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Abstract

Objectives

Allostatic load (AL) represents cumulative biological “wear and tear” that results from chronic stress exposure over time, ultimately increasing risk for chronic disease. A consensus is lacking regarding the

best operationalization of AL, particularly for younger, less studied populations. The purpose of this study was to test multiple hypothesized factor structures for AL to determine the best measurement approach for adolescents.

Methods

We analyzed biologic data for 1900 adolescents aged 12-18 from four waves (2003-2010) of the National Health and Nutrition Examination Survey. AL indicator variables included cardiovascular (systolic BP, creatinine), metabolic (HDL, LDL, triglycerides, insulin, fasting glucose, HA1C, body mass index [BMI], waist circumference), and immune (albumin, CRP, WBC, EBV) biomarkers. Structural equation modeling was used to test the fit of five hypothesized AL factor structures.

Results

The data best supported a unidimensional factor structure, where the AL construct directly influenced each of the indicator variables. All but two of the indicators (HDL and albumin) had positive factor loadings, thus, as AL increases the values for those indicators also increase. The best indicators for AL were those measuring metabolic dysregulation, with BMI and waist circumference having the highest factor loadings (0.95 and 0.982, respectively).

Conclusions

BMI and waist circumference may be some of the earliest clinical signs of elevated AL that manifest among adolescents. Future research should aim to include neuroendocrine biomarkers in their AL measures to have a more robust estimation of AL in younger populations.

1 INTRODUCTION

According to the World Health Organization (**2018**), the global burden of chronic diseases (ie, cardiovascular disease, cancer, obesity, diabetes) is rising, with projections that they will contribute to approximately 57% of global deaths by the year 2020. These diseases are common, costly, and often preventable health problems, affecting more than half of all individuals in the United States (Centers for Disease Control and Prevention, **2017**; Ward, Schiller, & Goodman, **2014**), with an estimated $1.3 trillion annual impact on our economy (Healthy People 2020, **2016**; Hunter & Reddy, **2013**). Although chronic diseases tend to be thought of as conditions of adulthood, roughly 25% of children and adolescents in the United States are also affected (Miller, Coffield, Leroy, & Wallin, **2016**), which has both immediate and lifelong effects on their optimal development and health. Health care professionals are interested in preventing the onset of chronic disease by better understanding and measuring key risk factors earlier in life to promote better health trajectories across all populations.

Allostatic load (AL) is a marker of cumulative biological “wear and tear” that captures the biological pathways through which social, behavioral, and environmental factors contribute to the development of chronic disease over time (Barboza Solís et al., **2015**; Friedman, Karlamangla, Gruenewald, Koretz, & Seeman, **2015**). AL expands on the concept of allostasis, proposing that the autonomic nervous system (ANS), the hypothalamic-pituitary-adrenal (HPA) axis, and the cardiovascular, metabolic, and immune systems protect the body by mounting adaptive responses to stressors to maintain homeostasis (McEwen, **1998**). Thus, AL is the biological result of chronic overactivity of these stress response pathways (Hux & Roberts, **2015**), which over time leads to systemic dysregulation across numerous

biological systems and increased risk for chronic disease. Indeed, a vast body of literature has linked elevated AL to a myriad of chronic diseases in adulthood, including a variety of psychological disorders (Beckie, Duffy, & Groer, **2016**; Kuhn et al., **2016**), cardiovascular disease (Havranek et al., **2015**; Steptoe & Kivimaki, **2013**), diabetes (Steptoe et al., **2014**), and adverse pregnancy outcomes (Hux, Catov, & Roberts, **2014**; Hux & Roberts, **2015**), as well as others. However, there is a lack of consistency across the literature in how AL is operationalized and scored, which makes the comparison and validity of findings across studies challenging (Beckie, **2012**). Moreover, few studies have evaluated whether AL is a valid construct of biological "wear and tear" in younger individuals, warranting further investigation into which biological indicators may be the most salient biomarkers of AL for younger populations.

2 SELECTION OF AL INDICATORS

AL is conceptualized as a latent construct that is best represented using a number of measured, biological indicator variables that represent stress-mediated systemic physiological dysregulation (Howard & Sparks, **2016**). In past research, a key determinant for selection of indicators included in AL measures has been the availability of and logistical access to various biomarkers that are believed to represent the key body systems involved in development of AL. Many population-based studies have therefore utilized available cardiovascular, metabolic, and inflammatory indicators when creating their AL constructs (Kobrosly, Seplaki, Cory-Slechta, Moynihan, & van Wijngaarden, **2013**; Masterson & Sabbah, **2015**; Theall, Drury, & Shirtcliff, **2012**), while excluding biomarkers of neuroendocrine function (ie, cortisol, dehydroepiandrosterone [DHEA]), which are comparatively more challenging to ascertain at the population level. In contrast, studies using clinical sample populations have been more likely to include assessment of neuroendocrine function within their AL indices, given they are better able to collect reliable and valid data on such measures (Chen, Miller, Brody, & Lei, **2015**; Howard & Sparks, **2016**). Despite decades of AL research, there remains a lack of consensus regarding which indicators of AL are necessary to include in the construct to remain consistent with its biological premise and predictive utility for health outcomes across different populations.

3 PREVIOUS ESTIMATION APPROACHES

In addition to AL indicator heterogeneity, estimation methods for AL also vary widely across the literature. Historically, the most common approach to measurement of AL has been a summative count method, with scores for each AL biomarker divided into risk quartiles based on AL psychometrics established in the foundational MacArthur Studies of Successful Aging (Seeman et al., **2010**), which first tested the AL construct in an older adult population. Using this approach requires dichotomization of each AL indicator (ie, into normal vs abnormal values) to create a summed total AL score, which leads to a loss of precision and explanatory power for each individual variable included. In addition, high-risk quartiles validated in adult populations may be less clinically meaningful for younger individuals whose distribution of values for AL biomarkers is likely to be different than those observed in adults. Other more complex scoring methods have been proposed, including summative measures based on clinical cutoffs, recursive partitioning, canonical correlation, and factor analysis (Gruenewald, Seeman, Ryff, Karlamangla, & Singer, **2006**; Karlamangla, Singer, McEwen, Rowe, & Seeman, **2002**; McCaffery, Marsland, Strohacker, Muldoon, & Manuck, **2012**; Seplaki, Goldman, Weinstein, & Lin, **2006**), but there is a lack of consensus on which statistical approach aligns best with the theoretical underpinnings of AL as a construct.

