Allostatic load and pain severity in older adults

DOI:
10.1016/j.exger.2016.12.013

Document Version
Accepted author manuscript

Allostatic load and pain severity in older adults: Results from the English Longitudinal Study of Ageing

Kimberly T. Sibille, PhD[a]; John McBeth, PhD[b]; Diane Smith, PhD[c]; Ross Wilkie, PhD[c]

[a] Assistant Professor, Department of Aging and Geriatric Research, College of Medicine, University of Florida, USA

[b] Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and Repair, Faculty of Medical and Human Sciences, Manchester Academic Health Sciences Centre, The University of Manchester

[c] Arthritis Research UK Primary Care Centre, Research Institute for Primary Care and Health Sciences, Keele University, Staffordshire, United Kingdom

Corresponding Author:
Kimberly Sibille, Ph.D.
Department of Aging and Geriatric Research, College of Medicine
University of Florida
P.O. Box 112610, Gainesville, FL 32610-3628
Phone: 352-294-5846, Fax: 352-273-5920
ksibille@ufl.edu

Conflicts of Interest: Kimberly Sibille, John McBeth, Diane Smith, and Ross Wilke have no conflicts of interest to declare.

Abstract

Pain is common in older adults, is frequently experienced as stressful, and is associated with increased morbidity and mortality. Stress regulatory systems are adaptive to challenge and change, allostasis, until demands exceed the adaptive capacity contributing to dysregulation, resulting in a high allostatic load. A high allostatic load is associated with increased risk of morbidity and mortality. Pain severity, based on the average intensity of frequent pain, was hypothesized to be positively associated with AL. Four formulations of AL were investigated. Cross-sectional data from Wave 4 (2008-2009) of the English Longitudinal Study of Aging (ELSA) were analysed. Covariates in the model included age, sex, education, smoking status, alcohol consumption, activity level, depression and common comorbid health conditions. A total of 5341 individuals were included; mean age 65.3(±9.2) years, 55% female, 62.4% infrequent or no pain, 12.6% mild pain, 19.1% moderate pain, and 5.9% severe pain. Severe pain was associated with greater AL defined by all four formulations. The amount of variance explained by pain severity and the covariates was highest when allostatic load was defined by the high risk quartile (12.9%) and by the clinical value (11.7%). Findings indicate a positive relationship between pain severity and AL. Further investigation is needed to determine if there is a specific AL signature for pain that differs from other health conditions.

Key words: pain severity, stress, allostatic load, older adults, health behaviors

Introduction

Up to 80% of adults aged 65 years and over report daily musculoskeletal pain [58,60] and 21-43% report pain at two or more sites [19]. Ninety percent of all pain complaints in older people relate to the musculoskeletal system [60], and chronic musculoskeletal pain accounts for more than 12% of all consultations to primary care in people aged ≥ 50 years [17]. With the aging of the population and increased incidence of pain in older adults, identifying a measure that can reflect the physiological toll of pain could be beneficial for clinical research and patient care.

Allostasis is theoretical construct of the relationship between stress and physiological functioning. The body is designed to be adaptive to challenge and change. The cumulative experience of life including genetics, emotional and behavioral functioning, and life events can contribute toward a physiological toll or "wear and tear" known as allostatic load [37]. When stress related systems: immune, metabolic, cardiovascular and neuroendocrine are persistently or extensively challenged without adequate recovery patterns of dysregulation become evident, indicating high allostatic load. It is important to note that extreme dysregulation in one system is not as likely to occur as subtle dysregulation across multiple systems, which is most predictive of negative health outcomes [22,51]. Allostatic load (AL) is evaluated by a composite measure that is empirically-supported, and is associated with and predictive of functional decline, disease, and death [18,21,49,52].

Pain is stressful. It is often perceived as aversive and threatening. As such it activates the stress response systems, and may contribute to an increased AL [6,23,47]. Consistent with the AL model, pain portends increased morbidity and mortality [2,9,29,33,61,62]. Altered immune, endocrine, and cardiovascular functioning has been demonstrated in individuals with persistent pain [15,27,43,46]. Psychosocial stress not only influences stress-system functioning, it is associated with increased risk for developing chronic pain [25,28,39] and exacerbating existing chronic pain conditions [26,43]. Aging is not only associated with increased experiences of chronic pain but also increased stress systems dysregulation [8,13,53]. Little is known about the consequences of pain on physiological functioning. A

significant and beneficial next step for research and patient care would be to understand and to measure the cumulative physiological toll of pain and aging on overall system functioning.

The relevance of measures of pain frequency, intensity, and duration on biological functioning is evident [3;13;24;29;30]. For example, dysregulated acute stress responses were demonstrated in individuals with *chronic pain* compared to those individuals with *episodic pain* [27]. Similarly, larger bilateral hippocampal volume and greater functional connectivity were found in individuals with *low frequency* chronic migraines compared to individuals with *high frequency* chronic migraines and healthy controls [30]. Consistent with the AL conceptualization, the experience of low frequency or episodic pain may facilitate an adaptive response and the experience of high frequency or persistent pain may promote physiological dysregulation and brain-related functional decline [37]. Nahin reported on pain prevalence and severity in a population-based study in the United States [38]. Based on a) pain persistence in the past three months and b) bothersomeness (little to a lot), one pain free and four pain severity categories
(1-low to 4-high) were identified. Approximately 39.8 million individuals reported a level 3 or 4 pain which was associated with worse health status and more disability compared to individuals with a level 1 or 2 of pain. As such it seems highly likely that the biological consequences of pain would differ across the groups. Although an initial investigation on the relationship between general definitions of pain and AL in a population based study reported supportive findings [57], further research evaluating the relationship between pain severity and AL is an important next step.

