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Clinical measures of allostatic load in children and adolescents with food allergy, depression, or anxiety

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ABSTRACT

Purpose: Sustained high stress exposure results in chronic activation of the stress response system, dysregulated stress responses, high allostatic load, and poor later-life health. Children and adolescents with chronic health conditions face stressors related to their condition in addition to those typical of childhood and adolescence, placing them at risk of high allostatic load. The purpose of this secondary analysis was to examine whether youth with chronic health conditions differ from controls on clinical measures of allostatic load.
Design and methods: A secondary analysis of two datasets, the electronic health record of a tertiary children's hospital and data from the Survey of the Health of Wisconsin, compared youth with chronic health conditions to controls on clinical measures of allostatic load. Additional analyses explored whether parental stress and mental health influenced these relationships.
Results: Analyses identified differences in BMI, blood pressure, and waist circumference between youth with food allergy, anxiety, or depression, and controls. These relationships differed for males and females and for those with comorbid mental and physical conditions, and were influenced by parent stress and mental health.
Conclusions: Results support future studies exploring whether high stress in youth with chronic health conditions leads to increased allostatic load. Incorporating biomarkers as well as genetic and epigenetic factors will provide critical insights.
Practice implications: Youth with mental and physical CHCs may be at increased risk of high allostatic load, reflected in clinical measures of metabolism, and should have regular assessments of their metabolic health.

Exposures to biological, psychological, and social factors affect health and well-being across the life course, making early life a critical determinant of biological function and later-life health (Haas & Oi, 2018; Harris & McDade, 2018). Diagnosis of a childhood-onset chronic health condition (CHC) is one factor influencing life course health outcomes: multiple studies have established that individuals with childhood-onset CHCs have worse later-life health, compared to peers without CHCs (Blackwell et al., 2001; Dalton et al., 2016; Delaney & Smith, 2012; Maatta et al., 2013; Zajacova et al., 2014). Factors influencing health trajectories also include cumulative stress exposures, which accumulate over time. Cumulative stress exposures increase risks of poor mental and physical health, evolve over the life course, and are specific to age and developmental stage (Harris & McDade, 2018; Kralik et al., 2006; Willis et al., 2018). Stress exposures, or stressors, may be particularly important during critical developmental stages, such as childhood and adolescence. All youth experience stressors in multiple domains that can affect life course health and well-being (Anda et al., 2006; Epel et al., 2018; Seeman et al., 2001). Some are at increased risk of multiple significant stress exposures, such as youth who experience adverse childhood experiences (ACEs) and chronic psychosocial stressors. Children and adolescents with mental and physical CHCs are also at increased risk of high cumulative stress exposure. They experience stressors related to their CHC in addition to those typical of childhood and adolescence (Ferro, 2014; Ferro & Boyle, 2015; Ferro, Van Lieshout, Ohayon, & Scott, 2016; Lebovidge et al., 2009).

Youth with different CHCs experience unique combinations of condition-specific stressors and those common to multiple diagnoses. For example, youth with food allergies (FA) face the ever-present risk of allergen exposure and severe, potentially fatal allergic reactions. This requires constant vigilance to avoid allergenic foods and readiness to respond to crisis situations but does not require daily medications. In contrast, type 1 diabetes (T1D) management requires careful

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monitoring and management of daily medications and diet to maintain normoglycemia (Ferro, Van Lieshout, Scott, et al., 2016; Mandell et al., 2005; Rose & Howard, 2014). Youth with CHCs report high levels of perceived stress from these variable stress exposures, and a subset have post-traumatic stress symptoms (PTSS) or disorder (PTSD) (Ferro, Van Lieshout, Scott, et al., 2016; Pinquart & Shen, 2011; Rechenberg et al., 2017). Parents of youth with CHCs also experience stressors related to the CHC, and are more likely to be diagnosed with depression, PTSS and PTSD than parents of children without these conditions (Ferro, 2015; Greening et al., 2006; Pinquart, 2019).

Parent stress and mental health, including depression, anxiety, and high perceived stress, are a critical component of the family environment. The family environment refers to characteristics of individual family members, their interactions and relationships, and other contextual factors, such as the family's socioeconomic status and local environment (Hohashi & Honda, 2011; Repetti et al., 2011). Some family environments are considered to be more risky than others. The family environment can also affect youth health and well-being (Belsky & Shalev, 2016; Brody et al., 2021; Repetti et al., 2002; Repetti et al., 2011). Children in high-stress families are more likely to be diagnosed with depression and have more anxiety, more internalizing symptoms, and higher perceived stress, than children in lower-stress families (Bettis et al., 2016; Bjorkenstam et al., 2015; Haltigan et al., 2017; Najman et al., 2017; Stone et al., 2016; Ulmer-Yaniv et al., 2018; Zandstra et al., 2015). Children of parents with anxiety disorder or a history of depression are at greater risk of anxiety and depressive disorders and higher levels of perceived stress (Morris et al., 2014; Sydsjö et al., 2018). Parental PTSD also alters child mental health (Cramm et al., 2019; Greene et al., 2018; Lambert et al., 2014; Maddoux et al., 2016).

