1)	3.8	(2.4)	3.5	(2.4)	3.5	(2.6)
	P value	*< 0.001*		*< 0.001*		*< 0.001*		*0.002*	
Education									
	High	2.7	(2.0)	3.0	(2.2)	2.8	(2.3)	2.9	(2.4)
	Middle	2.9	(2.0)	3.3	(2.3)	3.1	(2.3)	3.2	(2.4)
	Low	3.5	(2.1)	4.0	(2.3)	3.7	(2.3)	3.7	(2.5)
	P value for trend	*< 0.001*		*< 0.001*		*< 0.001*		*< 0.001*	
Household wealth									
	Q1 (highest)	2.6	(2.0)	2.8	(2.2)	2.7	(2.2)	2.6	(2.4)
	Q2	3.0	(2.0)	3.2	(2.2)	3.0	(2.2)	3.2	(2.4)
	Q3	3.2	(2.0)	3.6	(2.3)	3.4	(2.3)	3.4	(2.4)
	Q4	3.5	(2.1)	3.9	(2.3)	3.5	(2.3)	3.6	(2.4)
	Q5 (lowest)	3.9	(2.1)	4.3	(2.4)	4.1	(2.5)	4.3	(2.6)
	P value for trend	*< 0.001*		*< 0.001*		*< 0.001*		*< 0.001*	
Physical activity									
	Active	3.1	(2.1)	3.5	(2.3)	3.2	(2.3)	3.2	(2.5)
	Sedentary	3.8	(2.0)	4.2	(2.3)	4.6	(2.5)	4.7	(2.6)
	P value	*< 0.001*		*< 0.001*		*< 0.001*		*< 0.001*	
Alcohol intake									
	Rarely	3.8	(2.1)	4.2	(2.3)	3.9	(2.4)	4.0	(2.6)
	Frequently	3.2	(2.1)	3.4	(2.3)	3.2	(2.3)	3.3	(2.4)
	Daily	2.8	(2.0)	3.2	(2.3)	2.9	(2.2)	2.9	(2.4)
	P value for trend	*< 0.001*		*< 0.001*		*< 0.001*		*< 0.001*	
Smoking status									
	Never	2.9	(2.0)	3.2	(2.2)	3.0	(2.3)	3.0	(2.4)
	Former	3.2	(2.1)	3.6	(2.3)	3.4	(2.4)	3.5	(2.5)
	Current	3.6	(2.1)	3.7	(2.4)	3.4	(2.4)	3.3	(2.5)
	P value for trend	*< 0.001*		*< 0.001*		*< 0.001*		*0.001*	
IADL Limitations									
	None	3.0	(2.0)	3.3	(2.3)	3.1	(2.3)	3.1	(2.4)
	One	4.1	(2.2)	4.4	(2.4)	4.2	(2.3)	4.2	(2.5)
	Two or more	4.1	(2.0)	4.7	(2.3)	4.5	(2.5)	4.6	(2.6)
	P value for trend	*< 0.001*		*< 0.001*		*< 0.001*		*< 0.001*	
Number of comorbidities									
	None	2.7	(1.9)	3.0	(2.2)	2.7	(2.2)	2.9	(2.4)
	One	3.3	(2.1)	3.8	(2.3)	3.6	(2.3)	3.3	(2.4)
	Two or more	4.2	(2.2)	5.0	(2.2)	4.8	(2.4)	4.7	(2.6)
	P value for trend	*< 0.001*		*< 0.001*		*< 0.001*		*< 0.001*	

IADL: instrumental activities of daily living
[a] Student's t-test was used to compare two groups and Royston test was used to test for linear trends with ordered categories

and CES-D score (Table 3) were found according to smoking status, limitations in IADL and number of comorbidities whereas monotonic downward trends in both scores were found according to education, wealth and alcohol intake. Moreover, higher AL and CES-D scores were observed in non-married and sedentary participants than married and active participants. Higher scores in AL but not in CES-D were found among older adults whereas higher scores in CES-D but not in AL were found among women than men.