Another important consideration is that AL has been measured by a number of formulations with minimal differences found in predictive utility [18,51,53]. An AL sum score comprised of biological measures in the high risk quartile is the most frequently used measure. Other formulations include a standardized z-score, a lowest/highest 10%, and an index based on clinical ranges [18,53]. The formulation providing the greatest explanatory power and most associated with pain severity is unknown.

The purpose of our study was to: 1) investigate the relationship between pain severity and AL, and 2) evaluate four formulations of AL and associated biomarkers and identify which explains the greatest variance in the association with pain severity. We hypothesized that a positive relationship between pain severity and AL would be demonstrated.

Materials and Methods

The English Longitudinal Study of Ageing (ELSA) is a nationally representative panel study of adults aged 50 years and over in England. The ELSA sample was drawn from households who participated in the Health Survey for England. Data on biomarkers was collected at Wave 4 (2008-2009) and was used in this cross-sectional study. Although there were 10,336 participants who completed an interview in Wave 4, the analysis included only those with complete data on AL (i.e. collected during the nurse visit, n=5341). Compared to those subjects without complete AL data, those with complete AL data had obtained higher level of qualifications ($p<0.001$), were more likely to be a non-smoker ($p<0.001$), consume alcohol less frequently ($p<0.001$), were more active in vigorous ($p>0.001$), moderate ($p<0.001$) and mild activities ($p<0.001$) and less likely to be depressed ($p<0.001$) There was no difference for age ($p=0.16$) or sex ($p=0.58$). More detail on sampling and response rates for ELSA are provided elsewhere (Banks et al., 2010). All participants provided informed consent separately for the interview and nurse's visit. Data were accessed through the Economic and Social Data Service. Ethical approval for the ELSA study was obtained from the London Multicentre Research and Ethics Committee.

Allostatic load

Data on biomarkers were obtained during the nurse visit. Twelve biomarkers reflecting four systems (cardiovascular, immune, neuroendocrine, and metabolic) within the AL conceptualization were selected from the parent study and used to create an index of AL for this investigation [18,36]. Cardiovascular measures included systolic blood pressure, diastolic blood pressure, mean arterial pressure [54], and resting pulse rate. Immune measures included fibrinogen and C-reactive protein (CRP). Metabolic measures included high density lipoprotein (HDL), low density lipoprotein (LDL), glycosylated haemoglobin

(HBA1C), insulin-like growth factor-1 (IGF-1), and waist hip ratio (WHR). The neuroendocrine system was represented by Dehydroepiandrosterone (DHEAS),

To measure blood pressure, during the nurse visit, participants were seated and three readings of blood pressure were taken at one-minute intervals in the right arm using the OMRON HEM 907 blood pressure monitor. Participants were asked not to smoke, consume alcohol, or exercise at least 30 minutes prior to taking the blood pressure reading and room temperature was adjusted to between 15°C and 25 °C. The mean of the last two readings for systolic and diastolic blood pressure were used for analysis and to calculate mean arterial pressure. Resting pulse was also obtained using the OMRON HEM 907 blood pressure monitor. Waist hip ratio was measured from measurement of waist and hip circumference using a tape measure.

All other biomarkers were obtained from a blood sample. Participants who had a clotting or bleeding disorder and those on anti-coagulant medication were not asked to provide blood samples. Unless participants were older than 80 years, had diabetes, reported ever having had a seizure, were frail or seemed unwell, the nurse collected fasting blood samples, which were defined as not eating or drinking at least 5 h prior to the blood test. CRP was measured using the N Latex CRP mono immunoassay on the Behring Nephelometer II analyzer. Fibrinogen was analysed using a modification of the Clauss thrombin clotting method on the Organon Teknika MDA 180 analyzer. Hemoglobin levels were measured with two Abbott Diagnostics Cell-Dyn 4000 analysers. DHEAS measures were performed on the DPC Immulite 2000 analyser. IGF-1 measures were analysed using IDS-iSYS immunoassay analyser. The assay represents a new generation of assay which is calibrated to the new WHO international standard for insulin-like Growth Factor-I, NIBSC code: 02/254. The assay also conforms to the 2011 consensus statement on GH and IGF-I assays. Total cholesterol was analyzed using the cholesterol oxidase assay method and HDL cholesterol was analyzed using a direct method (no precipitation) on an Olympus 640 analyzer [7]. Calculation of LDL using the Friedewald formula was performed and incorporates the measured total cholesterol value as follows: LDL = Total Cholesterol - HDL Cholesterol - Triglycerides / 2.2. All blood samples were analyzed at the Royal Victoria Infirmary laboratory in Newcastle upon Tyne, UK (see [7] for a detailed description of blood analyses).