4 USE OF STRUCTURAL EQUATION MODELING

There are several potential advantages to using a structural equation modeling (SEM) approach for AL measurement, and specifically, the use of latent variable modeling with factor analysis. First, indicator variables can be treated as continuous variables, rather than the common practice of dichotomizing values at a high-risk cut-off level, leading to potential loss of information for the indicators (Beckie, **2012**; Rosemberg, Li, & Seng, **2017**). In addition, factor analysis allows researchers to test proposed factor structures for the AL construct through evaluation of local and global model fit statistics, modification indices, and parameter estimates (Booth, Starr, & Deary, **2013**). This type of complex modeling can also reduce the measurement error of the AL construct by reflecting only the common variance shared among the indicator variables, ultimately yielding a more reliable and valid measure.

To our knowledge, there are only a few studies that have utilized factor analysis to model the AL construct, with a variety of approaches and varying results. There are two studies that performed principle components analyses (PCA) (although methods were reported as exploratory factor analyses [EFA)) in which the authors aimed to determine the dimensionality (ie, how many distinct attributes the construct has) of the AL construct in an adult population using the original 10 indicators for AL (Howard & Sparks, **2016**; Johnston, **2004**). PCA is a data reduction analysis that aims to understand underlying dimensions that are implied by correlations among indicator variables, ultimately interpreting the dimensions found as "constructs" (Jain & Shandliya, **2013**). In contrast, EFA explains interrelationships among the indicator variables to determine which variables are more or less related to the larger latent construct through local and global fit testing, ultimately yielding indicator factor loadings and a latent factor structure (Jain & Shandliya, **2013**).

Keeping this in mind, the results from these two PCA studies reported different dimensionality of the AL construct, despite similar approaches and study populations (Howard & Sparks, **2016**; Johnston, **2004**). Howard and Sparks (**2016**) found evidence for a unidimensional AL construct that explained correlations between the indicators. In contrast, Johnston (**2004**) proposed that AL has three related subdimensions (cardiovascular, metabolic, and inflammation), with correlations between indicator variables relating directly to those three biological systems. Although these studies did not produce true factor structures for AL or factor loadings for indicator variables (given they utilized PCA and not EFA), they offered some preliminary insight into how a latent AL construct can be modeled.

Confirmatory factor analysis (CFA) is similar to EFA in that it produces true factor structures and factor loadings for indicators but is an approach that is driven by theory and empirical research, whereas EFA is purely data driven (Suhr, **2006**). There have been five CFA that have tested a variety of AL factor structures to determine the best measurement approach for this construct (Booth et al., **2013**; Gross, **2008**; McCaffery et al., **2012**; Seeman et al., **2010**; Wiley, **2015**). Booth et al. (**2013**) found support for a second-order three-subfactor AL structure, similar to that proposed by Johnston (**2004**), in an older adult population. The remaining four CFA studies tested a variety of AL factor structures, ultimately finding support for several different structures, including a second-order five-subfactor AL structure (Seeman et al., **2010**) as well as several residualized AL structures (Gross, **2008**; McCaffery et al., **2012**; Wiley, **2015**). In the study by Seeman et al. (**2010**), the retained AL factor structure had five subfactors, including heart rate variability, blood pressure, inflammation, metabolic, and cortisol, with

the individual indicators loading onto the subfactors and the subfactors loading onto an overall AL factor. In contrast, other studies found support for residualized AL structures where all indicators loaded onto a unidimensional AL construct, with those same indicators also sharing variance with other physiological systems (Gross, **2008**; McCaffery et al., **2012**; Wiley, **2015**). Given these differences in how AL has been operationalized in previous studies using SEM approaches and the lack of studies using such methods to generate AL constructs among younger populations, there is a clear need for further research on the ideal measurement approach, particularly in a less studied adolescent population.

5 STUDY PURPOSE

Given the heterogeneity in measurement of the AL construct across studies and the relative paucity of research parameterizing AL in younger populations, the purpose of this study is to test five hypothesized factor structures of AL using SEM among the US population-based sample of adolescents to determine the best measurement model for this construct.

6 METHODS

6.1 Study design and sample

Data for the present study were derived from four waves (2003 through 2010) of the National Health and Nutrition Examination Survey (NHANES), which is designed to assess the health and nutritional status of children, adolescents, and adults in the United States each year (National Center for Health Statistics, **2016**). Data were collected via in-home surveys conducted by trained interviewers and via a physical examination and laboratory testing completed by healthcare professionals in mobile examination centers (MECs) (NCHS, **2016**). The data are free, de-identified, and publicly available on the NHANES website.

6.2 Inclusion and exclusion criteria

The sole inclusion criterion for the current study was being 12-18 years of age, given that adolescence was the time period of interest for measuring the AL indicator variables. There were no specific exclusion criteria; therefore, any participant who met the inclusion criterion was retained. The final study sample that met inclusion and exclusion criteria was 1900 adolescents.

6.3 Study measures

6.3.1 Allostatic load

A total of 14 variables measuring dysregulation across several physiological systems were included as indictors of AL. Physical measurements included systolic blood pressure (SBP), body mass index (BMI), and waist circumference, which were collected by a trained health care professional in the MECs. Laboratory-assessed biomarkers included creatinine, insulin, fasting glucose, glycated hemoglobin (HA1C), high-density and low-density lipoprotein (HDL and LDL), triglycerides, albumin, C-reactive protein (CRP) level, white blood cell count (WBC), and Epstein-Barr viral index (EBV). All laboratory methods utilized to collect and analyze these biomarkers from NHANES were rigorously tested before data collection to ensure the reliability and validity of their protocols (Centers for Disease Control and Prevention, **2013**).

