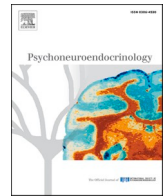


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Review

Evaluating measures of allostatic load in adolescents: A systematic review

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ABSTRACT

Background: Adolescents can experience heightened stress due to biopsychosocial changes that occur during this developmental stage. The 'wear and tear' of the physiological systems responsible for managing our stress response can lead to dysregulation of these systems, known as allostatic load (AL). AL is commonly measured within adult populations, however, inconsistencies exist across measures used to quantify the effects of stress on health. The aim of this review was to identify variations in measures across AL studies, and to consider how specific measures may be more appropriate for use within adolescent populations.

Method: Pubmed, PsycINFO, PsycARTICLES, Academic Search Complete, were searched in July 2020, using search terms 'allostatic load' and 'adolescence'. AL studies (1988–2020) with an adolescent population (age 10–24 years) were included. 354 records were screened by two reviewers and 41 full-text articles were assessed for eligibility.

Results: 25 studies were included in final synthesis. Biomarkers of AL ranged from 1 to 14. The most common index of AL consisted of 6 biomarkers; cortisol, epinephrine, norepinephrine, systolic blood pressure, diastolic blood pressure, and body-mass index.

Findings: Defining measures of AL during adolescence may help to identify vulnerabilities specific to adolescents, which may shape their lifelong health trajectories.

1. Introduction

The allostatic load (AL) framework was proposed by McEwen and Stellar (1993) to provide a conceptual and measurement model to consider the 'wear and tear' of the body over time that results from humans' responses to stressors. The MacArthur Studies (Seeman et al., 1997) originally proposed an index of AL that comprised of 10 biomarkers, depicting activity within and across four physiological systems; neuroendocrine, cardiovascular, metabolic, and immune. However, the original AL index was not proposed as a gold standard, but rather the first attempt to operationalise AL in a population of older adults. Since then, numerous studies have added to and revised the operationalisation of this latent construct (Guidi et al., 2021; McLoughlin et al., 2020; Li et al., 2019), and this has led to increasing variability, in the selection of measures used across studies, to represent allostatic load (Gallo et al., 2014). There is a general consensus that allostatic load measurement should include neuroendocrine and immunological biomarkers (Johnson et al., 2017), as the neuroendocrine and immune systems are involved in stress adaptation and affect health, however there is a wide

range of combinations of measures in use (Juster et al., 2010), and it is timely to pause and reflect on the construction and use, of allostatic load measures (Loucks et al., 2008).

Allostatic load has most often been used to examine the biological consequences of a range of stressors, including lower socio-economic status (Johnson et al., 2017; Szanton et al., 2005), discrimination due to minority group status (Chyu and Upchurch, 2011; Duru et al., 2012) and adverse childhood experiences (Slopen et al., 2016). In studies using allostatic load, the study populations are predominantly older adults, (Juster et al., 2011; Seplaki et al., 2006; Karlamangla et al., 2002). Implicit in the conceptualisation of allostatic load is the passage of time needed for the accumulation of the 'wear and tear' however, studies are now increasingly reporting on allostatic load in younger populations, including children and adolescents (Sun et al., 2020). It is possible that chronic stress may not be the only causal factor in allostatic load (Buss et al., 2011; Evans, 2003) and this delimits the concept of allostatic load as a condition of duration of exposure, in part as age, as a limiter of duration of stress exposure, may not be a strong determinant of consequences on markers of allostatic load. It does suggest

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though, that some physiological systems may be more disrupted by stress during periods of sensitivity, including adolescence (Joos et al., 2019; King et al., 2019a, 2019b), and so the combination of measures used to calculate allostatic load is a crucial consideration. Adolescence is a sensitive period of development, which involves changes across several physiological systems (Hastings et al., 2011). Evaluating the measures that most accurately indicate allostatic load during this developmental period is an important task, and would be served by determining the range and variability of allostatic load indicators used in adolescent populations (Fig. 1).