For this analysis four AL indices were created based on different methods for defining high risk for each biomarker. Table 2 provides a description for each formulation. Individuals with missing values for any biomarker were excluded from the analysis. Data on pain and putative confounders was collected using a standardised interview protocol.

Pain severity

Similar to the pain severity coding system implemented by Nahin [38], pain severity was characterized in this study based on two questionnaire items: frequency of pain and intensity of pain. If individuals responded "yes" to "*are you often troubled with pain*?" they were then queried to rate "*the intensity of their pain for most of the time*" as mild, moderate, or severe. As such there were four categories in the current study determined by frequency of pain: no pain or infrequent pain, mild pain, moderate pain, and severe pain.

Putative confounders

Age, sex, education, smoking status, frequency of alcohol consumption, activity levels, depression and health conditions common in older adults: cardiovascular disease, respiratory conditions, cancer, diabetes and arthritis were considered as putative confounders. Single items were used to measure all confounders other than depression. For educational attainment, participants were asked to specify their highest educational level and these were categorised as 1) a degree or equivalent; 2) higher education without a degree, National Vocational Qualification (NVQ) A level equivalent; 3) General Certificate of Secondary Education (GCSE); and 4) <GCSE, or 5) no qualification [3]. Past or present smoker status was determined by asking participants to indicate whether they 1) never smoked, 2) previously smoked or 3) currently smoke. Alcohol consumption was determined with a question about the frequency of alcohol consumption over the last 12 months. Responses were categorised as 1) 'not at all'(referent), 2) 'once or twice a year', 3) once every two months', 4) once or twice per week', 5) three or four days a week', 6) 'five or six days a week,' or 7) 'every day'. Frequency of vigorous physical activity was measured as 1) vigorous - more than twice a week (referent), 2) moderate - once or twice a week, and 3) mild - one to three times a month or hardly ever, were measured using single items.

Depression was measured using the eight item version of the Centre for Epidemiological Studies Depression (CES-D) scale [48]. Participants were asked to respond yes/no to eight questions regarding depressive symptoms experienced in the week prior to their ELSA interview. Responses were summed to give a score between 0 and 8 with a higher score indicating elevated depressive symptoms. Common health conditions in older adults (i.e. cardiovascular conditions, respiratory conditions, cancer, arthritis and diabetes) that may influence the relationship between pain severity and AL measures were assessed using single items that captured self-reported doctor-diagnosis (i.e. Has your doctor ever told you that you have had...).

Analysis

First, the distribution of each putative confounder was examined by pain status with differences tested for significance using Chi-square or Kruskal Wallis tests where appropriate. Mean AL index scores, for all 4 definitions were calculated overall and by pain severity.

The distribution of the AL scores had minimal skewness and kurtosis (high and lowest 25% skewness 0.44, kurtosis 2.66; 10^{th}/90^{th} percentile skewness 0.58, kurtosis 3.16; clinical values skewness 0.43, kurtosis 3.74; z-score skewness 0.63 kurtosis 3.44). To examine the association between pain severity and each of the four AL index scores linear regression was used. Initially, the association between pain severity and each AL formulation was adjusted for age, sex and educational attainment (Table 3: Model 1) and then cumulatively for all other confounders (i.e. age, sex, educational attainment, smoking status, frequency of alcohol consumption, frequency of mild, moderate and vigorous activity, depression, CVD, respiratory disease, cancer, diabetes and arthritis; Table 3: Model 2). Results for the allostatic load defined by high risk quartile, lowest/highest 10% and clinical values were expressed as unstandardized beta coefficients (B) with 95% confidence intervals. Results for the summary of allostatic load z-scores were expressed as standardized beta coefficients (β) with 95% confidence intervals.

Additionally, logistic regression was used to examine the association between pain severity and high risk of allostatic load for each of the 12 biomarkers defined by high risk quartile, lowest/highest 10% and clinical values, adjusting for age, sex, education, CVD, respiratory disease, cancer, diabetes and arthritis. Results are expressed as adjusted odds ratios with 95% confidence intervals. Linear regression was used to examine the association between pain severity and the summary of z-scores for allostatic load biomarkers adjusting for the same confounders in the logistic regression. Stata version 13 was used for all analyses. For all analyses the "infrequent/no pain" group was classified as the referent category. R squared was used to estimate the % of total variation within each model of AL that was explained by pain and the confounders.

Results

Subject characteristics

The mean age among the 5341 participants was 65.3 (SD 9.2) years, 55.0% were women and 25% had no formal qualifications (Table 2). A total of 3331 (62.4%) subjects had infrequent or no pain, 675 (12.6%) had mild pain, 1019 (19.1%) had moderate pain and 316 (5.9%) had severe pain. For moderate and severe pain, prevalence was higher in women ($p<0.001$). There was no relationship between pain severity and age.

The mean and standard deviation for the four allostatic load index scores are as follows: high risk quartile [3.2(2.0)], lowest/highest 10% [3.3(1.6)], clinical value [2.8(1.4)], and z-scores [0.1(4.4)]. The mean allostatic index score increased with increasing pain severity for all definitions (Table 1).