6.4 Protection of human subjects

The parent NHANES study was approved by the National Center for Health Statistics Research Ethics Review Board (NCHS, **2016**). The current study was reviewed by the Marquette University Institutional Review Board and declared exempt, given the study constituted secondary data analysis utilizing de-identified information.

6.5 Data analysis

The analysis for this study was performed in R (R Core Team, **2018**). We utilized structural equation modeling (SEM) with the R package lavaan (Rosseel, **2012**). As described by Raykov (**2012**), the SEM framework allows researchers to develop and test factors, such as evaluation of multidimensional structures, correlations between constructs, evaluation of multiple reliability measures, and reducing measurement error of the underlying measured indicators to estimate a more precise measure of the latent AL construct (Kline, **2016**; Little, **2013**). CFA was used within the SEM framework to test multiple factor structures for the AL indicators, which were compared based on their fit indices, proper estimation solution, and theoretical meaning of the parameter estimates.

Five AL factor structures were tested in this study to model the AL construct (see Figure **1**). First, we tested a unidimensional factor structure (model A), in which all of the indicators were explained by a single AL factor. We then tested three second-order factor structures (models B, C, and D), in which indicators loaded directly onto physiological systems or specific biological processes (subfactors), and then, these subfactors then loaded onto an overall AL factor. These factor structures included: (1) a second-order two-subfactor structure, whereby the indicators loaded onto cardiometabolic and inflammation first-order factors, (2) a second-order three-subfactor structure, in which the indicators loaded onto cardiovascular, metabolic, and inflammation first-order factors, and (3) a second-order five-subfactor structure, whereby the indicators loaded onto cardiovascular, insulin resistance, lipids, weight, and inflammation first-order factors. Finally, we tested a five correlated factors structure (model E) representing key physiological systems and processes that are associated with AL (using the same five subfactors as in model D), all of which were intercorrelated. These five AL factor structures were chosen based on the AL theoretical framework and previous empirical research that have utilized SEM to model this construct.

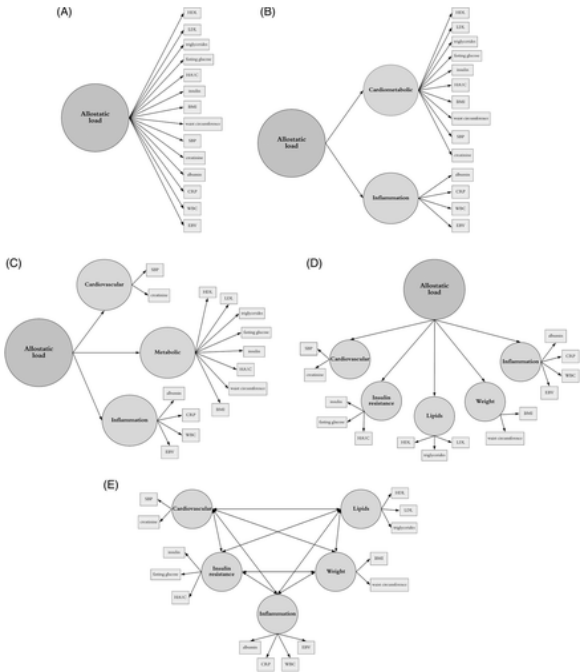

Figure 1 Proposed allostatic load factor structures. (A) Model A, unidimensional factor structure; (B) model B, second-order two-subfactor structure; (C) model C, second-order three-subfactor structure; (D) model D, second-order five-subfactor structure; (E) model E, five correlated factors structure

The reliability of the selected AL latent factor structure was then evaluated with the maximal reliability (MR) coefficient, which estimates the reliability of a factor or scale assuming the underlying indicators have different weights. Thus, MR is the maximal possible reliability for a linear combination of the indicator items and involves the estimation of the optimal linear combination (OLC) (ie, the weights for each item). MR was estimated with the R package semTools (semTools Contributors, **2018**).

All indicators for the AL latent construct were continuous measures. These indicators were transformed into a standard normal variable with mean = 0 and SD = 1, which was performed so that the indicators would all be in the same metric. SEM models were estimated with maximum likelihood (ML), and model fit was evaluated with multiple approximate fit indices (Fan & Sivo, **2007**; Kline, **2016**; West, Taylor, & Wu, **2012**). The effect of missing data was addressed with full information maximum likelihood (FIML), which is a modern method that properly handles missing data by improving parameter recoverability, reducing bias, and increasing power (Baraldi & Enders, **2010**; Enders, **2010**). The missing data recoverability was evaluated with the fraction of missing information (FMI), which quantifies the missing data's influence on the sampling variance of a parameter estimate as the proportion of the total sampling variance that is due to the missing data (Enders, **2010**).

Although historically it has been the standard to weight samples from large population datasets such as NHANES to account for complex sampling designs in less sophisticated analyses, there is evidence that it is not necessary to do so when using SEM. Work by Kaplan and Ferguson (**1999**) and Hahs-Vaughn and Lomax (**2006**) suggested that sampling weights in such study designs had a negligible effect on parameter estimates, so long as the probability of selection is not informative about the SEM parameters (Bollen, Turner, & Oberski, **2013**), which is up to the individual researcher to decide. We determined that including the sampling weights for the AL biomarkers would not likely have a

significant effect on parameter estimates and almost certainly would inflate the standard errors. To counter the increased risk for type I error, we utilized a conservative alpha level of 0.01 in all analyses.

7 RESULTS

7.1 Descriptive statistics

The mean age of the study participants was 15.036 years (SD = 2, range = 12-18), and there was an approximately equal distribution of females and males (48.3% female, 51.7% male) and racial/ethnic groups (27.6% White, 37.7% African American, 34.7% Hispanic) in the study population.
Table **1** provides additional descriptive statistics for each of the 14 biological indicator variables used to model the AL construct.

