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Mind versus body: Perceived stress and biological stress are independently related to cognitive decline

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ABSTRACT

Chronic stress may increase risk of age-related cognitive decline. 'Stress', however, is a multidimensional construct and few studies have investigated the inter-relationship of subjective stress and biological stress with cognitive decline. In this study, we examine the relationship between perceived stress and two measures of biological stress – allostatic load, indexing stress at the physiological level and leukocyte telomere length, indexing stress at the cellular level – with cognitive decline over a 12-year period in adults aged 50 and older.

3,458 participants (aged ≥ 50) from The Irish Longitudinal study on Ageing with measurements of allostatic load, telomere length and perceived stress at baseline and repeated measures of cognitive function were included. Hierarchical linear regression models with adjustment for multiple potential confounders were applied, and repeated stratified by sex in sensitivity analyses.

Higher perceived stress at baseline was associated with lower cognitive function (β = −0.10, 95 % CI −0.12, −0.07, p <.001), with similar strength of associations across waves. There were significant interactions between measures of biological stress and wave; higher allostatic load was associated ($X^2_{(18)}$ = 64.4; p <.001), and telomere length was borderline ($X^2_{(18)}$ = 9.4; p =.09) associated with cognitive decline from 4-year follow-up onward. Sex stratified analyses revealed that the association between telomere length and cognitive decline was present in women only. Mutual adjustment did not attenuate associations in either case. The interactions between allostatic load and telomere length with perceived stress were not significant.

Our findings suggest that subjective measures of stress and biological metrics may be independently related to cognitive function over time in older adults, hinting at the potential for different underlying mechanisms.

1. Introduction

Rapid global population ageing has led to a sharp increase in the current and projected prevalence of neurodegenerative conditions - most notably dementia (Collaborators GBDDF, 2022) – and an ever pressing need to target risk reduction at an individual and population level. Chronic stress is recognised as an important factor influencing how an individual ages and can have marked adverse effects both on physical and psychological health (Polsky et al., 2022). The literature on the effect of stress on cognitive function and decline in older adults suggests that stress of a persistent (chronic) or extreme nature is associated with an increased risk of accelerated cognitive decline (Kulshreshtha et al., 2023; Lupien et al., 2009; Christensen et al., 2023; Johansson et al., 2010; Donley et al., 2018). Divergent findings however exist, including observations that exposure to stressful events may have null or even beneficial effects on cognitive functioning in certain contexts (Feeney et al., 2013; McHugh Power et al., 2022; Kunzi et al., 2022; Xiang et al., 2022; Anderson et al., 2017). There is also no consensus as to which exposures are most likely to be deleterious to cognitive functioning, the precise mechanisms driving increased risk, and what exactly mitigates that risk.

An obstacle to moving research forward in elucidating the causal mechanisms underlying the relationships between stress and cognitive function is the heterogeneity in how stress can be operationalised and measured. Stress is a multidimensional concept with environmental, psychological, and biological indicators, and is conceptualised as either

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the exposure to a 'stressor' (some event or environmental context) or the individual's response to that stressor. Psychological stress, for example, has been measured using objectively reported adverse life events or subjective appraisals of stress over varying timescales (Weckesser et al., 2021). Both adverse exposures and perceived stress in adulthood have been independently associated with accelerated cognitive decline (Kulshreshtha et al., 2023; Christensen et al., 2023); however, the absence of subjective appraisal accompanying these'stressful' events often limits the potential for comparison across individuals, events and studies, contributing to the variable findings across different psychological stress measures (Shields et al., 2023).

Similarly, biological stress has been measured at different levels of resolution and with a focus on different physiological systems. Allostatic load, for example, captures biological stress at the level of multiple, interacting physiological systems (e.g., autonomic, cardiovascular, immune, metabolic), all of which influence brain structure and function. Decades of research has provided good evidence that chronic stress can lead to multi-system physiological dysregulation, secondary to prolonged exposure to elevated primary stress hormone, cortisol (McEwen, 2017; McEwen, 2008; McEwen et al., 1988). The extent of this multisystem dysregulation, or allostatic load, determines individual disease risk (McEwen, 1998, 1998; Seeman et al., 1997). At the cellular level, leukocyte telomere length has been advanced as a measure of stress-induced cellular ageing (Polsky et al., 2022). Telomeres are nucleotide segments on the ends of mammalian chromosomes which function to protect the chromosomes from the loss of coding base pairs during cell division, and physiological changes resulting from chronic perceived stress are thought to accelerate telomere attrition (Mathur et al., 2016). Both allostatic load and telomere length have been linked to cognitive function and decline, however discrepancies exist across studies. A recent systematic review and *meta*-analysis reported robust, albeit small, cross-sectional effects of allostatic load on cognitive function (D'Amico et al., 2020). Several longitudinal studies report higher allostatic load to be a risk factor for cognitive decline (Karlamangla et al., 2014; Perlman et al., 2022; Crook et al., 2018), while others show no association (Adedeji et al., 2023; Goldman et al., 2006). Regarding telomere length, while associations with mortality and a variety of major diseases are relatively well established, results are mixed in relation to cognitive decline and risk of dementia (Mahoney et al., 2019; Harris et al., 2016; Cai et al., 2013; Zhan et al., 2018; Topiwala et al., 2023).

