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Examination of the allostatic load construct and its longitudinal association with health outcomes in the Boston Puerto Rican Health Study

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Abstract

Objective: Despite evidence on allostatic load (AL) as a model explaining associations between stress and disease, there is no consensus on its operationalization. This study aimed to contrast various AL constructs and their longitudinal associations with disease and disability.

Methods: Baseline and 5-year follow-up data from 738 adults participating in the Boston Puerto Rican Health Study were used. Five AL scores were created by summing presence of 21 dysregulated multi-system physiological parameters using: (1) z-scores, (2) population-based quartile cutoffs, (3) clinical-based cutoffs, (4) ten pre-selected clinical-based cutoffs (AL-reduced); and (5) twelve clinical-based cutoffs selected *a posteriori* based on association with disease (AL-select). Adjusted logistic regression models examined associations between each AL score at baseline and 5-year incident type 2 diabetes (T2D), cardiovascular disease (CVD), activities (or instrumental activities) of daily living (ADL; IADL) for physical impairment, and cognitive impairment.

Results: AL-quartile was associated with greater odds of T2D (OR=1.20; 95%CI=1.07–1.35) and CVD (OR=1.14; 95%CI=1.06–1.22). AL-reduced was associated with higher odds of IADL (OR=1.21; 95%CI=1.07–1.37) and AL-clinical with CVD (OR=1.14; 95%CI=1.07–1.21), IADL (OR=1.11; 95%CI=1.04–1.19), and ADL (OR=1.15; 95%CI=1.04–1.26). AL-select showed associations with T2D (OR=1.35; 95%CI=1.14–1.61), CVD (OR=1.21; 95%CI=1.11–1.32), IADL (OR=1.15; 95%CI=1.04–1.26), and ADL, (OR=1.24; 95%CI=1.08–1.41). No associations were found with AL-zscore.

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Conflicts of Interest: None

Conclusion: AL scores computed with clinical-based cutoffs performed robustly in our sample of mainland Puerto Ricans, whereas z-scores did not predict disease and disability. AL-select was the most consistent predictor, supporting its use as a disease-predicting model. Future assessment of AL-select in other populations may help operationalize AL.

Keywords

allostatic load; type 2 diabetes; cardiovascular disease; physical impairment; cognitive impairment

Introduction

Allostatic load (AL), defined as the wear and tear of the body's regulatory systems due to chronic or repeated stress [1, 2], has emerged as a framework to understand how stress affects health disparities. AL is hypothesized as a chain of physiological changes that are initiated by primary mediators (i.e., catecholamines and glucocorticoids) secreted by the hypothalamic-pituitary-adrenal axis (HPA) and the sympathetic nervous system (SNS) due to chronic stress [2, 3]. Repeated activation of these systems results in abnormal secretion of primary mediators, which in turn affects multiple downstream secondary metabolic and physiological functions (secondary mediators). AL is, then, the chronic, cumulative dysregulation of these biological parameters, which may lead to development of chronic diseases and disability.

For almost three decades, researchers have documented significant associations between AL and disease outcomes [4–9]. For example, AL has been linked with cognitive and physical impairment (including impairment of activities of daily living (ADL) and impairment of instrumental activities of daily living (IADL)) [10–14], risk factors for cardiovascular disease (CVD) (i.e., obesity, type 2 diabetes (T2D), and hypertension) [15, 16], and eventual CVD [15, 17, 18]. Still, there are considerable differences across the literature on how to measure AL. Some studies do not include primary mediators in the AL construct, and thus fail to incorporate the systems that initiate AL [19]. Instead, these AL scores overlap with the metabolic syndrome or other cardiometabolic risk assessments. Furthermore, there is no consensus on which physiological markers should be included for each system, as well as on which systems should represent AL. The seminal MacArthur Successful Aging Study included cortisol (HPA axis activity), DHEA-S (HPA axis antagonist), epinephrine, and norepinephrine (SNS activity) in its AL construct [2, 3]; however, other studies have included other primary markers (e.g. aldosterone) [20, 21]. Similarly, studies differ in the selection of secondary markers. The vast majority include indicators of lipid metabolism, glucose metabolism, and the cardiovascular system. However, they differ in the specific markers used for each system [5, 22]. Some studies have included additional physiological systems, such as markers of renal dysfunction [5]. Lastly, there is wide variability in the approaches taken to calculate the AL score [5, 22, 23]. The most common method has been using population-based distribution quartiles as the cutoff to identify individuals with dysregulated indicators, while others use cutoffs based on clinical recommendations, when they exist, z-scores, or more sophisticated techniques (i.e., canonical correlation, recursive partitioning, grade of membership or cluster analysis).

Inconsistencies on assessing AL are mainly due to the absence of a “gold standard” and to the availability of parameters within a study. Such inconsistencies limit the ability to compare results between studies and to apply the AL framework to clinical practice. Thus, there is a need to evaluate the parameters and methodologies used to calculate AL, and to test which AL construct is the best predictor of developing chronic diseases and disability. In addition, there is a need to study AL in minority populations experiencing health disparities and who are constantly exposed to stressors. In particular, Puerto Ricans in the continental United States (US) experience profound health disparities [24], encounter numerous stressors (i.e., discrimination, racism, acculturation, poverty and language barriers) [25, 26], and have higher AL scores than other Latino groups [27]. Using data from the Boston Puerto Rican Health Study (BPRHS) [28], the present study aimed to evaluate four frequently-used AL constructs, with diverse inclusion of systems, indicators, and scoring approaches, and to determine longitudinal associations between these different AL constructs and eventual health outcomes (i.e., T2D, CVD, and physical and cognitive impairment). A second aim was to create a construct of AL by selecting the individual parameters and scoring methods that were most strongly associated with disease and disability outcomes.

Methods

Study design and study participants.

The present study used baseline and 5-year follow-up data from the BPRHS, a prospective cohort study of middle-aged Puerto Rican adults [28]. Briefly, the BPRHS recruited Puerto Rican adults in the Greater Boston area (ages 45 to 75 years) between June 2004–October 2009. Exclusions included severe cognitive impairment (Mini Mental State Examination (MMSE) score < 10) or plans to move out of the Boston area within the next two years. Participants were recruited using door to door enumeration, community events, and referrals from recruited individuals. After obtaining the participant’s written informed consent, trained bilingual study staff conducted study interviews and measurements at the participant’s home. The study was approved by the Institutional Review Boards of Tufts University and Northeastern University.

Data on socio-demographic factors (sex, education, income, and marital status), social and behavioral factors (acculturation, smoking, physical activity, diet), anthropometric measures (weight, height, and waist circumference), blood pressure, medical history (self-reported medical diagnoses and medication use), and biochemical specimens (12-hr urine collection and fasting blood samples) were obtained at each study visit. A total of 2,093 individuals were identified for the study, of these, 1,802 met the eligibility criteria and 1,500 agreed to participate (72% inclusion of those who were approached and 83% inclusion of those who were eligible). The present analysis included data on men and women at baseline and 2-year and 5-year follow up. Of the 1,500 participants enrolled in the study, 927 had records on all three study waves (62% retention). For the present study, we included individuals with records on the three study waves (2-year follow up data was used for imputation of missing covariates), complete data on AL parameters at baseline, and outcomes of interest at baseline and year 5. This resulted in a sample size of 738 participants.

