Children's Health Care

ISSN: 0273-9615 (Print) 1532-6888 (Online) Journal homepage: www.tandfonline.com/journals/hchc20

Symptoms, impairment and treatment needs among youth with orthostatic intolerance in a secondary care setting

Kristen G. Benito, Amrita Ramanathan, Debra Lobato, Barbara Jandasek, Erin Mamaril, Haley McBride & Lloyd R. Feit

To cite this article: Kristen G. Benito, Amrita Ramanathan, Debra Lobato, Barbara Jandasek, Erin Mamaril, Haley McBride & Lloyd R. Feit (2022) Symptoms, impairment and treatment needs among youth with orthostatic intolerance in a secondary care setting, Children's Health Care, 51:3, 316-335, DOI: 10.1080/02739615.2022.2047049

To link to this article: https://doi.org/10.1080/02739615.2022.2047049

CHILDREN'S HEALTH CARE
2022, VOL. 51, NO. 3, 316–335
https://doi.org/10.1080/02739615.2022.2047049

Taylor & Francis
Taylor & Francis Group

Symptoms, impairment and treatment needs among youth with orthostatic intolerance in a secondary care setting

Kristen G. Benito[a,b], Amrita Ramanathan[b], Debra Lobato[a], Barbara Jandasek[a,b], Erin Mamaril[a], Haley McBride[b], and Lloyd R. Feit[b,c]

[a]Department of Psychiatry and Human Behavior, Warren Alpert Medical School of Brown University, Providence, RI, USA; [b]Pediatric Heart Center, Hasbro Children's Hospital, Providence, RI, USA; [c]Department of Pediatrics, Warren Alpert Medical School of Brown University, Providence, RI, USA

ABSTRACT

Studies characterizing Orthostatic Intolerance (OI) have primarily focused on a specific subtype (e.g., Postural Orthostatic Tachycardia Syndrome, POTS) treated in tertiary care, yet many with impairing symptoms do not meet subtype criteria. Study 1 used structured coding of electronic medical records to explore symptoms and impairment among 226 youth with OI in a common care setting (outpatient cardiology) over a 1-year period. Impairment was evident for 54.7% of youth. Greater impairment was associated with female gender, higher number and frequency of symptoms, and specific symptoms of headache, weakness, or exercise intolerance. Study 2 examined symptoms, functional disability, and treatment interest in a subset of youth from Study 1 (n = 75); data were collected 1–2 years after initial visit via phone interview. Fifty-six percent of participants remained symptomatic, with mean disability exceeding "substantial impairment" and most (78.6%) expressing desire for treatment. Greater disability was associated with more symptoms and the symptom of weakness. Critically, disability was more than twice as high among racial and ethnic minority youth. Results suggest that OI impairment is common among youth in secondary care, and many experience symptoms warranting treatment 1–2 years later. Future studies should identify sources of health disparities and develop efficacious treatments.

Introduction

Orthostatic intolerance (OI) is characterized by symptoms that occur when standing upright and are relieved by recumbency. Symptoms always include dizziness or syncope/pre-syncope and can also include wide-ranging symptoms such as heart palpitations, blurred vision, or nausea (Sheldon et al., 2015). Some OI is attributed to normal physiology and up to 20% of youth will experience OI symptoms (Stewart et al., 2018). For some, these symptoms cause moderate to severe disability affecting quality of life in multiple domains

CONTACT Kristen G. Benito kbenito@lifespan.org Department of Psychiatry and Human Behavior, Warren Alpert Medical School of Brown University, Providence, RI, USA
Supplemental data for this article can be accessed on the publisher's website

(Benrud-Larson et al., 2002). Peak age of onset occurs in adolescence (Stewart et al., 2018), and youth with OI can experience significant difficulties in activities of daily living that interfere with age-appropriate milestones and may have cascading effects on development into adulthood (Bagai et al., 2011; Stewart, 2004). Impairment may be the direct result of symptoms (e.g., fatigue interfering with school performance) or occur secondary to avoidance of activities that trigger symptoms (e.g., withdrawal from social activities; Benarroch, 2012; Kritzberger et al., 2011).

OI subtypes

Physiologic mechanisms theorized to underlie primary OI (i.e., OI not due to another medical condition) are heterogeneous and not yet well understood, and may include both neurogenic and non-neurogenic forms of autonomic dysfunction (such as from inadequate release of norepinephrine from sympathetic neurons or from dehydration; Smit, Halliwill, Low, & Wieling, 1999). Most treatment development efforts have focused on one or more specific subtypes of OI thought to reflect different underlying mechanisms. These subtypes include orthostatic hypotension (OH; a sustained fall in blood pressure when standing upright; BP), postural vasovagal syncope (VVS; near or actual syncope that occurs after standing upright), and postural orthostatic tachycardia syndrome (POTS; chronic daily symptoms accompanied by sustained and excessive tachycardia when upright). In line with these subtype distinctions, OI diagnostic criteria are based on specific physiologic indicators that vary by subtype. However, there is considerable overlap of clinical features across subtypes and subtype-specific physiologic indicators often fail to predict functioning or clinical course. For example, HR increase during a tilt-table test (the "gold-standard" diagnostic procedure for POTS) has generally failed to predict symptom severity or impairment at any cutoff; this is particularly true among youth (e.g., Boris, Huang, & Bernadzikowski, 2020). Moreover, many youths with OI symptoms fail to meet criteria for any subtype (Boris et al., 2020) – a considerable number of whom may experience significant impairment that warrants treatment.

OI treatment

Consistent with the subtype-based conceptualization of OI, treatment studies have typically included those with a single subtype; the vast majority of these have focused on POTS. Most treatments target theorized pathophysiological mechanisms, such as beta-blockers to counter HR increase, alpha-adrenergic agents targeted at vascular resistance, mineralocorticoid agents targeted at blood volume, and salt/water supplementation targeted at blood volume expansion (Gordon, Opfer-Gehrking, Novak, & Low, 2000; Johnson et al.,

2010). Although there have been very few randomized controlled treatment trials (RCTs) for OI, there is evidence in support of modified salt and fluid intake (Johnson et al., 2010; Kizilbash et al., 2014), and some mixed support for beta-blockers and alpha agonists (Gordon et al., 2000). Matching patients to the right treatment based on probable mechanism is considered critical, yet more than one mechanism may be relevant for each individual and this is a challenging process for which clear guidelines do not exist (Mar & Raj, 2020). Moreover, some studies suggest that mechanism-based patient subgroups do not exhibit differential responses to these treatment approaches (Thieben et al., 2007). Altogether, available treatments only offer partial symptom relief in about half of adult patients (Thieben et al., 2007), and only 19% of adolescents report full symptom resolution 2 years after initiating treatment (Bhatia et al., 2016). Importantly, studies have yet to examine treatment options among those who are impaired but fail to meet OI subtype criteria.

