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Symptom Severity in POTS Patients Higher When Triggered by Physical Trauma than Infection or Other Triggers

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Abstract

Purpose: Postural orthostatic tachycardia syndrome (POTS) develops after varied environmental triggers, with little research exploring symptom severity related to POTS trigger. **Methods:** Electronic surveys were taken by 979 women, including a demographic questionnaire and the Malmo POTS Symptom Score (MAPS), Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT), and Gastrointestinal Symptom Rating Scale (GSRS). Participants were divided into four trigger groups associated with symptom onset: physical trauma, hormonal shift, immune response (infection and vaccine injury), and other triggers. **Results:** One-way ANOVAs revealed significant differences between trigger groups on the MAPS score, $F(3, 975) = 6.64$, $p<0.001$, with the physical trauma group reporting a significantly higher POTS severity score than the Immune Response and Other Triggers groups. Significant group differences in GSRS score, $F(3, 975) = 4.77$, $p<0.01$, were detected with the physical trauma group reporting significantly higher gastrointestinal discomfort scores than the immune response and other triggers groups. Finally, while significant group differences in FACIT scores were demonstrated, $F(3, 975) = 3.46$, $p<0.05$, no significant differences were found in post-hoc pairings. **Conclusion:** POTS symptom severity varies by an environmental trigger, with physical trauma leading to more severe overall POTS and gastrointestinal symptoms.

Keywords: Hormonal shift; Infection; Physical trauma; Postural orthostatic tachycardia syndrome (POTS); Vaccine injury

Introduction

Postural orthostatic tachycardia syndrome (POTS) is a broad, multisystem disorder due to malfunction of the autonomic nervous system. POTS is indicated by a supine-to-standing heart rate increase of ≥ 30 beats per minute (bpm) in adults and ≥ 40 bpm in adolescents in the absence of postural hypotension [1]. The symptom burden is particularly high in POTS, with significantly higher autonomic symptom burden in women [2], even when considering comparable long-term conditions [3]. More than 90% of POTS patients report lightheadedness, heart palpitations, brain fog, frequent nausea, headache and fatigue [4]. Approximately 30% of POTS patients require assistance with activities of daily living [5] and 25% are too sick to attend work or school [6].

The literature provides some insight on possible environmental triggers for POTS in likely predisposed individuals. In pediatric patients, 24% were triggered by infection, 11% by concussion, and 3% by surgery/trauma [7]. In a study of both pediatric and adult patients, 41% were triggered by infection, 12% by surgery, 9% by pregnancy, 6% by vaccination, 6% by car accident, 5% by puberty, 4% by concussion, and 3% by emotional stress or trauma [8]. These triggers vary widely but seem to fall naturally into several categories that we explore here: Infection, Vaccine Injury, Physical Trauma (surgery, accident, concussion), Hormonal Shift (puberty, pregnancy), and Other Triggers (unknown, stress, vitamin/mineral deficiency).

Perhaps the heterogeneity in symptom clusters and severity in POTS patients is related to the diversity of environmental triggers that manifest through different pathophysiological mechanisms. Those who developed POTS after infection or vaccine injury may have had an overactive or misdirected immune response, leading to autoimmunity in susceptible people [9]. Many triggers related to physical trauma can be linked to concussion and mild traumatic brain injury, which can directly impair the autonomic nervous system [10]. Finally, development of POTS is uncommon in women before puberty and after menopause, suggesting that hormonal shifts may play a role [11].

We hypothesized that the Immune Response (infection/vaccine injury) group will have increased POTS symptom severity when compared with the Physical Trauma, Hormonal Shift, and Other Triggers groups.

Methods

Participants

The participants were 979 women who completed an electronic survey available via the Standing Up to POTS® webpage and social media accounts. All participants were 18 years or older ($\bar{x}$= 35.7, SD = 12.1) and reported physician diagnosed POTS. These women had been symptomatic for approximately a decade ($\bar{x}$ = 10.7, SD=10.3) and averaged almost three diagnoses of chronic invisible illnesses ($\bar{x}$= 2.7, SD = 2.2). Most of our participants identified as White (n=939; 96.0%). There were 46 (4.7%) who identified as Latina, 17 (1.7%) as Asian, 15 (1.5%) as American Indian, and 12 (1.2%) participants who identified as Black.