Experiencing more stressors in multiple life domains may have a particularly detrimental effect on youth health and well-being. Sustained high cumulative stress, due to ACEs and chronic psychosocial stressors, affects physiology and biological function (Epel & Prather, 2018; Fava et al., 2019; McEwen & Getz, 2013). However, few studies have examined the physiological impact of stress and anxiety related to childhood diagnosis of a CHC (Ersig et al., 2016; Ferro, Van Lieshout, Ohayon, & Scott, 2016; Ravid et al., 2015).

This is a critical area for investigation: sustained high stress exposure can result in chronic activation of the stress response system, dysregulated stress responses, high allostatic load (AL), and poor later-life mental and physical health (Epel et al., 2018; McEwen, 2005; Seeman et al., 2001). Allostatic load, the cumulative biological burden of sustained high stress exposure, is frequently quantified using an index that includes biomarkers and clinical measures (Seeman et al., 2001). Ideally, measures reflect body systems involved in the stress response (Li & Rosemberg, 2020). These include the neuroendocrine, cardiovascular, and metabolic systems, as in the original allostatic load index (Seeman et al., 2001), as well as immune and inflammatory markers (Juster et al., 2010; King, Garnier-Villarreal, Simanek, & Johnson, 2019; Slavich, 2020). Measures selected for a study typically assess mechanisms of interest for that study. When comprehensive measures are not available, studies often use individual measures of AL (Eddington et al., 2012; Kuo et al., 2019).

A subset of clinical measures of AL reflect metabolism, including body mass index (BMI), blood pressure (BP), waist circumference (WC), and waist-hip ratio (WHR) (King et al., 2019; Seeman et al., 2001). Metabolic dysregulation due to high AL is evident in adolescents with high stress exposure, children with high levels of perceived stress, and youth who experience childhood poverty (Darling et al., 2019; Evans, 2003; Evans et al., 2007; Fahrenkamp & Sato, 2018; King et al., 2019; Wickrama et al., 2014). Metabolic indicators of AL are also dysregulated in youth with chronic mental health conditions: those with depression and anxiety are at increased risk of obesity, and adolescents with depression have greater WHR (Bitsko et al., 2018; Esposito et al., 2014; Fahrenkamp & Sato, 2018; Perry et al., 2020).

Multiple studies have established that children and adolescents with CHCs and their families experience substantial CHC-specific stress. However, the extent to which the challenges of living with and managing a CHC during childhood and adolescence affect AL and the physiological stress response is limited (Bahreinian et al., 2013; McEwen, 2017). This is a critical gap in knowledge, as high AL could be a mechanism underlying the increased incidence of poor health outcomes in individuals diagnosed with CHCs in childhood, and may compound risk of poor health resulting from CHCs themselves (Delaney & Smith, 2012).

Thus, the purpose of this secondary analysis was to examine whether youth with chronic mental or physical health conditions differ from controls on clinical measures of AL. Clinical measures of metabolism were selected because salivary and blood-based biomarkers of AL, such as cortisol and inflammatory cytokines, are not regularly assessed in youth, while clinical measures are often readily available in health records. Four research questions guided the analysis: (1) do adolescents with food allergy, which is a physical health condition, differ from controls on clinical measures of AL, (2) do adolescents with comorbid food allergy and mental health conditions differ from controls on clinical measures of AL, (3) do children and adolescents with anxiety and depression differ from controls on BMI and waist circumference, which are clinical measures of AL, and (4) does parent mental health, as a measure of family environment, affect relationships between child anxiety, depression, BMI and waist circumference?

Data were obtained from two datasets: (1) the electronic health record (EHR) of a tertiary Midwestern children's hospital (AFCH) and (2) the Survey of the Health of Wisconsin (SHOW) dataset. This secondary analysis was approved by the Minimal-Risk Health Sciences IRB at UW-Madison. Obtaining data from two separate datasets provided an opportunity to examine two cohorts with unique characteristics. Datasets differed in the way in which cases were identified, with ICD codes for the hospital sample and parent report for the survey. Using two separate datasets also supported analysis of AL in youth with a chronic physical condition, food allergy, as well as those with anxiety or depression, which are chronic mental health conditions. Data sources also differed: hospital data were obtained from the EHR and survey data from parent proxy and self-report data. The hospital dataset also provided an opportunity to examine clinical measures of AL in youth with comorbid chronic physical and mental conditions.