Table 1. Allostatic load indicator descriptive statistics

	Total sample (*N* = 1900)		**White (*N* = 525)**		**African American (*N* = 716)**		**Hispanic (*N* = 659)**	
AL indicators	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Systolic BP (mm Hg)	108.995	10.171	108.422	10.463	109.966	9.847	108.435	10.211
Creatinine (mg/dL)	0.746	0.162	0.753	0.158	0.785	0.162	0.7	0.154
HDL (mg/dL)	53.205	12.701	51.884	12.744	55.648	13.356	51.612	11.515
LDL (mg/dL)	89.106	26.606	89.521	28.201	88.901	27.815	89.035	23.855
Triglycerides (mg/dL)	85.797	50.815	96.288	60.613	71.26	34.176	95.004	55
HA1C (%)	5.217	0.442	5.163	0.385	5.275	0.5	5.197	0.409
Fasting glucose (mg/dL)	90.294	14.292	93.222	22.361	88.342	10.201	90.372	9.398
Insulin (uU/mL)	12.957	13.67	12.283	14.693	13.734	15.182	12.556	10.709
BMI (kg/m^2)	23.709	5.995	23.254	5.579	24.388	6.799	23.34	5.289
Waist circumference (cm)	81.152	15.009	81.569	14.413	80.388	16.454	81.642	13.779
Albumin (g/dL)	4.376	0.337	4.44	0.33	4.246	0.325	4.464	0.312
EBV	3.539	1.75	2.768	1.961	3.888	1.616	3.756	1.523
CRP (mg/dL)	0.256	0.623	0.21	0.369	0.369	0.665	0.259	0.715
WBC (1000 cells/uL)	6.873	2.125	7.35	2.17	5.887	1.877	7.565	1.934

† Abbreviations: AL, allostatic load; BMI, body-mass-index; CRP, C-reactive protein; EBV, Epstein-Barr viral index; HAIC, hemoglobin A1C (ie, glycated hemoglobin); HDL, high-density lipoprotein; LDL, low-density lipoprotein; systolic BP, systolic blood pressure; WBC, white blood cell count.

‡ Using unweighted NHANES data.

7.2 Tested factor structures

Table **2** reports the fit indices for the five tested factor structures. Models D and E presented the best fit indices, but the models both had unstable parameters. For model D, the standardized second-order factor loadings were at the boundary (1.00) for two of the first-order factors (WEI and INFL), which indicated that this factor solution did not have interpretable parameters. Model E presented negative residual variances (out of bounds) as well as low factor loadings for the INF second-order factor with a $p > .3$. Fit indices between models A, B, and C were equivalent, but models B and C also presented out of bounds parameters, meaning those parameters were also uninterpretable. Specifically, factor correlations for these two models were estimated to be higher than 1, indicating that some of the proposed first-order factors were not distinguishable, thus suggesting a unidimensional factor structure for AL. Model A was the only tested factor structure that had proper fit indices with no out of bounds parameters. Therefore, given the AL theoretical framework, fit indices, and parameter estimates for the five models, we selected model A as the preferred factor structure for the AL construct for this adolescent study population (see Figure **2**).

Table 2. Fit indices for tested factor structures

	χ^2 (df)	CFI	Gamma-hat	Adj. gamma-hat	RMSEA	SRMR
Model A	747.55 (75)	0.890	0.952	0.933	0.069 (0.064, 0.073)	0.067
Model B	732.09 (74)	0.890	0.952	0.932	0.069 (0.065, 0.077)	0.069
Model C	701.42 (85)	0.900	0.958	0.941	0.062 (0.058, 0.066)	0.065
Model D	596.12 (84)	0.921	0.966	0.953	0.055 (0.051, 0.059)	0.049
Model E	846.95 (81)	0.932	0.972	0.957	0.053 (0.048, 0.057)	0.056

† Abbreviations: χ^2, chi-square exact-fit; CFI, comparative fit index; df, degrees of freedom; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residual.
‡ Using unweighted NHANES data.

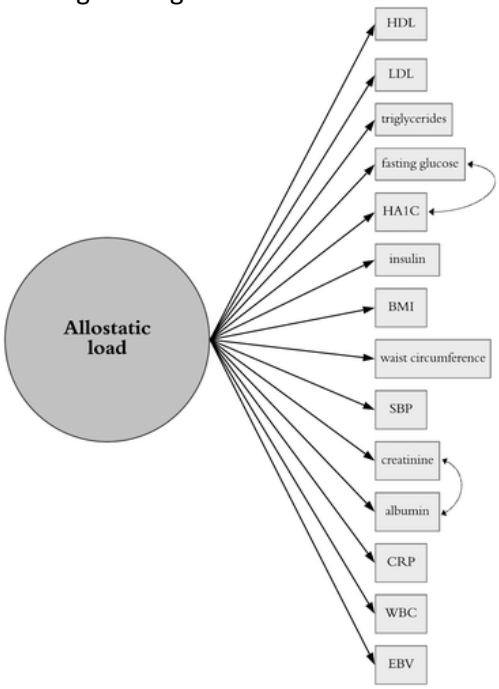

Figure 2 Unidimensional allostatic load (AL) factor structure. The 14 biomarkers that represent cardiovascular, metabolic, and immune system function load directly onto a single AL factor. The majority of the AL biomarkers had positive factor loadings, with high-density lipoprotein and albumin as the only negative factor loadings. Two

residual correlations were retained to improve model fit, which indicates these biomarkers share variance that is not related to AL. Fit indices for this unidimensional AL factor structure were as follows: $\chi 2$ (df) = 747.55 (75), CFI = 0.890, adj. gamma-hat = 0.933, root mean square error of approximation = 0.069 (0.064, 0.073), standardized root mean square residual = 0.067

Based on modification indices, two residual correlations between indicators were included (as shown in Figure **2**): between fasting glucose and HA1C (r = 0.628, p < .001) and between albumin and creatinine (r = 0.243, p < .001). These residual correlations were kept because of shared variance between those indicators that is attributable to other physiological processes than AL. Fasting glucose and HA1C share variance related to glucose metabolism, whereas albumin and creatinine share variance for conditions related to kidney function, both of which can be unrelated to stress and AL.