Procedure

Participants electronically read and agreed to the informed consent form before opening the online survey. Demographic questions included gender, age, race, ethnicity, years chronically ill, and physician diagnoses of chronic invisible illnesses commonly associated with POTS. Participants were asked about their initial environmental POTS trigger and completed validated survey instruments. The study protocol was approved by the Wittenberg University Institutional Review Board.

POTS Trigger Groups

Participants were asked "What do you think triggered your POTS in the first place?" Responses were initially divided into five categories: Infection, Vaccine Injury, Physical Trauma, Hormonal Shift, and Other Triggers. The makeup of each category can be found in Table 1. Ultimately, the Infection and Vaccine Injury groups were combined into the Immune Response group to increase statistical power since their underlying mechanisms are both likely mediated by the immune system.

Instruments

Functional Assessment of Chronic Illness Therapy Fatigue Scale, version 4 [(FACIT).12]. This validated 13 question self-report survey quantifies fatigue and its effect on quality of life for the past 7 days. Participants rated each question on a 0- (very much fatigued) to 4- (not at all fatigued) point Likert scale, in which higher values indicated better quality of life and lower scores indicated greater levels of fatigue (range 0-52). Scores < 30 indicate severe fatigue [13].

*Gastrointestinal Symptom Rating Scale [(GSRS).*14]. This validated 15 question self-report survey assesses the intensity and frequency of gastrointestinal symptoms in the past 7 days. Participants rated each symptom on a 1- (no discomfort) to 7- (severe discomfort) point Likert scale, in which higher scores indicated greater gastrointestinal distress (range 15-105). These items were used to construct the following five scales using mean scores: abdominal pain, reflux syndrome, diarrhea syndrome, indigestion syndrome, and constipation syndrome [15]. Mean scores ≥ 3 were used as the cut-off for bothersome gastrointestinal symptoms [16].

*Malmo POTS Symptom Score [(MAPS).*17]. This validated 12 question self-report survey quantifies the level of distress for 12 common POTS symptoms (e.g., dizziness, chest pain, headache). Participants rated each symptom on a 0- (no symptoms) to 10- (pronounced symptoms) point Likert scale, in which higher values indicated increased symptom severity (range 0-120). A MAPS score ≥ 42 can be used as a potential indicator of POTS [17].

Statistical Analysis

One-way Analyses of Variance (ANOVAs) compared the four trigger groups (Physical Trauma, Immune Response, Hormonal Shift, and Other Triggers) on age, years ill, age of POTS onset, total number of diagnoses, body mass index (BMI), incidence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), Ehlers-Danlos syndrome (EDS), mast cell activation syndrome (MCAS), and disability status, as well as MAPS score, FACIT score, and GSRS score. For analyses in which the Omnibus F ratio was significant ($p \leq 0.05$), Tukey's Honestly Significant Difference post hoc comparisons tested for significant differences between the trigger groups. A series of independent samples t-tests were conducted to detect differences between the Infection and Vaccine Injury groups, and within the Physical Trauma group to compare surgery and all other forms of physical trauma, and to detect differences within the Physical Trauma group related to the presence versus absence of EDS.

POTS Trigger	N	%
Immune Response	**376**	**38.40%**
Infection	**309**	**31.50%**
COVID	141	14.40%
Other illness	63	6.40%
Mononucleosis	62	6.30%
Influenza	28	2.90%
Lyme disease	9	0.90%
Mold exposure	6	0.60%
Vaccine Injury	**67**	**6.80%**
COVID vaccine	45	4.60%
HPV vaccine	19	1.90%
Influenza vaccine	3	0.30%
Physical Trauma	**131**	**13.40%**
Surgery	50	5.10%
Concussion	38	3.90%
Childhood abuse	17	1.70%
Auto accident	14	1.40%
Other trauma	8	0.80%
Domestic violence	4	0.40%
Hormonal Shift	**91**	**9.30%**
Puberty	44	4.50%
Pregnancy	42	4.30%
Menopause	4	0.40%
Other hormonal shift	1	0.10%
Other Triggers	**381**	**38.90%**
I don't know	327	33.40%
Other	34	3.40%
Stress/bereavement	14	1.40%
Medication	3	0.30%

Note. Immune Response = Infection + Vaccine injury

Table 1: POTS Trigger Categories by Frequency and Percentage.