Methods for AFCH data

In July 2018, we obtained deidentified electronic health record data on adolescents 12–18 years old from the American Family Children's Hospital (AFCH), Madison, WI. Eligible adolescents 1) visited the family medicine, allergy, pediatric allergy, or pediatric primary care clinics at AFCH in the last 2 calendar years; 2) had at least one clinical measure of AL available in the EHR; 3) did not have an admission to the emergency department for the 2 years for which data were retrieved; and 4) did not have an ICD-9 or ICD-10 code for trauma admission at any time. Clinical measures of AL in the EHR included weight and height, which were used to calculate BMI, and systolic and diastolic BP. Other clinical measures of AL were not available. Cases with food allergy, the physical CHC of interest, were identified based on ICD-9 and ICD-10 codes. Controls were adolescents who met the inclusion criteria but did not have a diagnosed food allergy or an ICD code for any one of a set of other serious chronic illnesses (e.g., Down syndrome, ventilator dependent). Additional data on mental health were obtained on cases and controls. Specific mental CHCs of interest included anxiety disorders, depression screening, single episode major depressive disorder (MDD), and recurrent MDD, identified using ICD-9 and ICD-10 codes. Adolescents could have more than one mental health diagnosis. Analyses compared adolescents with food allergy only, anxiety or depression only, and comorbid food allergy and anxiety or depression to controls without physical or mental CHCs. The final dataset included data on food allergy diagnosis, height, weight, calculated BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), and diagnosis of anxiety disorders, depression screening, recurrent MDD, or single episode MDD. Covariates included sex, self-identified race/ethnicity, and age.

AFCH sample

Deidentified data were available for 12,664 unique individuals who met inclusion and exclusion criteria. Some adolescents in the original dataset had more than one visit to AFCH in the two years for which data were obtained. To address this, an algorithm was used to identify the last visit and only data from this visit were analyzed. The mean age of the AFCH sample was 15.89 ± 0.01 years.

Of the unique individuals identified, there were 346 (2.7%) adolescents with an identified food allergy and 12,318 (97.3%) controls. Overall, 3436 (27.1%) had an anxiety disorder, 6 (0.05%) were screened for depression, 2104 (16.6%) had a single MDD episode, and 699 (5.5%) had recurrent MDD. Of the 346 youth who had food allergies, 95 (27.46%) had a diagnosis of anxiety disorder, 46 had been screened for depression, and 13 had recurrent MDD (Table 1). The sample was nearly evenly split between females and males. Of those who identified a race, the majority identified as White, with those who identified as Black as the next-largest group. Of those who provided data on ethnicity, 6.2% identified as Hispanic/Latino. Demographic and descriptive data are in Table 1.

Analysis of AFCH data

Analysis of AFCH data examined relationships between diagnosis of a mental and/or physical CHC (anxiety, depression and/or food allergy) and clinical measures of AL. Linear regression models were used to examine the relationship between CHC diagnosis and clinical measures of AL, as well as potential interactions among predictor variables. Covariates of interest included age, race, and sex. Due to between-sex differences in body composition and BMI in adolescents, we compared outcomes within sexes (Siervogel et al., 2003). Significance was set at $p = 0.05$. We report 95% confidence intervals (CI) for these analyses.

Table 1
Demographic & descriptive data, AFCH sample.

Variable	Total Sample (n = 12,664) Mean ± SD, N(%)	Male (n = 6359, 50.2%)	Female (n = 6305, 49.8%)
Age	15.89 ± 1.12		
BMI	23.6 ± 6.75		
Systolic BP	110.49 ± 12.26		
Diastolic BP	66.389 ± 8.89		
Race			
American Indian or Alaska Native	91 (0.7%)	48 (0.8%)	43 (0.7%)
Asian	572 (4.5%)	266 (4.2%)	306 (4.9%)
Black or African American	725 (5.7%)	341 (5.4%)	384 (6.1%)
Native Hawaiian or Other Pacific Islander	23 (0.2%)	13 (0.2%)	10 (0.2%)
White	10,660 (84.2%)	5392 (84.8%)	5268 (83.6%)
Multiracial	313 (2.5%)	160 (2.5%)	153 (2.4%)
Missing	280 (2.2%)	139 (2.2%)	141 (2.2%)
Ethnicity			
Not Hispanic / Latino	92.44%	92.61%	92.28%
Hispanic / Latino	6.24%	6.15%	6.33%
Food Allergy	346 (2.73%)	185 (1.21%)	161 (2.55%)
MDD – Single Episode	2104 (16.61%)	789 (12.41%)	1315 (20.86%)
MDD – Recurrent	699 (5.52%)	243 (3.82%)	456 (7.23%)
Screened for MDD	6 (0.05%)	3 (0.05%)	3 (0.05%)
All MDD	4109 (32.45%)	1608 (25.29%)	2501 (39.67%)
Other Anxiety Disorders	3436 (27.13%)	1301 (20.46%)	2135 (33.86%)

Results for AFCH data

Analyses examining group differences for systolic and diastolic BP were not significant. Initial analyses for BMI determined that males with food allergies had lower BMI, compared to male controls (mean BMI: male controls = 23.2, males with food allergies = 21.66; $p = 0.003$; 95% CI = −2.55, −0.53); however, there were no significant differences in BMI for female controls and females with food allergies. In contrast, both males and females with mental health conditions had higher BMIs than controls. Males with mental health conditions had an average BMI that was about 0.56 units higher than male controls (mean BMI: male controls = 23.2, males with mental health conditions = 23.76; $p = 0.006$; 95% CI = 0.95, 0.16), while females with mental health conditions had an average BMI about 0.57 units higher than female controls (mean BMI: female controls = 23.74, females with mental health conditions = 24.31; $p = 0.004$; 95% CI = 0.96, 0.19) (Table 2).