Independent variable: Allostatic load.

A total of 21 parameters available at baseline in the BPRHS were used to capture AL. These parameters have been previously used in AL studies [5] and represent multiple regulatory systems. Primary AL markers included parameters representing the HPA axis (serum dehydroepiandrosterone sulfate (DHEA-S) and urinary cortisol), SNS (urinary norepinephrine and epinephrine), and immune system (serum c-reactive protein (CRP) and white blood cells). Secondary markers included parameters of lipid metabolism (plasma HDL-C, total cholesterol, cholesterol:HDL ratio, LDL-C, and triglycerides), glucose metabolism (plasma hemoglobin A1c (HbA1c), fasting glucose, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) [29]), renal system (serum albumin and creatinine clearance) [30], cardiovascular system (systolic blood pressure (SBP), diastolic blood pressure (DBP) and plasma homocysteine), and adipose deposition (body mass index (BMI) and waist circumference). Detailed methodology and procedures used to collect overnight fasting blood and 12-hour urine samples are described elsewhere [28].

We evaluated five AL constructs (AL z-score, AL-quartile, AL-clinical, AL-reduced, and the *a posteriori*-selected AL-select) using parameters at baseline, which were calculated using different scoring approaches, strategies for establishing cutoffs of dysregulation, and inclusion of AL parameters (Table 1).

The AL z-score construct was created using the 21 AL parameters available. To calculate the z-score-based construct, baseline values of each parameter were standardized to have a mean of zero and a standard deviation of one. All standardized parameters were summed to create the summary AL z-score.

The AL-quartile construct was calculated from all 21 AL parameters using baseline top quartiles of the population distribution as high-risk cutoffs for all AL parameters to identify dysregulated parameters (except for DHEA-S, HDL-C, and creatinine clearance, for which the bottom quartiles were used as high-risk cutoffs). We assigned one point for each dysregulated parameter. Additionally, we assigned a point if a participant was taking medications at baseline for either testosterone, diabetes, hyperlipidemia, or hypertension and had parameters within normal values [15]. Points for dysregulated parameters were summed to calculate the baseline AL-quartile score, with plausible scores ranging from 0–21.

The AL-clinical construct was calculated from all 21 AL parameters using clinical guidelines as cutoffs to identify dysregulated parameters. For parameters for which there are no clinical recommendations (i.e., cortisol, epinephrine, norepinephrine, DHEA-S, white blood cells, cholesterol:HDL ratio, HOMA-IR, albumin, and homocysteine), we used the top (or bottom for DHEA-S) baseline population quartiles as cutoffs. We also assigned an additional point for medication use for parameters within normal values, similarly to AL-quartile. All points were summed, and the final AL-clinical score ranged from 0–21.

The AL-reduced construct consisted of 10 AL parameters that were selected *a priori*: cortisol, epinephrine, norepinephrine, DHEA-S, HDL-C, total cholesterol, HbA1c, diastolic and systolic blood pressure and waist circumference. This construct has been previously used in this population [15] and was tested in the present analysis as an alternative

AL summary score for when availability of AL parameters is limited. The AL-reduced score used the same cutoff criteria as AL-clinical. We summed all points for dysregulated parameters and the final AL-reduced score ranged from 0–10.

The AL-select construct was created *a posteriori* by selecting AL parameters (from among the original 21) associated with any of the measured health outcomes at $p < 0.10$. Based on this criterion, we identified twelve parameters that were predominately defined using clinical guidelines as cutoffs, and some quartile-based cutoffs for parameters without clinical guidelines. As in the AL-clinical construct, we assigned an additional point for use of medications for parameters within normal values. We summed all points for the dysregulated parameters and the final AL-select score ranged from 0–12.

Dependent variables.

T2D was defined according to the American Diabetes Association guidelines as having fasting glucose concentration ≥ 126 mg/mL [31] or use of anti-diabetes medication [28]. CVD cases were identified through self-reported diagnosis of heart attack, heart disease, or stroke. In addition to these three self-reported conditions, we further identified new CVD cases at 5-year follow-up by self-report of at least one of the following: chest pain or angina, heart failure, cardiac catheterization, heart or coronary bypass surgery, any procedure to unblock narrowed blood vessels to heart muscles (percutaneous transluminal coronary angioplasty, coronary angioplasty, or coronary stent), any procedures to unblock narrowed blood vessels in the neck (carotid endarterectomy, carotid angioplasty), poor blood circulation or blocked or narrowed blood vessels to the legs or feet, amputation because of poor circulation, blood clot or embolism in leg or lung.

Physical impairment was evaluated from two measures: ADL and IADL [32]. ADL asks about difficulty performing 12 basic self-care tasks (e.g. bathing, eating, dressing, etc.). The IADL questionnaire measures difficulty when performing six complex tasks (e.g. food shopping, doing chores, cooking, managing money, etc.). For each construct, response options ranged from no difficulty (0) to impossible to do (3) and a total score was calculated by adding all responses. Scores ranged from 0 to 36 for ADL and 0 to 18 for IADL. ADL and IADL were each categorized as no physical impairment (score=0) versus some degree of physical impairment (score>0).

Cognitive impairment was measured with the MMSE questionnaire [33–36]. The MMSE asks about orientation, attention, memory and language skills. We created a cognitive impairment variable from MMSE scores that were adjusted for educational level by classifying individuals experiencing cognitive impairment with a cutoff of 22 for individuals with middle school education or less, a cutoff of 23 for individuals with high school education, or a cutoff of 24 for individuals with some college education or greater [28]. Models evaluating cognitive impairment were done in a subsample of the study due to missing data on MMSE at 5-year follow-up (total missing $n=330$).

Covariates.

The following baseline covariates, identified *a priori* from the literature, were considered: age, sex, educational attainment, poverty-income ratio, smoking, physical activity,

psychological acculturation, and diet quality. Education was categorized as less than high school education versus high school education, GED, or higher. Poverty-income ratio, which was standardized using national data for household size and year of report, was categorized as $\leq 120\%$ or $>120\%$. Smoking was defined as never, former, or current smoker. A modified version of the Paffenbarger questionnaire was used to assess physical activity and a physical activity score was constructed and used as a continuous variable, with higher scores indicating higher levels of physical activity [37, 38]. The Psychological Acculturation Scale, which measures an individual's sense of belonging or attachment to the U.S.-American (highest score) or Puerto Rican (lowest score) culture, was used to measure acculturation [39]. Lastly, dietary intake was measured with a culturally-adapted food frequency questionnaire (FFQ) [40]. Foods and nutrients calculated from intake reported in this FFQ were used to calculate the Alternate Healthy Eating Index (AHEI) as a measure of diet quality [41].

Values for missing data at baseline for key covariates (poverty income ratio (n=28), AHEI (n=65), and acculturation (n=2)) were imputed with values from the nearest study timepoint (2-years), or the 5-year values if 2-year data were also missing (n=3 for poverty income ratio and n=1 for AHEI).

Statistical analysis.

A total of 189 participants were excluded for missing data on any of the AL parameters at baseline (n=124), covariates missing at any study wave (n=6) or outcomes of interest at baseline (n=6) and year 5 (n=53). A total of 738 participants were included in the present analysis.

