https://doi.org/10.5664/jcsm.8344

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Frequency and severity of autonomic symptoms in idiopathic hypersomnia

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Study Objectives: We aimed to quantify the symptoms of autonomic nervous system dysfunction in a large online cohort of patients with idiopathic hypersomnia, and to determine how the severity of these symptoms interacts with sleepiness, fatigue, and quality of life.

Methods: One hundred thirty-eight patients with idiopathic hypersomnia and 81 age- and sex-matched controls were recruited through the website of the Hypersomnia Foundation, a US-based patient advocacy group. Twenty-four patients with confirmed idiopathic hypersomnia were selected by the study investigators as a comparison group. All participants completed a battery of online sleep, autonomic, and quality of life questionnaires including the composite autonomic symptom score-31 (COMPASS-31).

Results: Online and confirmed patients reported significantly higher COMPASS-31 scores (median [interquartile range]) (43.6 [33.6–52.7] and 32.9 [21.7–46.8] vs 17.6 [11.7–27.9], $P < .001$), with the greatest symptom burden in the orthostatic and vasomotor domains. Online and confirmed patients reported more sleepiness (Epworth sleepiness scale), whereas only online patients reported more fatigue (Chalder fatigue scale). Both the Epworth sleepiness scale and Chalder fatigue scale positively correlated with COMPASS-31 scores. Patients reported lower quality of life as reflected by lower scores across all domains of the RAND 36-item health survey, which was negatively correlated with COMPASS-31 scores.

Conclusions: Symptoms of autonomic nervous system dysfunction are common in idiopathic hypersomnia. In addition, autonomic nervous system symptom burden was positively correlated with sleepiness and negatively correlated with quality of life.

Keywords: idiopathic hypersomnia, autonomic, orthostatic intolerance, POTS, syncope, fatigue

Citation: Miglis MG, Schneider L, Kim P, Cheung J, Trotti LM. Frequency and severity of autonomic symptoms in idiopathic hypersomnia. *J Clin Sleep Med*. 2020;16(5):749–756.

BRIEF SUMMARY

Current Knowledge/Study Rationale: The prevalence of autonomic nervous system dysfunction in idiopathic hypersomnia is unknown. Prior publications have described various symptoms of autonomic nervous system dysfunction in idiopathic hypersomnia; however, exploration of the character and severity of autonomic nervous system dysfunction in a large cohort of patients with idiopathic hypersomnia is lacking.

Study Impact: We provide the results of the first large-scale online study in idiopathic hypersomnia assessing the character and severity of autonomic nervous system dysfunction in this population, laying groundwork for future explorative studies. In addition, we correlate the severity of these symptoms with both excessive daytime sleepiness and worse quality of life.

INTRODUCTION

Idiopathic hypersomnia (IH) is a potentially debilitating central nervous system (CNS) hypersomnia of unknown etiology. Although the cardinal features of IH include excessive daytime sleepiness, lack of cataplexy, and unrefreshing sleep that is often prolonged,[1] it has been our experience that many patients with this condition also report symptoms of autonomic nervous system (ANS) dysfunction. Prior publications have described temperature intolerance, orthostatic intolerance, and Raynaud's phenomenon in patients with IH,[2,3] and more recent heart rate variability studies have demonstrated markers of increased parasympathetic tone during wake and sleep.[4] However, further exploration of ANS dysfunction in this population is lacking, with prior studies being limited to case series without healthy controls,[3] survey-based studies with limited focus on ANS dysfunction,[2] or small case-control heart rate variability (HRV) studies.[4] ANS dysfunction has been well described in type-1 narcolepsy (NT1), another CNS hypersomnia, which may be related to the underlying pathophysiology of hypocretin cell loss.[5] As the etiology of IH is not currently known, formally evaluating autonomic dysfunction as an associated feature of this disease would be of great value to further characterize its pathophysiology. We aimed to quantify the frequency and severity of ANS symptoms in a large online cohort of patients with IH, and to determine how the burden of these symptoms interacts with sleepiness, fatigue, and quality of life.

METHODS

Patient selection

Online patients and controls were recruited through the website of the Hypersomnia Foundation, a US-based patient advocacy

group. This method of convenience sampling is often necessary to recruit sufficient numbers of participants in the case of rare diseases, such as IH. A similar strategy of convenience sampling was performed to recruit the control group, which consisted of patients' spouses, friends, and nonblood relatives. All online participants self-reported a diagnosis of IH made by a physician and verified that this diagnosis was supported by polysomnogram and multiple sleep latency (MSLT) testing. An additional cohort of carefully phenotyped patients with confirmed IH were recruited as a validation group by the investigators at the sleep centers of Stanford (MGM, PK, LS, JC) and Emory (LMT). All confirmed patients were diagnosed by two of the study investigators (MGM, LMT) using current American Academy of Sleep Medicine criteria (mean sleep latency ≤8 minutes on MSLT with <2 sleep-onset rapid eye movement periods, or total sleep time ≥11 hours confirmed by 7-day actigraphy).[6] Participants under the age of 18 were excluded. After all three groups completed the online questionnaire, they were age- and sex-matched using the genetic search algorithm feature of the R package MatchIt, which utilizes an estimated propensity score based on logistic regression as one of the covariates.[7] Participants were excluded if they had untreated obstructive sleep apnea (OSA) or systemic exertional intolerance disease/chronic fatigue syndrome (SEID/CFS), such that self-reported diagnoses of OSA or SEID/CFS resulted in survey termination. We chose to exclude those with a pre-existing diagnosis of SEID/CFS due to the high rate of coexisting autonomic impairment in this patient population and concerns of biasing the data set. Controls were excluded if they had a pre-existing diagnosis of any CNS hypersomnia. Online patients were excluded from final analysis if they reported any symptoms of cataplexy or an average total sleep times less than 7 hours nightly (atypical in IH). Participants with clear outlier and implausible data (eg, total sleep time 25 hours) were also excluded from the final data set. Patients were not excluded if they were previously diagnosed with an autonomic disorder. In order to maintain consistency, we also included controls if they reported a pre-existing autonomic diagnosis.