Findings from the hybrid model showed that the between-person regression coefficient but not the within-person regression coefficient of the AL score was associated with CES-D score (Table 4). The positive between-person estimate (0.02, 95% CI: 0.01, 0.04) indicates that participants with greater AL scores also have higher CES-D scores. Within-person changes in age, marital status, physical activity and limitations in IADL were associated with higher CES-D scores. Within-person increases in age were associated with a decrease in the CES-D score (−0.02; 95% CI: −0.03, −0.01). In addition, transitioning from being married to non-married (0.69, 95% CI: 0.54, 0.84), from being active to sedentary (0.28, 95% CI: 0.10, 0.45) and from not having limitations in IADL to having 1 (0.34, 95% CI: 0.23, 0.45) or 2 + limitations (0.64, 95% CI: 0.48, 0.80) was associated with higher CES-D scores, all else being equal. Between-person differences in the CES-D score were found according to age, marital status, education, wealth, physical activity, smoking status, limitations in IADL and number of comorbidities. The negative coefficient for age (−0.02, 95% CI: −0.02, −0.01) indicates that older participants had lower CES-D scores than younger participants. Non-

Table 3
Cross-sectional associations between covariates and CES-D total score.

		Wave 2		Wave 4		Wave 6		Wave 8	
		Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Sex									
	Male	1.1	(1.6)	0.9	(1.5)	1.0	(1.6)	0.9	(1.5)
	Female	1.6	(1.9)	1.5	(1.9)	1.4	(1.9)	1.4	(1.8)
	P value[a]	*< 0.001*		*< 0.001*		*< 0.001*		*< 0.001*	
Age groups									
	50–59 years	1.4	(1.9)	1.2	(1.8)	1.4	(2.0)	1.3	(2.1)
	60–69 years	1.2	(1.7)	1.1	(1.7)	1.1	(1.7)	1.1	(1.6)
	70–79 years	1.4	(1.8)	1.3	(1.8)	1.2	(1.7)	1.0	(1.5)
	80 + years	1.7	(1.9)	1.6	(1.9)	1.5	(1.9)	1.5	(1.7)
	P value for trend[a]	*0.238*		*0.003*		*0.828*		*0.318*	
Ethnicity									
	White	1.4	(1.8)	1.2	(1.8)	1.2	(1.8)	1.2	(1.7)
	Non-white	2.0	(2.4)	1.4	(1.9)	1.4	(2.0)	1.1	(1.9)
	P value	*0.151*		*0.346*		*0.146*		*0.802*	
Marital status									
	Married	1.2	(1.6)	1.0	(1.6)	1.0	(1.6)	1.0	(1.5)
	Non-married	1.8	(2.1)	1.8	(2.1)	1.6	(2.1)	1.6	(2.0)
	P value	*< 0.001*		*< 0.001*		*< 0.001*		*< 0.001*	
Education									
	High	1.0	(1.6)	1.0	(1.6)	1.0	(1.6)	0.9	(1.5)
	Middle	1.3	(1.7)	1.2	(1.7)	1.2	(1.8)	1.1	(1.7)
	Low	1.6	(2.0)	1.5	(1.9)	1.4	(1.9)	1.4	(1.7)
	P value for trend	*< 0.001*		*< 0.001*		*< 0.001*		*< 0.001*	
Household wealth									
	Q1 (highest)	1.0	(1.6)	0.8	(1.4)	0.8	(1.4)	0.8	(1.4)
	Q2	1.1	(1.6)	1.0	(1.6)	1.0	(1.5)	0.9	(1.4)
	Q3	1.4	(1.8)	1.2	(1.7)	1.2	(1.8)	1.0	(1.3)
	Q4	1.6	(1.9)	1.5	(1.9)	1.5	(2.0)	1.5	(1.9)
	Q5 (lowest)	2.1	(2.2)	2.1	(2.2)	2.1	(2.3)	2.0	(2.2)
	P value for trend	*< 0.001*		*< 0.001*		*< 0.001*		*< 0.001*	
Physical activity									
	Active	1.3	(1.8)	1.2	(1.8)	1.2	(1.8)	1.1	(1.6)
	Sedentary	2.9	(2.4)	2.2	(2.2)	2.6	(2.4)	2.4	(2.2)
	P value	*< 0.001*		*< 0.001*		*< 0.001*		*< 0.001*	
Alcohol intake									
	Rarely	2.0	(2.1)	1.9	(2.2)	1.8	(2.1)	1.5	(1.8)
	Frequently	1.3	(1.8)	1.2	(1.7)	1.2	(1.8)	1.2	(1.7)
	Daily	1.2	(1.6)	0.9	(1.6)	0.9	(1.5)	0.9	(1.5)
	P value for trend	*< 0.001*		*< 0.001*		*< 0.001*		*< 0.001*	
Smoking status									
	Never	1.3	(1.8)	1.1	(1.7)	1.1	(1.7)	1.0	(1.5)
	Former	1.3	(1.8)	1.2	(1.7)	1.2	(1.7)	1.2	(1.6)
	Current	1.7	(2.1)	1.8	(2.2)	1.9	(2.3)	1.7	(2.2)
	P value for trend	*< 0.001*		*< 0.001*		*< 0.001*		*0.001*	
IADL Limitations									
	None	1.1	(1.6)	1.0	(1.6)	1.0	(1.6)	1.0	(1.5)
	One	2.3	(2.2)	2.3	(2.1)	2.2	(2.2)	1.9	(2.0)
	Two or more	3.4	(2.3)	3.3	(2.3)	3.2	(2.4)	2.7	(2.1)
	P value for trend	*< 0.001*		*< 0.001*		*< 0.001*		*< 0.001*	
Number of comorbidities									
	None	1.0	(1.6)	1.0	(1.6)	0.9	(1.6)	0.8	(1.5)
	One	1.6	(1.9)	1.4	(1.9)	1.4	(1.9)	1.4	(1.7)
	Two or more	2.1	(2.1)	2.1	(2.2)	2.1	(2.2)	1.7	(1.8)
	P value for trend	*< 0.001*		*< 0.001*		*< 0.001*		*< 0.001*	