1.1. Measuring allostatic load

Previous reviews have noted substantial variance amongst the number of biomarkers used, ranging from 6 to 17 measures used to calculate AL (Mauss et al., 2017). The allostatic load index (ALI) is based on 10 physiological measurements, comprising four primary mediators: dehydroepiandrosterone-sulfate (DHEA-S), epinephrine, norepinephrine, cortisol; and six secondary outcomes, systolic-blood pressure (SBP), diastolic-blood pressure, cholesterol, high-density-lipoprotein (HDL), glycosylated haemoglobin (HbA1c), and waist-hip ratio (WHR). The 10 biomarkers measured within this index are then transformed into summary scores, with higher values indicating greater evidence of physiological strain in response to stressors, and lower values indicating more successful adaptation (Liu et al., 2021). As the neuroendocrine system plays a central role in the stress response, and stress underpins the conceptual framework of AL, more recently, researchers have advocated that measures of AL should include neuroendocrine markers (Piazza et al., 2010). Johnson et al. (2017) noted the omission of HPA-axis activity markers in almost half of all studies retrieved in their review, and strongly advocated that these biomarkers should be included in order to align with McEwen and Stellar's (1993) original framework. The National Health and Nutrition Examination Survey (NHANES) data has been frequently drawn upon for studies of allostatic load (Duong et al., 2017) due to the number and range of biomarkers available including; systolic blood pressure (SBP), creatinine, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), insulin, fasting glucose, glycosylated haemoglobin (HbA1c), body-mass-index (BMI), waist circumference (WC), albumin, C-reactive protein (CRP), white blood cell count (WBC), and Epstein-Barr-virus (EBV). Although this database contains 14 biomarkers of AL, across three physiological systems, immune, metabolic, and cardiovascular, it does not contain markers of neuroendocrine function, yet it has been deemed a valid measure of AL in excess of 20 studies (Liu et al., 2021). The commonly argued inclusion of neuroendocrine markers,

versus the validity of AL indices that have failed to capture neuroendocrine function, only further contributes to this ongoing methodological debate. The number of studies that have used data from NHANES, or other large, longitudinal datasets (e.g. MIDUS), highlights a fundamental and persistent challenge encountered by AL researchers, in that biomarkers of physiological function, namely neuroendocrine and immune, are particularly difficult to ascertain due to participant and financial burden (Liu et al., 2021). The pre-existing methodological disparities, combined with access and availability of biomarkers, should be considered both in relation to the theoretical framework of allostatic load, but also in relation to determining sub-clinical, and clinically meaningful health outcomes (Loucks et al., 2008).

1.2. Allostatic load and adolescence

Allostatic load has been well documented in adult populations, when the long-term effects of stress on health are more pronounced (Juster et al., 2010; McEwen, 2002; Seeman et al., 2001) and may represent cumulative as well as severity of stress experienced. Measuring AL in younger populations may be more likely to indicate severity of stress, rather than duration, or an effect of timing of sensitive periods as the effects of stress on the mediators of AL may be amplified in early life (Bosch et al., 2012). Adolescence has been described as a sensitive period for both of these reasons, with both a change in biological responses to stress (Gunnar, 2020) and increased stress sensitivity (Ordaz and Luna, 2012; Sumter et al., 2010). In addition, adolescence is the transitional period between childhood and adulthood, during which adolescents acquire social, emotional, cognitive, and physical skills that lay the lifelong foundations for their health and wellbeing (Blakemore, 2012). It is important to consider stress, and stress responses, in the context of the developmental stage of adolescence, as patterns of stress reactivity during this period may foreground future patterns of physical health and psychobiological wellbeing (Yahfoufi et al., 2020).

The transitional stress of adolescence, combined with increasing demands across domains of school, family, work and social life (Wickrama et al., 2005) and the potential for the stress response to be recalibrated during adolescence (Engel and Gunnar, 2020) indicates adolescence is a critical period, demanding attention and effort to map the bio-behavioural stress responses during this life stage and describe how they may be distinct from earlier or later life stages (Dahl and Gunnar, 2009). The effects of acute stress, resulting from the release of primary mediators (e.g. cortisol), may present as problems with sleep, mood changes, and anxiety, all of which are frequently reported in adolescent populations (Majeno et al., 2018; Gradisar et al., 2011; Gunnar et al.,