Another area of divergence includes the emphasis placed on objective biological indicators versus the subjective reporting of stress and the mechanisms underpinning their relationships with cognitive function. It is a commonly held belief that perceived psychological stress translates into biological changes and that it is the biological effects that lead to increased risk of psychiatric and chronic physical health conditions, particularly in older adults as physiological decline is accelerating (Lupien et al., 2018). However, the observed associations between psychological and biological measures of stress are frequently weak or non-existent (Staufenbiel et al., 2013; Stalder et al., 2017; Epel et al., 2018). This lack of covariance makes it difficult to establish mechanisms. Whether perceived stress and biological stress have independent or additive effects on cognitive function and decline, and to what extent, if any, measures of biological stress mediate any association between perceived stress and cognitive decline, is not fully understood. It might be the case that both affect cognitive function in part through different pathways.

The brain is the key organ in perceiving a stressor and initiating a physiological stress response (McEwen et al., 2015). Cortisol has been shown to be neurotoxic in high concentrations and can impair cognitive function, with some evidence suggesting that it may accelerate cognitive decline or increase risk of dementia by a direct effect on neuronal cells and by triggering changes across the inflammatory/immune and cardiovascular systems (Ouanes and Popp, 2019; Lecca et al., 2022; Pascual et al., 2021; Bright et al., 2019). While decrements in cognitive functioning arising from these biological sequelae may take many years or even decades to manifest, there may also be rapid, maladaptive cognitive processes engaged in response to perceived chronic stressors, which can be detrimental to everyday cognitive functioning, and result in measurable deficits in cognitive performance across much shorter timescales. These processes include rumination, perseveration, and attentional deficits, known to be associated with a disengagement of the prefrontal cortex (PFC), leading to loss of 'top-down' cognitive control and reduced functional connectivity with other brain regions (Sole-Padulles et al., 2022). As well as sustaining the physiological stress response, engaging in these negative cognitions also reduces available resources to allocate competing cognitive tasks (Whitmer and Gotlib, 2013), and repetitive negative thinking is associated with poorer self-rated cognitive function (Schlosser et al., 2020). Long-term, negative cognitions putatively contribute to the accrual of 'cognitive debt', reducing resources and selective attention for cognitive tasks and increasing risk of cognitive decline and dementia (Marchant and Howard, 2015; Marchant et al., 2020).

In this study, we use a longitudinal design to conduct a detailed examination of the relationships between biological stress, perceived stress and cognitive decline over 12 years in a large population-based cohort of individuals aged 50 and older from the Irish Longitudinal Study on Ageing (TILDA). We explore the potential for independent and additive effects of perceived and biological stress on cognitive function, as well as the possibility that biological stress mediates the effects of perceived stress. We test two measures of biological stress: allostatic load as a measure of multi-system physiological dysregulation due to stress, and leukocyte telomere length indexing stress-induced cellular ageing. In supplementary analyses, we stratified by sex to test any differences between men and women in the association between stress and cognitive decline.

2. Methods

Ethical approval was granted by the Trinity College Faculty of Health Sciences Research Ethics Committee, Dublin, Ireland. Protocols conformed with the 1964 Declaration of Helsinki and its later amendments. Signed informed consent was obtained from all respondents prior to participation.

2.1. Study design

TILDA is a large population-based study of a nationally representative sample of community-dwelling older adults aged 50 years and older in Ireland. TILDA's random sampling procedure and study design have been described elsewhere (Donoghue et al., 2018). Participants have been followed biennially from wave 1 (2009–2011), and this study includes data up to wave 6 (2022). At each wave, a computer-assisted personal interview (CAPI) collected information on their social, health, and financial situations. Participants also completed a questionnaire (SCQ) which included questions on more sensitive matters such as quality of life, interpersonal relationships, and alcohol consumption. At wave 1 and wave 3, participants were invited to take part in an extensive nurse-administered health assessment in a dedicated health centre. The SCQ was completed after CAPI (mean = 0.59 days; SD = 12.09); mean time difference between CAPI and the health assessment was 109 days (SD = 74.2). Among the 8,173 participants aged 50 and older at baseline, 3,458 had measurements of allostatic load, telomere length and perceived stress at wave 1 and cognitive function at wave 1 and at least at any other wave (Fig. S1).

2.2. Allostatic load

Allostatic load (AL) was used as our measure of physiological stress. Twelve biomarkers measured across the cardiovascular, metabolic, renal and immune systems during the health assessment were used to construct the AL index. The average of two measurements of seated

systolic blood pressure (SBP), diastolic blood pressure (DBP), resting heart rate (RHR) and pulse wave velocity (PWV), a measure of vascular stiffness, were used to measure the cardiovascular system. SBP, DBP and RHR were obtained separated by a 1-minute interval using an automatic digital oscillometric blood pressure monitor (OMRONTM, M10-IT). PWV was obtained by capturing signal differences in flow between the carotid and femoral arteries using a Vicorder system (Skidmore Medical Ltd, Bristol, UK). Metabolic markers included waist-height ratio (WHR), body mass index (BMI), glycosylated haemoglobin (HbA1c), total cholesterol (TChol), and high-density lipoprotein. Weight and height were measured using a SECA electronic floor scales and a SECA 240 wall mounted measuring rod respectively. Non fasting blood samples were drawn at the health assessment for HbA1c, Tchol and HDL. HDL was reversed coded, i.e. multiplied by −1, prior to classification as high level of HDL is considered beneficial for health. Immunological dysregulation was measured using C-Reactive Protein (CRP), also obtained from non-fasting blood. Detection limits ranged from 0.3 to 350 mg/l. Renal markers included Creatinine (Crea) and Cyscatin C (Cysc), which were measured from frozen plasma.