Table **3** presents the factor loadings and R^2 for model A. The null hypothesis is rejected for every factor loading with all p values less than .01. AL is defined by positive factor loadings for every indicator except two (albumin and HDL), which means that individuals with higher AL will have higher values for positive loading indicators and lower values for negative loading indicators. The indicators that best represented AL were BMI and waist circumference, which had the highest absolute values of factor loadings, whereas the indicators that least represented AL were EBV and HA1C, which had the lowest factor loadings. Although the R^2 for some indicators were low in this study population, we decided to retain them given their theoretical and biological relevance to the AL construct.

Table 3. Factor loadings and R^2 for allostatic load indicators

Indicator	Factor loadings (SE)	*p*-value	R^2
CREAT	0.111 (0.025)	<.001	0.012
ALBUM	−0.255 (0.025)	<.001	0.065
CRP	0.164 (0.027)	<.001	0.027
HDL	−0.342 (0.024)	<.001	0.116
LDL	0.212 (0.035)	<.001	0.045
TRIGLY	0.317 (0.034)	<.001	0.101
EBV	0.083 (0.025)	.001	0.007
HAIC	0.079 (0.025)	.002	0.006
GLUC	0.121 (0.033)	<.001	0.013
INSUL	0.578 (0.030)	<.001	0.338
WBC	0.204 (0.025)	<.001	0.042
SBP	0.334 (0.026)	<.001	0.110
BMI	0.965 (0.018)	<.001	0.932
WAIST	0.982 (0.018)	<.001	0.949

† Abbreviations: ALBUM, albumin; BMI, body mass index; CREAT, creatinine; CRP, C-reactive protein; EBV, Epstein-Barr viral index; HA1C, glycated hemoglobin; HDL, high-density lipoprotein; INSUL, insulin; LDL, low-density lipoprotein; SBP, systolic blood pressure; TRIGLY, triglycerides; WAIST, waist circumference; WBC, white blood cell count.

‡ Using unweighted NHANES data.

When diagnosing the effect of missing data in the model, we found that the FMI was high (above 0.5) for the factor loadings of LDL, triglycerides, and insulin due to the large amount of missing data for these indicators (over 1000). The parameter estimates for those indicators are still reliable, but there is a penalty of larger standard errors for those indicators due to this missing data influence. FMI values for all other AL indicators were low; therefore, the effect of missing data in our study model was deemed to have little influence on our findings. In addition, the MR coefficient for the AL construct was 0.988, which demonstrated a high internal reliability.

8 DISCUSSION

The purpose of this study was to compare several factor structures for the AL construct in an adolescent population to determine the best measurement approach for this construct among younger individuals. Our findings provide support for a unidimensional AL structure such that the individual indicators that represent dysregulation of various body systems load onto a single AL factor. A unidimensional model implies that each AL biomarker is directly influenced by the AL construct, rather than indirectly influenced through a related physiological system. To our knowledge, this is the first SEM study in a pediatric population that supports a unidimensional AL factor structure.

Although our findings are consistent with that of the PCA study in an older adult population carried out by Howard and Sparks (**2016**), much of the adult AL literature that has utilized SEM supports either second-order factor structures (Booth et al., **2013**; Johnston, **2004**; Seeman et al., **2010**) or a residualized AL factor structure (Gross, **2008**; McCaffery et al., **2012**; Wiley, **2015**). This likely reflects differences in the age of the study population (adults or older adults vs adolescents) and the corresponding differences in how stress manifests physiologically over time. Given that AL is believed to represent the body's "wear and tear" over time (Booth et al., **2013**), it is logical that in an adolescent population, we may not see the widespread dysregulation of AL biomarkers across multiple-body systems that have been observed in studies utilizing adult populations. As a result, there was likely less variability in many of the AL indicators for this younger population, which likely contributed to fit indices supporting a unidimensional factor structure.

Overall, local and global fit indices for the selected unidimensional AL factor structure (model A) provided an adequate fit to the data (CFI 0.89, RMSEA 0.069, SRMR 0.067), which suggests that there is indeed a core of common shared variance among these biological markers of systemic dysregulation. This factor structure suggests that as AL increases in adolescents, the indicators with positive factor loadings also increase, whereas those with negative factor loadings decrease. A possible explanation for the lack of better model fit could be our inability to include all of the theorized biomarkers involved in the pathways between chronic stress and development of AL in adolescents. Specifically, this study was unable to include biomarkers from the neuroendocrine system (ie, cortisol, DHEA) given they were not available in NHANES. Inclusion of these biomarkers could have potentially improved fit indices and provided a more robust AL measure. However, in research carried out among adult populations in which such neuroendocrine biomarkers have been included in AL measures (Seeman et al., **2010**), those indicators had the lowest factor loadings compared to those from other physiological systems. The low factor loadings of the neuroendocrine indicators suggest that although it is ideal to include these biomarkers in AL measurement for theoretical purposes, models that do not include them are likely still valid and clinically meaningful for predicting chronic disease risk.

Consistent with previous AL literature using SEM, the biomarkers that were the best indicators of AL were those associated with dysregulation of the metabolic system (Booth et al., **2013**; Seeman et al., **2010**). Particular for this study, BMI and waist circumference had the highest factor loadings (0.965 and 0.982, respectively), with 93.2% and 94.9% of the variance in those indicators explained by AL. These two indicators suggest that an individual with higher AL is likely to have elevated BMI and waist circumference, both of which are associated with obesity (National Heart Lung and Blood Institute, **2017**). The high factor loadings in these AL indicators suggest that they are perhaps the earliest clinical signs of elevated AL that manifest in adolescent populations. Given that obesity among children and adolescents has become a serious health concern in the 21st century (Gungor, **2014**; Kelly et al., **2013**), this is an important finding that could aid health care providers in identifying individuals with elevated AL in its early phases where intervention might be more effective at reducing risk of developing chronic disease.