Results

Participants

Descriptive statistics indicate that of our 979 female participants, 98.9% reported scores indicative of fatigue or severe fatigue on the FACIT, 88.4% indicated symptoms indicative of POTS on the MAPS, and 71.0% reported indigestion syndrome on the GSRS (Table 2). Minimal skews (-2 to 2) and acceptable internal consistency reliabilities (alpha > 0.70) for the self-report measures, except for GSRS Abdominal Pain, are also shown in Table 2.

Comorbidities are common in this population. Self-reported comorbid diagnoses included 281 participants (28.7%) with EDS, 225 (23.0%) with ME/CFS, 201 (20.5%) with fibromyalgia, 197 (20.1%) with MCAS, 172 (17.6%) with orthostatic hypotension, 148 (15.1%) with vasovagal syncope, 25 (2.6%) with Chiari malformation, 24 (2.5%) with Lyme disease, and 7 (0.7%) with mitochondrial disorder. A total of 73 (7.4%) participants reported physician diagnosed autoimmune disorders: 30 (3.1%) with Sjogren's syndrome, 16 (1.6%) with lupus, 13 (1.3%) with Crohn's disease, 7 (0.7%) with Addison's disease, and 7 (0.7%) with ulcerative colitis.

Scale	Frequency (%)	Mean (SD)	α	Skew
Malmo POTS Symptom Score		68.9 (22.8)	0.86	-0.24
POTS ≥ 42	865 (88.4)			
Healthy < 42	114 (11.6)			
FACIT Fatigue Scale, version 4		21.7 (10.3)	0.87	-0.01
Severe fatigue < 30	723 (73.9)			
Fatigue 31-42	245 (25.0)			
Normal ≥ 43	11 (1.1)			
Gastrointestinal Symptom Rating Scale		2.9 (1.1)	0.87	0.41
Abdominal pain ≥ 3	563 (57.6)	3.2 (1.3)	0.65	0.40
Constipation syndrome ≥ 3	389 (39.8)	3.1 (1.6)	0.83	0.60
Diarrhea syndrome ≥ 3	399 (40.8)	2.7 (1.6)	0.87	0.84
Indigestion syndrome ≥ 3	701 (71.8)	4.0 (1.7)	0.72	0.63
Reflux syndrome ≥ 3	477 (48.8)	2.6 (1.7)	0.90	0.91

Table 2: Category frequencies and descriptive statistics for 979 POTS patients.

POTS Triggers

Participants were initially divided into five categories based on their external POTS trigger: Infection (n=309), Vaccine Injury (n=67), Physical Trauma (n=131), Hormonal Shift (n=91), and Other Triggers (n=381). Within the Infection group, COVID was the most prevalent trigger (n=141, 45.6% of this group). Within the Vaccination Injury group, COVID vaccine was the most prevalent trigger (n=45, 67.2% of group). Surgery (n = 50, 38.2%) had the highest individual incidence for the Physical Trauma group, although the remaining triggers within this group may have been related to concussion (61.8%; automobile accident, childhood abuse, concussion, domestic abuse, and other physical trauma). Puberty (n=44, 48.4%) and pregnancy (n=42, 46.2%) were nearly equal in the Hormonal Shift group. "I don't know" (n=327, 85.5%) was the most common answer for the Other Triggers group (Table 1).

To decrease complexity and increase statistical power, we investigated whether the Infection and Vaccine Injury groups could be combined since we believe that both triggers are likely driven by the immune system. Independent samples t-tests revealed no significant difference between the Infection and Vaccine Injury groups on the MAPS (t=0.68, p=0.50), FACIT (t = -1.31, p=0.19), or GSRS (t=0.62, p=0.54), and therefore we combined them into the Immune Response group.