AL was constructed using the high-risk quartile method (McLoughlin et al., 2020). For each biomarker, a dichotomous variable was created. Individuals were classified as high-risk and assigned a value of "1″ if above the sex-specified 75th percentile of the distribution of that marker. They were coded as "0" if below this threshold. Individuals were automatically reclassified as high-risk and assigned a value of 1 if they were taking medication: SBP was recoded as high risk if taking anti-hypertensive medication (Anatomic Therapeutic Classification codes C02, C03, C09); RHR was recoded as high risk if taking beta-blockers (C07) or calcium blockers (C08); HbA1c was recoded as high risk if taking diabetic medications (A10); and HDL was recoded as high risk if the participant was taking lipid modifying agents (C10). These dichotomous variables were then summed to create an index of AL for each participant (range: 0–12), with higher scores reflecting higher AL burden.

2.3. Leukocyte telomere length

Leukocyte telomere length (LTL) was used to index stress at the cellular level. Genomic DNA was extracted directly from the blood samples taken during the health assessment by standard procedures, and stored long-term at 4 °C. To determine LTL, a monochrome multiplex quantitative PCR (MMQPCR) method was performed (Cawthon, 2009). LTL was calculated as the mean telomere to single copy gene (T/S) ratio and is an approximation of the average telomere length per cell. More details regarding LTL quantification procedure and analytical methods can be found in Supplementary Text S1. Participants with an LTL 4 standard deviations below or above the mean were first excluded. Plate ID was used to adjust for batch effect and entered as a random effect in a linear mixed effect model with log-transformed LTL as outcome. Residuals were re-scaled back to T/S ratio by adding the mean to each value and these re-scaled LTL residuals were used for analysis.

2.4. Perceived stress

Perceived stress over the previous month was recorded using the four-item version of the Perceived Stress Scale (PSS-4) (Cohen, 1994) as part of the SCQ. The PSS, originally developed as a 14-item questionnaire, is a measure of chronic stress associated with global stress perception. The PSS-4 includes four questions, answered from "Never" (0) to "Very Often" (4) on a 5-point Likert scale. A composite stress score was derived by summing the four question responses (range 0–16), with higher scores representing more stress. The scale has adequate internal consistency for a short four-item scale, with a Cronbach's alpha in the current sample of 0.66.

2.5. Cognitive function

Cognitive function was assessed during the CAPI at each wave using 10-word immediate recall (2 trials), 10-word delayed recall and semantic verbal fluency (animal naming). Details on the individual tests are published elsewhere (Cronin et al., 2013). Briefly, word recalls assess an individual's episodic/verbal memory. The respondent is presented a list of 10 words and is asked to recall them immediately after being heard (immediate recall) or after a time delay (delayed recall). Animal naming draws on word knowledge, semantic memory and executive processes such as set shifting and inhibition (or the ability to suppress inappropriate/ incorrect items). The respondent is asked to generate as many animals as possible within one minute. A composite score per participant and per wave was derived by combining individual test scores. Composite scores are increasingly used to track longitudinal change in individuals who are largely healthy at baseline, as they have advantages over use of screening instruments such as the Mini-Mental State Examination (MMSE) in precluding ceiling effects, and being able to detect more subtle, often pre-clinical changes (Soldan et al., 2016; Malek-Ahmadi et al., 2018). The scores were generated based on an equally unit-weighted approach using standardized scores (*z*-scores), with higher scores reflecting better cognitive function.

2.6. Covariates

Covariates included baseline age, sex, education (none/primary, secondary, or tertiary/higher), lifestyle factors, levels of depressive symptoms, pre-existing self-reported physician-diagnosed cardiovascular diseases and events (CVDEs), long-term diseases and chronic diseases. Smoker status was defined as never, past, or current. The Cut down, Annoyed, Guilty, and Eye-opener (CAGE) questionnaire (Mayfield et al., 1974) was used as the measure of problematic alcohol consumption and was represented as a binary variable. Physical activity was recorded through the International Physical Activity Questionnaire (IPAQ (Hagströmer et al., 2006); short-form) and classified as low, moderate or high. Symptoms of depression were assessed using the Centre for Epidemiological Studies Depression Scale (CESD (Radloff, 1977) and are represented as a continuous variable. CVDEs included history of angina, heart attack, congestive heart failure, stroke, transient ischemic attack, and atrial fibrillation. Self-reported long-term diseases corresponded to any health problem, illness, disability, or infirmity that has troubled the respondent for a long period. Self-reported chronic conditions included lung disease, asthma, arthritis, osteoporosis, cancer, Parkinson's disease, stomach ulcer, varicose ulcer, liver disease, thyroid disease, or kidney disease. Data were pooled to create 3 separate dichotomous CVDEs, long-term and chronic disease measures, for absence (disease-free) or presence ($\geq$1) of CVDEs, long-term diseases, and chronic conditions, respectively.

2.7. Statistical analyses

All statistical analyses were performed using R software version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria (R: A language and environment for statistical computing, 2020). Descriptive characteristics are reported for the study sample and then expressed separately according to AL, LTL and perceived stress tertiles. Continuous variables are described as unadjusted means with standard deviations (SD); categorical variables are given as percentages (%). Spearman correlations were used to assess the relationship between biological and perceived stress. Ordered logistic regressions were used to assess differences between tertiles of AL, LTL and perceived stress separately. To estimate selection bias, the observed sample was also compared to the excluded cohort using independent *t*-tests and chi-squared tests.

Linear mixed effect models were used to examine the effect of baseline biological stress (at the physiological and cellular level) and perceived stress on cognitive decline (wave 1 to wave 6). Fixed effects

included, in separate models first, biological stress (continuous variables) and wave with an interaction term; and perceived stress (continuous variable) and wave with an interaction term. Biological stress x wave and perceived stress x wave were then mutually adjusted in subsequent models to assess putative mediating effects. Finally, three-way interactions between biological, perceived stress and wave were tested to assess the additive effect of biological stress and perceived stress on cognitive decline. AL was used as proxy of biological (physiological) stress in the first set of models and re-scaled LTL residuals were used as proxy of biological (cellular) stress in the second set of models. Minimally adjusted models included age, sex and education as covariates. Fully adjusted models accounted for lifestyle factors, depressive symptoms and diseases. In all models, participants constituted the random intercept.