Intervening on factors that maintain OI symptoms

Treatments aimed at factors contributing to OI symptom maintenance may offer benefit regardless of underlying cause and obviate the need for strict physiologic diagnostic criteria. Evidence suggests the involvement of several key factors in OI symptom maintenance that would be promising targets for intervention. Many individuals with impairing OI symptoms experience physical deconditioning as a function of avoiding physical activity (e.g., standing, exercise; Fu & Levine, 2018; Parsaik et al., 2012). This contributes to reduced cardiovascular efficiency and worsens symptoms over time. Evidence suggests that exercise training improves physical conditioning and clinical outcomes for those with POTS (Joyner & Masuki, 2008; Shibata et al., 2012), showing outcomes superior to propranolol (Fu et al., 2011). However, it has not yet been tested in youth or among those without a POTS diagnosis.

Specific types of thoughts and behaviors may also be implicated in the maintenance of OI symptoms (Benrud-Larson, Sandroni, Haythornthwaite, Rummans, & Low, 2003; Kluck, Junghans-Rutelonis, Jones, Fischer, & Weiss, 2017). The experience of OI symptoms is unpleasant and can be accompanied by heightened emotion and/or negative thoughts (e.g., catastrophizing). These are thought to contribute to symptom hypervigilance and excessive avoidance of triggers, which can worsen symptoms over time. This model of symptom maintenance is the basis for exposure-based cognitive-behavioral treatment (CBT), which has strong evidence of efficacy for other disorders characterized by unpleasant somatic sensations (e.g., chronic pain, panic disorder; Craske et al., 2011; Roy-Byrne, Craske, & Stein, 2006). Evidence suggests that this model is highly relevant

for OI; for example, pain catastrophizing has been associated with increased OI symptoms in youth (Junghans-Rutelonis et al., 2018; Raj, Opie, & Arnold, 2018). However, exposure-based CBT has yet to be tested for any OI subtype at any age.

Identifying youth with OI in need of treatment

Interventions that can reduce factors that maintain OI symptoms have the potential for wide-ranging benefit, including among youth that do not meet subtype criteria. However, little is known about how and where these youth would be best identified. The majority of studies characterizing individuals with OI have focused on POTS and occurred in highly specialized tertiary care settings (e.g., POTS or dysautonomia clinics) – where patients are predominantly female, White, and severely impaired (Boris & Bernadzikowski, 2018; Staples, Thompson, & Moodley, 2020). These patients report having already seen more than 10 doctors and spent more than 5 years trying to find an explanation for the symptoms they are experiencing (Kavi et al., 2016; Mar & Raj, 2020). Earlier identification of those needing treatment could occur in primary or secondary care; reports suggest that individuals with OI often present for evaluation and/or management in neurology, gastrointestinal, and cardiology specialty clinics (Mar & Raj, 2020). It will be important to characterize OI symptoms and treatment needs among youth presenting in these settings, so that they may be identified for appropriate care and inclusion in future treatment studies.

Current studies

The overarching goal of the current studies (studies 1 and 2) was to characterize OI symptoms, impairment, and treatment needs among youth presenting to a pediatric cardiology clinic – a common setting for evaluation of OI given the nature of symptoms (e.g., tachycardia) and the need to rule out serious cardiac causes (e.g., for syncope). In Study 1, we conducted an exploratory review of electronic medical records (EMR) for youth with primary OI presenting over a one-year period. Aims were as follows: (1) describe demographics and comorbidity, (2) characterize clinical features and related impairment, and (3) determine whether OI features relate to impairment. In Study 2, we conducted a brief survey with caregivers or youth from Study 1, between 1 and 2 years after initial evaluation. Aims were as follows: (1) characterize OI symptoms and concurrent functional disability, (2) examine relationships between symptoms and functional disability, and (3) describe treatment need.

Methods: Study 1

Participants

This study was approved by the Rhode Island Hospital IRB (Protocol # 891,176); written participant consent was not required given that this study involved collection of de-identified data from the EMR. Participants were 226 youth and young adults aged 8–21 presenting for evaluation of OI symptoms in an outpatient pediatric cardiology setting between January 2016 and January 2017. For parsimony, this paper will refer to participants of all ages as youth. Peak age of OI onset is thought to occur around 15 years (Stewart et al., 2018); however, this may have been influenced by setting in prior studies (e.g., data collected in tertiary care using retrospective report). Therefore, we included youth aged 8–21 so that we might characterize OI in youth at a wide range of ages. We screened 444 EMR records; youth with at least one core OI symptom (dizziness with standing or syncope/near syncope) documented at the time of initial evaluation were included; those with OI symptoms secondary to another medical condition were excluded. Inclusion/exclusion criteria were designed to capture a broad range of youth with primary OI symptoms, regardless of subtype or level of impairment. To establish the presence of OI symptoms, we first reviewed the EMR visit note and encounter summary from the initial evaluation office visit in pediatric cardiology (see EMR review for detail). Youth with at least one core OI symptom documented (dizziness with standing, syncope/pre-syncope, or close synonym) were included for further review (N = 326). Youth for whom the visit note described another medical condition as a cause of OI symptoms were excluded. When another medical condition was present (in the visit note, diagnosis code, or problem list) but contribution to OI symptoms was not documented, the record was reviewed by a cardiologist (last author) to determine whether OI symptoms were primary or secondary; youth with secondary symptoms were excluded (N = 100 excluded for secondary OI symptoms). Reasons for exclusion are presented in Supplementary Figure 1.

Setting

This study was conducted in an outpatient pediatric cardiology center (the Pediatric Heart Center; PHC) with three locations in the U.S. northeast, serving youth with demographic characteristics representative of the state (see Table 1). The PHC provides nearly all pediatric cardiology services in the state (>95%) and is embedded within a statewide multi-hospital system that uses a shared EMR (EPIC).

Table 1. Participant characteristics in Study 1 and Study 2.

			Study 2 $N = 75$		
		Study 1 $N = 226$	Symptomatic $n = 42$	Asymptomatic $n = 33$	Study 2 Total
Age (years)		$M = 14.1$ ($SD = 2.9$)	$M = 15.3$ ($SD = 2.8$)	$M = 14.8$ ($SD = 2.5$)	$M = 15.1$ ($SD = 2.7$)
Biological Sex	Male	35.4%	31.0%	51.5%*	40.0%
	Female	64.6%	69.0%	48.5%*	60.0%
Race[a]	White	79.2%[b]	64.3%	75.8%	67.5%[b]
	Black	5.3%	0.0%	3.0%	1.3%
	Asian	1.8%	2.4%	6.1%	3.9%
	Multiple/Other	11.9%	26.2%	12.1%	19.5%
	Declined	1.8%	9.5%	3.0%	5.2%
Ethnicity[a]	Latinx	15.9%	23.8%[c]	9.1%[c]	17.3%
	Not Latinx	82.3%	73.8%[c]	89.9%[c]	81.3%
	Declined	1.8%	2.4%	0.0%	1.5%

[a]State Demographics: 80.5% White, 6.8% Black, 3.4% Asian, 3.9% Multiple/Other; 15.4% Latinx (U.S. Census Bureau, 2019).
[b]Compared with Study 1, Study 2 included a lower proportion of youth identifying as White ($X^2(1) = 4.25$, $p = .04$).
[c]In Study 2, there was a marginally significant difference in the proportion of asymptomatic participants by sex ($X^2(1) = 3.26$, $p = .07$) and by ethnicity ($X^2(1) = 2.96$, $p = .08$).