POTS Trigger Groups: Demographic Variables

One-way ANOVAs showed no significant differences between our four trigger groups on age, F(3, 975) = 0.31, n.s., incidence of MCAS, F(3, 975) = 1.92, *n.s.*, or incidence of disability status, F(3, 975) = 2.06, *n.s.* (Table 3).

All other comparisons showed significant differences between the four trigger groups. Tukey's Honestly Significant Difference post-hoc tests were run for all statistically significant demographic variables (Table 3).

There were significant group differences in the number of years ill, F(3, 975) = 18.6, p<0.001. Post-hoc tests revealed that the Physical Trauma group had been chronically ill for a significantly shorter number of years than the Other Triggers group (p=0.005). In addition, the Immune Response group had been chronically ill for a significantly shorter number of years than the Hormonal Shift (p<0.001) and Other Triggers (p<0.001) groups. No significant differences were found in the other pairings.

There were significant group differences in age of onset, F(3, 975) = 14.6, p<0.001. Post-hoc tests revealed the Physical Trauma group had significantly higher age of onset than the Other Triggers group (p=0.004). In addition, the Immune Response group had a significantly higher age of onset than the Hormonal Shift group (p<0.001) and the Other Triggers group (p<0.001). No significant differences were found in the other pairings.

There were significant group differences in the total number of diagnoses, F(3, 975) = 3.0, p<0.05. However, post-hoc tests revealed no significant differences in the group pairings.

There were significant group differences in BMI, F(3, 975) = 3.2, p<0.001. Post-hoc tests revealed that the Hormonal Shift group had significantly higher BMI compared to the Other Triggers group (p = 0.047). No significant differences were seen in the remaining group pairings.

There were significant group differences in the incidence of ME/CFS, F(3, 975) = 4.1, p=0.007. Post-hoc tests revealed that the Physical Trauma group (p=0.043) and the Immune Response group (p=0.017) both had significantly higher incidence of ME/CFS compared to the Other Triggers group. No significant differences were seen in the remaining group pairings.

Significant group differences were found in the incidence of EDS, F(3, 975) = 2.9, p=0.036. However, post-hoc tests revealed no significant differences in the group pairings.

Variable	Physical Trauma n = 131 $\bar{x}$ (SD)	Hormonal Shift n = 91 $\bar{x}$ (SD)	Immune Response n = 376 $\bar{x}$ (SD)	Other Triggers n = 381 $\bar{x}$ (SD)	F
Mean (SD)					
Age	36.5 (12.1)	35.0 (10.4)	35.8 (12.3)	35.4 (12.4)	0.3
Years ill	$9.8_{a,b,c}$ (7.7)	$12.8_{a,b,d}$ (10.2)	$8.0_{a,c}$ (9.6)	$13.2_{b,d}$ (11.1)	18.6***
Age of onset	$26.6_{a,b,c}$ (11.8)	$22.2_{a,b,d}$ (9.8)	$27.8_{a,c}$ (13.4)	$22.2_{b,d}$ (12.9)	14.6***
Total diagnoses	3.1 (2.3)	3.0 (2.3)	2.5 (2.2)	2.6 (2.1)	3.0*
Body mass index	$27.6_{a,b,c}$ (8.4)	$28.4_{a,b}$ (8.9)	$26.3_{a,b,c}$ (7.2)	$26.1_{a,c}$ (7.0)	3.2*
ME/CFS incidence	$0.29_{a,b,c}$ (0.46)	$0.19_{a,b,c}$ (0.40)	$0.27_{a,c}$ (0.44)	$0.18_{b,c}$ (0.38)	4.1**
EDS incidence	0.35 (0.48)	0.37 (0.49)	0.25 (0.43)	0.28 (0.45)	2.7*
MCAS incidence	0.25 (0.44)	0.24 (0.43)	0.21 (0.41)	0.17 (0.37)	1.9
Disability incidence	0.23 (0.43)	0.19 (0.39)	0.16 (0.37)	0.14 (0.35)	2.1
MAPS	76.6_{a} (21.9)	$70.8_{a,b}$ (22.5)	67.9_{b} (23.1)	66.8_{b} (22.4)	6.6***
FACIT	19.4 (9.3)	20.9 (10.3)	21.6 (10.2)	22.7 (10.6)	3.0*
GSRS	48.2_{a} (14.4)	$44.5_{a,b}$ (15.0)	43.9_{b} (15.8)	42.4_{b} (15.9)	4.6**