2.8. Supplementary analyses

Women and men differ in both their vulnerability/ reactivity to stressors (Lupien et al., 2018) and their risk of dementia due to Azheimer's disease, with underlying mechanisms likely multifactorial (Ferretti et al., 2018). For these reasons, to assess potential differences between men and women in the observed relationships, the analyses described above were repeated, stratified by sex.

3. Results

3.1. Study sample characteristics

Participant characteristics at baseline are presented in Table 1. Mean age was 61.6 (8.2), 53 % of the participants were women. Mean AL was 3.6 (*SD* = 2.4; range = [0–11]); mean LTL was 1.03 (*SD* = 0.65; range = [0.08–9.3]); and mean perceived stress was 3.9 (*SD* = 3.1; range = [0–15]). AL was not associated with perceived stress (Spearman's rho = 0.01, p =.55) nor was LTL (Spearman's rho = -0.01, p =.55). For information purposes, the sample characteristics per AL, LTL and perceived stress tertile are provided in Supplementary Tables S1–S3.

3.2. The independent and additive effects of AL and perceived stress on cognitive decline

In minimally adjusted models higher AL was not associated with cognitive function at baseline (β = −0.01; 95 %CI = −0.03, 0.02, p =.55). The interaction between AL and wave was, however, significant ($X^2_{(18)}$ = 64.4; p <.001), with AL associated with lower cognitive function at wave 3, 4, 5 and 6 (Fig. 1; Table 2, Panel A). There was a significant main effect of perceived stress on cognitive function, such that higher stress was associated with lower cognitive scores (β = −0.10; 95 %CI = −0.12; −0.07; p <.001; Table 2, Panel B). The interaction between perceived stress and wave was not significant however ($X^2_{(17)}$ = 1.9; p =.85; Fig. 2). The strength of these associations did not substantially change when AL and perceived stress were adjusted for each other (Table 2, Panel C). The three-way interaction of AL x perceived stress x wave was not significant ($X^2_{(30)}$ = 8.54; p =.13). Similar associations were observed in fully adjusted models (Supplementary Table S4).

Table 1
Characteristics of the study sample in comparison with the excluded cohort.

	Study sample (N = 3,458)	Excluded sample (N = 4,711)	*p*
Age (mean, sd)	61.6 (8.2)	65.5 (10.5)	**0.000**
Sex (female, %)	53.4	54.7	0.213
Education (low, %)	19.3	38.9	**0.000**
Smoking (current, %)	13.5	21.6	**0.000**
Prob alcohol (yes, %)	13.9	9.8	**0.000**
Physical activity (low, %)	26.5	35.9	**0.000**
Depressive symptoms (mean, sd)	4.2 (3.8)	5.3 (4.4)	**0.000**
CVDEs (>1, %)	12.5	16.6	**0.000**
Chronic diseases (>1, %)	75.8	78.7	**0.002**
Long-term diseases (>1, %)	35.8	40.3	**0.000**
Perceived stress (mean, sd)	3.9 (3.1)	4.5 (3.1)	**0.000**
Allostatic load (mean, sd)	3.6 (2.4)	_	_
Leukocyte telomere length	1.0 (0.6)	_	_

Note: CVDEs = cardiovascular diseases and events; chronic diseases include lung disease, asthma, arthritis, osteoporosis, cancer, Parkinson's disease, stomach ulcer, varicose ulcer, liver disease, thyroid disease, or kidney disease. Long-term diseases corresponded to any health problem, illness, disability, or infirmity that has troubled the respondent for a long period. *p* indicates significant differences between samples.

3.3. The independent and additive effects of LTL and perceived stress on cognitive decline

Models with LTL as measure of biological stress show a non-significant interaction between LTL and wave ($X^2_{(18)}$ = 9.4; p =.09). LTL was not associated with cognitive decline at baseline but interaction terms with wave revealed that higher LTL was weakly associated with better cognitive function at wave 4 (β = 0.04, p =.01) and wave 5 (β = 0.03, p =.05) relative to baseline, in minimally adjusted models (Table 3, Panel A), in models adjusted for perceived stress (Table 3, Panel B) and in fully adjusted models (Table 3, Panel C). The interaction of LTL x Perceived stress x wave was not significant ($X^2_{(32)}$ = 1.6; p =.89).

3.4. Supplementary analyses

Sex-stratified analyses showed similar associations in minimally adjusted models between allostatic load and cognitive decline from wave 4 to wave 6 among men (Supplementary Table S5, Panel A) and women (Supplementary Table S6, Panel A), and similar associations among men (Supplementary Table S5, Panel B) and women (Supplementary Table S6, Panel B) between perceived stress and cognitive function too. These associations were robust to mutual adjustment (Supplementary Table S5/S6, Panel C) and further adjustment for covariates (Supplementary Table S5/S6, Panel D). Longer LTL was associated with higher cognitive function at wave 4 – 6 in women only (Supplementary Table S7; results for men not shown).