Further analyses examined between-group differences in BMI for males. Males with food allergies had an average BMI about 2.5 units lower than males with both food allergies and mental health conditions (mean BMI, males with food allergies and mental health conditions = 24.16, males with food allergies only = 21.66; $p = 0.027$; 95% CI = −4.72, −0.29). Males with mental health conditions only had an average BMI about 2.1 units higher than males with food allergies only (mean BMI: males with mental health conditions only = 23.76, males with food allergies only = 21.66; $p < 0.001$; 95% CI = 1.05, 3.15). However, there were no significant differences in BMI between males with food allergies and mental health conditions and controls.

Methods for SHOW dataset

The Survey of the Health of Wisconsin (SHOW) is an ongoing survey that obtains data on health determinants from statewide population-based samples of children and adults. This dataset was used to examine whether clinical measures of AL in children and adolescents with parent-reported mental health conditions differed from controls. The SHOW protocol and informed consent are approved by the UW-Madison Health Sciences IRB, and data are collected under a Certificate of Confidentiality from the US Department of Health and Human Services (Nieto et al., 2010).

SHOW has completed three waves of sample collection with over 6000 Wisconsin residents, and the pooled nine-year sample is largely representative of the state population. SHOW obtains data on adults 21–74 years old who are capable of giving written informed consent and able to communicate answers to interview questions. All household members, including children, are enumerated. SHOW does not include adults who live in nursing homes, hospitals, mental institutions, penal institutions, jails, halfway houses, or college dormitories, are fulltime

Table 2
Comparison of BMI between Adolescents with Food Allergies, Anxiety, or Depression and Controls.

	Coefficient	Std. Err.	t	P > |t|	[95% Conf. Interval]	
Males#						
Food Allergy + Mental Health Condition	0.96	1.02	0.95	0.34	−1.03	2.95
Food Allergy Only	−1.54	0.52	−2.99	**0.003**	−2.55	−0.53
Mental Health Condition Only	0.56	0.20	2.76	**0.006**	0.16	0.95
Females%						
Food Allergy + Mental Health Condition	0.24	0.98	0.24	0.81	−1.69	2.17
Food Allergy Only	−0.22	. 65	0.33	0.74	−1.49	1.06
Mental Health Condition Only	0.58	. 20	2.91	**0.004**	0.19	0.96

- Referent is male controls. % - Referent is female controls. Analyses controlled for race and age.

members of the armed forces or activated units of the National Guard stationed away from home, spend less than half their nights at the selected residence, or voluntarily disclose a diagnosis of mental incapacity and do not identify a proxy respondent (Nieto et al., 2010).

Children of SHOW participants were enrolled from 2014 to 2017, with over 700 children 0–17 years of age participating. Data are collected via parent proxy for children under 12 and are self-reported by children 12–17 years old. Physical exams on children six years of age and older included BP, height, weight, hip circumference (HC), and waist circumference (WC). Body measurements are obtained twice. Weight is measured in kilograms using digital scales with subjects wearing light clothing or surgical scrubs. Height, HC, and WC are measured in centimeters. Seated BP is measured using digital blood monitors, with three measurements taken one minute apart after a 5-min rest period (Survey of the Health of Wisconsin, 2021).

Dependent variables of interest included calculated BMI and WHR, as well as systolic and diastolic BP and WC. Parents' stress exposures in the last year were measured with the social readjustment rating scale (SRRS) (Holmes & Rahe, 1967). Parents' perceived stress was measured with the mental component score (MCS) of the SF-12, 6-item post-traumatic stress disorder (PTSD) checklist, global perceived stress scale (GPSS), and the stress subscale of the depression, anxiety, and stress scale (DASS-21) (Henry & Crawford, 2005; Jenkinson et al., 1997; Lang & Stein, 2005; Spruill et al., 2019; Weathers et al., 1993). Depression and anxiety were measured using the DASS-21. Depression was also assessed using the Patient Health Questionnaire (PHQ-8; PHQ-2) (Kroenke et al., 2003; Kroenke et al., 2009).

SHOW sample

This dataset included 54 children, ages 6–17 years, from Waves 1 and 2 (2008–2016), who had at least one biological, adoptive, or step-parent participate in SHOW (Table 4). Cases had a parent-reported provider diagnosis of depression or anxiety. Controls were matched to cases on age and sex and did not have a parent-reported provider diagnosis of depression or anxiety. This resulted in four groups of children and adolescents: (1) anxiety only; (2) depression only; (3) anxiety and depression; and (4) controls.

Two analyses were conducted, the first for all cases and controls ($n = 54$), and the second for cases and controls with available data on parents' stress and mental health ($n = 50$). Of the youth whose parents provided data on stress and mental health, two had data from fathers only, 18 from mothers only, and 30 from both fathers and mothers. Overall, 48 children had data from mothers and 32 had data from fathers (Table 5). Separate models were generated for data from mothers and fathers.

There were 27 cases with a parent-reported provider diagnosis of depression or anxiety. One had depression, 13 had anxiety, and 13 had depression and anxiety. For the entire sample (n = 54), there were 28 females and 26 males, with an average age of 13.41 (SD 2.92). The vast majority identified as White (77.8%).