We present baseline descriptive statistics for the total sample and by baseline AL categories defined as <0 vs. >1 for AL z-score, or below vs. above the median value for other AL constructs. Chi-square or Mann-Whitney tests were used to contrast baseline characteristics and median concentrations/measures of each parameter at baseline by AL category. Logistic regression models, adjusted for baseline covariates, were used to calculate the odds ratio (95% confidence interval (CI)) of having a health outcome at year 5 by each dysregulated parameter score (0 vs. 1 for quartile or clinical and continuous for z-score) at baseline, and each AL construct as a continuous score at baseline. For each model, we excluded individuals with the disease at baseline in order to predict incident disease at year 5. For the model predicting incident T2D, baseline AL parameters of glucose metabolism (HbA1c, HOMA-IR, and fasting glucose) were not evaluated and the AL constructs excluded these parameters. We adjusted the p value for multiple testing using a Bonferroni correction for the main models of this study evaluating the continuous baseline AL scores and incident disease at 5 years. The corrected p value for these models was 0.01. Additional models were performed with categorical AL-clinical, AL-reduced, and AL-select constructs to evaluate AL levels for high-risk of disease. According to cell size, AL-reduced and AL-select were categorized as 0–3, 4–5, or 6 or more dysregulated AL parameters and the AL-clinical score was categorized as 0–7, 8–10, or 11 or more dysregulated AL parameters. The p value for these models was also corrected for multiple testing using Bonferroni correction to a p value of 0.017. STATA version 14 was used for all analyses.

RESULTS

Median scores for each AL construct were 6 out of a 0–21 plausible range for AL-quartile, 9 out of a 0–21 range for AL-clinical, and 5 out of a 0–10 range for AL-reduced (Table 1). For the AL-quartile and AL-clinical constructs, participants had an observed maximum of 17 dysregulated parameters out of the 21 AL parameters, whereas for the AL-reduced construct, participants had an observed maximum of all possible 10 parameters dysregulated. Median and range for AL z-score were -0.32 and -16.2 to 21.5 , respectively.

Overall at baseline, median (25th percentile, 75th percentile) age was 56 (51.0, 62.0) years, nearly 75% of the sample was female, 71% had income at or below 120% poverty-income ratio, and 65% had less than a high school education (Table 2). At baseline, approximately 40% of participants had T2D, 21% had CVD, 71% had ADL physical impairment, about half had IADL physical impairment, and 29% were identified with cognitive impairment. According to the AL-quartile, AL-clinical, and AL-reduced constructs, individuals in the high AL categories tended to be older, female, at or below 120% poverty-income ratio, of lower acculturation to the U.S., and at lower physical activity level than individuals in the low AL categories. For all four AL constructs, individuals in the high AL category were more likely to have T2D and physical impairment for both ADL and IADL at baseline than individuals in the low AL groups. Additionally, for AL-quartile, AL-clinical and AL-reduced, individuals in the high AL group were more likely to have CVD at baseline than individuals in the low AL category.

We compared baseline median concentrations/measures of each parameter by low and high baseline AL categories (Table S1, Supplemental Digital Content). Overall, we observed higher concentrations of parameters (lower concentrations for DHEAS and HDL-C) in the high AL compared to the low AL category, with the exception of total cholesterol and LDL-C for which differences by AL category were the reverse. In addition, more individuals in the high AL categories reported using lipid lowering medications (except for AL z-score), and anti-hypertension and anti-diabetes medications, than in the low AL groups. No other differences were noted.

We evaluated associations between each dichotomized dysregulated parameter (or each parameter's z-score) at baseline with each health outcome at year 5 (Table 3). Using the AL-clinical score, dysregulated concentrations of DHEA-S, LDL-C, triglycerides, homocysteine, fasting glucose, and BMI were associated with higher odds of CVD; dysregulated CRP, HDL-C, BMI and waist circumference were associated with impairment of ADL; and dysregulated HDL-C, HbA1c, and waist circumference were associated with impairment of IADL. For parameters of the AL-quartile score, similar although weaker associations were noted. For AL z-score parameters, only some of these associations were observed, while additional associations were noted for white blood cells, HDL-C, total cholesterol, LDL-C, and BMI with T2D, HbA1c with CVD, and white blood cells, fasting glucose, and BMI with impairment of IADL (Table 3).

Results from Table 3 were used to create the AL-select construct. This construct included: cortisol, DHEA-S, CRP, HDL-C, LDL-C, triglycerides, HbA1c, fasting glucose, creatinine

clearance, homocysteine, BMI, and waist circumference, as defined with the AL clinical cutoffs because of stronger associations, except for cortisol, DHEA-S, and homocysteine, which lack clinical guidelines.

After adjusting for covariates, AL-quartile was significantly associated with higher odds of T2D and CVD at year 5, whereas AL-reduced was associated with higher odds of impairment of IADL (Table 4). The AL-clinical and AL-select constructs were associated with higher odds of CVD, and physical impairment of both IADL and ADL at year 5 after adjusting for covariates, and AL-select was additionally associated with higher odds of T2D. The AL-select score tended to show similar or slightly stronger associations, with each additional dysregulated parameter within the AL-select score being associated with 35% (95%CI: 1.14, 1.61) higher odds for T2D, 21% (95%CI: 1.11, 1.32) for CVD, 15% (95%CI: 1.04, 1.26) for IADL impairment, and 24% (95%CI: 1.08, 1.41) for ADL impairment. In sensitivity analyses, we evaluated the AL-select construct including SBP and DBP parameters which are commonly included in AL constructs, and results were similar but slightly attenuated (results not shown).

Lastly, we evaluated odds of disease at 5 years by categories of three of the AL scores: AL-clinical, AL-reduced and AL-select (Table 5). Adjusted models showed that, compared to individuals with 0–3 dysregulated AL-select parameters, individuals with 4–5 dysregulated AL parameters had almost three times the odds of incident T2D at year 5 (2.78, 95%CI: 1.42, 5.43), and individuals with more than 6 dysregulated AL parameters had three times the odds of incident T2D at year 5 (3.06, 95%CI: 1.35, 6.91). In addition, compared to individuals with 0–3 dysregulated AL-select parameters, individuals with more than 6 dysregulated AL parameters had twice the odds of CVD (2.32, 95%CI: 1.39, 3.87), impairment of IADL (2.10, 95%CI: 1.21, 3.64), and three times the odds of impairment of ADL (2.95, 95%CI: 1.42, 6.14) at year 5. For AL-clinical, individuals in the highest category of AL had twice the odds of CVD (2.28, 95%CI: 1.41, 3.68) and impairment of IADL (2.12, 95%CI: 1.22, 3.67) and ADL (2.76, 95%CI: 1.24, 6.13) compared to individuals in the lowest AL category. For AL-reduced, individuals in the highest AL group had more than twice the odds of T2D (2.92, 95%CI: 1.35, 6.31) and impairment of IADL (2.60, 95%CI: 1.42, 4.75) than individuals in the lowest AL group.

Discussion

This study evaluated five different AL scores, calculated through three different AL scoring approaches, that included various multi-system biological parameters to best predict diverse outcomes of disease and disability (i.e., T2D, CVD, and cognitive and physical impairment) in mainland Puerto Ricans. Overall, our results show that the AL z-score construct was the weakest predictor of disease and the AL-select, which included 12 parameters mostly defined with clinical cutoffs, was the most consistent predictor.