4. Discussion

The current study examined the association of biological and psychological measures of stress with cognitive function over a subsequent 12-year period in a large population-based sample of older adults. Results showed that biological stress as assessed using AL and LTL was unrelated to cognition at baseline, but higher AL predicted lower cognitive function from wave 3 (or 4-year follow-up) onward. There was a very weak but marginally significant association between LTL and cognitive decline at waves 4 and 5 in the full sample, but with subsequent sex stratified analyses revealing a clear association in females and not males. Baseline perceived stress was inversely associated with cognitive function and the strength of this association did not vary across waves. Adjusting for AL or LTL did not attenuate the associations, suggesting that these indices of biological stress do not mediate the association between perceived stress and cognitive function (and vice versa). Similarly, there was no evidence for additive effects of biological and psychological stress on cognitive function and decline. Taken together, these results suggest that the measures of biological stress in our study, measures of multisystem physiological dysregulation and cellular aging, predict cognitive decline, but that these effects may only appear with a lag. In contrast, higher perceived stress was consistently related to lower cognitive function, but it did not predict a decline in cognitive function over the 12-year period.

These different associations with cognitive function over the 12-year

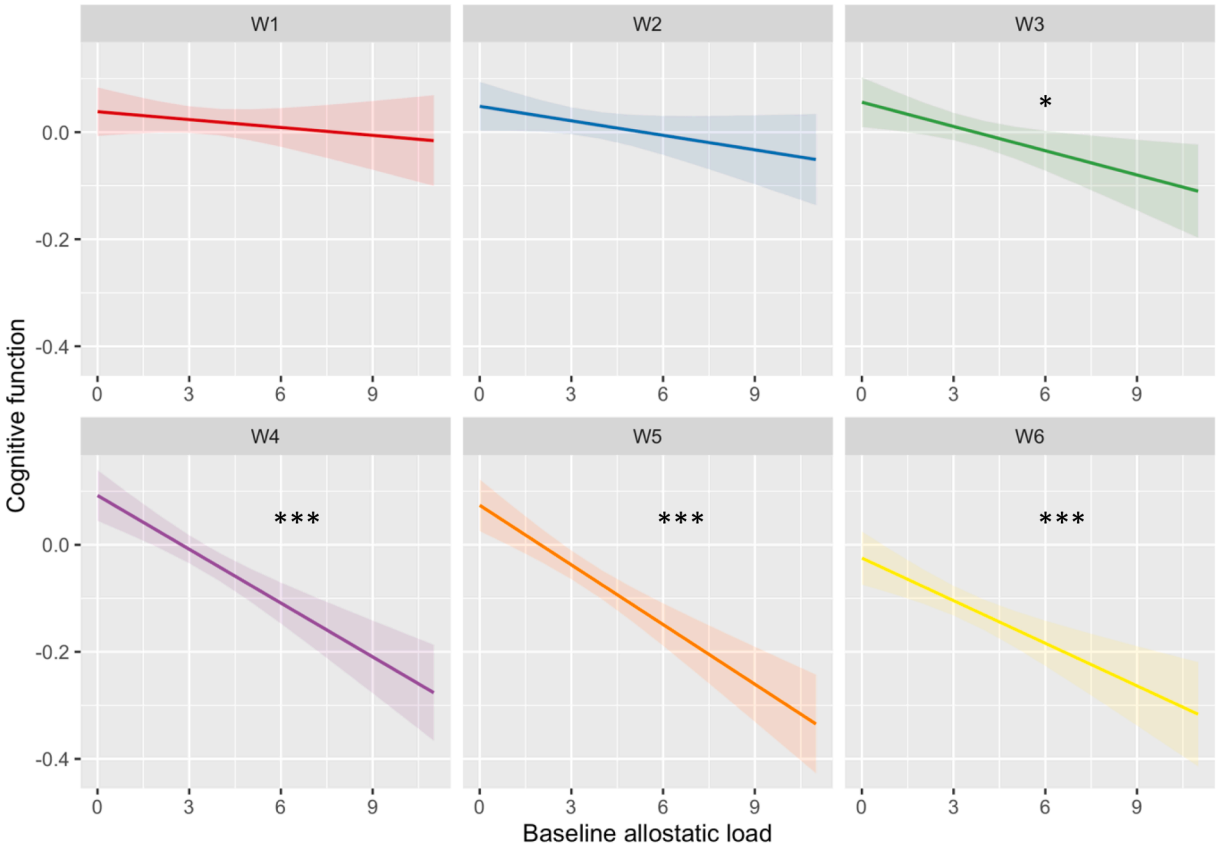

Fig. 1. The association between allostatic load and 12-year cognitive decline (wave 1 to wave 6), adjusted for age, sex and education (N = 3,458).

Table 2
Association of standardised allostatic load (**Panel A**) and perceived stress (**Panel B**) with 12-year cognitive decline (wave 1 to wave 6), adjusted for age, sex and education (minimally adjusted models). Mutual adjustments are given in **Panel C**.