Questionnaires

All participants completed a survey consisting of basic demographic information, a sleep questionnaire consisting of 7 hypersomnia-specific questions (supplemental material), the composite autonomic symptom score-31 (COMPASS-31), the Epworth Sleepiness Scale (ESS), the Chalder fatigue scale (CFQ), the morningness-eveningness questionnaire self-assessment (MEQ-SA), the STOP-Bang questionnaire, the insomnia severity index (ISI), the restless leg syndrome (RLS)–single item (RLS-SI) screen, and the RAND 36-item health survey (RAND-36). Data were collected via the online Research Electronic Data Capture platform.

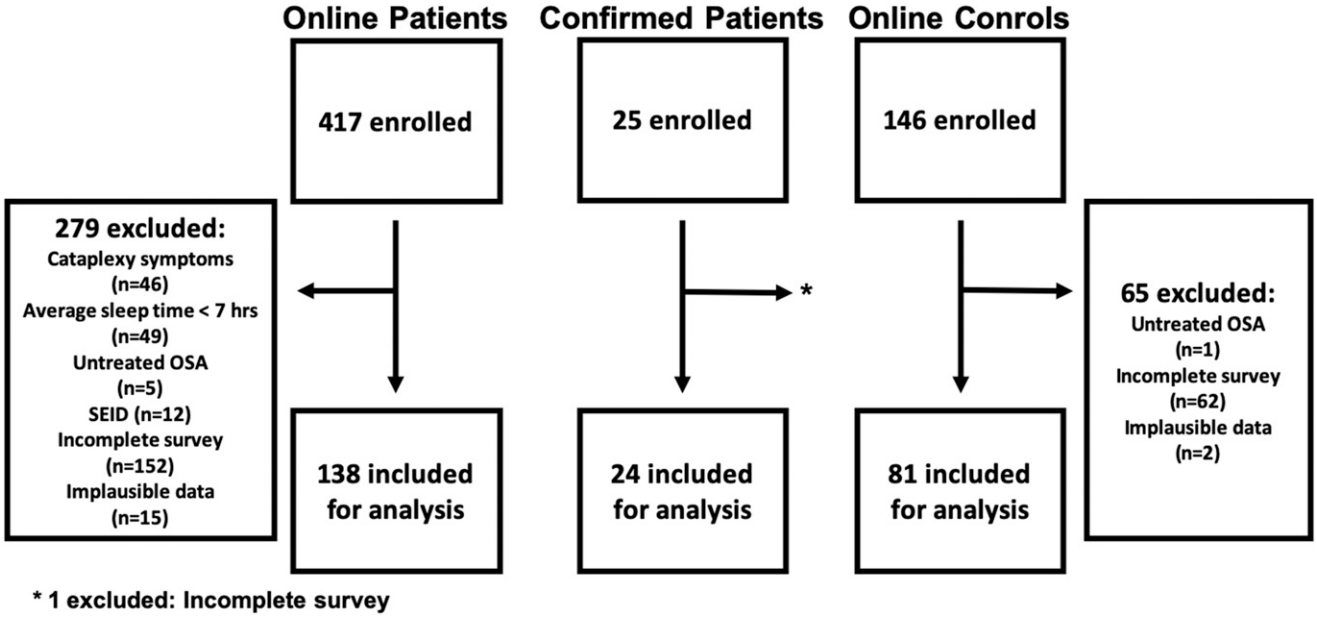
The COMPASS-31 is a widely used patient questionnaire that provides an abbreviated quantitative assessment of the severity and distribution of autonomic symptoms.[8] This questionnaire generates a weighted score from 0 to 100, and questions fall into one of six domains: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor function. Higher scores indicate greater symptom severity, with controls reporting a mean score of 8, and patients with mild, moderate, and severe autonomic dysfunction reporting mean scores of 15, 29, and 46, respectively (W. Singer, personal correspondence, May 2019). This questionnaire has proven to have good internal validity as well as good correlation with autonomic cardiovascular reflex testing in various patient populations.[7–10]