Electronic medical *r*ecord (EMR) *r*eview

We conducted an EMR search for youth in the selected age range with (1) a provider visit in the PHC between January 2016 and January 2017, and (2) ICD 9 or 10 visit diagnosis code matching OI symptoms [e.g., 780.2 (syncope), 785.0 (tachycardia), 785.1 (palpitations), 780.4 (dizziness); see Table 2 for full symptom list]. We used a structured coding system to further evaluate inclusion/exclusion criteria and to collect EMR data (coding manual available from

Table 2. Percent of patients endorsing OI symptoms in Study 1 and Study 2.

	Study 1[a] $N = 226$	Study 2[b] Symptomatic $N = 42$
Syncope/near syncope[c]	68.6%	38.1%
Dizziness with standing[c]	63.7%	81.0%
Altered Vision	35.0%	33.3%
Tachycardia/palpitations	30.1%	31.0%
Chest pain	27.9%	40.5%
Nausea/ GI distress	23.9%	52.4%
Short of breath	18.1%	31.0%
Sweating	16.4%	33.3%
Appears Pale	14.2%	33.3%
Headache	11.9%	71.4%
Fatigue	8.8%	66.7%
Weakness	7.1%	28.6%
Trouble exercising	4.0%	19.0%
Cognitive Disturbance	1.8%	28.6%

[a]Study 1 assessed symptoms using EMR review.
[b]Study 2 assessed symptoms using parent or self-report.
[c]Inclusion criteria required endorsement of at least one shaded symptom (all Study 1 participants and symptomatic Study 2 participants).

first author on request). A trained research assistant (2nd author) extracted data using this coding system and 10% of records were double coded by the first author; inter-coder reliability for all study variables described below was excellent (*K* or *ICC* range .88 to 1.0). Data were collected from visit notes, encounter summaries, procedure summaries, and problem lists.

Data collection

We extracted demographic information including age, gender, race, ethnicity, and insurance type (public or private). Using diagnoses in the problem list and visit note, we classified the presence of several specific medical or psychiatric comorbidities with high base rates and/or that have been associated with OI symptoms (GI, headache, cardiac, anxiety, mood, or ADHD diagnosis; yes/no for each). Although providers used a template for visit notes, the template was designed for general clinical care and did not include specific fields for systematic collection of the OI variables described in this study. We determined whether each OI symptom or a close synonym was documented in the visit note or diagnosis code (yes/no; see Table 2). Symptoms of interest were selected based on prior studies (Boris & Bernadzikowski, 2018; Fedorowski & Melander, 2013; Johnson et al., 2010; Stewart, 2013). When documented, we recorded duration in months since OI symptom onset and frequency of OI symptoms (classified as occurring *less than monthly, at least monthly but less than weekly, at least weekly but less than daily*, or *daily*). When notes documented evidence or absence of OI-related impairment (i.e. interference in social, physical, educational/occupational, or another critical domain that was attributed to OI symptoms), we coded this using a 0–3 scale (0 = *none, documented absence of impairment*; 1 = *mild, slight interference in at least one area*, e.g., using elevator instead of stairs due to OI symptoms; 2 = *moderate, definite interference in at least one area*, e.g., reduced sports participation, decline in academic performance but still attending school, difficulty with showering or other self-care; 3 = *severe, substantial impairment in at least one area*, e.g., not attending school, unable to socialize, unable to walk more than a few feet. These categories were based on conventions used with existing clinician-rated measures of global functioning (e.g., Clinical Global Impression-Severity scale, Guy, 1976; Global Assessment of Functioning, APA, 2000; World Health Organization Disability Assessment Schedule, Ustun et al., 2010).

POTS and OH criteria

When collected at initial evaluation, we extracted orthostatic vital signs including HR and systolic/diastolic BP (at supine and after 3 minutes standing). Although a tilt-table test is the "gold-standard" method for evaluating POTS criteria, these are infeasible in most practice settings (including the setting where this study took place). Multiple studies with adults show that a 3-

or 10-min standing test has similar sensitivity and specificity (Fedorowski, 2019; Kirbiš, Grad, Meglič, & Bajrovič, 2013). Therefore, we used supine and 3-min standing HR to calculate POTS criteria (standing HR > 120 bpm or HR change >40 bpm [age 8–17] or >30 bpm [age 18–21]; Stewart et al., 2018). We also calculated whether participants met OH criteria (BP decrease >20 mm Hg systolic or 10 mm Hg diastolic from supine to 3-min standing; Stewart et al., 2018).

Results: study 1

Analyses were conducted using SPSS (Version 25). Sample demographics and other study variables were characterized using descriptive statistics (Aims 1 and 2). Analyses for Aim 3 used correlation, independent samples *t*-test, or chi-square. When preliminary inspection of study variables revealed deviations from homoscedasticity or normality, we applied square root followed by cube root transformations until deviations were corrected (descriptive statistics are reported in original units for interpretability). We also explored whether demographic variables related to other studied variables of interest. Missing data were handled using listwise deletion. When variables were not documented for all participants in the sample, analyses were conducted with a subset of participants as follows: orthostatic vital signs (44%; 99/226), time since symptom onset (87%; 197/226), symptom frequency (67%; 153/226), OI impairment (71%; 161/226).

Demographic descriptive data (Aim 1)

For youth presenting to pediatric cardiology with primary OI symptoms are presented in Table 1. This sample includes youth with a mix of insurance types (60.6% private, 38.9% public, 0.4% uninsured). A majority of youth had at least one medical comorbidity (57.1%), including 4.9% with a cardiac diagnosis, 12.4% with a GI diagnosis, and 9.7% with a headache diagnosis. A sizable minority had at least one psychiatric comorbidity (21.2%), including 20.2% with an anxiety disorder, 8.0% with a mood disorder, and 11.1% with ADHD. These are slightly higher than rates for youth in the general population, where 15–20% have an anxiety disorder (Beesdo et al., 2009), 6.1% have a mood disorder (Bitsko et al., 2018), and 9.4% have ADHD (Danielson et al., 2018).

Characterizing OI symptoms and impairment (Aim 2)

After syncope/near-syncope and dizziness with standing (at least one of which was required for inclusion), the most commonly documented OI symptoms were altered vision, tachycardia/palpitations, chest pain, and nausea/GI distress (see Table 2). Other documented features (orthostatic vital signs,

Table 3. OI features and impairment in Study 1.