	Panel A: Minimally adjusted model with allostatic load x wave as fixed effects			**Panel B: Minimally adjusted model with perceived stress x wave as fixed effects**			**Panel C: Mutually adjusted model with allostatic load and perceived stress x wave as fixed effects**		
	Estimates	*95 % CI*	*p*	*Estimates*	*95 % CI*	*p*	*Estimates*	*95 % CI*	*p*
Fixed effects									
Allostatic load	−0.01	−0.03; 0.02	0.551				−0.00	−0.03; 0.02	0.748
Perceived stress				−0.10 ***	−0.12; -0.07	<0.001	−0.09***	−0.12; −0.07	<0.001
Allostatic load x wave 2	−0.01	−0.03; 0.01	0.364				−0.01	−0.03; 0.01	0.414
Allostatic load x wave 3	−0.03 *	−0.05; −0.00	0.037				−0.03*	−0.05; −0.00	0.046
Allostatic load x wave 4	−0.07 ***	−0.09; −0.04	<0.001				−0.07***	−0.09; −0.04	<0.001
Allostatic load x wave 5	−0.08 ***	−0.10; −0.05	<0.001				−0.10***	−0.04; −0.05	<0.001
Allostatic load x wave 6	−0.06 ***	−0.08; −0.03	<0.001				−0.08***	−0.04; −0.03	<0.001
Perceived stress x wave 2				0.00	−0.02; 0.02	0.993	0.00	−0.02; 0.02	0.989
Perceived stress x wave 3				0.01	−0.01; 0.03	0.371	0.01	−0.01; 0.03	0.357
Perceived stress x wave 4				−0.00	−0.03; 0.02	0.882	−0.00	−0.03; 0.02	0.916
Perceived stress x wave 5				0.01	−0.02; 0.03	0.463	0.01	−0.02; 0.03	0.439
Perceived stress x wave 6				0.01	−0.02 – 0.03	0.531	0.01	−0.02; 0.03	0.512
Covariates									
Age	−0.03 ***	−0.03; −0.03	<0.001	−0.03 ***	−0.04; -0.03	<0.001	−0.03***	−0.04; −0.03	<0.001
Sex: female	0.16 ***	0.12; 0.20	<0.001	0.16 ***	0.13; 0.20	<0.001	0.16***	0.13; 0.20	<0.001
Education: secondary	0.26 ***	0.21; 0.31	<0.001	0.25 ***	0.20; 0.30	<0.001	0.24***	0.19; 0.30	<0.001
Education: tertiary	0.61 ***	0.56; 0.67	<0.001	0.59 ***	0.54; 0.65	<0.001	0.58***	0.53; 0.64	<0.001
Intercept	1.52 ***	1.35; 1.70	<0.001	1.71 ***	1.55; 1.88	<0.001	1.63***	1.45; 1.79	<0.001
N participants	3458			3458			3458		
Observations	17,981			17,981			17,981		
Marginal R^2 / Conditional R^2	0.227 / 0.647			0.234 / 0.644			0.238 / 0.646		

period in older adults may be attributable to different underlying mechanisms. Higher AL and shorter LTL may be related to cognitive decline via common associated processes such as inflammation and oxidative stress (Yaffe et al., 2011) - taking many years for cognitive deficits to manifest. Conversely, increased chronic perceived stress may relatively quickly result in a decrease in cognitive performance, as cognitive resources are disproportionately allocated towards emotion regulation and reducing distress, and away from concurrent cognitive tasks (Sliwinski et al., 2006). In support of this, there is evidence that older adults engage in maladaptive emotion regulation strategies such as

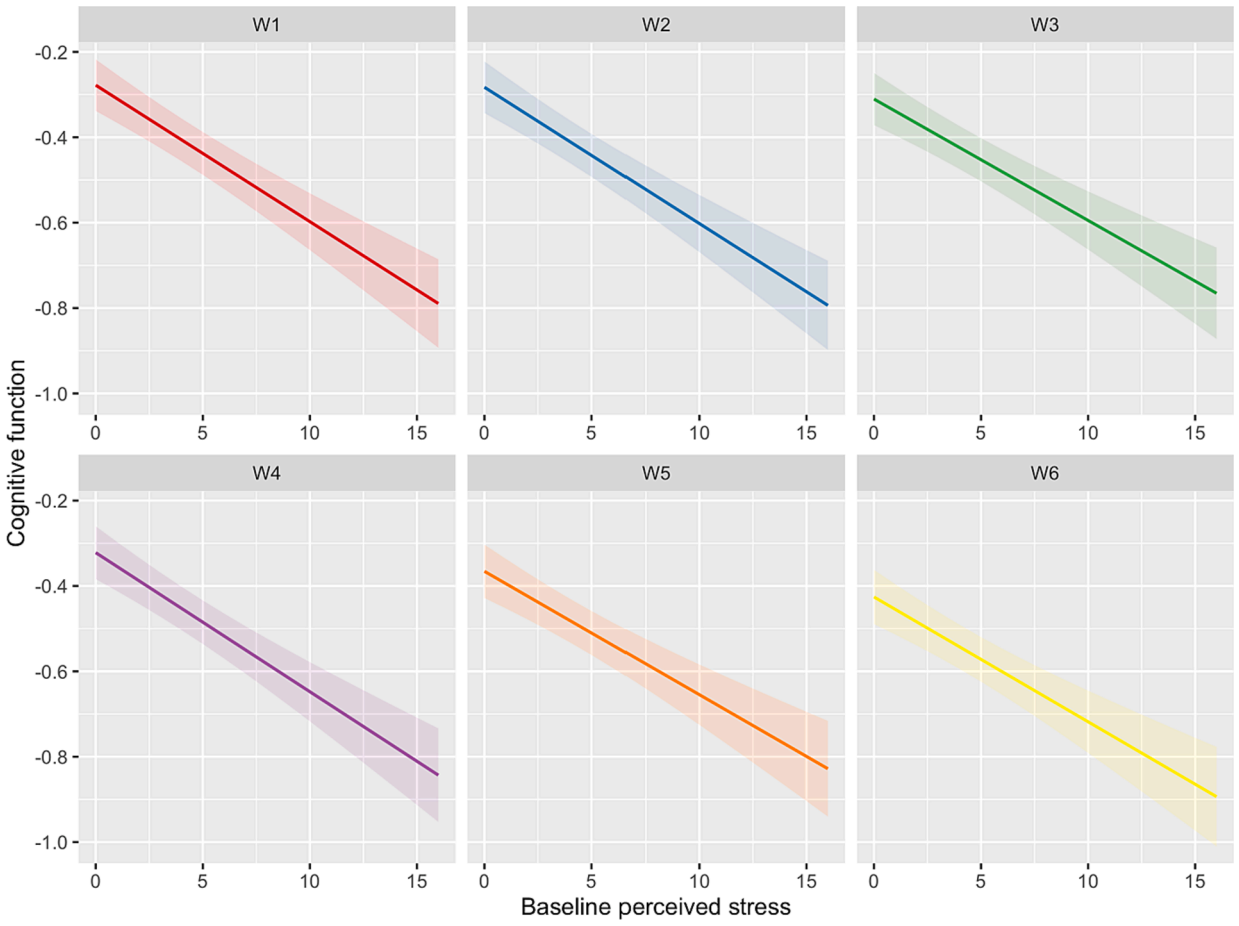

Fig. 2. The association between perceived stress and 12-year cognitive decline (wave 1 to wave 6), adjusted for age, sex and education (N = 3,458).