The ESS is a 24-point scale that quantifies the likelihood of dozing in various situations over the preceding 4 weeks. Scores ≥10 suggest excessive daytime sleepiness.[9] The MEQ-SA is a 19-item form that is used to predict circadian preference in individuals. Scores range between 16 and 86, with scores ≤41 indicating "evening" chronotypes, ≥59 indicating "morning" chronotypes, and scores 42–58 indicating "intermediate" chronotypes.[10] The CFQ is an 11-item questionnaire used to assess physical and mental fatigue validated in patients with SEID/CFS. Scores range from 0 to 33, with higher scores reflecting greater fatigue. A score ≤14 is considered normal, and a score >28 indicates significant fatigue, as experienced by those with SEID/CFS.[11,12] The RAND-36 is a health-related quality of life survey of 36 items that generates a numerical score from 0 to 100 for 8 different scales: physical functioning, role limitations caused by health problems, role limitations caused by emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health perceptions. Higher scores define a more favorable health state.[13] The ISI is a 7-item questionnaire assessing severity and impact of insomnia symptoms over the preceding month. Questions 1–3 address features unique to insomnia (difficulty falling asleep, staying asleep, and waking earlier than intended), whereas questions 4–7 address the effects of sleep disruption on quality of life. The total score ranges from 0 to 28, with ≤7 indicating the absence of insomnia, 8–14 subthreshold insomnia, 15–21 moderate insomnia, and ≥22 severe insomnia.[14] The RLS-SI is a single-item question developed by the RLS Study Group: "when you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by walking or movement?"[15] The STOP-Bang questionnaire is a widely used 8-item form that screens for obstructive sleep apnea, where a score of ≥3 indicates an increased risk.[16]

Statistical analysis

The primary outcome measure was defined as the total weighted COMPASS-31 score. Secondary outcomes included COMPASS-31 domain scores and correlations between total weighted COMPASS-31 score and ESS, CFQ, and RAND-36 domain scores. Categorical variables are presented as percentages, and continuous variables as median and interquartile range for non-Gaussian variables, as confirmed by the Shapiro-Wilk test for normality. Groupwise comparisons of continuous variables were performed using the Kruskal-Wallis test (multiple-group comparisons), and post hoc pairwise comparisons were performed with the Wilcoxon rank sum test only in instances where the Kruskal-Willis *P* value was below the significance threshold. Chi-square or Fisher's exact test (when counts fell below 5 in any category) were used to compare categorical variables between groups. Pearson correlation coefficients were calculated between scores of interest, and only those with at least moderate effect sizes were reported.

Figure 1—Participant flow diagram.



Correlations for the entire sample were performed due to sample size limitations, limiting statistical power in subgroup analyses. A statistical threshold of $\alpha = 0.05$ was set, and Bonferroni correction for multiple comparisons was performed for each major analysis. All methods were implemented in the R programming language v3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).[17]

Standard protocol approvals, registrations, and patient consents

All participants gave written informed consent, and the study was approved by the local institutional review boards of Stanford University and Emory University.

RESULTS

After exclusion criteria were applied, a total of 138 online patients, 24 confirmed patients, and 81 controls were included in the final analysis (**Figure 1**). Online patients included participants from all geographic areas of the United States as well as regions of Canada, England, Australia, and Russia. Online patients were more likely to report long sleep times (>11 hours) than confirmed patients, and both patient groups were more likely to report longer sleep times than online controls ($P < .001$). Twenty of 138 (15%) online patients reported pre-existing autonomic disorders, including "postural tachycardia syndrome" (POTS; n = 9), "inappropriate sinus tachycardia" (n = 2), "tachycardia" (n = 1), "chronic tachycardia" (n = 1), "orthostatic hypotension" (n = 2), "vasovagal syncope" (n = 1), "syncope" (n = 1), "autonomic neuropathy" (n = 1), "vegetative vascular dystonia" (n = 1), and "dysautonomia" (n = 1). A similar percentage of confirmed patients—4 of 24 (17%)—reported pre-existing autonomic diagnoses, including POTS (n = 3), and syncope (n = 1). No controls reported a pre-existing autonomic diagnosis. The demographics of the three groups are listed in **Table 1**.

Online and confirmed patients reported significantly higher COMPASS-31 scores, with the highest scores reported by online patients (43.6 [33.6–52.7] and 32.9 [21.7–46.8] vs 17.6 [11.7–27.9] online controls; $P < .001$) (**Table 2**, **Figure 2**). When compared with controls, online patients reported higher scores in all 6 autonomic domains, whereas confirmed patients reported higher scores in the orthostatic and vasomotor domains only ($P < .001$ for both) (**Figure 3**). Symptoms of sympathetic impairment were just as common as parasympathetic impairment (diarrhea vs constipation) in most domains, although it should be noted that the COMPASS-31 was not designed to make this distinction but rather to quantify the severity of autonomic impairment by subdomain.