Association between pain severity and allostatic load index scores

After adjusting for age, sex and education, severe pain was associated with each of the four allostatic index scores (Table 3; Model 1). Mild pain was associated with allostatic load defined by the lowest/highest 10% (0.10; 0.01, 0.18). Moderate pain was associated with allostatic index score defined by the high risk quartile (unstandardized beta coefficient 0.15; 95% confidence interval 0.08, 0.22) and clinical values (0.17; 0.07, 0.27) but not the lowest/highest 10% (0.07; -0.00, 0.14) or the summarised z-score (standardised beta

coefficient 0.19; 95% confidence interval -0.12, 0.50). The association between severe pain and each of the four allostatic load scores attenuated with adjustment for all confounders but remained significant (Table 3, Model 2). The associations for mild and moderate pain attenuated with the additional confounders to non-significance for all four definitions of allostatic load (Table 3, Model 2).

The relationship between covariates and increasing allostatic load differed by AL formulation (Model 2, supplemental data). Age was associated with increasing allostatic load score defined by high risk quartile and the summary of z-scores. Male sex was associated with increasing allostatic load score defined by high risk quartile, lowest/highest 10% and clinical values. Depression was only associated with increasing allostatic load defined by clinical values. Diabetes was associated with higher allostatic load index scores for all four formulations and cardiovascular disease was associated with three formulations. Arthritis and cancer were not associated with any formulation of allostatic load.

Extent of variance of allostatic load explained by pain severity and covariates

The amount of variance explained by pain and the covariates was highest when allostatic load was defined by the high risk quartile (12.9%) and by the clinical value (11.7%), Supplemental Data. The amount of variance explained by pain and covariates when allostatic load was defined by the lowest/highest 10% and z-score were <5%.

Association between pain severity and individual biomarkers

Additional analyses were completed to determine the association between pain severity and individual biomarkers. Adjusting for age, sex, education, and comorbid conditions, seven biomarkers were significantly associated with pain severity when high risk was defined by the high risk quartile (fibrinogen, HDL, CRP, HBA1c, DHEAS, IGF-1 and WHR), five when defined by clinical values (fibrinogen, HDL, CRP, HBA1c, and WHR), seven when high risk was defined by the lowest/highest 10% (resting pulse, fibrinogen, HDL, LDL, CRP, DHEAS, and IGF-1) and seven when defined by a z score (fibrinogen, HDL, LDL, CRP, HBA1c, DHEAS, WHR) (Table 4). Systolic blood pressure, diastolic blood pressure, and mean arterial pulse were not associated with pain severity.

Discussion

In line with the proposed hypotheses, two novel and important findings were generated from this study. First, consistent with the AL model, there was a positive relationship between pain severity and AL regardless of the formulation. Second, of the four formulations, the extent of variance explained by pain severity and covariates was greater with the high risk quartile and clinical values index than when defined by lowest/highest 10% and z score formulations. Our findings indicate that an AL composite may be able to capture the physiological toll of pain and associated biological, behavioral, and psychosocial factors on overall system functioning.

Pain Severity and AL

Goertzel and colleagues reported a positive relationship between AL and pain intensity and frequency in adults with chronic fatigue syndrome [12]. In 2012, Slade and colleagues expanded on these findings demonstrating an association between AL and pain across three different categories in a population based study: severe headaches/migraines within three months, pain more than 24 hours within the previous month, and widespread bodily pain was reported [57]. Importantly, neurobiological findings emphasize the importance of considering frequency, intensity, and duration in the interpretation of biological changes in response to pain experiences. Nahin's work further endorses these implications [38]. Pain severity was measured in community dwelling adults and based on two criteria: persistence (or frequency of pain) and the "bothersomeness" of pain. Adults with greater pain severity reported greater disability, worse health status, and more health care usage compared to those with less pain severity [38]. We extend previous findings by applying a similar definition of pain severity in a large population-based study of older adults and demonstrate that adults with greater pain severity also show a greater biological burden as indicated by a greater allostatic load.
As such, our findings align with pain-related neurobiological changes reported [5,30,31] and extend previous findings by demonstrating the importance of considering pain severity, specifically frequency and intensity, when evaluating the biological interface of pain and associated biological, behavioural, and psychosocial stressors.

Age is associated with an increasing AL resulting from decreasing physiological reserves [8,53]. The clinical ranges applied in the development of the clinical value index varied by age, thus, age differences were addressed within the formulation. An increase in AL with age was demonstrated in the high risk quartile and the z score formulation but not the highest/lowest 10% index formulations. Sex differences in pain [11] and biological measures [64] were indicated in our findings. Women had a greater prevalence of pain across moderate and severe categories and demonstrated a lower AL on three of four formulations.

Mood disturbances are frequently associated with chronic pain. In this study, symptoms of depression over the past week were measured, associations with AL were limited to the clinical value formulation. Findings are not surprising; a short-term measure of depressive symptoms would not be expected to be associated with physiological dysregulation. Symptoms of depression over the previous week would not differentiate acute transient symptoms of depression from those meeting a threshold of Major Depressive Disorder, if recurrent, may be of the intensity, persistence, and duration that could contribute to maladaptive biological changes.