The factor loadings for the remaining AL biomarkers in this adolescent population were relatively low (ranging from 0.06 to 0.338), with the lowest primarily found among those associated with dysregulation of the cardiovascular and immune systems, similar to previous research using NHANES data (Gross, **2008**). The studies that did observe higher factor loadings for the cardiovascular and inflammatory indicators (Booth et al., **2013**; Seeman et al., **2010**) were carried out among adult and older adult study populations; therefore, these individuals would have had more time to develop elevated AL across multiple systems, whereas adolescents have not. As such, drastic systemic alterations in the stress regulatory systems observed in adult populations may be unlikely to be present in a younger, relatively healthy study sample.

Moving forward with AL research in pediatric populations, an argument could be made to modify the biomarkers included in measures of AL to include biological indicators that are more likely to become dysregulated earlier in life to have a more robust estimation of AL. Although measuring the neuroendocrine mediators can be logistically challenging, these are theoretically antecedent to biomarkers reflecting systemic dysregulation in the cardiovascular, metabolic, and immune systems (such as those focused on in this study). Thus, dysregulation of neuroendocrine stress hormones, such as cortisol, may be more likely to emerge in childhood and adolescence than biomarkers linked to other downstream physiological systems and processes. Although these neuroendocrine AL biomarkers have not had high factor loadings for adult populations, they might be more relevant indicators of elevated AL in pediatric populations. A suggestion for future pediatric AL research utilizing an SEM approach would be to incorporate a measure of hair cortisol as an indicator of more long-term HPA axis dysregulation, which overcomes the measurement challenges of salivary or serum cortisol use and provides a more stable measurement of chronic stress (Fischer et al., **2017**). In addition, if we are to better understand why some children develop elevated AL while others do not under similar stressful conditions, DHEA has been proposed to be a potentially important marker for stress resilience (Juster, McEwen, & Lupien, **2010**) and is involved in turning off the HPA axis, thus warranting consideration for inclusion in future AL constructs in younger populations.

The findings of this study provide preliminary evidence for how best to model the AL construct within an adolescent study population. Moving forward in future research, given the low factor loadings for many of the AL indicators that are often used in adult AL research, this unidimensional AL factor

structure should be validated in other pediatric populations. In addition, researchers might want to consider paring down the number of biomarkers that are included in the AL construct to facilitate transition of this concept over into clinical practice. Future research could help determine the ideal combination of weighted biomarkers through use of SEM and factor analyses to promote consensus on the best two or three indicators from each of the key AL systems that are relevant for pediatric populations. Limiting of included AL indicators could help contain research costs and make it more feasible to follow children long-term in longitudinal biobehavioral studies, which are better able to capture development of elevated AL over time.

8.1 Study strengths and limitations

The findings from this study should be interpreted in the context of several strengths and limitations. Strengths of the study include its focus on a younger adolescent population, use of a wide variety of AL biomarkers in a large study sample, and incorporation of a sophisticated SEM modeling strategy with little influence of missing data on findings, which together are not found in the existing AL measurement literature. However, a key limitation is that NHANES data are cross-sectional, which did not allow assessment of whether the currently observed levels of the AL indicators truly reflected a cumulative process of dysregulation developing over time. In addition, there was no measurement of neuroendocrine hormones in NHANES, which serve as mediators in the development of AL through their effects on the HPA axis. Although there are significant logistical challenges for measuring such biomarkers at the population level, hormones that reflect dysregulation of HPA axis activity would have been ideal to include in the AL latent construct for this adolescent population. Lastly, there is some research suggesting that individual AL indicators might contribute differently to the AL construct based on race/ethnicity, an aspect that was not considered in the present analysis. Examination of AL construct measurement across different racial/ethnic groups, particularly in younger populations, should be another focus area for future work in this field.

9 CONCLUSION

This is the first known AL study using SEM for an adolescent population that supports a unidimensional AL factor structure reflecting common shared variance among several biological indicators representing this construct. Further research in adolescent and pediatric populations is warranted to better delineate which biologic pathways contributing to elevated AL emerge first in life, why this is the case, and how we could best intervene earlier in life to mitigate chronic disease risk over the life course. AL is a promising theoretical framework that allows better understanding for how social and environmental stressors can become biologically embedded and negatively impact the health of children and adolescents, which could program for ill health in adulthood. Ultimately, health care providers may be able to utilize the AL theoretical framework to identify adolescents at greatest risk for developing chronic disease and thereby focus preventative efforts on these individuals to best mitigate disease risk.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare in conducting this research or preparing this manuscript for publication.

AUTHOR CONTRIBUTIONS

This study was conceived by AK, MGV, and NJ. AK and MGV were responsible for all statistical analyses, and AK drafted the manuscript. AK, MGV, NJ, and AS all participated in manuscript revisions, and all authors approved the final manuscript.

REFERENCES

Barboza Solís, C., Kelly-Irving, M., Fantin, R., Darnaudery, M., Torrisani, J., Lang, T., & Delpierre, C. (2015). Adverse childhood experiences and physiological wear-and-tear in midlife: Findings from the 1958 British Birth Cohort. *Proceedings of the National Academy of Sciences of the United States of America*, **112**(7), E738– E746. https://doi.org/10.1073/pnas.1417325112

Baraldi, A. N., & Enders, C. K. (2010). An introduction to modern missing data analyses. *Journal of School Psychology*, **48**(1), 5– 37. https://doi.org/10.1016/j.jsp.2009.10.001

Beckie, T. M. (2012). A systematic review of allostatic load, health, and health disparities. *Biological Research for Nursing*, **14**(4), 311– 346. https://doi.org/10.1177/1099800412455688

Beckie, T. M., Duffy, A., & Groer, M. W. (2016). The relationship between allostatic load and psychosocial characteristics among women veterans. *Women's Health Issues*, **26**(5), 555– 563. https://doi.org/10.1016/j.whi.2016.05.008

Bollen, K., Turner, S., & Oberski, D. (2013). Issues in the structural equation modeling of complex survey data. In *Proceedings of the 59th World Statistics Congress* (p. 2013). 25–30 August 2013, Hong Kong (session ST2010).