rumination in response to chronic stress to a greater extent than younger individuals (Sliwinski et al., 2021), while at the same time they also have decreasing neural resources to compensate for increased cognitive demands (Cabeza et al., 2018). Connectivity between the medial PFC and amygdala plays an important role in emotion processing and is related to stress responses (Thayer et al., 2021). Higher functional connectivity between these regions in older adults is associated with more positive mood, memories and normal cortisol profiles (Mather, 2016). Structural and functional changes in the PFC in older adults may therefore affect both stress/emotion regulation and general cognitive performance contemporaneously, whereas downstream, physiological sequelae of chronic stress may exert further slower-acting wear and tear on brain structure. Supporting evidence for this also comes from the literature showing rapid benefits to general cognitive performance of stress-reduction techniques such as mindfulness (Zeidan et al., 2010; Gard et al., 2014).

The results concerning perceived stress accord with other studies of older adults that have examined associations of a baseline measure of perceived stress with cognitive function and subsequent decline. Several previous studies found that baseline perceived stress was associated with prevalent cognitive impairment or lower cognitive scores but not with cognitive decline or incident cognitive impairment (Kulshreshtha et al., 2023; Chen et al., 2019); however, increasing perceived stress over time was associated with cognitive decline (Kulshreshtha et al., 2023; Johansson et al., 2010; Aggarwal et al., 2014). Previous research by our group also found that a 2-year increase in perceived stress was associated with a decline in cognitive performance over the same period (Feeney et al., 2018). An effect of perceived stress on cognitive decline may only manifest in older adults for whom stress is increasing over time. We did, however, investigate changes in perceived stress across the 6 waves of data and found it to be relatively stable across the waves. K means cluster analysis revealing high stable, moderate stable and low stable groups only. It is also possible that differences in trajectories of cognitive decline by baseline perceived stress would be evident with a longer term of follow-up than the 12-year period examined in our study (i.e. over two or more decades), as the strongest results concerning cognitive impairment and dementia have emerged from studies with follow-up over decades (Kulshreshtha et al., 2023; Johansson et al., 2010). Of course, reverse causation cannot be fully ruled out and the converse may also be true - that the individuals in our study with higher perceived stress levels may have already undergone stress associated declines in cognition. This possibility is consistent with a study by Christensen and colleagues which found that higher midlife perceived stress was associated with a faster decline in cognitive function from early- to mid-adulthood (Christensen et al., 2023).

The association between higher allostatic load and cognitive decline from 4 years onwards accords with the findings of D'Amico and colleagues, who noted that longitudinal associations between AL and cognition were more likely to be evident in studies with longer durations of follow-up (D'Amico et al., 2020), and suggests the possibility of slower acting effects of AL on the brain. The weak association between LTL and cognitive decline in the overall sample echoes findings of recent *meta*-analyses in similar older adult cohorts (Zhan et al., 2018); however, sex was not explored as a moderator of the association in these studies.

Sex differences in the association of stress biomarkers and subjective reports with mental health and cognitive function have previously been reported. Higher prevalence of depression and dementia among older females has previously been linked to differences in stress vulnerability and biology (Albert and Newhouse, 2019), though males may be more

Table 3
Association of standardised leukocyte telomere length (LTL) with 12-year cognitive decline (wave 1 to wave 6), adjusted for age, sex and education (minimally adjusted model: **Panel A**), further adjusted for perceived stress (mutually adjusted model: **Panel B**) and further adjusted for lifestyle factors, depressive symptoms and diseases (fully adjusted model: **Panel C**).