Pain can be a consequence of and contribute to other morbidities. The inclusion of comorbid conditions in the fully adjusted model resulted in an attenuation of some AL associations and strengthening of others. A diagnosis of cardiovascular disease and/or diabetes was positively associated with AL while cancer and/or arthritis were not. The resulting pattern may be related to the biomarkers included in the AL composite. However, there is significant variability in the stage of the health condition and associated contributions to biological functioning. Importantly, the AL formulations appear to be sensitive to the pain severity that extends through these various comorbid conditions, consistent with other recent findings [56]. Additionally, as noted in the methods, some blood samples were collected from non-fasting participants. We explored the possible influences of non-fasting samples, adjusting all analyses for fasting. There were no differences in the associations between pain severity and AL and pain severity and individual biomarkers. Further, excluding non-fasting participants from the analyses resulted in minimal changes. Thus, even after

controlling for conditions that can contribute to biological measure variance, the evidence remains that pain severity is associated with all formulations of AL.

AL formulations

The merits and limitations of different AL formulations have been investigated and reviewed [18]. Regardless of the formulation, a multisystem approach has demonstrated better predictive utility compared to formulations with fewer systems represented [20,51,52]. In this study, the high risk quartile index was the strongest model with the clinical value index a close second. The associations between these formulations and age and sex were in the anticipated direction, providing further evidence of construct validity. Based on sample distribution, the high risk quartile is useful with large population-based studies [57], however, clinical application and utility in smaller studies is limited. Similar in the extent of variation in AL score explained, the clinical value index is based on population norms and reported ranges. Thus, the index is generalizable, accommodates age and sex differences, and can be implemented clinically. Two formulations were lower in the extent of variance explained: the lowest/highest 10% index and the z score formulation. The lowest/highest 10% index might be more applicable if specific clinical ranges were used for the values rather than a 10% cut-off of the highest and lowest sample values. In regard to the z score formulation, the overall value is difficult to interpret, did not outperform other formulations, and would be difficult to implement clinically.

Individual biomarkers

Questions have been raised as to whether the AL index should be comprised of a standard set of biomarkers by system (immune, cardiovascular, neuroendocrine, metabolic) or whether the biomarkers incorporated in an index should vary by condition [4,55]. Determining which biological measures are associated with pain severity is important, investigations specific to pain and AL and the biological measures which best capture that relationship are minimal [55,57].

The study included a comprehensive array of biomarkers from multiple systems [18,36]. Six biomarkers were repeatedly indicated as associated with pain severity in the fully

adjusted models. Fibrinogen, CRP, and HDL were significant in all four formulations and three additional biomarkers were associated with pain severity in three of the four formulations: HbA1c, DHEAS, and WHR. DHEAS is an androgen with numerous benefits to include functioning as a HPA-axis antagonist, suppressing inflammatory cytokines, promoting lean muscle mass, among others [18]. Fibrinogen is a biomarker not typically referenced in pain research, it is a measure of inflammation and frequently identified as an indicator of cardiovascular disease risk. CRP is also a measure of inflammation and is associated with cardiovascular disease risk and cancer but unlike fibrinogen, CRP has been investigated in pain research and is associated with experimental pain, chronic pain, and functional disability [1,14,59]. Findings regarding HBA1c are interesting, even after controlling for diabetes, the associations with pain severity remained strong. HDL is a measure reflective of metabolic functioning. High levels of HDL are protective. Thus, low levels are identified as a risk factor. WHR is a measure of adipose fat distribution, frequently conceptualized as a metabolic measure, high levels of WHR contribute to AL.

Interestingly, Slade and colleagues (2012) reported CRP, triglycerides, and BMI were strongly associated with pain across three categories and HBA1c, serum albumin and urinary creatinine with two. In a study of symptoms of chronic fatigue syndrome and allostatic load, CRP was the best predictor of bodily pain, based on the Medical Outcome Study 36-item Short Form Health Survey [12]. Noteworthy, the cardiovascular measures (systolic blood pressure, diastolic blood pressure, resting pulse, and mean arterial pulse), were not associated with pain severity. Olsen and colleagues reported that cardiovascular stress responsiveness was minimally associated with chronic pain in a large population-based study [44]. The inclusion of cardiovascular measures in future allostatic load and pain studies requires further investigation. Although mean arterial pressure is highly correlated with systolic and diastolic blood pressure, there was some evidence of predictive utility [54] and it has been included in pain-related studies [44]. The findings do not support the inclusion of mean atrial pressures in future allostatic load formulations. Importantly, results are encouraging and highlight biomarkers to consider in future investigations.

Strengths, Limitations, and Future Directions

There are a number of strengths in the study design. ELSA is a large and well-characterized sample of older adults living in England. Established study protocols ensure high quality data is available. In this analysis we have adjusted the relationship between pain and AL for relevant putative confounders at each stage. Consistent with prior studies, age, sex, and education were included in the adjusted model as well as adaptive and maladaptive behaviours such as smoking, alcohol use, and physical activity. We also considered confounding by comorbid conditions: cardiovascular and respiratory diseases, cancer, arthritis, and diabetes on the biomarkers included in the formulations. By doing so, we also control for medications associated with the treatment of those conditions [20].