Orthostatic Vital Signs *n* = 99[a]	Standing HR (3 min)	*M* = 96.2 (*SD* = 16.3)
	HR change (supine to standing, 3 min)	*M* = 21.9 (*SD* = 13.2)
	BP change, systolic (supine to standing, 3 min)	*M* = −0.8 (*SD* = 8.5)
	BP change, diastolic (supine to standing, 3 min)	*M* = −5.1 (*SD* = 7.6)
Time since onset (months) *n* = 197[a]		*M* = 17.1 (*SD* = 25.8)
Symptom Frequency *n* = 153[a]	Daily	19.6%
	< Daily to weekly	28.1%
	< Weekly to monthly	18.3%
	< Monthly	34.0%
OI Impairment *n* = 161[a]	None	45.3%
	Mild	34.2%
	Moderate	14.9%
	Severe	5.6%

[a]Number of participants for whom relevant variable was documented.

duration and frequency of symptoms) and impairment are presented in Table 3. Only 4.0% of participants met POTS HR criteria. Given this, we explored a less conservative HR change >30 bpm criterion for adolescents (recent studies suggest using this threshold with adolescents to avoid underdiagnosis; Boris et al., 2020). Using this approach, 12.8% met POTS criteria. 24.2% met OH criteria.

Exploring demographic relationships

Age was significantly related to HR change such that older youth had greater HR increase with standing (r = .26, p = .01). Age was also related to impairment such that older youth were more impaired (r = .22, p = .006). Females had greater impairment ($t(159)$ = 2.61, p = .01, M = 1.0 (0.9)) compared with males (M = 0.6(0.9). There was a trend toward females having more frequent symptoms ($t(151)$ = 1.97, p = .051, M = 2.7(1.4)) than males (M = 3.2(1.3)), higher standing HR ($t(97)$ = 1.91, p = .06, M = 98.4(16.4)) than males (M = 91.9(15.4)), and a greater number of symptoms ($t(222)$ = 1.93, p = .06, M = 3.8 (1.4)) than males (M = 3.4(1.4)). We did not find any other significant differences related to age, sex, ethnicity, race, or insurance type.

Relationships between OI features and impairment (Aim 3)

The following analyses were conducted with N = 161 participants for whom impairment was documented in the EMR. Number of symptoms (r = .41, p < .001) and frequency of symptoms (r = .38, p < .001) were significantly related to impairment. Holding the number of OI symptoms constant, the following specific symptoms related to higher impairment: dizziness with standing (r = .24, p = .002), headache (r = .20, p = .01), weakness (r = .20, p = .01), and

exercise intolerance (r = .20, p = .01). Holding the number of OI symptoms constant, the presence of any of the following symptoms related to lower impairment: syncope/near syncope (r = −.27, p = .001), altered vision (r = −.22, p = .005), and appearing pale (r = −.16, p = .04). Too few participants met strict POTS criteria to test for differences based on POTS status. OI-related impairment was not significantly different among youth meeting a less conservative POTS criterion (HR change > 29 bpm) or those meeting criteria for OH (p > .05).

Methods: Study 2

Participants

This study was approved by the Rhode Island Hospital IRB (Protocol # 1,068,109). Participants were 75 youths (age 9–20) that had been included in Study 1 and agreed to participate in a brief phone survey. Caregiver participants (for youth aged 9–17) or patient participants (for young adults age 18–20) provided verbal consent. Given that the budget and project period were limited (i.e., not sufficient for proper translation of measures or hiring Spanish-speaking staff), caregivers (for youth age 9–17) or patients (for young adults age 18–20) were required to speak English. Participant flow and reasons for study exclusion are presented in Supplementary Figure 1 (could not reach, N = 106; declined study, N = 38; not English-Speaking, N = 6). Two participants did not finish study measures and were not included in analyses.

Procedures

All families who had participated in Study 1 were invited to participate in Study 2, following consent procedures, they provided demographic information (age, gender, race, and ethnicity), and verbally completed study measures. Surveys were conducted between December 2017 and February 2018. Caregiver participants completed study measures for youth aged 9–17 (n = 63) and patient participants age 18–20 completed study measures for themselves (n = 12). Participants were instructed to respond to all measures based on experiences over the past 2 weeks. To encourage a high rate of participation, we designed study procedures to minimize participant burden. As such, the surveys were brief (approximately 15 minutes) and administered by phone; we did not require youth-report in addition to caregiver-report. Given IRB limitations on the type of data that may be obtained with verbal consent (vs. with in-person, written consent), data collected in Study 2 could

not be linked to individual participant data from Study 1 (e.g., for examining EMR data collected in Study 1 as predictors of functioning reported in Study 2).

Measures

OI symptom checklist

Participants were asked to report whether they/their child had experienced each OI symptom over the previous 2 weeks (yes or no; symptoms listed in Table 2). This symptom list was generated based on prior studies documenting common OI symptoms (e.g., Benarroch, 2012; Boris et al., 2020; Fedorowski, 2019) and mirrors those symptoms assessed in Study 1.

Functional disability inventory (FDI)

The FDI is a 15-item measure assessing difficulty with functioning related to health status in home, school, social, and physical domains. Items are rated on a scale of 0 (*no trouble*) to 4 (*impossible*) and summed to create a total score (0–60). The FDI has good psychometric properties, including internal consistency, reliability across youth and caregiver reporters, and construct validity (Claar & Walker, 2006; Walker & Greene, 1991). Internal consistency was excellent in this sample (Cronbach's $\alpha = 0.94$). The FDI is widely used for youth with chronic pain and other health conditions; it has also been used with young adults in pediatric medical settings (Walker, Guite, Duke, Barnard, & Greene, 1998).

Treatment interest and acceptability

Participants answered four questions assessing interest in treatment, including general interest in OI treatment ("How interested are you in getting treatment for these symptoms?") and specific interest in medication (How interested are you in a medication to treat these symptoms?), exercise ("How interested are you in an exercise treatment for these symptoms?," and behavioral health ("How interested are you in a behavioral treatment for these symptoms?") forms of treatment. When participants were unfamiliar with behavioral treatment, the interviewer described it as a treatment approach that focuses on learning new thought patterns, behaviors, and lifestyle adjustments. Reponses were rated on a 0 (*not at all interested*) to 5 (*extremely interested*) scale.

Results: Study 2

Analyses were conducted as in Study 1. Demographic descriptive data for youth in Study 2 are presented in Table 1. Compared with the Study 1 sample, Study 2 included a lower proportion of youth identifying as White ($\chi^2(1) = 4.25$, $p = .04$). Study 1 and 2 samples did not differ on any other demographic characteristics ($ps > .05$).

Characterizing OI symptoms (Aim 1)

A large minority of participants (44.0%, n = 33) were asymptomatic (i.e., reported no longer experiencing core OI symptoms of syncope/near-syncope, dizziness with standing, or light-headedness). Among those who were symptomatic (i.e., endorsing at least one core OI symptom; 56.0%, n = 42), the other most commonly endorsed symptoms included headache, fatigue, and nausea/GI distress (see Table 2).