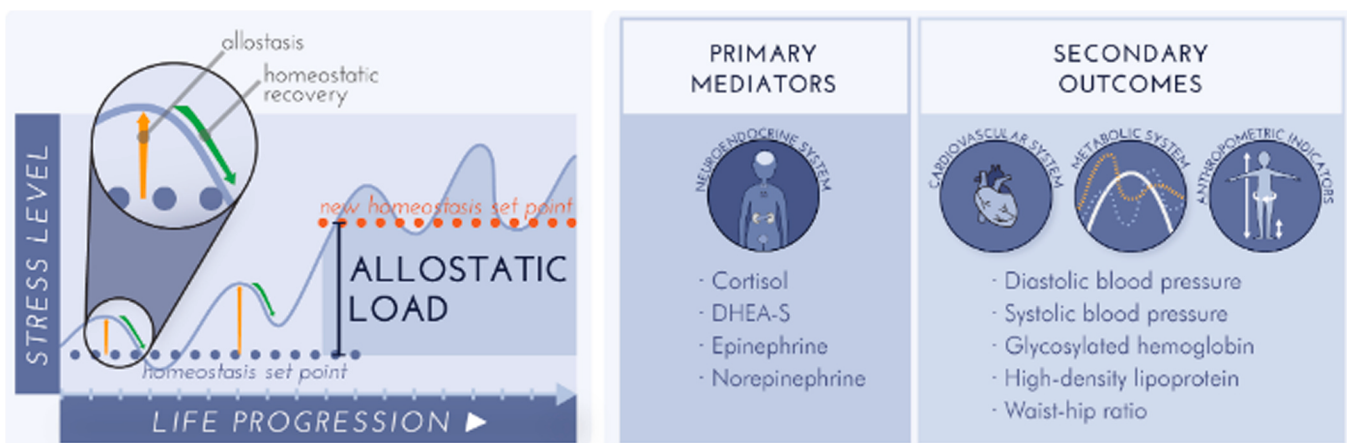


Fig. 1. The experience of stress initiates physiological and behavioural responses to support adaptive response, in the process of allostasis. With repeated stress experiences across time, allostatic load accumulates, which may alter set points across multiple physiological systems. These effects are wrought by primary mediators of the neuroendocrine system, and measurable as secondary outcomes across multiple systems of the body. The original allostatic load index (McEwen, 1998) contains ten measures of allostatic load.

2009), and in turn predict changes in psychological and biological function (Peper and Dahl, 2013; Colrain and Baker, 2011). For example, poorer quality sleep may be a consequence of stress, placing adolescents at greater risk of experiencing adverse psychological and physical health outcomes (McEwen and Karatsoreos, 2015). As sufficient sleep is required for optimal functioning of the hypothalamic-pituitary-adrenal (HPA) axis, and the HPA axis plays a crucial role in regulation of the stress response, the HPA axis activity has been proposed as a potential key mechanism contributing to negative health outcomes experienced in adolescence (Minkel et al., 2012). The HPA axis has a central role within the theoretical model of allostatic load, and biomarkers of HPA axis activity, primarily cortisol, have been proposed as a central measure to include in any index of allostatic load (Badanes et al., 2011). In addition to the acute stressors experienced during this developmental period, some adolescents may also experience chronic stress, stemming from adverse childhood experiences (Berg et al., 2017), poverty (Blair et al., 2011), and/or discrimination (Brody et al., 2014a, 2014b), and these experiences may also lend to differences in how AL manifests during this period (Currie et al., 2019).

Previous studies conducted with paediatric populations (Cedillo et al., 2019; Calcaterra et al., 2019) support the inclusion of metabolic and anthropometric age-specific measures in an index of AL, due to associations between higher AL and higher body-mass-index (BMI), total body fat mass, and waist circumference (WC) in early life. Due to the prevalence of overweight and obesity experienced during childhood and adolescence (Shin and Miller, 2012), the inclusion of metabolic markers, for risk of adiposity and the onset of disordered eating patterns, may be necessary to articulate the potential mechanisms through which stress-related, adverse health outcomes can emerge during this developmental stage (Miller and Luk, 2019; Eisenberg and Neumark-Sztainer, 2010). Developing a core set of measures for AL in adolescence may enhance the predictive power of the AL framework in indicating future health risk. However, the formation and direct translation of a single AL index created with reference to people in mid- or older-life to the adolescent period may not be appropriate. Beyond this, tailoring sets of AL measures to represent the age- and stage- specificities (Currie et al., 2019) of anthropometric, metabolic, neuroendocrine, and immune measures, may be necessary to fully articulate how and when stressful experiences contribute to AL.

1.3. Current study

The focus of AL literature to date has directed much of its attention to the onset of tertiary outcomes and cognitive decline in older adults (Karlama et al., 2002). The most commonly reported adverse health outcomes, such as cardiovascular diseases and cancers, experienced in this population are often measured via markers of cardiovascular function, for example blood pressure. Although these biomarkers provide useful insight into health status in younger populations, they may not represent the most sensitive, early signs of AL as a sub-clinical measure of health during adolescence. In line with suggestions from recent studies (Liu et al., 2021; Calcaterra et al., 2019), the aims of this review are 1) to describe what physiological markers of stress have been included in studies of AL in adolescence, 2) to determine the frequency of use of primary mediators and secondary outcomes, and 3) describe the consistency of measurement used in describing the physiological consequences of stress during adolescence. As a result, the implications of this review should shed light on future applications of AL measures for use within adolescent populations, to identify the presence of AL at an earlier stage of life, and in turn lend to the development of interventions which help to promote adolescent health and minimise future disease risk.