There are also limitations for consideration. First, our analysis was limited to those individuals with complete allostatic load data. Second, the AL index is a measure to capture signs of physiological dysregulation due to challenges exceeding adaptive capacity over time. As such, quantifying the burden of a challenge is essential. The pain groups are not differentiated by duration or extent of pain. Additional measures (e.g. extent, duration) to characterize pain experiences may help differentiate level of stress-system burden. Third, pain severity and the covariates explained the greatest variance in the high risk quartile (12.9%) and the clinical value (11.7%) AL formulations. Hence, approximately 87% of the variance in the model remains unaccounted for. Additional measures to characterize pain burden may increase strength of the model in addition to inclusion of other measures such as sleep quality [34]. Fourth, this study is cross-sectional, a prospective investigation is an important next step. Fifth, inclusion of additional stress-related biological measures may provide an improved understanding of biological system functioning. Sixth, sex was included as a covariate in this study, future investigations would benefit by evaluation of the possible effect modification of sex. Additionally, the relationship between stress and health is adaptive with high AL indicated as a result of persistent, prolonged, and excessive stress, an important consideration when evaluating biomarkers and interpreting statistical models [20,21,35,37]. Lastly, AL is demonstrating utility as an indicator of the biological interface of a

person's life experience [18,36]. As such, the AL index may be most useful as a measure to reflect current multi-system functioning and to serve as a biomarker to evaluate the impact of various biopsychosocial and behavioral interventions [23].

Conclusions

This study provides an important next step in understanding the relationship between pain severity and physiological dysregulation in aging adults. There are three key findings in this study: 1) a positive relationship between pain severity and the AL was demonstrated across all four formulations; 2) the high risk quartile and the clinical values index explained the greatest variance with AL when included with putative confounders; and 3) six biomarkers were consistently associated with pain severity. Importantly, a pain-related AL index may serve as a useful clinical and research measure indicating dysregulated stress-system functioning and evaluating the physiological benefits of clinical interventions.

Acknowledgements

Funding for this research is supported by the National Institute on Aging Grants 2R01AG7644-01A1 and 2R01AG017644 and a consortium of UK government departments coordinated by the Office for National Statistics. KTS is funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under Award Number NIAMS K23AR062099. JM is funded by an Arthritis Research UK Centre grant. DS is funded by an Acorn studentship, Keele University. RW is funded by the Institute of Primary Care and Health Sciences, Keele University.

ELSA data were made available through the UK Data Archive (UKDA). ELSA was developed by a team of researchers based at the NatCen Social Research, University College London and the Institute for Fiscal Studies. The data were collected by NatCen Social Research. The funding is provided by the National Institute of Aging in the United States, and a consortium of UK government departments co-ordinated by the Office for National Statistics. The developers and funders of ELSA and the Archive do not bear any responsibility for the analyses or interpretations presented here.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The funding sources had no involvement in development and presentation of the submitted manuscript.

An expression of thanks is extended to Hari Parvataneni MD for assistance with identification of clinical measure values, Roger B. Fillingim PhD for content suggestions, and John Marks DHSc for formatting assistance.

References

[1] Afari N, Mostoufi S, Noonan C, Poeschla B, Succop A, Chopko L, Strachan E. C-reactive protein and pain sensitivity: Findings from female twins. Ann Behav Med 2011;42:277-83.

[2] Andersson H. The course of non-malignant chronic pain: a 12-year follow-up of a cohort from the general population. European Journal of Pain 2004;8:47-53.

[3] Banks J, Muriel A, Smith J. Disease prevalence, disease incidence, and mortality in the United States and in England. Demography 2010;47:S211-31.

[4] Behavioral and Social Research Program. NIA Exploratory Workshop on Allostatic Load., 2007.

[5] Bushnell MC, Case LK, Ceko M, Cotton VA, Gracely JL, Low LA, Pitcher MH, Villemure C. Effect of environment on the long-term consequences of chronic pain. Pain 2015;156:S42-S49.

[6] Chapman C, Tuckett R, Song C. Pain and stress in a systems perspective: Reciprocal neural, endocrine, and immune interactions. J Pain 2008;9:122-45.

[7] Craig R, Deverill C, Pickering K. Quality control of blood, saliva and urine analytes. Health Survey for England 2004, Methodology and Documentation, vol 2. London: The Information Centre, 2006. pp. 34-41.

[8] Crimmins E, Johnston M, Hayward M, Seeman T. Age differences in allostatic load: an index of physiological dysregulation. Exp Gerontol 2003;38:731-34.

[9] Dominick C, Blyth F, Nicholas M. Unpacking the burden: Understanding the relationships between chronic pain and comorbidity in the general population. Pain 2012;153:293-304.

[10] Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Executive summary of the third report of the National Cholesterol Education Program (NCEP). JAMA 2001;285:2486-97.

[11] Fillingim RB. Sex, gender and pain: women and men really are different. Current Review of Pain 2000;4:24-30.

[12] Goertzel B, Pennachin C, de Souza Coelho L, Maloney E, Jnes J, Gurbaxani B. Allostatic load is associated with symptoms in chronic fatigue syndrome patients. Pharmacogenomics 2006;7:485-94.