ESS and CFQ scores followed a similar trend, with the highest scores reported by online patients. Online patients reported not only more substantial daytime sleepiness (online patients 16 [12–19] vs controls 6 [4–8]; $P < .001$) but also greater levels of fatigue (online patients 30 [24–34] vs controls 15 [13–18]; $P < .001$). Compared with controls, confirmed patients also demonstrated more substantial daytime sleepiness (15 [13–18]; $P < .001$) but not fatigue (confirmed patients 17 [13–28]; $P = .2$); however, the mean CFQ score was still reflective of increased fatigue. Across all individuals, both ESS and CFQ scores were positively correlated with COMPASS-31 scores in online patients ($\rho = 0.60$, $P < 2.2*10^{-16}$ and $\rho = 0.64$, $P < 2.2*10^{-16}$, respectively) (**Figure 4**). As a result of higher levels of insomnia symptoms being reported by ISI in online patients and a moderate correlation between CFQ and ISI ($\rho = 0.57$, $P < 3.7*10^{-19}$), partial correlations among all relevant correlations were performed in order to adjust for confounding effects of the ISI. Although all correlation coefficients

Table 1—Demographics and core hypersomnia symptoms.

	Online Patients (n = 138)	Confirmed Patients (n = 24)	Online Controls (n = 81)	*P*	Pairwise Comparisons
Age (years)	35.5 (27–50)	40 (31.5–46.25)	40 (30–51)	.367	N/A
Female:male (%)	126:12 (91)	20:4 (83)	72:9 (88)	.39	N/A
BMI (kg/m^2)	25.27 (21.98–30.88)	24.49 (21.48–29.2)	28.12 (23.47–32.48)	.05	N/A
Long sleep time (≥ 11 h)	64	21	1	***< .001***	OC<CP<OP
Hypnagogic hallucinations	50	45	17	***< .001***	OC<OP, CP
Sleep paralysis	35	42	12	***< .001***	OC<OP<CP
Nonrefreshing naps	96	83	27	***< .001***	OC<OP, CP
Sleep drunkenness	89	68	30	***< .001***	OC<OP, CP

Values are presented as the median (interquartile range) or percentage. Comparisons of continuous measures with Kruskal-Wallis test and categorical data with χ^2/Fisher's exact test. Groupwise differences that remained significant after Bonferroni correction for multiple comparisons ($\alpha = 0.0022$) are bold and italicized. CP = confirmed patients, OC = on-line controls, OP = on-line patients, N/A = not applicable.

Table 2—Questionnaire results.