Analysis of SHOW data

Initial analyses of general population-based survey data from SHOW examined relationships between case status and clinical measures of AL in all cases and controls. Follow up analyses of youth with available parental data examined associations of parent stress and mental health with child AL and child mental health conditions. For analyses including parent data, separate best subset models were generated for mothers and fathers because of the small sample size (n = 54) and large set of possible predictor variables. Best subset regression identifies fewer optimal predictors from a large initial set, which were selected for each outcome using the TRYEM Stata algorithm to run all possible subset regressions (Boston College Department of Economics, 2012). The algorithm located the three best fitting predictors, controlling for covariates of child age and case status and parent education, age, and income. Predictors selected for each outcome of interest had the best R^2 value. Because of this, predictor variables varied across outcomes.

The pool of possible predictor variables included measures of parent stress and mental health from the GPSS, the depression, anxiety, and stress subscales of the DASS21, PHQ-2, PTSD 6-item checklist, and MCS 12. The primary outcomes were clinical measures of youth AL, which included BMI, systolic BP, diastolic BP, WC, and WHR. For each outcome, optimal predictors were identified as described. Case status was forced into each model to determine the effect of child mental health conditions on AL, as were four covariates of interest (child age, parent age, parent education level, parent income). An additional analysis examined the association between parent stress and mental health and child mental health diagnosis. Due to the small sample size for the SHOW data (n = 54 total; n = 50 with parental data), analyses used Bayesian regression models. Bayesian linear regression models were used to analyze clinical measures of AL, while Bayesian logistic regression models were used to examine the relationship between parent stress and mental health and child mental health diagnosis. Significance was set at $p = 0.05$. We report mean Beta values or odds ratios, as well as 95% credible intervals (CrI), for these analyses.

Results for SHOW data

Initial analyses compared cases with anxiety or depression to controls and did not include parental data or covariates. Compared to controls, youth with a mental health condition had a slightly larger WHR (p = 0.05) and slightly higher SBP (p = 0.05), although these results did not reach statistical significance. Children and adolescents with comorbid anxiety and depression had higher weight ($p = 0.001$), BMI ($p < 0.001$), and DBP ($p = 0.04$), and larger WC ($p = 0.03$), compared to those with anxiety only, depression only, and controls (Table 3).

Subsequent analyses examined the relationship of parental stress and mental health with clinical measures of AL in youth and included covariates. Contrary to expectations, children of fathers with more stress and worse mental health on several measures were less likely to have clinical measures that reflected high AL (Table 6). Children of fathers with more stress from caring for someone else had lower systolic BP (β = −4.05; 95% CrI = −7.18, −0.86). Waist circumference was smaller in children whose fathers had more stress in their relationships (β = −11.16; 95% CrI = −11.27, −11.06), higher scores on the depression scale of the DASS21 (β = −13.98; 95% CrI = −14.01, −13.93), and worse mental health on the MCS-12 (β = −4.21; 95% CrI = −4.22, −4.19).

In contrast, high maternal stress and worse mental health were associated with clinical measures reflecting higher AL in children for most measures (Table 7). Children of mothers with more stress from meeting basic needs had higher SBP (β = 3.64; 95% CrI = 0.95, 6.52). Those whose mothers had higher scores on the PTSD6 checklist (β = 1.43; 95% CrI =0.76, 2.13) or worse mental health on the MCS-12 (β = 0.46; 95% CrI =0.17, 0.75) had higher DBP. Youth whose mothers had higher scores on the depression scale of the DASS21 (β = 0.007; 95% CrI =0.003, 0.01) had larger WHR. Children of mothers with more stress from meeting basic needs (β = 1.73; 95% CrI =0.53, 2.96), and those whose mothers had worse scores on the MCS-12 (β = 0.23; 95% CrI =0.11, 0.36) had higher BMI. Contrary to expectations, children whose mothers had depressive symptoms based on the PHQ-2 had smaller WC (β = −9.33; 95% CrI = −14.71, −2.59).

The final set of analyses examined relationships between parent stress and mental health and youth anxiety and depression. Several measures of parent stress from the GPSS were eliminated to improve model fit. Remaining items included stress in relationships, from caring for someone else, and from medical problems. All other predictors remained the same. Results indicated that children of fathers with more depressive symptoms, measured using the PHQ2, and children whose mothers have more PTSD symptoms, have higher odds of being

Table 3
Clinical measures of AL in youth with comorbid anxiety and depression, compared to youth with anxiety only, depression only, and controls.