IADL: instrumental activities of daily living
[a] Student's t-test was used to compare two groups and Royston test was used to test for linear trends with ordered categories

Table 4
Linear hybrid model for the association between AL score and CES-D total score (n = 17,335 repeated assessments over 12 years in 8291 adults).

		Between-person effects			Within-person effects		
		Coef.	[95%CI]	P value	Coef.	[95%CI]	P value
Sex							
	Male	0.00	[Reference]				
	Female	0.35	[0.28, 0.41]	< 0.001			
Ethnicity							
	White	0.00	[Reference]				
	Non-white	0.24	[0.03, 0.45]	0.025			
Age, in years		-0.02	[− 0.02, − 0.01]	< 0.001	-0.02	[− 0.03, − 0.01]	< 0.001
AL score		0.02	[0.01, 0.04]	0.007	0.01	[− 0.01, 0.03]	0.535
Marital status							
	Married	0.00	[Reference]		0.00	[Reference]	
	Non-married	0.34	[0.26, 0.41]	< 0.001	0.69	[0.54, 0.84]	< 0.001
Education							
	High	0.00	[Reference]		0.00	[Reference]	
	Middle	0.02	[− 0.06, 0.11]	0.555	-0.11	[− 0.30, 0.08]	0.239
	Low	0.09	[0.00, 0.17]	0.039	-0.15	[− 0.32, 0.02]	0.089
Household wealth							
	Q1 (highest)	0.00	[Reference]		0.00	[Reference]	
	Q2	0.02	[− 0.08, 0.12]	0.704	0.01	[− 0.10, 0.12]	0.874
	Q3	0.16	[0.06, 0.26]	0.003	0.08	[− 0.06, 0.21]	0.267
	Q4	0.20	[0.09, 0.31]	< 0.001	0.10	[− 0.07, 0.27]	0.237
	Q5 (lowest)	0.42	[0.30, 0.54]	< 0.001	-0.07	[− 0.31, 0.18]	0.595
Physical activity							
	Active	0.00	[Reference]		0.00	[Reference]	
	Sedentary	0.33	[0.13, 0.52]	0.001	0.28	[0.10, 0.45]	0.002
Alcohol intake							
	Rarely	0.00	[Reference]		0.00	[Reference]	
	Frequently	-0.24	[− 0.34, − 0.15]	< 0.001	-0.05	[− 0.18, 0.08]	0.444
	Daily	-0.28	[− 0.37, − 0.18]	< 0.001	-0.13	[− 0.29, 0.02]	0.099
Smoking status							
	Never	0.00	[Reference]		0.00	[Reference]	
	Former	0.06	[− 0.01, 0.13]	0.086	0.18	[− 0.03, 0.40]	0.093
	Current	0.34	[0.23, 0.44]	< 0.001	0.15	[− 0.11, 0.41]	0.265
IADL Limitations							
	None	0.00	[Reference]		0.00	[Reference]	
	One	1.10	[0.96, 1.24]	< 0.001	0.34	[0.23, 0.45]	< 0.001
	Two or more	1.84	[1.68, 2.00]	< 0.001	0.64	[0.48, 0.80]	< 0.001
Number of comorbidities							
	None	0.00	[Reference]		0.00	[Reference]	
	One	0.27	[0.19, 0.35]	< 0.001	0.05	[− 0.04, 0.14]	0.276
	Two or more	0.57	[0.45, 0.70]	< 0.001	-0.01	[− 0.16, 0.13]	0.858