Note. Immune Response = Infection + Vaccine Injury groups; ME/CFS = chronic fatigue syndrome/myalgic encephalomyelitis; EDS = Ehlers-Danlos syndrome; MCAS = mast cell activation syndrome; MAPS = Malmo POTS Symptom Score; FACIT = Functional Assessment of Chronic Illness Therapy Fatigue Scale, version 4; GSRS = Gastrointestinal Symptom Rating Scale. For the univariate Fs, * $p \leq 0.05$; ** $p \leq 0.01$, *** $p \leq 0.001$. For the post hoc comparisons (within rows), means with different subscripts differ significantly ($p < .05$; Tukey's Honestly Significant Difference).

Table 3: ANOVAs by environmental trigger category for demographics and self-report scales.

POTS Trigger Groups: Self-Reported Symptom Scales

All comparisons on the symptom scales showed significant differences between the four trigger groups.

The results of Tukey's Honestly Significant Difference post hoc tests comparing the four trigger groups on the self-report symptom scales are presented in Table 3.

Malmo POTS Symptom Score. There were significant group differences in MAPS score between the four trigger groups, F(3, 975) = 6.64, p<0.001. Post-hoc tests revealed that the Physical Trauma group had a significantly higher score compared to the Immune Response (p<0.001) and Other Triggers (p<0.001) groups for POTS symptom severity.

No significant differences were seen in the remaining group pairings.

Functional Assessment of Chronic Illness Therapy, version 4. There were significant group differences in FACIT scores between the four trigger groups, F(3, 975) = 3.46, p<0.05. However, post-hoc tests revealed no significant differences in fatigue severity in the group pairings.

Gastrointestinal Symptom Rating Scale. There were significant group differences in GSRS scores, F(3, 975) = 4.77, p<0.01. Post-hoc tests revealed that the Physical Trauma group had a significantly higher mean score compared to the Immune Response (p=0.028) and Other Triggers (p=0.001) groups, indicating higher levels of gastrointestinal discomfort. No significant differences were seen in the remaining group pairings.

Investigating Potential Confounds within the Physical Trauma Group

When we divided the Physical Trauma group into surgery versus all other physical trauma (automobile accident, childhood abuse, concussion, domestic violence, and other physical trauma), independent samples t-tests found no significant difference in the MAPS (t=1.79, p=0.08) or FACIT scores (t = -1.41, p=0.16). There was, however, a significant difference between surgery and all other physical traumas on the GSRS (t=2.00, p=0.048), with all other physical traumas having a higher level of gastrointestinal discomfort than those with surgery as a trigger.

When we divided the Physical Trauma group into those with and without EDS, independent samples t-tests revealed no significant difference on the MAPS (t = -1.27, p=0.21), FACIT (t=0.84, p=0.40), or GSRS (t = -0.71, p=0.48) scores.

Bivariate Correlations

Both the MAPS and GSRS scores correlated significantly and positively with total diagnoses, BMI, and incidence of ME/CFS, EDS, MCAS, and disability status. MAPS and GSRS scores were also significantly positively correlated with each other. MAPS and GSRS scores both correlated significantly and negatively with age, age of symptom onset and FACIT scores (Table 4).

FACIT scores correlated significantly and positively with age and age of symptom onset. FACIT scores correlated significantly and negatively with total diagnoses, BMI, incidence of ME/CFS, EDS, MCAS and disability status, MAPS score and GSRS score. Lower FACIT scores indicate more severe fatigue, leading to the change in direction for these correlations compared with the MAPS and GSRS scores (Table 4).