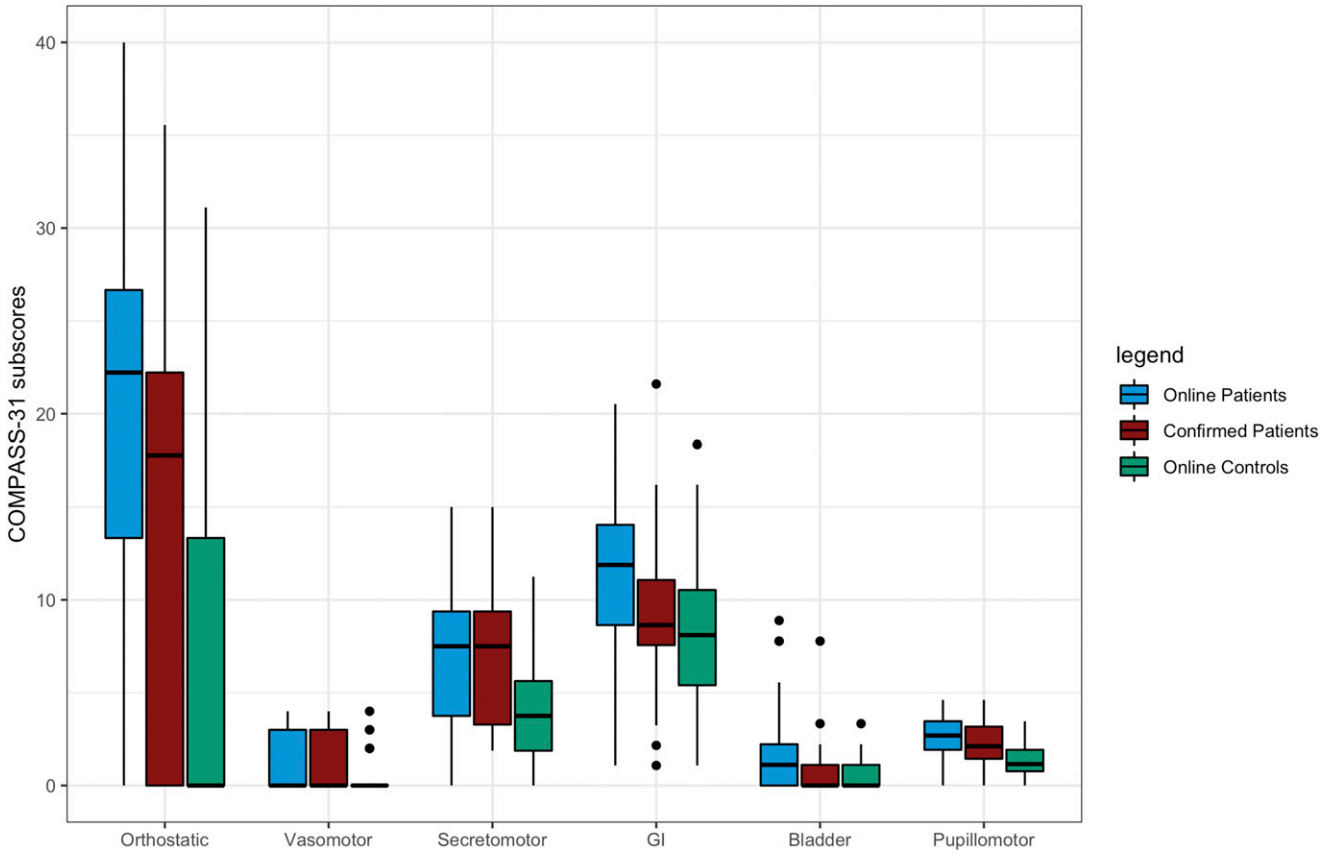
	Online Patients (n = 138)	Confirmed Patients (n = 24)	Online Controls (n = 81)	*P*	Pairwise Comparison Summary
COMPASS-31					
Orthostatic intolerance	22.2 (13.3–26.7)*	17.8 (0–22.2)†	0 (0–13.3)	< .001	OP&CP>OC
Vasomotor	0 (0–3)*	0 (0–3)†	0 (0–0)	< .001	OP&CP>OC
Secretomotor	7.5 (3.8–9.4)*	7.5 (3.3–9.4)	3.8 (1.9–5.6)	< .001	OP>OC
Gastrointestinal	11.9 (8.6–14.0)*	8.6 (7.6–11.1)	8.6 (5.4–11.9)	< .001	OP>OC
Bladder	1.1 (0–2.2)*	0 (0–1.1)	0 (0–1.1)	< .001	OP>OC
Pupillomotor	2.7 (1.9–3.5)*	2.1 (1.4–3.2)	1.15 (0.7–1.9)	< .001	OP>OC
Total weighted score	43.6 (33.6–52.7)*	32.9 (21.7– 46.8)†	17.6 (11.7– 27.9)	< .001	OP&CP>OC
Epworth sleepiness scale	16 (12–19)*	13 (8–16.5)†	6 (4–8)	< .001	OP&CP>OC
Fatigue severity scale	30 (24–34)*§	17 (13–28)	15 (13–18)	< .001	OP>CP&OC
Morningness-eveningness questionnaire	44 (38–51)*	54 (43–62)	55 (46–62)	< .001	OP>OC
Restless legs syndrome–single item (years)	29	26	25	.657	N/A
STOP-Bang	1 (1–2)	1 (0–1)	1 (0–2)	< .001	N/A
Insomnia severity index	9 (7–12)*§	5 (1–7)	4 (2–7)	< .001	OP>CP&OC
RAND-36					
Physical functioning	65 (45–80)*	80 (58–95)	90 (80–95)	< .001	OP<OC
Role limitations due to physical health	25 (0–25)*§	75 (25–100)	100 (75–100)	< .001	OP<CP&OC
Role limitations due to emotional problems	50 (0–100)*	100 (50–100)	100 (75–100)	< .001	OP<OC
Energy/fatigue	10 (5–20)*	50 (15–56)	55 (40–65)	< .001	OP<OC
Emotional well-being	60 (44–76)*	66 (60–80)	72 (60–80)	< .001	OP<OC
Social functioning	44 (25–63)*	75 (50–100)	75 (63–100)	< .001	OP<OC
Pain	68 (45–90)*	85 (68–90)	90 (68–90)	< .001	OP<OC
General health	35 (25–60)*	60 (38–79)	70 (60–80)	< .001	OP<OC

Values are presented as the median (interquartile range) or percentage. Comparisons of results for questionnaires between groups using Kruskal-Wallis test. Post hoc pairwise comparisons were only performed with the Wilcoxon rank sum test for measures demonstrating significant groupwise differences with a Bonferroni-corrected threshold of $\alpha = 0.00086$. *Significant difference between online patients and online controls. †Significant difference between confirmed patients and online controls. §Significant difference between online patients and confirmed patients. CP = confirmed patients, OC = on-line controls, OP = on-line patients, N/A = not applicable.

were expectedly diminished, they all remained of equivalent strength (0.5–0.7: moderate correlation; 0.3–0.5: weak correlation) (**Table 3**).

MEQ-SA scores were lower in online patients, suggesting a tendency to an eveningness chronotype, though failing to meet the predefined effect size cutoff. Comparatively, confirmed

Figure 2—Total weighted COMPASS-31 scores.



GI = gastrointestinal.

patients did not demonstrate a significant difference in chronotype from either online patients or controls, even though the chronotype scores were more aligned with online controls. RLS symptoms were common in both patients and controls, whereas STOP-Bang scores were low in both patients and controls. Online patients were more likely to report insomnia symptoms than were online controls. Finally, online patients reported lower quality of life relative to online controls, as reflected by lower scores across all domains of the RAND-36. Comparatively, online patients were more severely affected than confirmed patients only in assessments of role limitations due to physical health. The most significantly affected domains were those of role limitations due to physical health ($\eta^2 = 0.28$), energy/fatigue ($\eta^2 = 0.29$), and social functioning ($\eta^2 = 0.2$; **Table 2**).