AL: allostatic load; IADL: instrumental activities of daily living

married, sedentary and smoking participants and those with less education and wealth, with limitations in IADL and comorbidities had higher CES-D scores than their corresponding counterparts. On the contrary, participants who drank daily and frequently had lower CES-D scores than those who rarely drank alcohol, all other things being equal.

Similar results were observed when: (i) including participants with full data on AL biomarkers only (n = 7632; between-person coefficient: 0.02, 95% CI: 0.01, 0.04; within-person coefficient: 0.00, 95% CI: −0.03, 0.02), (ii) excluding waist circumference from the calculation of the AL score (n = 8278; between-person coefficient: 0.02, 95% CI: 0.01, 0.04; within-person coefficient: 0.01, 95% CI: −0.02, 0.03) and (iii) reducing the follow-up period from 12 to 8 years (n = 8134; between-person coefficient: 0.02, 95% CI: 0.01, 0.04; within-person coefficient: 0.01; 95% CI: −0.02, 0.03).

4. Discussion

Our analysis of this large population-based cohort of older English adults aged 50 + years showed that AL was associated with more depressive symptoms over 12 years. However, most of the association was driven by differences in AL between individuals rather than changes in AL over time. In particular, the between-person estimate indicated that participants with greater AL score also had a slightly higher CES-D score (cross-sectional association). The within-person estimate indicated that changes in the AL score were not associated with changes in the CES-D score.

Chronic stress is one of the most significant influences on depression (Lupien et al., 2009; Yang et al., 2015). Our finding that chronic stress, as indicated by AL, was not prospectively associated with depressive symptoms disagrees with previous studies showing that exposure to adverse life events and perceived chronic stress are related to late-life depression (Fiske et al., 2009; Köhler et al., 2018; Yang et al., 2015). This contradicting finding could be attributed to methodological differences in the measurement of chronic stress; while we used a physiological measure (AL index) previous studies were based on self-reports. That said, it is possible that the subjective experience of stressful events influences the occurrence of depressive symptoms in a different way to the physiological dysregulation caused by chronic stress (Kobrosly et al., 2014). Repeated exposure to stress could trigger physiological dysfunction and depressive symptoms via independent mechanisms, which in turn explains why they are associated cross-sectionally albeit not causally (Rodriquez et al., 2018).

Juster et al. (2011) suggested that AL could be associated with acute rather than prospective depressive symptoms among older adults. This claim is supported by evidence showing that an association between AL and depression was more consistently found in longitudinal studies with shorter (Goldman et al., 2006; Kobrosly et al., 2014; McClain et al., 2022) than longer follow-ups (Juster et al., 2011). However, an association was reported in a recent 9-year follow-up study among middle-age adults (Beydoun et al., 2023). Taken together, these findings suggest

that the effect of AL could occur at younger ages, particularly in middle adulthood as opposed to late adulthood. There is evidence that AL increases steadily from young to middle adulthood and remains remarkably constant in older groups (Yang and Kozloski, 2011). If that is the case, our cohort was too old (50 + years) to capture the effects of AL on depressive symptoms.