	1	2	3	4	5	6	7	8	9	10	11
1 Age											
2 Years ill	0.35†										
3 Onset age	0.66†	-0.47†									
4 Diagnoses	0.10†	0.27†	-0.12†								
5 BMI	0.14†	0.05	0.09†	0.07*							
6 ME/CFS	0.02	0.06	-0.02	0.44†	0.04						
7 EDS	-0.01	0.19†	-0.16†	0.44†	0.04	0.16†					
8 MCAS	0.09*	0.13†	-0.02	0.47†	0.03	0.20†	0.34†				
9 Disability	0.25†	0.05	0.19†	0.18†	0.13†	0.09*	0.08*	0.11†			
10 MAPS	-0.16†	-0.03	-0.13†	0.27 †	0.08*	0.19†	0.16†	0.13†	0.14†		
11 FACIT	0.08*	-0.01	0.08*	-0.23 †	-0.11†	-0.23†	-0.13†	-0.14†	-0.18†	-0.61†	
12 GSRS	-0.10†	0.01	-0.11†	0.28 †	0.08*	0.17†	0.14†	0.15†	0.11†	0.61†	-0.41†

Note. BMI = Body mass index; ME/CFS = chronic fatigue syndrome/myalgic encephalomyelitis; EDS = Ehlers-Danlos syndrome; MCAS = mast cell activation syndrome; MAPS = Malmo POTS Symptom Score; FACIT = Functional Assessment of Chronic Illness Therapy Fatigue Scale, version 4; GSRS = Gastrointestinal Symptom Rating Scale; * $p<0.05$, † $p\leq0.001$.

Table 4: Correlations between self-report instruments.

Discussion

Little research to date has investigated the connection between the initial environmental trigger and symptom severity in people with POTS. We hypothesized that the Immune Response group (infection and vaccine injury) would have a higher symptom burden than the other environmental trigger groups due to the immune response, but the surprising finding was that those whose POTS symptoms were initially triggered by Physical Trauma - automobile accident, childhood abuse, concussion, domestic violence, surgery and other physical trauma – had the most severe symptoms. In fact, those in the Physical Trauma group had more severe overall POTS symptoms and gastrointestinal problems than patients whose environmental trigger was Immune Response, Hormonal Shift or Other Triggers.

To our knowledge, only one study has previously looked at the symptom load of POTS based on the initial environmental trigger. In that study, people who identified physical trauma as their initial trigger were more likely to be male than those in the viral illness group. Despite the gender disparity, there was no difference in autonomic symptom burden, fatigue severity or gastrointestinal symptoms between people reporting viral illness or physical trauma as their initial environmental trigger [18]. This differs from our study, in which women with concussion and other physical trauma reported significantly higher symptom burden than women in other groups. Perhaps their sample size for physical trauma (n=19) was not large enough to capture a difference in symptom burden compared with the viral group (n=199) [18].

Physical Trauma and POTS

What might account for increased symptomology in POTS following physical trauma? In this study, 61.8% of the Physical Trauma group could be related to concussion, a mild form of traumatic brain injury, while the remaining 38.2% was related to surgery, in which physical trauma is more controlled using anesthesia. We wondered if there was a difference in POTS symptom severity between those with a surgery trigger versus those with concussion related traumas. Interestingly, we found no significant difference in overall POTS symptoms or fatigue between those whose trigger was surgery versus all other forms of physical trauma. There was, however, a significant decrease in gastrointestinal symptoms for those who indicated surgery as their trigger compared with all other concussion-related forms of physical trauma.

Post-operative orthostatic intolerance appears in 60% of major surgical cases, and especially in women with low BMI [19]. General anesthesia may lead to both autonomic and baroreflex dysfunction, thereby causing orthostatic intolerance, and postoperative opioids may exacerbate orthostatic symptoms [20]. Further, significant blood loss during surgery is also linked with orthostatic intolerance, perhaps due to hypovolemia and reduced cerebral blood flow [19]. Finally, postsurgical inflammation might also impair the blood pressure responses to standing [20]. Taken together, several physiological factors appear to be involved in postsurgical orthostatic intolerance, which may continue in some patients and contribute to the development of their POTS.