Our finding of AL z-score being the weakest disease predictor agrees with other studies [42, 43]. For example, a study that used data from the National Health and Nutrition Examination Survey (NHANES) to evaluate different scoring methods of composite scores measuring multi-system physiological dysregulation in U.S. women found that the z-score

approach had weaker associations with general health, diabetes, and hypertension, compared to other constructs of physiological dysregulation (i.e., logistic regression and count-based methods) [42]. Another cross-sectional study conducted in Taiwanese individuals found that AL z-score was associated with physical impairment of ADL, depression, and self-reported health, but its R^2 and pseudo- R^2 statistics were smaller than those for AL defined with population based cutoffs (i.e., deciles) [43]. Thus, although the z-score approach is simpler and more standardized than other statistical techniques, it may not be the most effective to predict disease outcomes.

A review that evaluated 21 NHANES studies on multi-system physiological dysregulation and health outcomes noted that there was great variability in the approaches taken to capture dysregulated parameters [23]. Duong *et al.* (2017) reported that a total of 5 constructs of physiological dysregulation used clinical cutoffs to identify dysregulated parameters, 9 used population-based cutoffs, and 4 combined both clinical and population-based cutoffs. Another review study that evaluated AL and socio-economic status found that 73% of the studies used population-based quartiles to identify dysregulated AL parameters [22]. We observed AL-clinical yields similar but slightly higher estimates than AL-quartile in predicting 5-year disease and disability. Thus, using clinical cutoffs (when available) over population-based cutoffs appears to be preferable, and provides consistency across studies. The caveat is that not all AL parameters have clinical guidelines, and thus population-based cutoffs may need to be used for parameters lacking clinical guidelines.

We also observed that the AL-reduced construct produced similar estimates with the tested disease and disability outcomes compared to AL-clinical, albeit not significant after adjusting for multiple testing. AL-reduced had approximately half of the parameters included in AL-clinical. A study by Seplaki *et al.* (2005) also observed comparable results when testing the association between an AL construct that included 10 available parameters vs. one that included 16 parameters with health outcomes (physical impairment of ADL, depression, and self-reported health) [43]. This finding is particularly relevant to observational studies limited by the availability of AL parameters. As analyzing more biological samples is costly and may increase participant burden, using fewer, but relevant, parameters to define AL may still be valid for disease-prediction.

Lastly, the *a posteriori*-defined AL-select construct was, expectedly, the most consistent predictor of disease and disability, as it included AL parameters more strongly associated with the tested outcomes. Most of the parameters included in AL-select have been shown to be individually associated with our tested outcomes. For example, dysregulated cortisol and CRP have been linked with higher odds of diabetes, and some secondary parameters are known diabetes risk factors [44–47]. Similarly, dysregulated cortisol, CRP, creatinine clearance, and homocysteine have been shown to be associated with CVD [48–51], while other secondary parameters are known CVD risk factors [52]. Associations for some parameters of the AL-select construct also have been noted with cognitive [53–57] and physical [58–61] impairment. Due to the nature of an *a posteriori* defined and calculated score, the AL-select construct may be overfitting and specific to our study sample. Thus, future studies should test and validate the AL-select score in other populations and with other disease outcomes.

In our sample, systolic and diastolic blood pressure, two important risk factors for CVD [62] and commonly included in most AL constructs, did not meet the criteria to be included in the AL-select construct. In sensitivity analysis, including those parameters in the AL construct did not improve disease and disability prediction. It is possible that, in our sample, systolic and diastolic blood pressure are not essential predictors of the tested outcomes. However, future studies should evaluate if these parameters are relevant for AL in other populations and other diseases.

It is important to note that AL is defined as a pre-clinical measure of disease, as it is conceptualized as the mediator between stress and disease [19, 63]. Thus, defined by either population-based quartiles or by clinical cutoff points, it is a summary index of progression to final disease. AL measures specifically incorporate risk factors for disease endpoints, thus they include parameters associated with the outcomes but they do not include markers of the disease itself [64]. For example, our T2D models specifically excluded all components of glucose metabolism in the AL definition. Future studies need to be aware of this matter.

One limitation of this study is that there are other AL parameters that have been used in the literature but that were not available in our dataset (i.e., dopamine, insulin-like growth factor-1, aldosterone, fibrinogen, and peak expiratory flow) and thus we were unable to test them. Similarly, there are additional complex methods of computing AL that we did not analyze [5]. These parameters and complex computations are seldom used in the AL literature. Another limitation is that not all parameters have clinical guidelines available, thus we used population-based cutoffs, which reduces true standardization of an AL constructs. In addition, the generalizability of our findings may be limited to Puerto Rican adults, primarily women, residing in the mainland US.

A major strength of our study is that all the AL constructs we evaluated included primary and secondary AL parameters, representing multiple regulatory systems. These criteria are essential when evaluating AL, in order to capture the cumulative impact on multiple physiological functions [19]. Another study strength is the use of longitudinal analyses to evaluate the association between the different AL constructs and development of disease and disability, as few studies have done so. In addition, very few studies have examined AL by Latino heritage. Each Latino heritage in the US has a unique history, culture and acculturation process that may influence stress exposure and health outcomes, and thus need to be examined separately. Thus, another strength of the present study is its focus on mainland Puerto Ricans, a population with multiple stressors and health disparities [24–26]. Finally, the AL model is used as a framework of health disparities, and our study provides a template for its use in disease-prediction for Puerto Ricans and similar populations that experience multiple stress-related health disparities.

In conclusion, we evaluated five AL constructs and their association with diverse outcomes of diseases and disability. Our study identifies an AL construct (AL-select) with 12 multi-system parameters, defined predominantly using clinical-based cutoffs, as the most consistent predictor of disease and disability at 5-year follow-up in a sample of Puerto Rican adults. Future studies should validate this AL-select construct in other populations using additional and longer-term outcomes. Creating a standardized AL construct will

help decrease inconsistency of AL measurement and allow clinical application of the AL framework to identify individuals at high risk of disease for timely intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Acronyms:

ADL	impairment of activities of daily living
AHEI	alternative healthy eating index
AL	allostatic load
BMI	body mass index
BPRHS	Boston Puerto Rican Health Study
CI	confidence interval
CRP	c-reactive protein
CVD	cardiovascular disease
DBP	diastolic blood pressure
DHEA-S	dehydroepiandrosterone sulfate
FFQ	food frequency questionnaire
HbA1c	plasma hemoglobin A1c
HOMA-IR	homeostatic model assessment of insulin resistance
HPA	hypothalamic pituitary-adrenal axis
IADL	impairment of instrumental activities of daily living
MMSE	mini mental state examination
NHANES	national health and nutrition examination survey
SBP	systolic blood pressure
SNS	sympathetic nervous system
T2D	type 2 diabetes

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Table 1.

Sex-specific cut-off scores for AL quartile and clinical constructs.