2. Method

In line with PRISMA guidelines, the following databases were searched in July 2020; PubMed, PsycINFO, Cochrane Library, and PsycARTICLES, using search terms, key words, and MeSH terms. Search

terms were generated based on 'allostatic load' and 'adolescents' (see Table 1). Searches were contained to 1988–2020 in line with the coining of the term 'allostasis' (Sterling and Eyer, 1988). An additional list of authors was generated from the searching of references, to identify any authors who may have published or unpublished outputs relevant to this review. A grey literature search was conducted on Google Scholar, using the same overarching search terms 'allostatic load' and 'adolescents'. Four additional papers were retrieved from this search. Following screening of both titles and abstracts, none of the four papers from the grey literature search were deemed eligible and were therefore excluded from the final synthesis.

Given the recent developments in neuroscience and in psychology, and to account for the onset of puberty, changes in the brain, and culturally defined roles, the period of adolescence has been extended, and now ranges from 10 to 24 years (Sawyer et al., 2018). As the population of interest for this study was adolescents, we adopted the Lancet Commission's (Patton, 2016) definition of adolescence, and therefore our specified age range spanned from 10 to 24 years. Where studies contained data that extended beyond this range, authors were contacted directly for data on measures limited to the specified age band of 10–24 years. A total of 552 studies were retrieved in the initial search, after the removal of duplicates, 354 records were screened for title/abstract (see Fig. 2: PRISMA Flowchart). Following eligibility screening (see Table 2), 25 studies were included in the review. Animal studies were excluded, as was research on children and adults (participants aged less than 10 and above the age of 24). Articles were screened by two independent reviewers (EW & JOS). A third reviewer (SD) was on standby to resolve any disagreements between included studies, however, no discrepancies arose. After reviewing the full text of each article, the following elements were extracted: authors, year of publication, population, gender, number of biomarkers, nature of biomarkers (primary or secondary), systems measured (cardiovascular, neuroendocrine, immune, metabolic), study design, number of participants, age of the sample (mean, standard deviation, and range), and study findings.

3. Results

25 studies were deemed eligible and included in the final synthesis (see Table 3). Participants ranged in age from 10 to 24 ($M = 17.5$). The majority (92%) of studies included both male and female adolescents, two studies were completed with only males. Studies were conducted in Nepal, India, England, China, and Australia, with the majority of studies carried out across the USA (80%). The vast majority of studies, 88% ($n = 22$), were carried out with adolescents living below the poverty line, and/or minority groups. Sample sizes ranged from 107 to 2400.

Almost half of the studies ($n = 11$) included in this review were secondary analyses, including data from National Health and Nutrition Examination Survey (NHANES), Strong African American Families Healthy Adult Panel (SHAPE) study, Determinants of Adolescent Social well-being and Health (DASH) study, National Institute of Child Health and Human Development Study of Early Child Care and Youth

Table 1
Search terms.

allostasis	AND	Adolescen*
OR		OR
allostatic load		child*
OR		OR
allostatic overload		youth*
OR		OR
allostatic load index		young*
		OR
		teen*
		OR
		paediatric*
		OR
		pediatric*