It is well established that certain AL biomarkers tend to be dysregulated in people with depression, spanning the neuroendocrine, inflammatory, metabolic and cardiovascular systems (Kokkeler et al., 2022; Lupien et al., 2009; McEwen, 2000, 2003). There is no consensus on how best to operationalise AL although the key challenge is to capture physiological dysregulation across multiple systems. Our AL measure included nine biomarkers from the metabolic, cardiovascular and inflammatory systems. As such, it was based on secondary outcomes rather than primary mediators. Primary mediators are those released during activation of the HPA axis, such as dehydroepiandrosterone sulfate and cortisol, and the SNS, such as epinephrine, norepinephrine and dopamine (McEwen, 2000, 2003). Increased activity of the HPA axis and SNS could lead to altered states of brain chemistry and function (Lupien et al., 2009; McEwen, 2003). There is also evidence that low-frequency heart rate variability, an indicator of autonomic nervous system function, is negatively associated with depression (Brown et al., 2018). It is thus possible that the lack of primary mediators and/or biomarkers in the parasympathetic nervous system in our AL index, due to data availability in ELSA, could have attenuated our estimates of the AL-depression association. The possibility of reverse causation (depressive symptoms increasing AL) cannot be ruled out either. Common inflammatory markers, such as IL-6 and CRP, are typically elevated in clinical samples with depression (Haapakoski et al., 2015) and depression can exacerbate inflammation (Beurel et al., 2020), suggesting that the association between AL and depression might be bidirectional (McClain et al., 2022). However, several risk factors for depression (such as adverse childhood experiences and poor socioeconomic circumstances) are also pro-inflammatory (Köhler et al., 2018; Wu et al., 2022). It is thus possible that common determinants play a role in their comorbidity. Our finding implies that other factors may better explain the incidence of depressive symptoms among older adults.

The strengths of our study are the long follow-up, the large sample of community-dwelling older adults and the advance data modelling to disentangle between- and within-individual effects. Our analysis is not without limitations though. As with any longitudinal study, selection bias could have been introduced from non-response and attrition. Our estimates may be conservative because participants who provided blood samples could be more likely to be healthier than those who did not. Similarly, there were differences between participants included and excluded from the analysis, which reduces the generalisability of our findings. Measurement bias should also be considered. The lack of primary mediators of stress in our AL measure was discussed extensively above. In addition, we used a short version of the CES-D with binary responses, which has been validated and extensively used among older adults (O'Halloran et al., 2014; Steffick, 2000). However, it is possible that the fewer items and response options in our instrument yielded less variability than the full 20-item scale, which could have reduced our ability to identify the hypothesised association. Finally, the risks of unmeasured and residual confounding cannot be fully ruled out from any observational study.

In conclusion, our study showed for the first time in a large English sample of older adults that AL was associated with depressive symptoms over a 12-year period. However, most of the association was driven by cross-sectional differences between individuals rather than changes in AL over time.

Conflict of interest

The authors declare no conflict of interest regarding this work.

Acknowledgement

The English Longitudinal Study of Ageing was developed by a team of researchers based at the University College London, NatCen Social Research, the Institute for Fiscal Studies and the University of Manchester. The data were collected by NatCen Social Research. ELSA is funded by the National Institute on Aging (R01AG017644), and by UK Government Departments coordinated by the National Institute for Health and Care Research (NIHR).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2023.106100.