[13] Graham J, Christian L, Kiecolt-Glaser J. Stress, age, and immune function: Toward a lifespan approach. J Beh Med 2006;29:389-400.

[14] Haren M, Malmstrom T, Miller D, Patrick P, Perry III H, Herning M, Banks W, Morley J. Higher c-reactive protein and soluble tumor necrosis factor receptor levels are associated with poor physical function and disability: A cross-sectional analysis of a cohort of late middle-aged African Americans. Journal of Gerontology 2010;65A:274-81.

[15] Hasselhorn H, Theorell T, Vingàrd E, Group M-NS. Endocrine and immunologica parameters indicative of 6-month prognosis after the onset of low back pain or neck/shoulder pain. Spine 2001;26:D1-D6.

[16] James P, Oparil S, Carter B, Cushmnan W, Dennison-Himmeelfarb C, Handler J, Lackland D, LeFevre M, MacKenzie T, Ogedegbe O, Smith S, Svetkey L, Taler S, Townsend R, Wright J, Narva A, Ortiz E. 2014 Evidence-based guideline for the management of high blood pressure in adults Report from the panel members appointed to the eighth joint national committee (JNC8). JAMA 2014;311:507-20.

[17] Jordan K, Kadam U, Hayward R, Porcheret M, Young C, Croft P. Annual consultation prevalence of regional musculoskeletal problems in primary care: an observational study. BMC Musculoskeletal Disorders 2010;11:144.

[18] Juster R, McEwen B, Lupien S. Allostatic load biomarkers of chronic stress and impact on health and cognition. Neuroscience and Biobehavioral Reviews 2010;35:2-16.

[19] Kamaleri Y, Natvig B, Ihlebaek CM, Benth JS, Bruusgaard D. Number of pain sites is associated with demographic, lifestyle, and health-related factors in the general population. Eur J Pain 2007.

[20] Karlamangla A, Singer B, McEwen B, Rowe J, Seeman T. Allostatic load as a predictor of functional decline. MacArthur studies on successful aging. J CLin Epidemiol 2002;55:696-710.

[21] Karlamangla A, Singer B, Seeman T.

Reduction in allostatic load in older adults is associated with all-cause mortality risk: MacArthur Studies of Successful Aging. Psychosomatic Medicine 2006;68:500-07.

[22] Karlamangla A, Tinetti M, Guralnik J, Studenski S, Wetle T, Reuben D. Comorbidity in older adults: nosology of impairment, diseases, and conditions. J Gerontol A Biol Sci Med Sci 2007;62(3):296-300.

[23] King C, Keil A, Sibille K. Chronic pain and perceived stress. In: F G, editor. Stress: Concepts, cognition, emotion, and behavior: Elsevier, 2016. pp. 413-21.

[24] Koenig W. Fibrinogen in cardiovascular disease: an update. Thromb Haemost 2003;89:601-09.

[25] Kopec J, Sayre E, Esdaile J. Predictors of back pain in a general population cohort. Spine 2004;29(1):70-77.

[26] Lampe A, Sollner W, Krismer M, Rumpold G, Kantner-Rumplmair W, Ogon M, Rathner G. The impact of stressful life events on exacerbation of chronic low-back pain. J Psychosom Res 1998;44(5):555-63.

[27] Leistad R, Nilsen K, Stovner L, Westgaard R, Rø M, Sand P. Similarities in stress physiology among patients with chronic pain and headache disorders: Evidence for a common pathophysiological mechanism? J Headache Pain 2008;9:165-75.

[28] Linton SJ. A review of psychological risk factors in back and neck pain. Spine 2000;25(9):1148-56.

[29] Macfarlane GJ, McBeth J, Silman AJ. Widespread body pain and mortality: prospective population based study. BMJ 2001;323(7314):662-65.

[30] Maleki N, Becerra L, Brawn J, McEwen B, Burstein R, Borsook D. Common hippocampal structure and functional changes in migraine. Brain Struct Funct 2013;218(4):903-12.

[31] May A. Chronic pain may change the structure of the brain. Pain 2008;137:7-15.

[32] Mayo Clinic. Interpretive Handbook; Test 35100:Insulin-Like Growth Factor 1 (IGF-1) and Insulin-Like Growth Factor Binding Protein 3 (IGFBP-3) Growth Panel; Clinical Information., Vol. 2014, 1995.

[33] McBeth J, Silman A, Macfarlane G. Associations of widespread body pain with an increased risk of cancer and reduced cancer survival: A prospective, population-based study. Arthritis & Rheumatism 2003;48:1686-92.

[34] McEwen B. Sleep deprivation as a neurobiologic and physiologic stressor: allostasis and allostatic load. Metabolism Clinical and Experimental 2006;55:S20-S23.

[35] McEwen B. Physiology and neurobiology of stress and adaptation: Central role of the brain. Physiol Rev 2007;87:873-904.

[36] McEwen B. Biomarkers for assessing population and individual health and disease related to stress and adaptation. Metabolism 2015;64:S2-S10.

[37] McEwen B, Seeman T. Protective and damaging effects of mediators of stress. Annals New York Academy of Sciences 1999;896:30-47.

[38] Nahin R. Estimates of Pain Prevalence and Severity in Adults: United States, 2012. J of Pain 2015;16:769-80.