DISCUSSION

The result of this study demonstrated two important principal findings: (1) symptoms of ANS dysfunction were more common and severe in clinically confirmed and online IH patients than in sex- and age-matched online controls; (2) the severity of these symptoms was positively correlated with both excessive daytime sleepiness and fatigue, and negatively correlated with quality of life. Online patients reported COMPASS-31 scores nearly as high as those reported by patients with severe autonomic failure (total weighted score ≥ 46), and confirmed patients reported scores higher than those reported by patients with moderate autonomic failure (total weighted score ≥ 29). This suggests a significant burden of ANS dysfunction. Whereas online patients reported higher scores than controls in all 6 autonomic domains, confirmed patients reported higher scores in orthostatic and vasomotor domains only. Although this suggests that the confirmed patient group may have been underpowered to detect changes in the other 6 domains, it also confirms our clinical experience that orthostatic intolerance is the most commonly reported autonomic symptom in patients with IH.

Prior publications have reported similar results with more limited questionnaire assessments. Roth's original publication on IH describes autonomic imbalance including resting tachycardia in a significant number of patients.[18] More recently, in a cohort of 62 French patients with IH, 32% reported a "feeling of faintness," consistent with orthostatic intolerance.[2] Twenty-three percent of these patients reported palpitations, 25% temperature intolerance, 22% digestive problems, and 46% cold extremities. Another smaller Australian cohort of 13 patients with IH reported migraine headaches, cold extremities, and syncope in some patients, with no difference in symptom frequency when compared with patients with NT1.[19]

A single HRV study in patients with IH demonstrated an elevation of high-frequency power during both wake and sleep,

Figure 3—Weighted COMPASS score by diagnostic category.

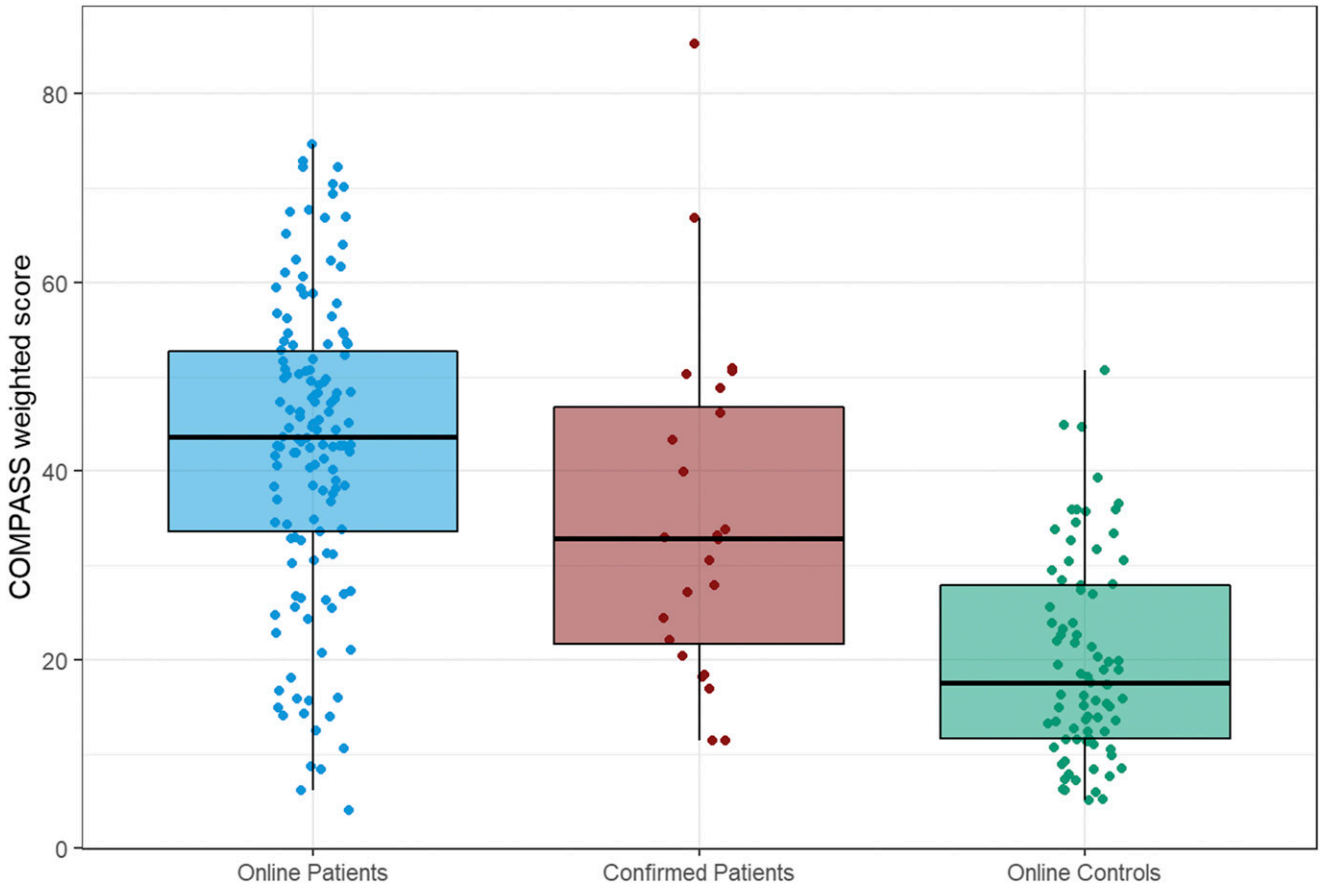
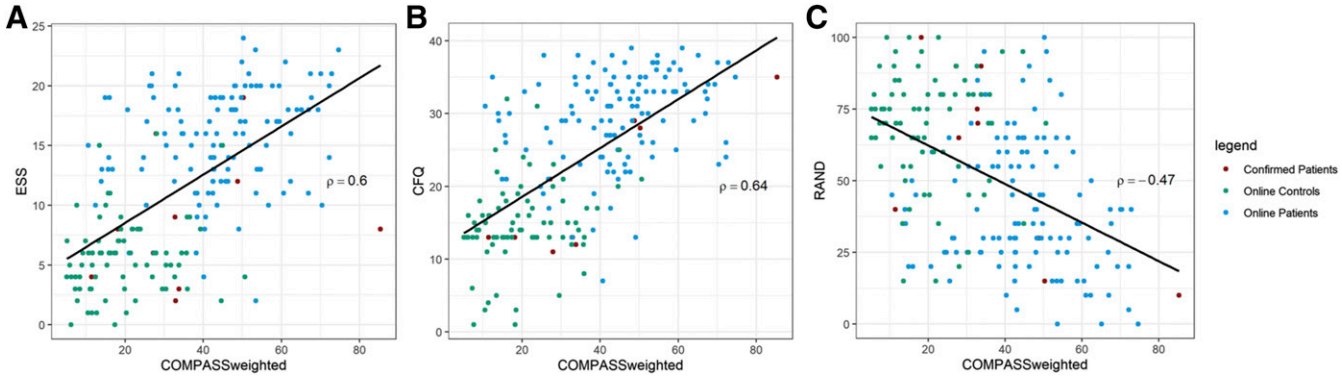