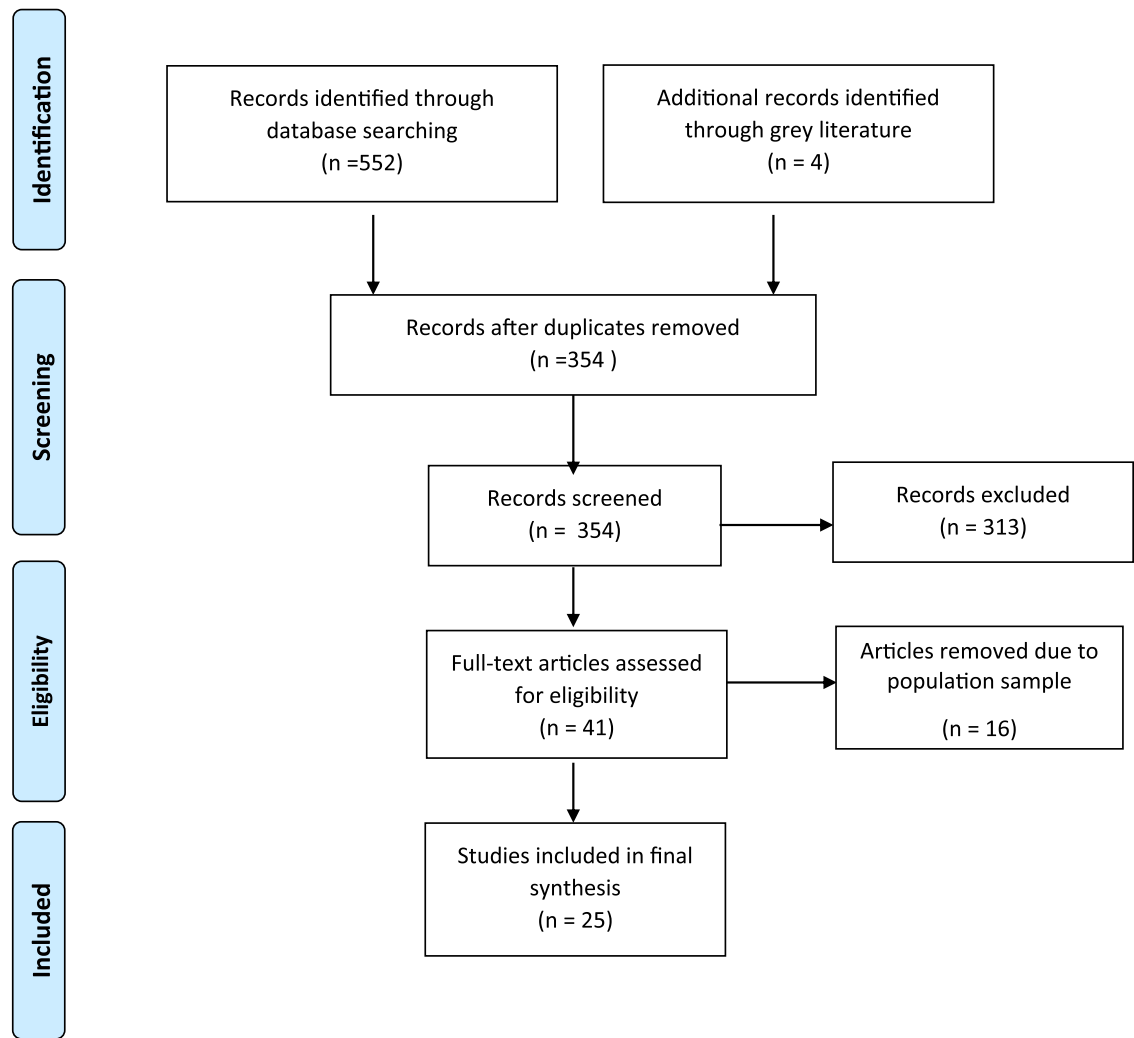


Fig. 2. PRISMA flowchart.

Table 2
Inclusion and exclusion criteria.

Inclusion Criteria
• Must be adolescent population within specified age ranges (10–24 years) • Must identify biomarkers as indicators of allostatic load (title/abstract) • Studies conducted between 1988 and 2020 • English language studies
Exclusion Criteria
• Any studies conducted with children or adults (under 10 and over 24) • Studies that did not identify biomarkers as indicators of allostatic load • Studies conducted prior to 1988 • Studies not in English language

Development (NICHD SECCYD), [Evans \(2003\)](#), and [Evans and Kim \(2007\)](#). The remaining empirical studies comprised of 36% longitudinal studies (n = 9) and 20% cross-sectional studies (n = 5). The number of biomarkers measured across studies ranged from 1 to 14 (M = 7.5, Median = 7, Mode = 6). The most frequently used AL index (n = 13) consisted of 6 biomarkers: three primary mediators, including cortisol, epinephrine, and norepinephrine, and three secondary outcomes including, SBP, DBP, and BMI (see [Table 4](#)). Only 20% of studies (n = 5) included biomarkers of neuroendocrine, cardiovascular, metabolic, and immune systems. The majority of studies (n = 17), contained markers of cardiovascular, metabolic, and neuroendocrine systems, but did not include a marker of immune function. The majority of studies (84%)

included markers of HPA and/or Sympathetic-Adreno-Medullar (SAM) axis function; 16% of studies included no measure of stress reactivity. Only 1 study used the original 10 biomarkers from the MacArthur study. One study included markers of cardiovascular and metabolic systems only. One study measured diurnal cortisol only and referred to as an index of AL.