Variable		M ± SD	95% CI	*p*-value
Weight	Comorbid Anxiety & Depression	74.37 ± 23.21	60.35, 88.39	
	Anxiety only, Depression only, & Controls	51.03 ± 21	44.40, 57.66	**0.001**
BMI	Comorbid Anxiety & Depression	26.6 ± 5.53	23.26, 29.93	
	Anxiety only, Depression only, & Controls	20.45 ± 5.28	18.78, 22.11	**<0.001**
SBP	Comorbid Anxiety & Depression	116.85 ± 13.27	108.83, 124.87	
	Anxiety only, Depression only, & Controls	109.06 ± 12.39	104.98, 113.12	0.06
DBP	Comorbid Anxiety & Depression	65.85 ± 8.82	60.52, 71.18	
	Anxiety only, Depression only, & Controls	60.37 ± 7.56	57.88, 62.85	**0.04**
Waist Circ	Comorbid Anxiety & Depression	88.22 ± 15.69	76.16, 100.28	
	Anxiety only, Depression only, & Controls	72.88 ± 17.91	65.93, 79.82	**0.03**
WHR	Comorbid Anxiety & Depression	0.88 ± 0.08	0.82, 0.94	
	Anxiety only, Depression only, & Controls	0.85 ± 0.08	0.82, 0.88	0.34

diagnosed with depression or anxiety (paternal: OR = 20.78; 95% CrI = 1.46, 109.61; maternal: OR = 1.57; 95% CrI = 1.08, 2.48).

Discussion

This secondary analysis of two datasets explored whether children and adolescents with physical and mental CHCs have high AL. Additional analyses of data from a general population survey of children and their parents explored whether parental stress and mental health also influence these outcomes. Results suggest that clinical measures of AL that reflect metabolic health may vary between children and adolescents with mental or physical CHCs compared to controls and that there may be differences between males and females**.** In addition, the effects of having comorbid mental and physical CHCs may differ from effects due to either type of CHC alone.

Analyses of clinical data from a children's hospital EHR indicate that youth with food allergies and mental health conditions differ from controls on clinical measures of AL. These results align with studies identifying dysregulated biomarkers of stress and clinical measures of AL in youth with other CHCs (Bitsko et al., 2018; Davis et al., 2019; Esposito et al., 2014; Fahrenkamp & Sato, 2018; Perry et al., 2020). CHCs generate unique stressors, such as physical difficulties, feeling different from others, and loss of social connections (Kralik et al., 2006; Patel et al., 2017). These may not be traumatic, but they persist for an extended length of time and can have a significant impact on health and well-being (Koffer et al., 2016). Youth with CHCs also experience developmentally normative stressors. Exposure to both types of stressors could increase risks of high cumulative stress exposure, which may be a mechanism linking CHC diagnosis with poor later-life health outcomes (Delaney & Smith, 2012; Pearlin, 2010). However, because measures of stress exposure and perceived stress were not included in the datasets analyzed, we were unable to examine this relationship, and additional studies are needed to examine this possibility.

Regardless of source, stress exposures in different life domains occur simultaneously, interact throughout the life course, and accumulate over time, increasing risks of poor mental and physical health (Epel et al., 2018; Evans et al., 2007; Harris & McDade, 2018; Juster et al., 2010; Koffer et al., 2016; Slopen et al., 2018). Studies in adults show that multimorbidity is associated with higher perceived stress and less effective coping, as well as dysregulated biomarkers of AL and advanced biological age (Friedman & Shorey, 2019; Ghimire et al., 2019; Swartz & Jantz, 2014; Vancampfort et al., 2017). Similar results emerged from a study of youth with physical and mental CHCs who reported significantly lower psychological well-being (Butler et al., 2018). In this study, children and adolescents with co-occurring anxiety and depression were more likely to have dysregulated clinical measures consistent with high AL, compared to youth with anxiety only, depression only, and controls. Future research leveraging longitudinal data would provide insights into how diagnosis of multiple CHCs could affect psychological and physiological stress responses across the life course, with a particular focus on critical developmental stages, such as childhood and adolescence (Law et al., 2013).

Table 5
Demographic Data for SHOW Dataset for subjects whose parent(s) provided data.

Variable	Father Group (n = 32)	Mother Group (n = 48)
Age	13.16 ± 3.08	13.44 ± 2.92
Gender		
Male	14 (43.8%)	23 (47.9%)
Female	18 (56.3%)	25 (52.1%)
BMI	21.03 ± 5.24	21.37 ± 5.51
Systolic BP	108.73 ± 13.66	110.43 ± 12.58
Diastolic BP	61.27 ± 8.05	61.37 ± 7.15
Waist-Hip Ratio	0.84 ± 0.07	0.84 ± 0.06
Race		
White	27 (84.4%)	37 (77.1%)
African American	2 (6.3%)	4 (8.3%)
Hispanic/Latino	1 (3.1%)	2 (4.2%)
Other	2 (6.3%)	5 (10.4%)