Characterizing functional disability (Aim 1)

Average disability among symptomatic participants (FDI M = 12.9, SD = 10.8) exceeded a threshold for "substantial impairment" (FDI score > 7; Roma et al., 2019). Individually, 60.0% of symptomatic participants had FDI scores exceeding this threshold. Supplementary Table 1 presents means for each FDI item; areas of greatest impairment included being up all day without a nap or rest (M = 1.3, SD = 1.3), being at school/work all day (M = 1.3, SD = 1.1), doing activities in gym or playing sports (M = 1.3, SD = 1.2), running the length of a football field (M = 1.7, SD = 1.4) and getting to sleep/staying asleep (M = 1.6, SD = 1.2).

Exploring demographic relationships

Although descriptive data suggest a disproportionately higher number of females among symptomatic participants (Table 1), the difference did not reach statistical significance ($X^2(1) = 3.26$, $p = .07$). Among symptomatic participants, females endorsed a higher number of OI symptoms ($t(40) = -2.8$, $p = .009$, $M = 6.8(3.0)$) compared with males ($M = 4.1(2.7)$). No other gender differences emerged. Although there was a trend suggesting that Latinx participants were more likely to be symptomatic (Table 1), the difference did not reach significance, $X^2(1) = 2.96$, $p = .08$. Among those with symptoms, Latinx participants had functional disability scores more than two times higher ($t(39) = -3.07$, $p = .004$, $M = 21.4(12.3)$) than those of non-Latinx participants ($M = 10.5(9.0)$). Latinx participants also endorsed a greater number of OI symptoms ($t(39) = -3.40$, $p = .002$, $M = 8.6(2.7)$) compared with non-Latinx participants ($M = 5.1(2.9)$). Given the low number of participants in some racial groups, we examined differences by race with respect to White participants vs. Black, Indigenous, and People of Color (BIPOC) participants (those identifying as Black, Asian, or multiple/other race). Similar to findings bases on ethnicity, BIPOC participants had disability scores more than two times higher ($t(40) = 3.61$, $p = .001$, $M = 20.2(11.2)$) than those of White participants ($M = 8.8(8.2)$). BIPOC participants endorsed a higher number of OI symptoms ($t(40) = 2.76$, $p = .009$,

M = 7.6(2.8)) compared with White participants (M = 5.0(3.0)). Accordingly, BIPOC participants expressed stronger interest in treatment ($t(40)$ = 2.63, p = .012, M = 3.9(1.7)) compared with White participants (M = 2.3(1.9). We did not find any other significant differences related to age, ethnicity or race.

Relationships between OI symptoms and functional disability (Aim 2)

Among symptomatic participants, number of symptoms was strongly related to disability (r = .65, p < .001). Holding the number of symptoms constant, weakness was specifically related to higher disability (r = 0.39, p = .01). No other symptoms were significantly related to impairment.

Describing treatment needs (Aim 3)

Most symptomatic participants (78.6%) reported being interested in treatment. Stronger interest in treatment was associated with a higher number of symptoms (r = .38, p = .017) and a higher functional disability (r = .40, p = .008). Interestingly, a number of participants falling below the "substantial impairment" threshold (i.e. with FDI score < 7) expressed a desire for treatment (n = 11 of 17). Understanding the need for treatment despite lower levels of overall impairment may be important for identifying these youth in practice. As such, we further explored the rate at which these 11 youth endorsed individual areas of impairment on the FDI. Most (n = 9) did endorse "moderate" or greater impairment in at least one major area of functioning, most commonly for difficulty being up all day without a nap or rest (n = 3), being at school/work all day (n = 4), doing activities in gym/playing sports (n = 2), and getting to sleep/staying asleep (n = 2). Of those interested in treatment (n = 33), there was strong interest in behavioral (M = 3.8, SD = 1.7) or exercise (M = 3.7, SD = 1.3) interventions, and somewhat less interest in medication (M = 2.2, SD = 1.8).

Discussion: studies 1 and 2

Results from these studies shed light on the symptoms, impairment, and treatment needs among a broad range of youth presenting with OI symptoms in secondary care. Specifically, findings suggest that a number of youth experience OI-related impairment that can persist for up to 2 years after evaluation in this setting. These youths and their families describe a high level of interest in treatment for OI and are particularly interested in behavioral health and/or exercise interventions. Results also point to specific OI features that may signal poorer functioning, including endorsement of weakness, headache, or exercise intolerance. Finally, demographic data from these

studies suggests that OI symptoms occur at similar rates across racial and ethnic groups – but that racial and ethnic minority youth go on to experience disproportionately higher rates of impairment over time.

Exploratory results from EMR review (Study 1) show that youth had been experiencing symptoms for 17 months on average at the time of initial cardiac evaluation, and more than half (54.7%) were experiencing OI-related impairment in at least one area. While study 1 results should be considered exploratory given missing data for some EMR variables, it is notable that more than half of youth participating in Study 2 remained symptomatic. Although response bias may have influenced this rate (i.e., those with symptoms were more likely to respond to our survey request), it suggests that at least 19% (and up to 56%) of youth will continue to experience OI symptoms 1–2 years after first presenting to cardiology for evaluation. Altogether, these findings suggest that a broad range of youth with OI symptoms could benefit from treatment and confirm that pediatric cardiology is an appropriate setting in which to identify them.

Youth in Study 2 experienced functional disability exceeding a threshold for "substantial impairment," reporting the most trouble with being at school or work all day, physical activity, and sleep. While significant disability was clearly present in this sample, the average level of disability appears lower than reported in tertiary care settings (Benrud-Larson et al., 2002; Mar & Raj, 2020; Staples et al., 2020). This underscores the benefit of identifying youth for OI treatment in secondary care settings, potentially before symptoms become severe. Interestingly, some participants wanted treatment but had low functional disability scores. On closer inspection, these youth exhibited moderate impairment in at least one essential area (e.g., being at school or work all day). Altogether, results suggest that youth with OI who exhibit moderate impairment in at least one important domain may be appropriate candidates for treatment.

In striking contrast to prior work, our findings suggest that OI symptoms occur at similar rates across demographic groups and that racial and ethnic minority youth experience disproportionately higher rates of impairment over time. In Study 1, participant demographics were similar to local census data; we also did not find any racial or ethnic differences in clinical presentation. This is a departure from several studies suggesting that OI predominantly affects White individuals (>94% White, e.g., Boris & Bernadzikowski, 2018). However, most prior data has come from tertiary care clinics that may be difficult to access for minority youth or adults. A higher proportion of BIPOC youth participated in Study 2 when compared with Study 1 and local census rates. This may be related to greater symptom burden among minority youth; critically, Study 2 findings suggest that racial and ethnic minority youth may be more likely to remain symptomatic 1–2 years after initial evaluation. They also reported rates of disability more than two times higher than their non-

minority counterparts. This may even be an underestimate given that participants not comfortable speaking English were excluded in Study 2. Altogether, findings suggest that racial and ethnic minority youth initially present with OI symptoms at proportionate rates but are more likely to experience a protracted symptom course characterized by higher levels of impairment. There are a number of factors that might contribute to this disparity (e.g., access to appropriate care, Flores & Tomany-Korman, 2008; racial bias in somatic symptom assessment, Hoffman, Trawalter, Axt, & Oliver, 2016; economic or neighborhood stressors that could impact functioning; Mezuk et al., 2010), and future studies should seek to understand these in detail. These findings suggest a critical need for early and appropriate treatment of OI symptoms in minority youth.