Figure 4—Correlations between COMPASS-31 scores.



(**A**) ESS, (**B**) CFQ, and (**C**) RAND-36. CFQ = Chalder fatigue scale, ESS = Epworth Sleepiness Scale.

suggestive of increased parasympathetic tone.[4] The authors noted that, when compared with controls, the heart rate acceleration during arousals was greater in patients with IH, consistent with a heightened sympathetic response during arousals.

The mechanism of ANS dysfunction in IH is unknown. One possible explanation is that excessive sleepiness and fatigue lead to reduced physical activity and deconditioning, a well-established source of ANS dysfunction and orthostatic intolerance.[20] Another more intriguing possibility is a shared pathophysiologic mechanism, and the possibility that ANS dysfunction is part of the IH phenotype. The most common comorbid ANS diagnosis in our patients was that of POTS, a disorder that affects a similar demographic of younger, predominantly Caucasian women. In addition, common ANS

Table 3—Correlation and partial correlation coefficients.

COMPASS Correlate	ρ	*P*	ρ_{ISI}	*P* $value_{ISI}$
ESS	0.60	< .001	0.51	< .001
CFQ	0.64	< .001	0.53	< .001
RAND	−0.47	< .001	−0.34	< .001

Correlation coefficients for correlations between weighted COMPASS scores and ESS, CFQ, and the RAND-36. Partial correlations, adjusted for ISI score, are included for reference.

symptoms reported in prior publications of IH cohorts included orthostatic intolerance, palpitations, and temperature intolerance, all of which are also common symptoms of POTS. Interestingly, one-third of patients in the French cohort reported an allergy compared with 14% of controls.[2] Mast cell activation syndrome, an allergic disorder of inappropriate histamine release, is a common comorbidity in POTS,[21] raising the suspicion that some patients with IH may be predisposed to these overlapping conditions. It has been reported that allergies and autoinflammatory disorders are more common in IH, suggesting an immune dysregulation mechanism.[22] Although POTS is also a syndrome in which the mechanism is unknown, more recent studies suggest an autoimmune etiology in a subgroup of patients. Several publications have described autoantibodies targeting cardiovascular G-protein-coupled adrenergic, muscarinic, and angiotensin II type 1 receptors,[23,24] resulting in sympathetic activation. It is also worth noting that the typical demographic of both POTS and IH (Caucasian woman of childbearing age) is the same demographic of a typical patient with an autoimmune disorder. A third mechanistic explanation is a genetic predisposition, as a family history of IH is noted in over 30% of patients;[3,25] however, genetic autonomic syndromes in this demographic are rarely identified. Further research is ultimately needed to help distinguish these phenotypes and any underlying pathophysiology they might share.

Patients in our online cohort reported both excessive daytime sleepiness and excessive fatigue, and the severity of both correlated with autonomic symptom burden. The magnitude of fatigue reported by online patients was comparable with that reported by patients with SEID/CFS,[11,12] even after those with a pre-existing diagnosis were excluded in the final analysis. Although there was no statistical difference between fatigue scores of confirmed patients and controls, it should be noted that both had mildly elevated CFQ scores. Under the current SEID criteria, patients must have not only fatigue but also unrefreshing sleep, postexertional malaise, and either cognitive dysfunction or orthostatic intolerance. These criteria describe many symptoms commonly experienced by patients with IH; therefore, it is not surprising that a diagnostic overlap exists between these two conditions. In fact, it has been reported that over 20% of patients with CNS hypersomnias also meet criteria for SEID/CFS.[26] Whether these symptoms are cause or consequence of autonomic dysfunction remains unclear.