4. Discussion

The findings from this review identified 25 eligible articles and evaluated them in light of how AL has been quantified in research with adolescent populations, including determining the number of measures used to construct each individual index, the number of physiological systems represented, the frequency of use of each measure, and if measures were used as primary mediators or secondary outcomes. The AL framework was developed and originally applied in an adult sample ([Seeman et al., 1997](#)) and measures dysregulation across four physiological systems, metabolic, cardiovascular, neuroendocrine, and immune, from which an index was derived. Empirical evidence has demonstrated the value of the AL index for predicting subclinical states of a variety of health outcomes in older populations ([Beckie, 2012](#)), yet less is known about the utility and validity of the AL index within adolescent populations. The original index included 10 markers; SBP, DBP, LDL, HDL, total cholesterol, HbA1c, WHR, cortisol, DHEA-S, epinephrine and norepinephrine ([Seeman et al., 1997](#)). There has been substantial variation in the combination and range of measures used to

Table 3

Full-text articles included in review.

	Authors	Title	Type of Study	No. of measures
1	Augustine et al. (2016)	Exploring the bio-behavioural link between stress, allostatic load & micronutrient status: A cross-sectional study among adolescent boys	Cross-sectional	9
2	Berger et al. (2019)	Hair cortisol, allostatic load, and depressive symptoms in Australian Aboriginal and Torres Strait Islander people	Cross-sectional	14
3	Brody et al. (2014a)	Neighborhood poverty and allostatic load in African American youth	Longitudinal	6
4	Brody et al. (2014b)	Perceived Discrimination Among African American Adolescents and Allostatic Load: A Longitudinal Analysis With Buffering Effects	Longitudinal	7
5	Brody et al. (2013a)	Is Resilience Only Skin Deep?: Rural African Americans' Socioeconomic Status-Related Risk and Competence in Preadolescence and Psychological Adjustment and Allostatic Load at Age 19	Longitudinal	6
6	Brody et al. (2013b)	Cumulative socioeconomic status risk, allostatic load, and adjustment: a prospective latent profile analysis with contextual and genetic protective factors	Longitudinal	6
7	Brody et al. (2013c)	Supportive family environments, genes that confer sensitivity, and allostatic load among rural African American emerging adults: a prospective analysis	Longitudinal	6
8	Chen et al. (2015)	Neighborhood poverty, college attendance, and diverging profiles of substance use and allostatic load in rural African American youth	Secondary analysis	6
9	Chen et al. (2016)	The Great Recession and health risks in African American youth	Secondary analysis	7
10	Dich et al. (2015a)	Children's emotionality moderates the association between maternal responsiveness and allostatic load: Investigation into differential susceptibility	Secondary analysis	6
11	Dich et al. (2015b)	Children's negative emotionality combined with poor self-regulation affects allostatic load in adolescence	Secondary analysis	6
12	Dich et al. (2017)	In risky environments, emotional children have more behavioral problems but lower allostatic load	Longitudinal	6
13	Doan et al. (2016)	Stress of stoicism: Low emotionality and high control lead to increases in allostatic load	Longitudinal	6

Table 3 (continued)

	Authors	Title	Type of Study	No. of measures
14	Doan and Evans (2011)	Maternal responsiveness moderates the relationship between allostatic load and working memory	Secondary analysis	6
15	Evans and Fuller-Rowell, 2013	Childhood poverty, chronic stress, and young adult working memory: The protective role of self-regulatory capacity	Longitudinal	6
16	Evans and Kim, 2012	Childhood poverty and young adult's allostatic load: The mediating role of cumulative risk exposure	Secondary analysis	6
17	Fuller-Rowell et al. (2012)	Poverty and health: The mediating role of perceived discrimination	Secondary analysis	6
18	Harding et al. (2016)	Longitudinal study of cardiometabolic risk from early adolescence to early adulthood in an ethnically diverse cohort	Longitudinal	7
19	King et al. (2019a, 2019b)	Testing allostatic load factor structures among adolescents: A structural equation modelling approach	Secondary analysis	14
20	Skinner et al. (2011)	Allostasis model facilitates understanding race differences in the diurnal cortisol rhythm	Cross-sectional	1
21	Theall et al. (2012)	Cumulative neighbourhood risk of psychosocial stress and allostatic load in adolescents	Secondary analysis	11
22	Rainisch and Upchurch (2013)	Sociodemographic correlates of allostatic load amongst a national sample of adolescents: findings from the National Health and Nutrition Examination Survey, 1999–2008	Secondary analysis	8
23	Wolpert (2014)	The relation of chronic stress during middle childhood to allostatic load in adolescents	Secondary analysis	6
24	Worthman and Panter-Brick (2008)	Homeless street children in Nepal: use of allostatic load to assess the burden of childhood adversity	Cross-sectional	7
25	Tian et al. (2020)	Discrimination Increases the Association Between Parental and Adolescent Allostatic Load in Chinese Rural-to-Urban Migrants	Cross-sectional	10