Female participants had higher documented impairment in Study 1 and endorsed more symptoms in Study 2. This is consistent with prior literature showing that females are disproportionately affected by OI (Stewart et al., 2018). We observed a slightly more pronounced difference in sex distribution in Study 2 (69% female), with females marginally more likely to be symptomatic. This is consistent with prior work showing that females comprise 80% of the adult patients and 65–70% of adolescent patients (Johnson et al., 2010), suggesting that the sex difference may widen across development. Older age was also associated with higher impairment, consistent with the known peak age of OI symptoms occurring in late adolescence/early adulthood (Stewart et al., 2018).

Several clinical features were associated with greater impairment, including the overall number of OI symptoms and some specific symptoms, including weakness (Studies 1 and 2) as well as dizziness, headache, and exercise intolerance (Study 1). Several symptoms (e.g., headache, fatigue) were notably more common in Study 2 vs. Study 1 samples. This difference could result from the influence of care context in Study 1 (i.e., cardiac-relevant symptoms more likely to be documented). However, the overall pattern of findings is consistent with those in other studies, where fatigue, headache, and cognitive dysfunction have been associated with poorer short-term prognosis among those with POTS (Jarjour, 2013). Youth with these symptoms may warrant closer monitoring and/or earlier intervention to mitigate the impairment caused by symptoms.

Of Study 1 participants with orthostatic vital signs documented in the EMR, only 4.0% met accepted POTS HR criteria; 12.8% met criteria using a less conservative approach (Boris et al., 2020). Nearly one-quarter met the BP criterion for OH. However, there were no significant differences in OI symptoms or impairment based on POTS or OH criteria. This is consistent with several other studies (e.g., Boris et al., 2020), and adds to a body of the literature suggesting that orthostatic vital signs may not be helpful for understanding symptom burden. It is important to note that the present study did not use

a tilt-table test and could have underestimated the number of youth meeting POTS criteria. However, this test is infeasible in most practice settings. This study used a more feasible standing test, which has comparable accuracy among adults (Fedorowski, 2019; Kirbiš et al., 2013). Importantly, orthostatic vital signs were only documented for a portion of youth (44%) that presented for care, and future studies will be needed to confirm these exploratory results. Overall, findings suggest that – when using tests readily available in practice settings – formal assessment of OI subtype criteria does not add clinical value.

Results should be interpreted in light of several limitations. In study 1, information about symptoms and impairment was based on unstandardized clinical interviews as documented by providers in the EMR. Rates of symptom endorsement should be interpreted considering the setting, where evaluation likely focused more on cardiac-related symptoms (e.g., tachycardia, dizziness, syncope) than on others (e.g., nausea) and likely did not include a thorough assessment of impairment in all possible domains. Additionally, impairment ratings relied on subjective coding rather than standardized assessment. Not all variables of interest were documented in the EMR for every participant, resulting in some missing data. As a result, study 1 findings should be considered exploratory. In study 2, procedures were designed to encourage a high rate of participation. For example, we did not require youth-report in addition to caregiver-report because youth were often not available when parents were reached by phone. Youth ratings can differ from those of their caregivers (Vetter, Bridgewater, & Ascherman et al., 2014), and it will be important to collect these data in future studies. Nevertheless, caregivers play a central role in symptom reporting and treatment decisions for youth, and their perspective is valuable for characterizing this population. Finally, we were unable to link individual participant data across studies 1 and 2 due to IRB guidelines for verbal consent. This precluded some longitudinal analyses that may have been helpful for understanding symptom trajectory (e.g., identifying clinical features in study 1 that predict subsequent impairment in study 2). However, the primary goal of this study was to characterize symptoms, impairment, and treatment needs among youth with OI. Finally, there may be important differences in symptom presentation, impairment, and/or treatment need among youth presenting in other settings (e.g., GI, primary care); future studies in this area will be needed. Limitations notwithstanding, this is one of the first studies to characterize a broad range of youth who present with OI in a common care setting–an important step toward developing effective treatments for this population.

Implications for practice

To identify youth in need of treatment, providers should evaluate whether moderate OI-related impairment is present in at least one important domain (e.g., academic, social, family, or physical functioning). Youth endorsing

symptoms of weakness, headache, or exercise intolerance may exhibit poorer functioning and benefit from closer monitoring and/or earlier intervention. Racial and ethnic minority youth are at higher risk for increased impairment over time and may also benefit from closer monitoring and/or earlier referral for treatment. Although additional research is needed to understand the specific factors that contribute to this disparity, clinics and/or providers that evaluate youth with OI could consider deploying strategies designed to bolster healthcare equity. These might include staff training in perspective taking during somatic symptom assessment (Drwecki, Moore, Ward, & Prkachin, 2011), offering transportation vouchers or telehealth services for families with transportation barriers (Zuckerman, Perrin, Hobrecker, & Donelan, 2013), use of care coordination services in the clinic or through insurance providers (Toomey, Chien, Elliott, Ratner, & Schuster, 2012), and/or developing a referral list of follow-up service providers (e.g., behavioral health) that can meet some common needs for minority families (e.g., Spanish-speaking, accepts public insurance). In making referrals for OI treatment, providers should consider that behavioral health and/or exercise interventions appear to be more acceptable than medication for youth with OI and their families, although future studies will need to evaluate the relative efficacy of these treatments for this population.

Acknowledgments: This work was supported by funding from the Department of Pediatrics at Hasbro Children's Hospital.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the Hasbro Children's Hospital Department of Pediatrics. This is the correct funding source. Authors do not have any conflicts of interest to disclose.