[39] Nahit ES, Hunt IM, Lunt M, Dunn G, Silman AJ, Macfarlane GJ. Effects of psychosocial and individual psychological factors on the onset of musculoskeletal pain: common and site-specific effects. Ann Rheum Dis 2003;62(8):755-60.

[40] Nathan D, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine R. Translating the A1c assay into estimated average glucose values. Diabetes Care 2008(31):1473-78.

[41] National Institute for Clinical Excellence. Hypertension: Clinical management of primary hypertension in adults., 2013.

[42] NIH - National Cancer Institute. Pulse (Heart Rate): PubMed Health.

[43] Okifuji A, Turk DC. Stress and psychophysiological dysregulation in patients with fibromyalgia syndrome. Appl Psychophysiol Biofeedback 2002;27(2):129-41.

[44] Olsen R, Bruehl S, Nielsen C, Rosseland L, Eggen A, Stubhaug A. Chronic pain and cardiovascular stress responses in a general population: the Tromsø study. J Behav Med 2014;37:1193-201.

[45] Pearson T, Mensah G, Alexander R, Cannon R, Criqui M, Fadl Y, Fortmann S, Hong Y, Myers G, Rifai N, Smith S, Taubert K, Tracy R, Vinicor F. Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice: A Statement for Healthcare Professionals From the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003(107):499-511.

[46] Pontari M, Ruggieri M. Mechanisms in prostatitis/chronic pelvic pain syndrome. J Urol 2008;179:S61-S67.

[47] Price D. Psychological and neural mechanisms of the affective dimension of pain. Science 2000;288:1769-72.

[48] Radloff L. The CES-D scale: A self-report depression scale for research in the general population. Journal of Applied Psychological Measurement 1977;1:385-401.

[49] Reuben D, Cheh A, Harris T, Ferrucci L, Rowe J, Tracy R, Seeman T. Peripheral blood markers of inflammation predict mortality and functional decline in high-functioning community-dwelling older persons. J Am Geriatr Soc 2002;50:638-44.

[50] Roche Diagnostics. DHEAS Kit: Roche Modular E Reference Ranges. Available in ELSA, 2008.

[51] Seeman T, Gruenewald T, Karlamangla A, Sidney S, Liu K, McEwen B, Schwartz J. Modeling multisystem biological risk in young adults: The coronary artery risk development in young adults study. American Journal of Human Biology 2010;22:463-72.

[52] Seeman T, McEwen B, Rowe J, Singer B.

Allostatic load as a marker of cumulative biological risk: MacArthur Studies of Successful Aging. Proc Natl Acad Sci 2001;98:4770-75.

[53] Seplaki C, Goldman N, Glei D, Weinstein M. A comparative analysis of measurement approaches for physiological dysregulation in an older population. Exp Gerontol 2005;40:438-39.

[54] Sesso HD S, MJ, Rosner B, Hennekens C, Gaziano J, Manson J, Glynn R. Systolic and diastolic blood pressure, pulse pressure, and mean arterial pressure as predictors of cardiovascular disease risk in men. Hypertension 2000(36):801-07.

[55] Sibille K, Riley III J, McEwen B. Authors build an important foundation for further research. J Pain 2012;13:1269-70.

[56] Sibille K, Steingrímsdóttir O, Fillingim R, Stubhaug A, Schirmer H, Chen H, McEwen B, Nielsen C. Investigating the burden of chronic pain: An inflammatory and metabolic composite. Pain Research & Management 2016;2016.

[57] Slade GD, Sanders AE, By K. Role of allostatic load in sociodemographic patterns of pain prevalence in the u.s. Population. J Pain 2012;13(7):666-75.

[58] Soldato M, Liperoti R, Landi F, Finne-Sovery H, Carpenter I, Fiaova D, Bernabei R, Onder G. Non-malignant daily pain and risk of disability among older adults in home care in Europe. Pain 2007;129:304-10.

[59] Stürmer T, Raum E, Buchner M, Gebbhardt K, Schiltenwolf M, Richter W, Brenner H. Pain and high sensitivity C reactive protein in patients with chronic low back pain and acute sciatic pain. Ann Rheum Dis 2005;64:921-25.

[60] Thomas E, Peat G, Harris L, Wilkie R, Croft PR. The prevalence of pain and pain interference in a general population of older adults: cross-sectional findings from the North Staffordshire Osteoarthritis Project (NorStOP). Pain 2004;110(1-2):361-68.

[61] Torrance N, Elliott A, Lee A, Smith B. Severe chronic pain is associated with increased 10 year mortality. A cohort record linkage study. European Journal of Pain 2010;14:380-86.

[62] Wilkie R, Tajar A, McBeth J. The onset of widespread musculoskeletal pain is associated with a decrease in healthy ageing in older people: a population-based prospective study. PLoS One 2013;8.

[63] World Health Organization. Waist circumference and waist-hip ratio: report of a WHO expert consultation, Geneva, 2008.

[64] Yang Y, Kozloski M. Sex differences in age trajectories of physiologicl dysregulation: Inflammation, metabolic syndrome, and allostatic load. J of Gerontology: Biological Sciences 2011;66:493-500.