MEQ-SA scores fell within the "intermediate" chronotype category for all groups, though online patients had lower mean scores, suggesting a tendency toward an eveningness chronotype. These results are in line with prior publications on chronotype in patients with IH in which most patients are either intermediate or evening chronotypes, with few morning chronotypes.[2,27] Symptoms of RLS were common in both patients and controls, and not unexpected given the high sensitivity of the RLS single-item screen. Prevalence estimates of RLS vary from 4% to 29%, and the condition is 35%–50% more common in women.[28] It was initially surprising that online patients reported ISI scores reflective of subclinical insomnia. On further analysis, however, patients scored much higher on questions 4–7, which deal with the effects of any sleep problem on quality of life, not necessarily just insomnia, as opposed to questions 1–3, which assess insomnia symptoms more directly (difficulty falling asleep, staying asleep, early morning awakenings). This likely explains the slightly diminished, but of similar strength, correlations that were noted after adjustment for total ISI score. In addition, other cohorts have described frequent sleep disruption in patients with IH, with some reporting that almost half of patients described restless sleep with frequent arousals.[3]

The primary limitations of our study were related to the use of an online survey. These include a situation in which patients may be more apt to overreport than under-report, as reflected in the greater symptom burden reported by online patients across all surveys administered; however, this may also reflect sample bias in which online patients did not have access to tertiary sleep centers and optimal treatment. Even while accounting for this, confirmed patients also demonstrated a significantly greater autonomic symptom burden when compared with controls. We had a greater percentage of long sleepers in our online patient group, and although both reported significant ANS dysfunction, it is possible that these groups represent slightly different phenotypes.

Although we made every attempt to exclude those patients without appropriate diagnostic workups, we did not analyze individual online patient records, and thus we relied on accurate self-reporting. As such, we made every attempt to exclude those patients with data incongruent with a diagnosis of IH (eg, short sleep times). As we did not analyze the medical records of our online cohort, we were not able to assess comorbid medical disorders which may have contributed to hypersomnia, nor did we assess comorbid mood disorders or medication usage, all of which may have potentially influenced participants' responses. In addition, the online survey may have created selection bias for those English-speaking patients with internet access and knowledge of the Hypersomnia Foundation. Although we attempted to validate our results with a carefully phenotyped cohort of confirmed patients at multiple institutions, our sample size in this group was small, which speaks to the rarity of IH. Because of this, we feel that the benefits of utilizing an online survey to access a large, global population of patients with IH outweigh the limitations inherent in such a survey and provide a novel perspective of this poorly understood condition.

In conclusion, we found that autonomic symptoms are common in IH, with the greatest symptom burden in the orthostatic and vasomotor domains. In addition, ANS symptom burden correlates moderately with higher levels of sleepiness and fatigue and is inversely correlated with quality of life. Future analysis will focus on objective autonomic testing to help

identify symptomatic domains, with the goal of more focused therapeutic targets for patients with IH.

ABBREVIATIONS

ANS, autonomic nervous system
CFQ, Chalder fatigue scale
CNS, central nervous system
COMPASS 31, composite autonomic symptom score-31
ESS, Epworth Sleepiness Scale
HRV, heart rate variability
IH, idiopathic hypersomnia
ISI, insomnia severity index
MEQ-SA, morningness-eveningness questionnaire self-assessment
MSLT, multiple sleep latency testing
NT1, Narcolepsy type-1
OSA, obstructive sleep apnea
POTS, postural tachycardia syndrome
RAND-36, RAND 36-item health survey
RLS, restless legs syndrome
RLS-SI, restless legs syndrome–single item
SEID/CFS, systemic exertional intolerance disease/chronic fatigue syndrome

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ACKNOWLEDGMENTS

Mitchell G. Miglis designed and conceptualized the study and drafted and revised the manuscript; Paul Kim drafted and revised the manuscript; Logan Schneider designed and conceptualized the study, analyzed the data, and revised the manuscript; Joseph Cheung designed and conceptualized study and revised the manuscript; Lynn Marie Trotti designed and conceptualized study and revised the manuscript.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication October 28, 2019
Submitted in final revised form January 9, 2020
Accepted for publication January 9, 2020
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DISCLOSURE STATEMENT

All authors have seen and approved this manuscript. This work was performed at the Stanford Sleep Disorders Clinic and the Emory Sleep Clinic. This work was supported by NIH grants #K23 NS083748 (Lynn Marie Trotti) and #K23 NS101094 (Joseph Cheung). Writing of this manuscript was supported by the Office of Academic Affiliations, Advanced Fellowship Program in Mental Illness Research and Treatment, Department of Veterans Affairs (Logan Schneider). Dr. Trotti is the chair of the medical advisory board for the Hypersomnia Foundation, an unpaid position. All authors report no financial conflicts to declare.