References

Bagai, K., Song, Y., Ling, J. F., Malow, B., Black, B. K., Biaggioni, I., . . . Raj, S. R. (2011). Sleep disturbances and diminished quality of life in posturaltachycardia syndrome. *Journal of Clinical Sleep Medicine*, *7*(2), 204–210. doi:10.5664/jcsm.28110

Beesdo, K., Knappe, S., & Pine, D. S. (2009). Anxiety and anxiety disorders in children and adolescents: Developmental issues and implications for DSM-V. *Psychiatric Clinics of North America*, *32*(3), 483–524. doi:10.1016/j.psc.2009.06.002

Benarroch, E. E. (2012). Postural tachycardia syndrome: A heterogeneous and multifactorial disorder. *Mayo Clinic Proceedings*, *87*(12), 1214–1225. doi:10.1016/j.mayocp.2012.08.013

Benrud-Larson, L. M., Dewar, M. S., Sandroni, P., Rummans, T. A., Haythornthwaite, J. A., & Low, P. A. (2002). Quality of life in patients with postural tachycardia syndrome. *Mayo Clinic Proceedings*, *77*(6), 531–537. doi:10.4065/77.6.531

Benrud-Larson, L. M., Sandroni, P., Haythornthwaite, J. A., Rummans, T. A., & Low, P. A. (2003). Correlates of functional disability in patients with postural tachycardia syndrome: Preliminary cross-sectional findings. *Health Psychology*, *22*(6), 643–648. doi:10.1037/0278-6133.22.6.643

Bhatia, R., Kizilbash, S. J., Ahrens, S. P., Killian, J. M., Kimmes, S. A., Knoebel, E. E., … Fischer, P. R. (2016). Outcomes of adolescent-onset postural orthostatic tachycardia syndrome. *The Journal of Pediatrics*, *173*, 149–153. doi:10.1016/j.jpeds.2016.02.035

Bitsko, R. H., Holbrook, J. R., Ghandour, R. M., Blumberg, S. J., Visser, S. N., Perou, R., & Walkup, J. T. (2018). Epidemiology and impact of health care provider-diagnosed anxiety and depression among US children. *Journal of Developmental & Behavioral Pediatrics*, *39*(5), 395–403. doi:10.1097/DBP.0000000000000571

Boris, J. R., & Bernadzikowski, T. (2018). Demographics of a large paediatric postural orthostatic tachycardia syndrome program. *Cardiology in the Young*, *28*(5), 668–674. doi:10.1017/S1047951117002888

Boris, J. R., Huang, J., & Bernadzikowski, T. (2020). Orthostatic heart rate does not predict symptomatic burden in pediatric patients with chronic orthostatic intolerance. *Clinical Autonomic Research*, *30*(1), 19–28. doi:10.1007/s10286-019-00622-y

Claar, R. L., & Walker, L. S. (2006). Functional assessment of pediatric pain patients: psychometric properties of the functional disability inventory. *Pain*, *121*(1–2), 77–84. doi:10.1016/j.pain.2005.12.002

Craske, M. G., Wolitzky-Taylor, K. B., Labus, J., Wu, S., Frese, M., Mayer, E. A., & Naliboff, B. D. (2011). A cognitive-behavioral treatment for irritable bowel syndrome using interoceptive exposure to visceral sensations. *Behaviour Research and Therapy*, *49*(6–7), 413–421. doi:10.1016/j.brat.2011.04.001

Danielson, M. L., Bitsko, R. H., Ghandour, R. M., Holbrook, J. R., Kogan, M. D., & Blumberg, S. J. (2018). Prevalence of parent-reported ADHD diagnosis and associated treatment among U.S. children and adolescents, 2016. *Journal of Clinical Child & Adolescent Psychology*, *47*(2), 199–212. doi:10.1080/15374416.2017.1417860

Drwecki, B. B., Moore, C. F., Ward, S. E., & Prkachin, K. M. (2011). Reducing racial disparities in pain treatment: The role of empathy and perspective-taking. *PAIN*, *152*(5), 1001–1006. doi:10.1016/j.pain.2010.12.005

Fedorowski, A. (2019). Postural orthostatic tachycardia syndrome: Clinical presentation, aetiology and management. *Journal of Internal Medicine*, *285*(4), 352–366. doi:10.1111/joim.12852

Fedorowski, A., & Melander, O. (2013). Syndromes of orthostatic intolerance: A hidden danger. *Journal of Internal Medicine*, *273*(4), 322–335. doi:10.1111/joim.12021

Flores, G., & Tomany-Korman, S. C. (2008). Racial and ethnic disparities in medical and dental health, access to care, and use of services in US children. *Pediatrics*, *121*(2), e286–e298. doi:10.1542/peds.2007-1243

Fu, Q., & Levine, B. D. (2018). Exercise and non-pharmacological treatment of POTS. *Autonomic Neuroscience: Basic and Clinical*, *215*, 20–27. doi:10.1016/j.autneu.2018.07.001

Fu, Q., VanGundy, T. B., Shibata, S., Auchus, R. J., Williams, G. H., & Levine, B. D. (2011). Exercise training versus Propranolol in the treatment of the postural orthostatic tachycardia syndrome. *Hypertension*, *58*(2), 167–175. doi:10.1161/HYPERTENSIONAHA.111.172262

Gordon, V. M., Opfer-Gehrking, T. L., Novak, V., & Low, P. A. (2000). Hemodynamic and symptomatic effects of acute interventions on tilt in patients with postural tachycardia syndrome. *Clinical Autonomic Research*, *10*(1), 29–33. doi:10.1007/BF02291387

Guy, W. (1976). *ECDEU assessment manual for psychopharmacology*. Rockville, MD: U.S. Department of Health, Education, and Welfare.

Hoffman, K. M., Trawalter, S., Axt, J. R., & Oliver, M. N. (2016). Racial bias in pain assessment and treatment recommendations, and false beliefs about biological differences between blacks and whites. *Proceedings of the National Academy of Sciences of the United States of America (PNAS)*, *113*(16), 4296–4301. doi:10.1073/pnas.1516047113

Jarjour, I. T. (2013). Postural tachycardia syndrome in children and adolescents. *Seminars in Pediatric Neurology*, *20*(1), 18–26. doi:10.1016/j.spen.2013.01.001

Johnson, J. N., Mack, K. J., Kuntz, N. L., Brands, C. K., Porter, C. J., & Fischer, P. R. (2010). Postural orthostatic tachycardia syndrome: A clinical review. *Pediatric Neurology*, *42*(2), 77–85. doi:10.1016/j.pediatrneurol.2009.07.002

Joyner, M. J., & Masuki, S. (2008). POTS versus deconditioning: The same or different? *Clinical Autonomic Research*, *18*(6), 300–307. doi:10.1007/s10286-008-0487-7

Junghans-Rutelonis, A. N., Craner, J. R., Ale, C. M., Harbeck-Weber, C., Fischer, P. R., & Weiss, K. E. (2018). Youth with chronic pain and postural orthostatic tachycardia syndrome (POTS): Treatment mediators of improvement in functional disability. *Journal of Clinical Psychology in Medical Settings*, *25*(4), 471–484. doi:10.1007/s10880-018-9558-7

Kavi, L., Nuttall, M., Low, D. A., Opie, M., Nicholson, L., Caldow, E., & Newton, J. L. (2016). A profile of patients with postural tachycardia syndrome and their experience of healthcare in the UK. *British Journal of Cardiology*, *23*(1), 1–6. doi:10.5837/bjc.2016.010