Components	AL-quartile		AL-clinical		AL-reduced	
	Cutoff for dysregulation	Percent meeting cutoff for dysregulation (%)	Cutoff for dysregulation	Percent meeting cutoff for dysregulation (%)	Cutoff for dysregulation	Percent meeting cutoff for dysregulation (%)
Median	6		9		5	
Observed range	0-17		0-17		0-10	
Possible range	0-21		0-21		0-10	
Neuroendocrine:						
Cortisol (ug/g creatinine)	45.4M 38.5F	25.3M 24.8F	45.4M 38.5F	25.3M 24.8F	45.4M 38.5F	25.3M 24.8F
Epinephrine (ug/g creatinine)	4.95M 4.68F	25.3M 24.8F	4.95M 4.68F	25.3M 24.8F	4.95M 4.68F	25.3M 24.8F
Norepinephrine (ug/g creatinine)	43.9M 49.4F	24.8M 25.0F	43.9M 49.4F	24.8M 25.0F	43.9M 49.4F	24.8M 25.0F
DHEAS (ng/mL) ^a	590M 350F	25.8M 25.0F	590M; 350F	25.8M 25.0F	590M; 350F	25.8M 25.0F
Immune system:						
CRP (mg/L)	4.70M 8.70F	24.8M 25.4F	>3.0	40.4M 63.2F	-	-
White blood cells 1000/uL	8.28M 8.0F	25.3M 26.1F	8.28M 8.0F	25.3M 26.1F	-	-
Metabolic: Lipid metabolism^a						
HDL (mg/dL)	32.0M 39.0F	27.3M 24.8F	<40.0M <50.0F	57.6M 66.9F	<40.0M <50.0F	57.6M 66.9F
Total cholesterol (mg/dL)	204 213F	24.2M 25.4F	200.0	28.8M 37.0F	200	28.8M 37.0F
Cholesterol:HDL ratio	5.40M 4.69F	24.8M 25.0F	5.40M 4.69F	24.8M 25.0F	-	-
LDL (mg/dL)	130M 133F	25.3M 25.6F	190 no T2D 70 yes T2D	31.8M 30.4F	-	-
Triglycerides (mg/dL)	200M 183F	24.8M 25.0F	150	46.5M 40.9F	-	-
Glucose metabolism^a						

Components	AL-quartile		AL-clinical		AL-reduced	
HbA1c (%)	7.4M 7.63F	28.3M 24.6F	>6.5%	42.9M 42.6F	>6.5%	42.9M 42.6F
HOMA-IR	2.64M 2.65F	25.3M 24.6F	2.64M 2.65F	25.3M 24.6F	-	-
Fasting glucose (mg/dL)	135M 128.0F	25.8M 25.2F	126.0	30.3M 26.3F	-	-
<i>Renal system</i>						
Albumin (g/dL)	4.6M 4.4F	26.8M 35.9F	4.6M 4.4F	26.8M 35.9F	-	-
Creatinine clearance (mL/min)	88.9M 82.2F	26.3M 24.4F	<60.0	5.1M 6.9F	-	-
Cardiovascular						
Systolic blood pressure (mmHg) ^a	149M 146F	25.3M 24.4F	130.0	58.1M 57.2F	130	58.1M 57.2F
Diastolic blood pressure (mmHg) ^a	89.3M 87.3F	24.8M 24.3F	80.0	61.6M 52.2F	80.0	61.6M 52.2F
Homocysteine (μmol/L)	11.4M 9.2F	26.3M 24.8F	11.4M 9.2F	26.3M 24.8F	-	-
Anthropometric:						
BMI (kg/m ²)	33.6M 36.9F	24.8M 25.0F	30.0	48.5M 64.4F	-	-
Waist circumference (cm)	111M 111F	25.8M 25.0F	102M 88F	51.0M 82.8F	102M 88F	51.0M 82.8F

M=male; F=female; AL=allostatic load; DHEA-S= serum dehydroepiandrosterone sulfate; CRP=C-reactive protein; HDL=high-density lipoproteins; LDL=low-density lipoproteins; T2D=type 2 diabetes; HbA1c=glycosylated hemoglobin; HOMA-IR= Homeostatic Model Assessment of Insulin Resistance; BMI=body mass index. Total n=738. Quartiles were used for those parameters without clinical cutoffs.

^a Medication use for system/parameter was accounted for in the computed AL constructs.

Table 2.

Baseline characteristics in the total sample and by AL categories in the BPRHS.

Characteristics	Total sample n=738 (%)	AL z-score		AL-quartile		AL-clinical		AL-reduced	
		Low AL (Z score <0) n=386 (52.3%)	High AL (Z score >0) n=352 (47.7%)	Low AL (score=0-6) n=383 (51.9%)	High AL (score 7) n=355 (48.1%)	Low AL (score: 0-9) n=423 (57.3%)	High AL (score: 10) n=315 (42.7%)	Low AL (score: 0-5) n=443 (60.0%)	High AL (score: 6) n=295 (40.0%)
Age; median (P25, P75)	56.0 (51.0, 62.0)	56.0 (51.0, 62.0)	56.0 (51.0, 62.0)	58.0 ^{***} (53.0, 64.0)	54.0 (50.0, 60.0)	54.0 (50.0, 61.0)	58.0 (53.0, 64.0) ^{***}	55.0 (50.0, 61.0)	58.0 (52.0, 64.0) ^{***}
Female	546 (74.0)	295 (76.4)	251 (71.3)	263 (74.1)	283 (73.9)	300 (70.9)	246 (78.1) [*]	319 (72.0)	227 (79.0)
Poverty-income ratio 120%	521 (70.6)	280 (72.5)	241 (68.5)	262 (73.8)	259 (67.6)	286 (67.6)	235 (74.6) [*]	305 (68.9)	216 (73.2)
< High school education	477 (64.6)	255 (66.1)	222 (63.1)	236 (66.5)	241 (62.9)	263 (62.2)	214 (67.9)	281 (63.4)	196 (64.4)
PAS; median (P25, P75)	18.0 (12.0, 22.0)	18.0 (12.0, 22.0)	17.5 (12.0, 22.0)	16.0 (11.0, 22.0) ^{**}	19.0 (13.0, 22.0)	18.0 (13.0, 22.0)	16.0 (11.0, 22.0)	19.0 (13.0, 22.0)	16.0 (11.0, 22.0) ^{**}
Smoking status									
Never	356 (48.2)	199 (51.6)	157 (44.6)	157 (44.2)	199 (52.0)	211 (49.9)	145 (46.0)	220 (49.7)	136 (46.1)
Former	214 (29.0)	102 (26.4)	112 (31.8)	117 (33.0)	97 (25.3)	109 (25.8)	105 (33.3)	117 (26.4)	97 (32.9)
Current	168 (22.8)	85 (22.0)	83 (23.6)	81 (22.8)	87 (22.7)	103 (24.4)	65 (20.6)	106 (23.9)	62 (21.0)
PA; median (P25, P75)	30.4 (28.2, 33.2)	31.1 (28.3, 33.2)	30.6 (28.1, 33.2)	29.9 (28.0, 32.3) ^{***}	30.8 (28.4, 34.3)	30.8 (28.5, 33.9)	29.8 (28.0, 32.4) ^{***}	30.8 (28.4, 33.9)	30.0 (28.0, 32.5) ^{**}
AHEI; median (P25, P75)	54.1 (48.2, 59.7)	54.1 (48.6, 59.7)	54.2 (47.8, 59.8)	54.2 (47.8, 59.8)	54.1 (48.6, 59.6)	54.1 (48.2, 59.7)	54.2 (48.2, 59.5)	54.4 (48.4, 59.7)	53.8 (47.8, 59.8)
T2D	288 (39.0)	108 (28.0)	180 (51.1) ^{***}	218 (61.4) ^{***}	70 (18.3)	63 (14.9)	225 (71.4) ^{***}	107 (24.2)	181 (61.4) ^{***}
CVD	158 (21.4)	78 (20.2)	80 (22.7)	108 (30.4) ^{***}	50 (13.1)	62 (14.7)	96 (30.5) ^{***}	61 (13.8)	97 (32.9) ^{***}
Impairment of ADL	521 (70.6)	259 (67.1)	262 (74.3) [*]	271 (76.3) ^{**}	250 (65.3)	268 (63.4)	253 (80.3) ^{***}	290 (65.5)	231 (78.3) ^{***}
Impairment of IADL	353 (47.8)	171 (44.3)	182 (51.7)	187 (52.7) [*]	166 (43.3)	178 (42.1)	175 (55.6) ^{***}	198 (44.7)	155 (52.5) [*]
Cognitive impairment	120 (29.4)	62 (28.8)	58 (30.1)	56 (27.9)	64 (30.9)	74 (30.6)	46 (27.7)	76 (31.2)	44 (26.8)