References

Banks, J., Breeze, E., Lessof, C., Nazroo, J., 2008. Living in the 21st Century: Older People in England: The 2006 English Longitudinal Study of Ageing. The Institute of Fiscal Studies, London.
Beurel, E., Toups, M., Nemeroff, C.B., 2020. The bidirectional relationship of depression and inflammation: double trouble. Neuron 107, 234–256.
Beydoun, H.A., Beydoun, M.A., Kwon, E., Hossain, S., Fanelli-Kuczmarski, M.T., Maldonado, A., Evans, M.K., Zonderman, A.B., 2023. Longitudinal association of allostatic load with depressive symptoms among urban adults: healthy aging in neighborhoods of diversity across the life span study. Psychoneuroendocrinology 149, 106022.
Blazer 2nd, D.G., Hybels, C.F., 2005. Origins of depression in later life. Psychol. Med 35, 1241–1252.
Brown, L., Karmakar, C., Gray, R., Jindal, R., Lim, T., Bryant, C., 2018. Heart rate variability alterations in late life depression: a meta-analysis. J. Affect Disord. 235, 456–466.
Carbone, J.T., Clift, J., Alexander, N., 2022. Measuring allostatic load: approaches and limitations to algorithm creation. J. Psychosom. Res. 163, 111050.
van Deurzen, I., Vanhoutte, B., 2019. A longitudinal study of allostatic load in later life: the role of sex, birth cohorts, and risk accumulation. Res. Aging 41, 419–442.
Fava, G.A., McEwen, B.S., Guidi, J., Gostoli, S., Offidani, E., Sonino, N., 2019. Clinical characterization of allostatic overload. Psychoneuroendocrinology 108, 94–101.
Firebaugh, G., Warner, C., Massoglia, M., 2013. Fixed effects, random effects, and hybrid models for causal analysis. In: Morgan, S.L. (Ed.), Handbook of Causal Analysis for Social Research. Springer, Dordrecht, the Netherlands.
Fiske, A., Wetherell, J.L., Gatz, M., 2009. Depression in older adults. Annu. Rev. Clin. Psychol. 5, 363–389.
GBD 2019 Mental Disorders Collaborators, 2022. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry 9, 137–150.
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, 862–870.
Guidi, J., Lucente, M., Sonino, N., Fava, G.A., 2021. Allostatic load and its impact on health: a systematic review. Psychother. Psychosom. 90, 11–27.
Haapakoski, R., Mathieu, J., Ebmeier, K.P., Alenius, H., Kivimäki, M., 2015. Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. Brain Behav. Immun. 49, 206–215.
Johnson, S.C., Cavallaro, F.L., Leon, D.A., 2017. A systematic review of allostatic load in relation to socioeconomic position: poor fidelity and major inconsistencies in biomarkers employed. Soc. Sci. Med 192, 66–73.
Juster, R.P., Marin, M.F., Sindi, S., Nair, N.P., Ng, Y.K., Pruessner, J.C., Lupien, S.J., 2011. Allostatic load associations to acute, 3-year and 6-year prospective depressive symptoms in healthy older adults. Physiol. Behav. 104, 360–364.
Kobrosly, R.W., van Wijngaarden, E., Seplaki, C.L., Cory-Slechta, D.A., Moynihan, J., 2014. Depressive symptoms are associated with allostatic load among community-dwelling older adults. Physiol. Behav. 123, 223–230.
Köhler, C.A., Evangelou, E., Stubbs, B., Solmi, M., Veronese, N., Belbasis, L., Bortolato, B., Melo, M.C.A., Coelho, C.A., Fernandes, B.S., Olfson, M., Ioannidis, J.P. A., Carvalho, A.F., 2018. Mapping risk factors for depression across the lifespan: an umbrella review of evidence from meta-analyses and Mendelian randomization studies. J. Psychiatr. Res 103, 189–207.
Kohout, F.J., Berkman, L.F., Evans, D.A., Cornoni-Huntley, J., 1993. Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index. J. Aging Health 5, 179–193.
Kokkeler, K.J.E., Marijnissen, R.M., Wardenaar, K.J., Rhebergen, D., van den Brink, R.H. S., van der Mast, R.C., Oude Voshaar, R.C., 2022. Subtyping late-life depression according to inflammatory and metabolic dysregulation: a prospective study. Psychol. Med. 52, 515–525.
Lupien, S.J., McEwen, B.S., Gunnar, M.R., Heim, C., 2009. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat. Rev. Neurosci. 10, 434–445.
McClain, A.C., Xiao, R.S., Tucker, K.L., Falcón, L.M., Mattei, J., 2022. Depressive symptoms and allostatic load have a bidirectional association among Puerto Rican older adults. Psychol. Med 52, 3073–3085.