Kirbiš, M., Grad, A., Meglič, B., & Bajrovič, F. F. (2013). Comparison of active standing test, head-up tilt test and 24-h ambulatory heart rate and blood pressure monitoring in diagnosing postural tachycardia. *Functional Neurology*, *28*(1), 39–46. doi:10.11138/FNeur/2013.28.1.039

Kizilbash, S. J., Ahrens, S. P., Bruce, B. K., Chelimsky, G., Driscoll, S. W., Harbeck-Weber, C., … Fischer, P. R. (2014). Adolescent fatigue, POTS, and recovery: A guide for clinicians. *Current Problems in Pediatric and Adolescent Health Care*, *44*(5), 108–133. doi:10.1016/j.cppeds.2013.12.014

Kluck, B. N., Junghans-Rutelonis, A. N., Jones, A. E., Fischer, P. R., & Weiss, K. E. (2017). Adolescent chronic fatigue and orthostatic intolerance: Relationships between parental attributes and child functioning. *Clinical Pediatrics*, *56*(1), 85–89. doi:10.1177/0009922816644730

Kritzberger, C. J., Antiel, R. M., Wallace, D. P., Zacharias, J. D., Brands, C. K., Fischer, P. R., & Harbeck-Weber, C. (2011). Functional disability in adolescents with orthostatic intolerance and chronic pain. *Journal of Child Neurology*, *26*(5), 593–598. doi:10.1177/0883073810390366

Mar, P. L., & Raj, S. R. (2020). Postural orthostatic tachycardia syndrome: Mechanisms and new therapies. *Annual Review of Medicine*, *71*(1), 235–248. doi:10.1146/annurev-med-041818-011630

Mezuk, B., Rafferty, J. A., Kershaw, K. N., Hudson, D., Abdou, C. M., Lee, H., … Jackson, J. S. (2010). Reconsidering the role of social disadvantage in physical and mental health: Stressful life events, health behaviors, race, and depression. *American Journal of Epidemiology*, *172*(11), 1238–1249. doi:10.1093/aje/kwq283

Parsaik, A., Allison, T. G., Singer, W., Sletten, D. M., Joyner, M. J., Benarroch, E. E., … Sandroni, P. (2012). Deconditioning in patients with orthostatic intolerance. *Neurology*, *79*(14), 1435–1439. doi:10.1212/WNL.0b013e31826d5f95

Raj, V., Opie, M., & Arnold, A. C. (2018). Cognitive and psychological issues in postural tachycardia syndrome. *Autonomic Neuroscience: Basic and Clinical*, *215*, 46–55. doi:10.1016/j.autneu.2018.03.004

Roma, M., Marden, C. L., Flaherty, M. A., Jasion, S. E., Cranston, E. M., & Rowe, P. C. (2019). Impaired health-related quality of life in adolescent myalgic encephalomyelitis/chronic fatigue syndrome: The impact of core symptoms. *Frontiers in Pediatrics*, *7*, 26. doi:10.3389/fped.2019.00026

Roy-Byrne, P. P., Craske, M. G., & Stein, M. B. (2006). Panic disorder. *The Lancet*, *368*(9540), 1023–1032. doi:10.1016/S0140-6736(06)69418-X

Sheldon, R. S., Grubb, B. P. I. I., Olshansky, B., Shen, W.-K., Calkins, H., Brignole, M., … Kanjwal, K. (2015). 2015 Heart Rhythm Society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *HeartRhythm*, *12*(6), e41–e63. doi:10.1016/j.hrthm.2015.03.029

Shibata, S., Fu, Q., Bivens, T. B., Hastings, J. I., Wang, W., & Levine, B. D. (2012). Short-term exercise training improves the cardiovascular response to exercise in the postural orthostatic tachycardia syndrome. *The Journal of Physiology*, *590*(15), 3495–3505. doi:10.1113/jphysiol.2012.233858

Smit, A. A., Halliwill, J. R., Low, P. A., & Wieling, W. (1999). Pathophysiological basis of orthostatic hypotension in autonomic failure. *The Journal of Physiology*, *519*(1), 1–10. doi:10.1111/j.1469-7793.1999.0001o.x

Staples, A., Thompson, N. R., & Moodley, M. (2020). Pediatric-onset postural orthostatic tachycardia syndrome in a single tertiary care center. *Journal of Child Neurology*, *35*(8), 526–535. doi:10.1177/0883073820916260

Stewart, J. M. (2004). Chronic orthostatic intolerance and the postural tachycardia syndrome (POTS). *The Journal of Pediatrics*, *145*(6), 725–730. doi:10.1016/j.jpeds.2004.06.084

Stewart, J. M. (2013). Common Syndromes of Orthostatic Intolerance. *Pediatrics*, *131*(5), 968–980. doi:10.1542/peds.2012-2610

Stewart, J. M., Boris, J. R., Chelimsky, G., Fischer, P. R., Fortunato, J. E., Grubb, B. P., … Chelimsky, T. C.; The Pediatric Writing Group of the American Autonomic Society. (2018). Pediatric disorders of orthostatic intolerance. *Pediatrics*, *141*(1), 1–13.

Thieben, M. J., Sandroni, P., Sletten, D. M., Benrud-Larson, L. M., Fealey, R. D., Vernino, S., … Low, P. A. (2007). Postural orthostatic tachycardia syndrome: The Mayo clinic experience. *Mayo Clinic Proceedings*, *82*(3), 308–313. doi:10.4065/82.3.308

Toomey, S. L., Chien, A. T., Elliott, M. N., Ratner, J., & Schuster, M. A. (2012). Disparities in unmet need for care coordination: The national survey of children's health. *Pediatrics*, *131*(2), 217–224. doi:10.1542/peds.2012-1535

U.S. Census Bureau. (2019). *American community survey demographic and housing estimates* (Table ID. DP05). Retrieved May 6, 2021, from https://data.census.gov/cedsci/table?tid=ACSDP5Y2019.DP05&g=0400000US44

Vetter, T. R., Bridgewater, C. L., Ascherman, L. I. Avi Madan-Swain & Gerald L McGwin . (2014). Patient versus parental perceptions about pain and disability in children and adolescents with a variety of chronic pain conditions. *Pain Research Management*, *19*(1), 7–14. doi:10.1155/2014/736053

Walker, L. S., & Greene, J. W. (1991). The functional disability inventory: Measuring a neglected dimension of child health status. *Journal of Pediatric Psychology*, *16*(1), 39–58. doi:10.1093/jpepsy/16.1.39

Walker, L. S., Guite, J. W., Duke, M., Barnard, J. A., & Greene, J. W. (1998). Recurrent abdominal pain: A potential precursor of irritable bowel syndrome in adolescents and young adults. *The Journal of Pediatrics*, *132*(6), 1010–1015. doi:10.1016/S0022-3476(98)70400-7

Zuckerman, K. E., Perrin, J. M., Hobrecker, K., & Donelan, K. (2013). Barriers to specialty care and specialty referral completion in the community health center setting. *The Journal of Pediatrics*, *162*(2), 409–414. doi:10.1016/j.jpeds.2012.07.022