AL=alostatic load; P=percentile; PAS=psychological acculturation score; PA=physical activity; AHEI=alternative healthy eating index; T2D=type 2 diabetes; CVD=cardiovascular disease; ADL=activities of daily living IADL= instrumental activities of daily living. Values are n (%) unless otherwise indicated.

* Indicates significant differences between low and high AL groups within each AL construct.

** <0.010 p <0.05;

*** <0.001 p <0.01;

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Table 3.

Adjusted odds ratios (95% CI) of the association between each dysregulated AL parameter at baseline and health outcomes at 5 years.

	T2D		CVD		Impairment of IADL		Impairment of ADL		Cognitive impairment	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Neuroendocrine AL-quartile, AL-clinical										
Cortisol ^a	1.71 (0.98, 2.99)	0.57 (0.36, 0.90)*	1.25 (0.76, 2.05)	0.85 (0.45, 1.60)	1.11 (0.57, 2.17)					
Epinephrine ^a	1.16 (0.64, 2.09)	0.88 (0.56, 1.37)	1.26 (0.76, 2.10)	0.88 (0.45, 1.70)	0.78 (0.40, 1.52)					
Norepinephrine ^a	1.04 (0.56, 1.92)	0.91 (0.59, 1.42)	1.10 (0.67, 1.82)	1.23 (0.62, 2.41)	0.80 (0.40, 1.58)					
DHEAS ^a	1.26 (0.70, 2.26)	1.65 (1.07, 2.55)*	1.02 (0.60, 1.73)	0.82 (0.38, 1.80)	1.34 (0.69, 2.62)					
Neuroendocrine AL z-score										
Cortisol	1.15 (0.93, 1.43)	0.78 (0.62, 0.98)*	1.14 (0.89, 1.44)	1.04 (0.79, 1.36)	1.12 (0.83, 1.50)					
Epinephrine	0.88 (0.66, 1.18)	0.93 (0.77, 1.12)	1.10 (0.87, 1.39)	0.99 (0.71, 1.36)	0.83 (0.60, 1.13)					
Norepinephrine	1.00 (0.77, 1.31)	0.89 (0.73, 1.09)	0.99 (0.79, 1.23)	1.02 (0.73, 1.41)	0.75 (0.54, 1.05)					
DHEA-S	0.94 (0.69, 1.29)	0.77 (0.62, 0.96)*	1.17 (0.94, 1.45)	0.98 (0.72, 1.34)	0.97 (0.68, 1.37)					
Immune system AL-clinical										
CRP	1.80 (1.04, 3.11)*	1.31 (0.89, 1.93)	1.19 (0.78, 1.83)	2.09 (1.17, 3.74)*	0.90 (0.49, 1.64)					
White blood cells	1.63 (0.90, 2.99)	1.09 (0.70, 1.68)	1.45 (0.88, 2.41)	1.06 (0.52, 2.16)	0.93 (0.47, 1.82)					
Immune system AL-quartile										
CRP	1.76 (0.97, 3.20)	1.00 (0.64, 1.55)	1.58 (0.95, 2.62)	2.32 (1.04, 5.20)*	0.76 (0.36, 1.57)					
White blood cells	1.63 (0.90, 2.99)	1.09 (0.70, 1.68)	1.45 (0.88, 2.41)	1.06 (0.52, 2.16)	0.93 (0.47, 1.82)					
Immune system AL z-score										
CRP	1.27 (0.92, 1.74)	0.86 (0.67, 1.10)	1.08 (0.89, 1.30)	2.09 (1.24, 3.52)**	0.82 (0.56, 1.22)					
White blood cells	1.37 (1.04, 1.80)*	0.97 (0.79, 1.19)	1.43 (1.13, 1.81)**	1.17 (0.84, 1.61)	1.29 (0.96, 1.74)					
Lipid metabolism AL-clinical										
HDL ^a	1.32 (0.760, 2.28)	1.13 (0.76, 1.69)	1.68 (1.06, 2.68)*	2.46 (1.33, 4.58)**	1.03 (0.54, 1.96)					
Total cholesterol ^a	0.71 (0.41, 1.22)	1.01 (0.68, 2.44)	0.80 (0.50, 1.27)	0.80 (0.44, 1.44)	0.89 (0.46, 1.70)					
Cholesterol:HDL ratio	0.85 (0.47, 1.52)	1.16 (0.76, 1.79)	1.04 (0.63, 1.71)	1.44 (0.72, 2.87)	1.49 (0.78, 2.86)					
LDL	1.17 (0.12, 11.0)	1.82 (1.21, 2.73)**	1.26 (0.78, 2.05)	1.77 (0.86, 3.62)	1.29 (0.67, 2.51)					