Concussion symptoms overlap with other medical conditions that involve autonomic nervous system dysfunction and compromise cerebral perfusion [10]. The autonomic nervous system controls blood vessel diameter in the brain itself and modifies both cardiac function and the baroreflex [10, 21], particularly in females [21]. Concussion is the second leading cause of POTS in adolescents [7], with 7-10% developing orthostatic intolerance [22, 23] and high autonomic symptom burden that impacts quality of life [18]. In adolescents with post-concussion syndrome, nearly 70% had abnormal response on the tilt table test [24]. Together, these indicate that concussion can trigger POTS symptoms.

Potential Confounds to Physical Trauma: Age and EDS

Age could be a factor in the development of POTS symptoms, especially after physical trauma. Due to the ongoing development of the frontal lobe, the adolescent brain is more susceptible to long term deficits following concussion than the adult brain [25]. In this study, no significant difference in age between trigger groups was detected and the average age of participants was 35.7 years, when brains are fully mature [26]. When considering the age of symptom onset, the Physical Trauma group was significantly older than the Other Triggers group and not significantly different from the Hormonal Shift or Immune Response groups. Therefore, it's not likely that brain development related to the current age or age of symptom onset is driving the severity of symptoms in the Physical Trauma group.

The presence of EDS may also be important in physical trauma due to the excessive hyperextensibility of their connective tissues, including those of the arachnoid layer of the meninges. Indeed, EDS can increase symptom severity related to concussion [27], and may slow the recovery from brain injury [28]. In our study, the incidence of physician-diagnosed EDS was at least 30% in each group, with no significant differences between the trigger groups.
When we divided the physical trauma group by the presence or absence of an EDS diagnosis, we found no significant difference in overall POTS symptoms, fatigue or gastrointestinal symptoms. Therefore, the presence of EDS does not seem to drive these findings in the Physical Trauma group.

Immune Response and POTS

Our hypothesis that the Immune Response group would be significantly different in symptom severity from the other groups was not supported in this study. Like previous findings [18], the Immune Response group was highly symptomatic in overall POTS severity and associated fatigue and gastrointestinal problems. We found no significant difference in symptom severity between the Infection and Vaccine Injury groups for the overall POTS symptom severity, fatigue, or gastrointestinal problems, likely because both triggers are mediated by an immune response. This result might indicate that literature addressing symptom severity for infection could generalize to vaccine injury triggers as well. This finding is important, as many people have developed POTS due to vaccine injury in recent years.

Hormonal Shifts and POTS

Hormonal shifts, including puberty and pregnancy, can trigger POTS. In general, women are more likely than men to develop POTS, and have a higher autonomic burden across orthostatic intolerance, pupillary motor, bladder, and gastrointestinal symptoms [2] which could be related to hormonal differences. Rising estrogen and progesterone levels during pregnancy may initiate or exacerbate existing POTS symptoms [29]. In our study, there were no significant differences in autonomic burden, fatigue or gastrointestinal symptoms between the Hormonal Shift and other groups.

Limitations

One major limitation of this study is that our data were taken from online self-report measures, rather than objective medical testing or direct physician diagnosis. Only women were included in this analysis, and these findings may not generalize to other gender categories. Because our participants were partially solicited from online support groups, our sample may have been biased toward those with more debilitating POTS symptoms and not generalize to the entire POTS population.

Implications for Clinical Practice

Consideration of the environmental trigger for POTS may be helpful clinically. While all environmental trigger groups were highly symptomatic, the Physical Trauma group reported the most severe symptomology on overall POTS symptoms and gastrointestinal problems when compared with the Hormonal Shift, Immune Response, and Other Triggers groups. While the mechanisms driving this finding are currently unknown, treatment of concussion and other physical trauma needs to be taken seriously. When orthostatic intolerance and POTS symptoms begin to arise, adding appropriate POTS treatments to the regimen early is warranted to prevent further exacerbation of symptoms.

Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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