	Panel A: Minimally adjusted model with telomere length x wave as fixed effects			**Panel B: Mutually adjusted model with telomere length and perceived stress x wave as fixed effects**			**Panel C: Fully adjusted model with telomere length and perceived stress x wave as fixed effects**		
	Estimates	*95 % CI*	*p*	*Estimates*	*95 % CI*	*p*	*Estimates*	*95 % CI*	*p*
Fixed effects									
Telomere length	−0.01	−0.04; 0.01	0.304	−0.01	−0.04; 0.01	0.211	−0.01	−0.05; 0.01	0.211
Perceived stress				−0.09	−0.12; −0.07	<0.001	−0.08	−0.11; −0.06	<0.001
Telomere length x wave 2	0.01	−0.01; 0.04	0.320	0.01	−0.01; 0.04	0.320	0.01	−0.01; 0.04	0.298
Telomere length x wave 3	−0.00	−0.03; 0.03	0.998	0.00	−0.02; 0.02	0.988	0.00	−0.02; 0.02	0.951
Telomere length x wave 4	0.04	0.00; 0.06	0.017	0.04	0.00; 0.06	0.017	0.04	0.00; 0.06	0.017
Telomere length x wave 5	0.03	−0.00; 0.06	0.056	0.03	−0.00; 0.06	0.056	0.03	−0.00; 0.06	0.053
Telomere length x wave 6	0.02	−0.01; 0.05	0.181	0.02	−0.01; 0.05	0.178	0.02	−0.01; 0.05	0.176
Perceived stress x wave 2				0.00	−0.02; 0.02	0.979	0.00	−0.02; 0.02	0.978
Perceived stress x wave 3				0.01	−0.01; 0.03	0.370	0.01	−0.01; 0.03	0.367
Perceived stress x wave 4				−0.00	−0.03; 0.02	0.920	0.00	−0.02; 0.02	0.999
Perceived stress x wave 5				0.01	−0.01; 0.04	0.436	0.01	−0.01; 0.04	0.399
Perceived stress x wave 6				0.00	−0.02; 0.04	0.512	0.00	−0.02; 0.04	0.471
Covariates									
Age	−0.03	−0.04; −0.03	<0.001	−0.03	−0.04; −0.03	<0.001	−0.03	−0.04; −0.03	<0.001
Sex: female	0.16	0.12; 0.19	<0.001	0.16	0.12; 0.20	<0.001	0.18	0.14; 0.22	<0.001
Education: secondary	0.26	0.21; 0.32	<0.001	0.25	0.19; 0.30	<0.001	0.24	0.18; 0.29	<0.001
Education: tertiary	0.62	0.57; 0.68	<0.001	0.59	0.53; 0.64	<0.001	0.57	0.52; 0.63	<0.001
Smoking: past							0.00	−0.04; 0.05	0.839
Smoking: current							−0.06	−0.12; 0.00	0.036
Problematic alcohol: yes							0.09	0.03; 0.14	0.002
Physical activity: mid							0.04	−0.00; 0.09	0.070
Physical activity: high							0.05	−0.00; 0.09	0.056
Depressive symptoms							−0.01	−0.01; −0.00	0.009
CVDEs							−0.04	−0.10; 0.01	0.140
Chronic conditions							−0.04	−0.08; 0.01	0.130
Long-term diseases							−0.00	−0.04; 0.04	0.892
Intercept	1.62	1.45; 1.78	<0.001	1.84	1.67; 2.01	<0.001	1.67	1.49; 1.84	<0.001
N participants	3458			3458			3458		
Observations	17,981			17,981			17,981		
Marginal R^2 / Conditional R^2	0.234 / 0.646			0.237 / 0.644			0.240 / 0.646		

susceptible to adverse effects in early life (Hodes and Epperson, 2019). We found no evidence of different associations of stress markers with cognitive decline by sex when the predictors of interest were AL and perceived stress, suggesting that the results with respect to these indices generalise to both males and females. In the case of LTL length, however, sex stratified analyses revealed an association between shorter telomeres and cognitive decline in females only. This finding is consistent with a recent systematic review and *meta*-analysis of telomere length and brain ageing which found that the association between LTL and measures of brain ageing and cognitive function was stronger for females compared with males (Gampawar et al., 2022). In addition, LTL may have effects on brain development which result in higher brain and cognitive reserve (Gampawar et al., 2022) – preserving cognitive function in older adults with longer telomeres for longer in the face of age-related and neuropathological brain changes. As accelerated telomere attrition is known to take place during development as well as later life, early life environmental factors together with genetics will undoubtedly influence LTL in late-life also (Gampawar et al., 2022).

Our study has a number of key strengths. The unique, interdisciplinary nature of the research - operating at the interface between cognitive epidemiology, stress physiology, and cellular biology - allowed us to simultaneously test the relationship of stress operationalised at different levels of resolution with cognitive decline, in a large, population-based sample of older adults. Additional strengths include the follow-up period of 12 years with 6 repeated cognitive assessments and adjustment for multiple confounders, including demographics, health behaviours and chronic diseases. We must also acknowledge some limitations. Firstly, despite multiple adjustment, we cannot exclude the possibility of residual confounding by other factors not controlled for in this study like familial factors (e.g. APoE). Secondly, we examined two indicators of biological stress, indexing multi-system physiological dysregulation and accelerated cellular ageing. It may the case that other possible indices of biological stress are more (or less) closely related to cognitive decline and perceived stress. However, in the case of the AL index, it captures measures from several different stress sensitive systems. Thirdly, our measure of cognitive function was based on three tests only (two measuring verbal memory and one assessing verbal fluency/ executive function) which may not fully reflect an individual's cognitive function. These tests were chosen over other tests in TILDA to allow for longer follow-up, however the addition of other tests in the future is warranted. Fourthly, instrument to assess perceived stress was the 4-item version of the Perceived Stress Scale. This was included in TILDA over longer versions because of its brevity, with a view to ensuring a good response rate: however, it is likely that the 14- or 10-item version of the Perceived Stress scale may exhibit superior psychometric properties (though this is currently untested in an older adult population to the best of our knowledge). Finally, our analytic sample differed from those individuals with missing data on a number of key characteristics which limits the strength of conclusions with respect to the older adult population in general. It is a possibility that selective attrition may have resulted in loss to follow-up of the individuals with high baseline perceived stress and pronounced decline in cognition over time, leading to an absence of apparent association with cognitive decline. Nonetheless, mixed effects models allow for the inclusion of all data from individuals who are subsequently lost from the study up until their point of exit, which reduces the likely bias somewhat.

5. Conclusion

Perceived stress and indicators of biological stress were independently and differently associated with cognitive function and decline over 12 years in older adults from a population representative study, albeit with small effect sizes. These findings emphasise that different types of 'stress' measures are not interchangeable when investigating effects on cognition in later life, and suggest potential separable processes underlying observed associations.

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Author contributions

C.D.L. and J.F conceived, designed and performed the analyses and drafted the article; C.M.C. helped shape the research and assisted with data measurement; A.OH. assisted with blood biomarkers; All authors provided feedback on the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2023.10.017.

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