	T2D		CVD		Impairment of IADL		Impairment of ADL		Cognitive impairment	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Triglycerides	1.04 (0.61, 1.77)	1.56 (1.06, 2.29)*	1.38 (0.89, 2.14)	1.10 (0.61, 1.98)	1.81 (1.00, 3.28)					
Lipid metabolism AL-quartile										
HDL	1.90 (1.03, 3.50)*	0.95 (0.60, 1.51)	1.11 (0.67, 1.83)	1.95 (0.94, 4.02)	1.47 (0.76, 2.85)					
Total cholesterol	0.78 (0.44, 1.38)	1.27 (0.84, 1.94)	1.04 (0.63, 1.72)	0.80 (0.42, 1.53)	1.01 (0.51, 1.99)					
Cholesterol:HDL ratio	0.85 (0.47, 1.52)	1.16 (0.76, 1.79)	1.04 (0.63, 1.71)	1.44 (0.72, 2.87)	1.49 (0.78, 2.86)					
LDL	0.59 (0.33, 1.07)	0.83 (0.54, 1.28)	0.70 (0.42, 1.16)	0.68 (0.36, 1.30)	1.21 (0.62, 2.37)					
Triglycerides	1.69 (0.96, 3.00)	1.42 (0.92, 2.18)	0.99 (0.60, 1.63)	1.01 (0.50, 2.03)	1.43 (0.74, 2.78)					
Lipid metabolism AL z-score										
HDL	0.68 (0.50, 0.92)*	0.97 (0.80, 1.19)	0.83 (0.66, 1.06)	0.56 (0.47, 0.92)*	0.86 (0.62, 1.20)					
Total cholesterol	0.72 (0.54, 0.95)*	1.08 (0.89, 1.31)	0.86 (0.68, 1.07)	0.84 (0.62, 1.14)	1.01 (0.74, 1.39)					
Cholesterol:HDL ratio	1.15 (0.88, 1.50)	1.09 (0.91, 1.32)	1.04 (0.83, 1.31)	1.29 (0.94, 1.80)	1.19 (0.90, 1.57)					
LDL	0.70 (0.53, 0.92)*	0.99 (0.81, 1.20)	0.83 (0.66, 1.04)	0.92 (0.68, 1.24)	0.96 (0.71, 1.30)					
Triglycerides	1.29 (1.00, 1.67)	1.25 (1.04, 1.52)*	1.15 (0.91, 1.46)	1.04 (0.79, 1.36)	1.23 (0.93, 1.65)					
Glucose metabolism AL-clinical										
HbA1c ^d	-	1.11 (0.68, 1.82)	1.79 (1.00, 3.19)*	1.74 (0.74, 4.04)	1.27 (0.59, 2.75)					
HOMA-IR	-	1.22 (0.78, 1.92)	1.04 (0.62, 1.74)	0.73 (0.35, 1.51)	1.02 (0.51, 2.06)					
Fasting glucose	-	2.05 (1.24, 3.39)**	1.51 (0.83, 2.74)	1.42 (0.62, 3.24)	1.28 (0.60, 2.76)					
Glucose metabolism AL-quartile										
HbA1c	-	1.63 (0.95, 2.80)	2.56 (1.17, 4.36)*	1.62 (0.61, 4.31)	0.97 (0.42, 2.25)					
HOMA-IR	-	1.22 (0.78, 1.92)	1.04 (0.62, 1.74)	0.73 (0.35, 1.51)	1.02 (0.51, 2.06)					
Fasting glucose	-	2.11 (1.27, 3.50)**	1.80 (0.99, 3.29)	1.27 (0.55, 2.93)	1.36 (0.64, 3.00)					
Glucose metabolism AL z-score										
HbA1c	-	1.30 (1.05, 1.61)*	1.44 (1.10, 1.88)**	1.50 (0.96, 2.34)	1.18 (0.82, 1.67)					
HOMA-IR	-	1.04 (0.86, 1.25)	1.12 (0.83, 1.51)	0.76 (0.51, 1.12)	1.07 (0.83, 1.37)					
Fasting glucose	-	1.31 (1.08, 1.60)**	1.28 (1.01, 1.62)*	1.17 (0.83, 1.65)	0.96 (0.69, 1.33)					
Renal system AL-clinical										
Albumin	0.89 (0.51, 1.55)	0.84 (0.56, 1.26)	0.89 (0.57, 1.39)	1.02 (0.56, 1.84)	0.81 (0.42, 1.54)					
Creatinine clearance	0.54 (0.18, 2.60)	1.63 (0.75, 3.54)	2.24 (0.89, 5.60)	1.18 (0.29, 4.72)	1.68 (0.49, 5.76)					

	T2D		CVD		Impairment of IADL		Impairment of ADL		Cognitive impairment	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Renal system AL-quartile										
Albumin	0.89 (0.51, 1.55)	0.84 (0.56, 1.26)	0.89 (0.57, 1.39)	0.89 (0.57, 1.39)	1.02 (0.56, 1.84)	0.81 (0.42, 1.54)				
Creatinine clearance	0.96 (0.51, 1.77)	2.00 (1.27, 3.15)**	0.90 (0.53, 1.52)	0.90 (0.53, 1.52)	0.59 (0.29, 1.19)	1.48 (0.73, 3.01)				
Renal system AL z-score										
Albumin	0.88 (0.67, 1.13)	0.92 (0.77, 1.12)	0.90 (0.71, 1.13)	0.90 (0.71, 1.13)	0.97 (0.74, 1.27)	0.79 (0.60, 1.06)				
Creatinine clearance	1.24 (0.89, 1.73)	0.92 (0.74, 1.15)	1.06 (0.80, 1.41)	1.06 (0.80, 1.41)	1.16 (0.77, 1.74)	0.80 (0.56, 1.14)				
Cardiovascular AL-clinical										
Systolic blood pressure ^a	0.79 (0.46, 1.37)	1.04 (0.70, 1.53)	1.23 (0.79, 1.94)	1.23 (0.79, 1.94)	0.99 (0.55, 1.78)	0.91 (0.50, 1.69)				
Diastolic blood pressure ^a	0.93 (0.54, 1.60)	1.05 (0.72, 1.55)	1.05 (0.67, 1.63)	1.05 (0.67, 1.63)	1.31 (0.72, 2.39)	0.88 (0.48, 1.62)				
Homocysteine	1.30 (0.74, 2.28)	1.77 (1.16, 2.68)**	1.17 (0.71, 1.93)	1.17 (0.71, 1.93)	2.04 (1.00, 4.16)	1.06 (0.53, 2.12)				
Cardiovascular AL-quartile										
Systolic blood pressure	0.94 (0.51, 1.73)	1.48 (0.95, 2.29)	0.92 (0.55, 1.53)	0.92 (0.55, 1.53)	1.05 (0.52, 2.10)	1.52 (0.78, 2.93)				
Diastolic blood pressure	1.07 (0.59, 1.91)	1.14 (0.74, 1.76)	1.19 (0.72, 1.98)	1.19 (0.72, 1.98)	1.03 (0.52, 2.04)	0.98 (0.49, 1.94)				
Homocysteine	1.30 (0.74, 2.28)	1.77 (1.16, 2.68)**	1.17 (0.71, 1.93)	1.17 (0.71, 1.93)	2.04 (1.00, 4.16)	1.06 (0.53, 2.12)				
Cardiovascular AL z-score										
Systolic blood pressure	0.84 (0.63, 1.11)	1.14 (0.94, 1.38)	0.93 (0.74, 1.15)	0.93 (0.74, 1.15)	0.99 (0.75, 1.31)	1.11 (0.82, 1.49)				
Diastolic blood pressure	0.92 (0.69, 1.21)	1.15 (0.95, 1.39)	1.06 (0.85, 1.32)	1.06 (0.85, 1.32)	1.05 (0.77, 1.43)	0.90 (0.66, 1.24)				
Homocysteine	0.99 (0.77, 1.27)	1.21 (1.01, 1.44)*	1.06 (0.86, 1.31)	1.06 (0.86, 1.31)	0.99 (0.71, 1.36)	1.17 (0.87, 1.59)				
Adipose deposition AL-clinical										
BMI	1.43 (0.84, 2.46)	1.69 (1.13, 2.55)*	1.48 (0.95, 2.30)	1.48 (0.95, 2.30)**	2.23 (1.24, 4.03)**	1.03 (0.56, 1.89)				
Waist circumference ^a	2.11 (1.07, 4.17)	1.29 (0.81, 2.05)	1.70 (1.03, 2.81)*	1.70 (1.03, 2.81)**	2.43 (1.33, 4.42)**	0.71 (0.36, 1.40)				
Adipose deposition AL-quartile										
BMI	1.85 (0.98, 3.49)	1.16 (0.75, 1.82)	1.75 (1.02, 3.00)*	1.75 (1.02, 3.00)*	1.77 (0.81, 3.87)	0.61 (0.29, 1.32)				
Waist circumference	2.29 (1.23, 4.24)**	1.01 (0.64, 1.60)	2.14 (1.24, 3.71)**	2.14 (1.24, 3.71)**	2.19 (0.86, 5.57)	0.77 (0.37, 1.63)				
Adipose deposition AL z-score										
BMI	1.47 (1.11, 1.94)**	1.14 (0.94, 1.39)	1.35 (1.03, 1.75)*	1.35 (1.03, 1.75)*	1.67 (1.14, 2.46)**	0.92 (0.66, 1.27)				
Waist circumference	1.70 (1.27, 2.28)***	1.12 (0.92, 1.36)	1.48 (1.16, 1.90)**	1.48 (1.16, 1.90)**	1.55 (1.09, 2.20)*	1.01 (0.75, 1.36)				