quantify AL in adult populations ([Rodriguez et al., 2019](#)), as well as in adolescent populations, evidenced in the number of biomarkers included across different studies, ranging from 1 to 14 in the studies identified in this review. Only one study on adolescent AL used the original index of 10, ([Tian et al., 2020](#)) with the remaining 24 studies varying widely in the number and combination of measures used. Earlier AL studies were more adherent to the original index ([Weinstein et al., 2003](#); [Karlman et al., 2002](#)), but more recently, the high level of variation may be partly enabled by advances in measurement, and evolving models, whereby consequences of stress have been refined and may be reflected in a more condensed set of measures ([Mauss and Jarczok, 2021](#)). However, the inconsistency of markers of AL used

Table 4
Range of measures of allostatic load across studies.

S	DHE	COR	IL-6	CRP	CHO	HDL	LDL	BMI	SBP	DBP	HR	TNF	TRI	FG	HbA	EPI	NOR	WHR	CRE	INS	WC	ALB	WBC	EBV	ACT	SM	AD	T
1	x		x	x	x	x		x	x	x																		9
2		x	x	x	x	x	x				x																	14
3		x						x	x	x																		6
4		x		x				x	x	x																		7
5		x						x	x	x																		6
6		x						x	x	x																		6
7		x						x	x	x																		6
8		x						x	x	x																		6
9		x		x				x	x	x																		7
10		x						x	x	x																		6
11		x						x	x	x																		6
12		x						x	x	x																		6
13		x						x	x	x																		6
14		x						x	x	x																		6
15		x						x	x	x																		6
16		x						x	x	x																		6
17		x						x	x	x																		6
18								x	x	x																		6
19								x	x	x																		7
20								x																				14
21		x		x				x	x	x																		1
22				x				x	x	x																		11
23		x						x	x	x																		8
24		x						x	x	x																		6
25		x						x	x	x																		7
T	1	21	2	7	5	7	4	22	24	23	3	1	4	4	5	15	15	2	1	2	3	2	1	2	1	1	1	10

within adolescent populations, as shown in the results, draws our attention to the need to evaluate the consequences of various combinations of AL markers on the conceptual and methodological rigour in research on adolescent AL. The addition of new measures or omission of well-established measures may affect the sensitivity with which AL is detected, as well as the usefulness and overall strength of the AL framework in predictive and explanatory models of psychobiological health during adolescence.

The variations in structure of the AL Index suggests there may be differences in the robustness of the AL structure. The most frequently used index contained three primary mediators, cortisol, epinephrine, and norepinephrine, and three secondary outcomes, systolic blood pressure, diastolic blood pressure, and body-mass-index. Rather than interpret inclusion and frequency as an indication of the validity of the measure, it is important to note that many of the papers using these measures share a common-source dataset, as they are secondary analyses of longitudinal studies (Evans and Kim, 2007; Evans, 2003). That is, the pattern of what is included in the AL Index across many of the studies included in this review arises from the constraints of the same original data. The inclusion of AL indicators can be influenced by pragmatic considerations including cost, convenience, or availability of the measures in a dataset, rather than guided solely by the contribution of the measure to the validity of the overall index (Liu et al., 2021). These limitations are illustrated when studies using data from the National Health and Nutrition Examination Survey (NHANES) were reviewed (King et al., 2019a, 2019b; Rainisch and Upchurch, 2013; Theall et al., 2012). Although these studies used an AL Index comprising 14 biomarkers, the original, longitudinal study did not include markers of the neuroendocrine system via measures of HPA axis function, and so, in turn these markers were then not available for use in secondary analyses. In line with its conceptual underpinnings, the optimum AL index should include measures of neuroendocrine function, as central to stress reactivity (McEwen and Stellar, 1993). However, a large number of studies (Duong et al., 2017) have used the NHANES data to measure AL, and despite the exclusion of neuroendocrine measures, these studies have successfully demonstrated the validity of this index in predicting health outcomes.