Booth, T., Starr, J. M., & Deary, I. (2013). Modeling multisystem biological risk in later life: Allostatic load in the Lothian Birth Cohort Study 1936. *American Journal of Human Biology*, **25**(4), 538– 543. https://doi.org/10.1002/ajhb.22406

Centers for Disease Control and Prevention. (2013). *National Health and Nutrition Examination Survey: Plan and operations, 1999-2010*. Retrieved from https://www.cdc.gov/nchs/data/series/sr_01/sr01_056.pdf

Centers for Disease Control and Prevention. (2017). Chronic disease overview. *Chronic Disease Prevention and Health Promotion*. Retrieved from https://www.cdc.gov/chronicdisease/overview/index.htm

Chen, E., Miller, G. E., Brody, G. H., & Lei, M. (2015). Neighborhood poverty, college attendance, and diverging profiles of substance use and allostatic load in rural african american youth. *Clinical Psychological Science*, **3**(5), 675– 685. https://doi.org/10.1177/2167702614546639

Enders, C. K. (2010). *Applied missing data analysis*. New York: Guilford Press.

Fan, X., & Sivo, S. A. (2007). Sensitivity of fit indices to model misspecification and model types. *Multivariate Behavioral Research*, **42**(3), 509– 529. https://doi.org/10.1080/00273170701382864

Fischer, S., Duncko, R., Hatch, S. L., Papadopoulos, A., Goodwin, L., Frissa, S., . . . Cleare, A. J. (2017). Sociodemographic, lifestyle, and psychosocial determinants of hair cortisol in a south

London community sample. *Psychoneuroendocrinology,* **76**, 144– 53. doi:https://doi.org/10.1016/j.psyneuen.2016.11.011

Friedman, E. M., Karlamangla, A. S., Gruenewald, T. L., Koretz, B., & Seeman, T. E. (2015). Early life adversity and adult biological risk profiles. *Psychosomatic Medicine*, **77**(2), 176– 185. https://doi.org/10.1097/psy.0000000000000147

Gross, K. S. (2008). Measuring allostatic load in children: Exploring the pathway between biomarkers and educational outcomes. In *Doctor of Philosophy*. Ann Arbor: University of Pennsylvania.

Gruenewald, T. L., Seeman, T. E., Ryff, C. D., Karlamangla, A. S., & Singer, B. H. (2006). Combinations of biomarkers predictive of later life mortality. *Proceedings of the National Academy of Sciences of the United States of America*, **103**, 14158– 14163.

Gungor, N. K. (2014). Overweight and obesity in children and adolescents. *Journal of Clinical Research in Pediatric Endocrinology*, **6**(3), 129– 143. https://doi.org/10.4274/Jcrpe.1471

Hahs-Vaughn, D. L., & Lomax, R. G. (2006). Utilization of sample weights in single-level structural equation modeling. *The Journal of Experimental Education*, **74**(2), 161– 190.

Havranek, E. P., Mujahid, M. S., Barr, D. A., Blair, I. V., Cohen, M. S., Cruz-Flores, S., . . . Stroke, C. (2015). Social determinants of risk and outcomes for cardiovascular disease: A scientific statement from the American Heart Association. *Circulation,* **132**(9), 873– 98. doi:https://doi.org/10.1161/CIR.0000000000000228

Healthy People 2020. (2016). Healthy people 2020. Retrieved from https://www.healthypeople.gov/sites/default/files/HP2020Framework.pdf

Howard, J. T., & Sparks, P. J. (2016). Does allostatic load calculation method matter? Evaluation of different methods and individual biomarkers functioning by race/ethnicity and educational level. *American Journal of Human Biology*, **28**(5), 627– 635. https://doi.org/10.1002/ajhb.22843

Hunter, D. J., & Reddy, K. S. (2013). Noncommunicable diseases. *New England Journal of Medicine*, **369**(14), 1336– 1343. https://doi.org/10.1056/NEJMra1109345

Hux, V., & Roberts, J. (2015). A potential role for allostatic load in preeclampsia. *Maternal & Child Health Journal*, **19**(3), 591– 597. https://doi.org/10.1007/s10995-014-1543-7

Hux, V. J., Catov, J. M., & Roberts, J. M. (2014). Allostatic load in women with a history of low birth weight infants: The National Health and Nutrition Examination Survey. *Journal of Women's Health*, **23**(12), 1039– 1045. https://doi.org/10.1089/jwh.2013.4572

Jain, P. M., & Shandliya, V. K. (2013). A survey paper on comparative study between principal component analysis (PCA) and exploratory factor analysis (EFA). *International Journal of Computer Science and Applications*, **6**(2), 373– 375.

Johnston, M. L. (2004). Age, sex, and race/ethnic differences in biological risk: Allostatic load and metabolic syndrome. In *Doctor of Philosophy*. Los Angeles, CA: University of Southern California.

Juster, R. P., McEwen, B. S., & Lupien, S. J. (2010). Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neuroscience & Biobehavioral Reviews*, **35**(1), 2– 16. https://doi.org/10.1016/j.neubiorev.2009.10.002

Kaplan, D., & Ferguson, A. J. (1999). On the utilization of sample weights in latent variable models. *Structural Equation Modeling: A Multidisciplinary Journal*, **6**(4), 305– 321.

Karlamangla, A. S., Singer, B. H., McEwen, B. S., Rowe, J. W., & Seeman, T. E. (2002). Allostatic load as a predictor of functional decline: MacArthur studies of successful aging. *Journal of Clinical Epidemiology*, **55**, 696– 710.