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AL=allostatic load; DHEA-S= serum dehydroepiandrosterone sulfate; CRP=C-reactive protein; HDL=high-density lipoproteins; LDL=low-density lipoproteins; HbA1c=glycosylated hemoglobin; HOMA-IR= Homeostatic Model Assessment of Insulin Resistance; BMI=body mass index; T2D=type 2 diabetes; CVD=cardiovascular disease; ADL=activities of daily living IADL= instrumental activities of daily living.

Parameters used for the AL-reduced construct. All models adjusted for baseline covariates and medications (except for components of AL z-score). Excluded individuals with disease at baseline. Excluded individuals with disease at baseline. Sample size for models of each disease are: Diabetes: n=450; CVD: n=580; IADL: n=385; ADL: n=217; cognitive impairment: n=288.

* <0.010 p <0.05;

** <0.001 p <0.01;

*** p<0.001.

Table 4.

Odds ratios (95% CI) for the association between the baseline AL constructs and health outcomes at 5 years.

	AL z-score	P value	AL-quartile	P value	AL-clinical	P value	AL-reduced	P value	AL-select	P value
	OR (95% CI)		OR (95% CI)		OR (95% CI)		OR (95% CI)		OR (95% CI)	
T2D	1.01 (0.96, 1.07)	0.620	1.20 (1.07, 1.35)	0.002	1.15 (1.02, 1.29)	0.017	1.22 (1.03, 1.45)	0.020	1.35 (1.14, 1.61)	0.001
CVD	1.02 (0.98, 1.05)	0.322	1.14 (1.06, 1.22)	<0.001	1.14 (1.07, 1.21)	<0.001	1.12 (1.003, 1.25)	0.044	1.21 (1.11, 1.32)	<0.001
Impairment of IADL	1.04 (1.00, 1.08)	0.035	1.11 (1.02, 1.20)	0.012	1.11 (1.04, 1.19)	0.003	1.21 (1.07, 1.37)	0.003	1.15 (1.04, 1.26)	0.004
Impairment of ADL	1.03 (0.98, 1.08)	0.310	1.08 (0.98, 1.21)	0.133	1.15 (1.04, 1.26)	0.005	1.17 (1.00, 1.28)	0.054	1.24 (1.08, 1.41)	0.001
Cognitive impairment	0.99 (0.95, 1.04)	0.792	1.07 (0.97, 1.18)	0.186	1.06 (0.98, 1.16)	0.206	1.05 (0.89, 1.23)	0.583	1.12 (0.98, 1.27)	0.086

AL=allostatic load. T2D=type 2 diabetes; CVD=cardiovascular disease; ADL=activities of daily living IADL= instrumental activities of daily living. All models adjusted for baseline covariates. Excluded individuals with disease at baseline. For T2D, none of the AL constructs contain fasting glucose, HOMA-IR, glycosylated hemoglobin and diabetes medications. Excluded individuals with disease at baseline. Sample size for models of each disease are: Diabetes: n=450; CVD: n=580; IADL: n=385; ADL: n=217; cognitive impairment: n=288. Corrected significance for multiple comparisons: p<0.01.

Table 5. Odds ratio (95% CI) of association between categories of baseline AL constructs and health outcomes at 5 years.

	T2D		CVD		Impairment of IADL		Impairment of ADL		Cognitive impairment	
	OR (95%CI) p value	Reference	OR (95%CI) p value	Reference	OR (95%CI) p value	Reference	OR (95%CI) p value	Reference	OR (95%CI) p value	Reference
AL-select										
0-3	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
4-5	2.78 (1.42, 5.43) 0.003	1.06 (0.61, 1.85) 0.837	1.39 (0.79, 2.44) 0.255	1.87 (0.93, 3.75) 0.078	1.76 (0.73, 4.24) 0.209	Reference	1.76 (0.73, 4.24) 0.209	Reference	1.76 (0.73, 4.24) 0.209	Reference
6+	3.06 (1.35, 6.91) 0.007	2.32 (1.39, 3.87) 0.001	2.10 (1.21, 3.64) 0.008	2.95 (1.42, 6.14) 0.004	2.49 (1.12, 5.53) 0.025	Reference	2.49 (1.12, 5.53) 0.025	Reference	2.49 (1.12, 5.53) 0.025	Reference
AL-clinical										
0-7	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
8-10	1.77 (1.01, 3.10) 0.045	1.55 (0.96, 2.50) 0.075	1.08 (0.64, 1.83) 0.763	1.50 (0.76, 2.94) 0.239	2.11 (1.00, 4.47) 0.051	Reference	2.11 (1.00, 4.47) 0.051	Reference	2.11 (1.00, 4.47) 0.051	Reference
11+	1.60 (0.64, 4.02) 0.315	2.28 (1.41, 3.68) 0.001	2.12 (1.22, 3.67) 0.008	2.76 (1.24, 6.13) 0.013	1.44 (0.68, 3.05) 0.347	Reference	1.44 (0.68, 3.05) 0.347	Reference	1.44 (0.68, 3.05) 0.347	Reference
AL-reduced										
0-3	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
4-5	2.04 (1.00, 4.14) 0.049	1.14 (0.68, 1.91) 0.626	1.87 (1.03, 3.39) 0.040	1.45 (0.75, 2.96) 0.300	1.45 (0.61, 3.42) 0.400	Reference	1.45 (0.61, 3.42) 0.400	Reference	1.45 (0.61, 3.42) 0.400	Reference
6+	2.92 (1.35, 6.31) 0.007	1.61 (0.95, 2.72) 0.079	2.60 (1.42, 4.75) 0.002	1.69 (0.80, 3.59) 0.172	1.45 (0.62, 3.41) 0.395	Reference	1.45 (0.62, 3.41) 0.395	Reference	1.45 (0.62, 3.41) 0.395	Reference

AL=allostatic load; T2D=type 2 diabetes; CVD=cardiovascular disease; ADL=activities of daily living IADL= instrumental activities of daily living. All models adjusted for baseline covariates and excluded individuals with disease at baseline. For diabetes, none of the AL constructs contain fasting glucose, HOMA-IR, glycosylated hemoglobin and diabetes medications were included. T2D: n=450; CVD: n=580; IADL: n=385; ADL: n=217; cognitive impairment: n=288. Corrected significance for multiple comparisons: p<0.017.