Less consistency exists regarding the inclusion of other physiological systems, particularly the immune system. Less than one third of studies ($n = 8$) included markers of immune function, despite its central role in the stress response (Szanton et al., 2005). These findings align with a previous review on AL which reported inclusion of immune markers in approximately only one-third of all studies (Johnson et al., 2017). C-reactive protein (CRP) was the most commonly measured marker of inflammation ($n = 7$), whilst interleukin-6 (IL-6) was measured only once. Given the role of IL-6 in regulating CRP, their combined use as an indicator of inflammation may provide a better predictor of associated risk than the use of either indicator alone (Del Giudice and Gangestad, 2018). The robust research linking chronic stress to inflammation, particularly evidenced in elevated IL-6 scores (Seplaki et al., 2006), indicates that markers of immune function should be represented in an index designed to measure the physiological effects of stress. The current study highlights the omission of immune-markers in previous studies of AL in adolescents, once again, highlighting constraints in access to empirical data, particularly amongst this cohort, which presents a challenge to research on AL. The multi-systemic nature of AL calls for a multidisciplinary approach, access to resources, equipment and the theoretical knowledge as well as practical training that is required in designing and conducting studies of AL in adolescence, not least as it requires expertise in both developmental science and physiology. For example, there are changes in the immune system, metabolic processes, as well as rapid changes in body size, including waist circumference, that occur during adolescence as a result of puberty and so adopting a developmental perspective on AL is necessary (Worthman et al., 2019). There may be other challenges related to the type of measures required, for example, markers of inflammation, such as CRP, IL-6, albumin, and

TNF alpha, are assayed via blood samples, which may pose additional challenges in terms of recruitment. These challenges may be particularly pertinent to consider when conducting research within an adolescent population, as they may present additional barriers in gaining consent and commitment from both the adolescent themselves, as well as their primary caregiver.

As the relationship between the functions of a system, and in turn markers of system function, is nonlinear and reciprocal, it is important to be able to articulate this interconnectedness when evaluating measures of AL for inclusion within an AL index. For example, IL-6 stimulates the HPA axis, activation of which is associated with central obesity, hypertension and insulin resistance (Yudkin et al., 2000). Due to the multi-systemic nature of AL, and the existing knowledge gap on the most effective means of measurement, it is advisable that studies contain markers of each of the four systems; neuroendocrine, cardiovascular, metabolic, and immune, to demonstrate the degree and extent of dysregulation. In order to move toward a consensus on the essential index of AL, we must ascertain which measures act as the best indicators of disease risk at a population level, and then more specifically at critical developmental stages such as adolescence. A recent factor analysis (King et al., 2019a, 2019b), included in the current study, found that the best indicators for AL within an adolescent population were those measuring metabolic dysregulation, with BMI and waist circumference (WC) having the highest factor loadings (0.95 and 0.982, respectively). The results from this study are notable but present a further research and conceptual complexity, arising from the increasing prevalence of obesity in adolescence (Hales et al., 2017; Güngör, 2014). These findings may act as a crucial reminder to further studies of AL, as to determine the most appropriate measurements, we should look at tertiary outcomes, and specific vulnerabilities of target populations, and then work backwards to identify what the most effective measurements of disease risk may be. Structural equation modelling approaches have been used to evaluate AL indicators in relation to efficiency as predictors of health risk in adults, indicating that cardiovascular and inflammatory markers had the highest risk loadings (Booth et al., 2015; Seeman et al., 2010). The difference in loadings and significance of systems between the adolescent and adult populations, may be a reflection of the cumulative cost of AL on cardiovascular and immune function, which may be nascent at earlier stages of life. The high factor loadings of BMI and WC may reflect the earliest, clinical signs of elevated AL that manifest in adolescent populations and are therefore essential markers to consider in future research with adolescents. In addition, these measures may not only reflect elevated AL, but may also be considered as outcomes related to health behaviours, the social context, and epigenetic factors, as much as a manifestation of stress, or in combination with stress.

5. Conclusion

The measurement of AL at adolescence may help to identify vulnerabilities specific to adolescent populations, which may shape both their current health, as well as lifelong health trajectories. In turn, studies should aim to include a wide range of measures across multiple systems, to ensure the cumulative cost of stress on physiological function is adequately measured. The selection of biomarkers should be considered within the context of specific populations, to take into consideration current health status and to tailor the development of interventions to promote and improve future health of target populations. In the same manner that disruption to one system can cascade into the dysregulation of multiple systems, the inverse may also be true, and interventions that stabilize one system to a healthy range may have benefits to other systems. Therefore, identifying the essential measures to include in an allostatic load index for use in adolescent populations is an important goal for accurate, specific measurement for research, but may also have implications for prevention and intervention science.

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