Table 4
Demographic Data for SHOW Dataset by Sex and Case Status.*

Variable	Total Sample (n = 54) Mean ± SD, N(%)	Male (n = 26, 48.1%)	Female (n = 28, 51.9%)	Cases	Controls
Age	13.41 ± 2.92	13.31 ± 3.33	13.50 ± 2.53	13.41 ± 2.97	13.41 ± 2.97
BMI	21.93 ± 5.92	22.28 ± 7.56	21.59 ± 3.95	22.97 ± 6.32	20.88 ± 5.40
Systolic BP	111.04 ± 12.95	113.76 ± 15.27	108.42 ± 9.86	114.42 ± 13.69	107.52 ± 11.35
Diastolic BP	61.76 ± 8.17	62.24 ± 9.74	61.31 ± 6.48	63.23 ± 8.62	60.24 ± 7.55
Waist-Hip Ratio	0.86 ± 0.07	0.86 ± 0.09	0.85 ± 0.06	0.88 ± 0.07[a]	0.83 ± 0.07[a]
Race					
White	42 (77.8%)	22 (84.6%)	20 (71.4%)	21 (77.8%)	21 (77.8%)
African American	4 (7.4%)	2 (7.7%)	2 (7.1%)	2 (7.4%)	2 (7.4%)
Hispanic/Latino	2 (3.7%)	2 (7.7%)	0	1 (3.7%)	1 (3.7%)
Other	6 (11.1%)	0	6 (2.14%)	3 (11.1%)	3 (11.1%)

* There were no significant differences between males and females for variables analyzed.
[a] $p < 0.05$.

Table 6
Relationship between Paternal Stress & Mental Health & Youth Waist Circumference, Bayesian parameter estimates.

Youth Outcome Variable	Paternal Stress/Mental Health Measure	Mean Parameter Estimate	Std. Dev.	[95% Cred. Interval]	
Waist circumference	Stress in your relationships	−11.16	0.06	−11.2766	−11.06
	Depression Score (DASS21)	−13.98	0.02	−14.01	−13.93
	Mental Health (MCS-12)	−4.21	0.01	−4.22	−4.19
Systolic BP	Stress from caring for someone else	−4.05	1.62	−7.18	−0.86

Analyses control for child age and case status, and parent education, age, and income.

Results also indicated differences in BMI between adolescents with food allergies and mental health conditions and controls that could have clinical significance. Compared to controls, males with food allergies had lower BMI, while males and females with mental health conditions had higher BMI than same-sex controls. The relationship between food allergies and lower BMI may be due to more restricted diets for individuals with food allergies (Hubbard, 2003). The relationship between BMI and mental health conditions is bidirectional and more complex. Individuals with anxiety or depression may be more likely to have higher BMI, while those who have high BMI may be more likely to develop anxiety or depression (Bharti & Malhi, 2021; Lindberg et al., 2020; Thaker et al., 2020; Zhang, 2021). Additional studies are needed to examine biomarkers of AL not related to dietary intake in adolescents with food allergies and mental health conditions, such as cytokines and epigenetic modifications, and to examine whether stress affects these relationships.

This analysis also identified potential differences in the relationship between CHCs and clinical measures of AL for males vs. females. Biological sex influences relationships between stress exposures and measures of AL in adults (Edes & Crews, 2017; Juster et al., 2019; Rincon-Cortes et al., 2019). Although preliminary, results from this analysis indicate that these differences may be evident before adulthood. However, although the current study had a restricted age range, and age was controlled for in study analyses, data were not available on pubertal status, which can differ between individuals of the same chronological age and could affect clinical measures of AL (Palmert & Boepple, 2001). In addition, this analysis did not examine the effect of gender identity and gender roles on clinical measures of AL, which influence clinical measures of AL in adults, providing another direction for future research with youth who have CHCs (Juster et al., 2019; Rincon-Cortes et al., 2019).

The family environment is another critical factor influencing stress exposure, stress response, and AL in children and adolescents with mental and physical CHCs. Families in which a child or adolescent has a CHC experience shared and unique stress exposures (Kazak, 1989; Mattson et al., 2019). These can affect parent stress and mental health, which impacts the family environment and child health and well-being (Katz et al., 2012). Analyses from a general population survey of youth and their parents identified differences in clinical measures of AL for youth with anxiety or depression whose parents reported higher stress, compared to those whose parents had lower stress. Youth whose parents reported higher stress were also more likely to be diagnosed with anxiety or depression. These results align with other studies showing that youth with CHCs are more likely to have families with poor functioning (Ferro, Van Lieshout, Ohayon, et al., 2016). Those whose mothers had depressive symptoms are also at increased risk of having anxiety or depression (Ferro & Boyle, 2015).

Studies of the family environment often include data only from mothers. Analyses of the effects of paternal and maternal stress and poor mental health on youth AL and mental health found differences in youth outcomes for paternal and maternal data, highlighting the importance of including multiple family members in studies of the family environment. While results for maternal stress and mental health were in the expected direction, those for paternal stress and mental health were not. These differences should be explored further, as they may be due to the relationships that youth have with each parent, or parental roles within families. What is not known from this analysis is whether high parental stress preceded youth diagnosis of anxiety or depression; longitudinal datasets incorporating parent and child data would provide additional insights. Interventions aimed at improving family functioning could have a positive effect on mental health of adolescents with CHCs and their mothers (Ferro, Van Lieshout, Ohayon, et al., 2016).