McEwen, B.S., 2000. Allostasis and allostatic load: implications for neuropsychopharmacology. Neuropsychopharmacology 22, 108–124.
McEwen, B.S., 2003. Mood disorders and allostatic load. Biol. Psychiatry 54, 200–207.
O'Halloran, A.M., Kenny, R.A., King-Kallimanis, B.L., 2014. The latent factors of depression from the short forms of the CES-D are consistent, reliable and valid in community-living older adults. Eur. Geriatr. Med. 5, 97–102.
de Oliveira, C., Sabbah, W., Schneider, I.J.C., Bernabé, E., 2021. Complete tooth loss and allostatic load changes later in life: a 12-Year follow-up analysis of the english longitudinal study of ageing. Psychosom. Med. 83, 247–255.
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. 63, 131–140.
Perlman, G., Cogo-Moreira, H., Wu, C.Y., Herrmann, N., Swardfager, W., 2022. Depression interacts with allostatic load to predict cognitive decline in middle age. Psychoneuroendocrinology 146, 105922.
Read, S., Grundy, E., 2014. Allostatic load and health in the older population of England: a crossed-lagged analysis. Psychosom. Med. 76, 490–496.
Rodriquez, E.J., Livaudais-Toman, J., Gregorich, S.E., Jackson, J.S., Nápoles, A.M., Pérez-Stable, E.J., 2018. Relationships between allostatic load, unhealthy behaviors, and depressive disorder in U.S. adults, 2005-2012 NHANES. Prev. Med. 110, 9–15.
Schempf Hirai, A., Kaufman, J.S., 2017. Fixed versus random effects models for multilevel and longitudinal data. In: Oakes, J.M., Kaufman, J.S. (Eds.), Methods in social epidemiology. John Wiley & Sons, San Francisco, pp. 369–397 (CA, pp).
Schunck, R., Perales, F., 2017. Within- and between-cluster effects in generalized linear mixed models: A discussion of approaches and the xthybrid command. Stata J. 17, 89–115.
Shiels, P.G., Stenvinkel, P., Kooman, J.P., McGuinness, D., 2017. Circulating markers of ageing and allostatic load: a slow train coming. Pr. Lab Med. 7, 49–54.
Shiels, P.G., Buchanan, S., Selman, C., Stenvinkel, P., 2019. Allostatic load and ageing: linking the microbiome and nutrition with age-related health. Biochem Soc. Trans. 47, 1165–1172.
Steffick, D.E., 2000. Documentation of affective functioning measures in the Health and Retirement Study (HRS/AHEAD Documentation Report DR-005). Survey Research Center. University of Michigan, Ann Arbor, MI, USA.
Steptoe, A., Breeze, E., Banks, J., Nazroo, J., 2013. Cohort profile: the English longitudinal study of ageing. Int. J. Epidemiol. 42, 1640–1648.
Turvey, C.L., Wallace, R.B., Herzog, R., 1999. A revised CES-D measure of depressive symptoms and a DSM-based measure of major depressive episodes in the elderly. Int. Psychogeriatr. 11, 139–148.
Twisk, J.W.R., de Vente, W., 2019. Hybrid models were found to be very elegant to disentangle longitudinal within- and between-subject relationships. J. Clin. Epidemiol. 107, 66–70.
Wu, Q., Feng, J., Pan, C.W., 2022. Risk factors for depression in the elderly: an umbrella review of published meta-analyses and systematic reviews. J. Affect Disord. 307, 37–45.
Yang, L., Zhao, Y., Wang, Y., Liu, L., Zhang, X., Li, B., Cui, R., 2015. The effects of psychological stress on depression. Curr. Neuropharmacol. 13, 494–504.
Yang, Y., Kozloski, M., 2011. Sex differences in age trajectories of physiological dysregulation: inflammation, metabolic syndrome, and allostatic load. J. Gerontol. A Biol. Sci. Med. Sci. 66, 493–500.