Kelly, A. S., Barlow, S. E., Rao, G., Inge, T. H., Hayman, L. L., Steinberger, J., … Council on Clinical, C. (2013). Severe obesity in children and adolescents: Identification, associated health risks, and

treatment approaches: A scientific statement from the American Heart Association. *Circulation*, **128**(15), 1689– 1712. https://doi.org/10.1161/CIR.0b013e3182a5cfb3

Kline, R. B. (2016). *Principles and practice of structural equation modeling* (4th ed.). New York: Guilford Press.

Kobrosly, R. W., Seplaki, C. L., Cory-Slechta, D. A., Moynihan, J., & van Wijngaarden, E. (2013). Multisystem physiological dysfunction is associated with depressive symptoms in a population-based sample of older adults. *International Journal of Geriatric Psychiatry*, **28**(7), 718– 727. https://doi.org/10.1002/gps.3878

Kuhn, M., Scharfenort, R., Schümann, D., Schiele, M. A., Münsterkötter, A. L., Deckert, J., … Lonsdorf, T. B. (2016). Mismatch or allostatic load? Timing of life adversity differentially shapes gray matter volume and anxious temperament. *Social Cognitive & Affective Neuroscience*, **11**(4), 537– 547. https://doi.org/10.1093/scan/nsv137

Little, T. D. (2013). *Longitudinal structural equation modeling*. New York: Guilford Press.

Masterson, E. E., & Sabbah, W. (2015). Maternal allostatic load, caretaking behaviors, and child dental caries experience: A cross-sectional evaluation of linked mother-child data from the third National Health and Nutrition Examination Survey. *American Journal of Public Health*, **105**(11), 2306– 2311. https://doi.org/10.2105/AJPH.2015.302729

McCaffery, J. M., Marsland, A. L., Strohacker, K., Muldoon, M. F., & Manuck, S. B. (2012). Factor structure underlying components of allostatic load. *PLoS One*, **7**(10), 1– 8. https://doi.org/10.1371/journal.pone.0047246

McEwen, B. S. (1998). Protective and damaging effects of stress mediators. *The New England Journal of Medicine*, **338**(3), 171– 179.

Miller, G. F., Coffield, E., Leroy, Z., & Wallin, R. (2016). Prevalence and costs of five chronic conditions in children. *The Journal of School Nursing*, **32**(5), 357– 364. https://doi.org/10.1177/1059840516641190

National Center for Health Statistics. (2016). National Health and Nutrition Examination Survey (NHANES). Retrieved from http://www.cdc.gov/nchs/nhanes/

National Heart Lung and Blood Institute. (2017). Assessing your weight and health risk. Retrieved from https://www.nhlbi.nih.gov/health/educational/lose_wt/risk.htm

Raykov, T. (2012). Scale construction and development using structural equation modeling. In R. H. Hoyle (Ed.), *Handbook of Structural Equation Modeling* (pp. 472– 494). New York: Guilford Press.

R Core Team. (2018). R: A language and environment for statistical computing. Retrieved from https://www.R-project.org/

Rosemberg, M. S., Li, Y., & Seng, J. (2017). Allostatic load: A useful concept for advancing nursing research. *Journal of Clinical Nursing*, **26**, 1– 15. https://doi.org/10.1111/jocn.13753

Rosseel, Y. (2012). lavaan: An R package for structural equation modeling. *Journal of Statistical Software,* **48**(2), 1- 36.

Seeman, T., Gruenewald, T., Karlamangla, A., Sidney, S., Liu, K., McEwen, B., & Schwartz, J. (2010). Modeling multisystem biological risk in young adults: The Coronary Artery Risk Development in Young Adults Study. *American Journal of Human Biology*, **22**(4), 463– 472. https://doi.org/10.1002/ajhb.21018

semTools Contributors. (2018). semTools: Useful tools for structural equation modeling. Retrieved from https://CRAN.R-project.org/package=semTools

Seplaki, C. L., Goldman, N., Weinstein, M., & Lin, Y. H. (2006). Measurement of cumulative physiological dysregulation in an older population. *Demography*, **43**, 165– 183.

Steptoe, A., & Kivimaki, M. (2013). Stress and cardiovascular disease: An update on current knowledge. *Annual Review of Public Health*, **34**, 337– 354. https://doi.org/10.1146/annurev-publhealth-031912-114452

Steptoe, A., Hackett, R. A., Lazzarino, A. I., Bostock, S., Marca, R. L., Carvalho, L. A., & Hamer, M. (2014). Disruption of multisystem responses to stress in type 2 diabetes: Investigating the dynamics of allostatic load. *Proceedings of the National Academy of Sciences of the United States of America*, **111**(44), 15693– 15698. https://doi.org/10.1073/pnas.1410401111

Suhr, D. D. (2006). *Exploratory or confirmatory factor analysis?* Cary: SAS Institute.

Theall, K. P., Drury, S. S., & Shirtcliff, E. A. (2012). Cumulative neighborhood risk of psychosocial stress and allostatic load in adolescents. *American Journal of Epidemiology*, **176**(Suppl 7), S164– S174.

Ward, B. W., Schiller, J. S., & Goodman, R. A. (2014). Multiple chronic conditions among US adults: A 2012 update. *Preventing Chronic Disease*, **11**, 130389. https://doi.org/10.5888/pcd11.130389

West, S. G., Taylor, A. B., & Wu, W. (2012). Model fit and model selection in structural equation modeling. In R. H. Hoyle (Ed.), *Handbook of structural equation modeling* (pp. 209– 231). New York: Guilford Press.

Wiley, J. F. (2015). Measurement of psychosocial resources, allostatic load, and their relations. In *Doctor of Philosophy*. Los Angeles, CA: University of California Los Angeles.

World Health Organization. (2018). The global burden of chronic diseases. Retrieved from http://www.who.int/nutrition/topics/2_background/en/