Limitations

Although this study provides preliminary evidence of altered AL in children and adolescents with mental and physical CHCs, there are also limitations. One of the primary limitations is that there are no measures of stress exposure and stress in youth from either dataset. However, multiple studies have found that children and adolescents with mental and physical CHCs report high levels of stress due to their conditions (Ferro, 2014; Ferro & Boyle, 2015; Pinquart & Shen, 2011; Rechenberg et al., 2017), and the same is likely for subjects in these datasets. As both datasets included subjects who live in the state of Wisconsin, there is a remote possibility that a subject may be included in both datasets. However, the survey recruits participants statewide, while the hospital's patients live in a much smaller area. Because the datasets were also analyzed separately, data for any subjects in both datasets would not have been analyzed twice. Subjects in this analysis were mostly White, limiting the generalizability of the results to other racial and ethnic groups. Future studies of similar relationships in children and adolescents with chronic health conditions should seek to recruit more diverse subject pools in order to examine the potential

Table 7
Relationship between Maternal Stress/Mental Health and Youth Allostatic Load, Bayesian parameter estimates.

Youth Outcome Variable	Maternal Stress/Mental Health Measure	Mean Parameter Estimate	Std. Dev.	[95% Credible Interval]	
BMI	Stress from meeting basic needs	**1.73**	0.61	**0.53**	**2.96**
	Depression Score (DASS21)	0.34	0.22	−0.09	0.81
	Mental Health (MCS-12)	0.**23**	0.06	**0.11**	**0.36**
Systolic BP	Stress from meeting basic needs	3.64	1.34	**0.95**	**6.52**
Diastolic BP	Post-traumatic stress symptoms (PTSD Checklist)	1.43	0.35	**0.76**	**2.13**
	Mental Health (MCS-12)	0.46	0.14	**0.17**	**0.75**
Waist-Hip Ratio	Depression Score (DASS21)	0.007	0.002	**0.003**	**0.01**
Waist circumference	Mental Health (MCS-12)	−9.33	2.93	**−14.70**	**−2.59**

Analyses controlled for child age and case status, and parent education, age, and income.

effects of race and ethnicity on allostatic load. The SHOW sample provided opportunities to examine key outcomes in children with mental health conditions; however, the case-control design led to a small sample size, limiting opportunities to examine other relationships of interest and the number of covariates assessed. Body composition and BMI change during puberty, potentially limiting how informative BMI is as a clinical measure of AL in this age group (Araújo et al., 2014; Siervogel et al., 2003; Tu et al., 2015). Finally, food allergy could affect food choices and nutrient intake, which could affect metabolic outcomes.

Implications for nursing research

Nurse researchers have a holistic perspective ideal for exploring connections between individual and contextual factors and health outcomes. Future studies should include comprehensive examination of the relationships among stress exposures, CHC-specific and general stress, and AL. Multiple measures of AL are available, including clinical measures that can be readily obtained in a clinic setting, highlighting their utility for future research on AL in youth with high stress exposure (Katz et al., 2012). Comprehensive assessment of AL should also incorporate relevant biomarkers and genetic and epigenetic variants (Epel et al., 2018; McEwen, 2015). These biological measures provide additional information on AL in individuals with CHCs, and some are also less likely to affected by pubertal development, compared to clinical measures such as BMI. Future studies examining AL in youth with other CHCs are also needed to determine if similar relationships between CHC diagnosis and clinical measures of AL are evident for other conditions.

Future studies should also incorporate a life course approach (Pearlin, 2010), exploring potential relationships between cumulative stress exposure and health outcomes in individuals with CHCs. A life course approach would also support a more comprehensive assessment of the relationships between contextual factors, stress exposure, perceived stress, and AL over time and across multiple life transitions (Pearlin, 2010). Research across the life course will also help determine whether high cumulative stress in individuals with CHCs leads to high AL, as this could be a mechanism for poor health outcomes in individuals with childhood-onset CHCs (Delaney & Smith, 2012).

Implications for nursing practice

Studies building on these preliminary results could provide a foundation for development and testing of interventions designed to mitigate the potentially detrimental effects of high cumulative stress exposure on AL and individuals' health and well-being. Nurses in practice should be aware that youth with mental and physical CHCs may be at increased risk of metabolic dysregulation due to high AL and should ensure that assessments of metabolic health are completed regularly in this population. Of particular importance are assessing nutritional status and BMI in adolescents with food allergies, and the bidirectional relationship of obesity and mental health in adolescents.

Conclusions

Many studies have evaluated the relationship of chronic and acute stress with measures of AL. Children and adolescents with chronic health conditions are at increased risk of experiencing greater cumulative stress exposure, compared to youth without CHCs, placing them at risk of increased allostatic load and poor later-life health. However, studies of the relationship between CHCs in children and adolescents and AL are limited. This analysis provides preliminary evidence of dysregulation in metabolic biomarkers of AL in children and adolescents with chronic physical and mental health conditions. Given the importance of health in childhood and adolescent for life course health trajectories, studies evaluating the relationship of chronic health conditions in children and adolescents with an expanded index of allostatic load indicators are needed. Nurses are ideally positioned to conduct future studies of these relationships and implement interventions designed to mitigate the impact of chronic health conditions in youth on stress, allostatic load, and later life health.

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Declaration of Competing Interest

The authors have no conflict of interest to report.

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