Self-reported symptom burden in postural orthostatic tachycardia syndrome (POTS): A narrative review of observational and interventional studies

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ABSTRACT

Background and objective: Postural Orthostatic Tachycardia Syndrome (POTS) is a chronic health condition affecting mostly women of childbearing age, and significantly impacting their health and quality of life. It is currently poorly understood with no approved licensed treatments. The aim of this systematic review was to contextualize the symptom burden of POTS, and review factors associated with this burden that may guide future treatments. The specific questions were (1) How does symptom burden in POTS compare to the burden in other long term conditions (LTCs), (2) Which factors are associated with POTS symptom burden, and (3) Which interventions show promise in reducing symptom burden in POTS.

Databases and data treatment: Electronic databases (CENTRAL, MEDLINE, EMBASE, CINAHL, PsycINFO, Web of Science, APA PsycArticles, OpenGrey) were searched from inception to January 2022 for observational studies reporting on the association between any biological, psychological or social factors and symptom burden, and randomized controlled trials reporting on interventions in adults with POTS. Two reviewers independently conducted eligibility screening, data extraction and quality assessment. A narrative synthesis was undertaken.

Results/Conclusion: 5159 entries were screened for eligibility. Twenty-nine studies were included (1372 participants with POTS of a total sample size of 2314, 17 High-, 12 Medium-quality), seventeen were observational and twelve were randomized controlled experimental and intervention trials. Overall methodological quality of the evidence was medium-high but heterogeneity was high and sample sizes modest, allowing moderately robust conclusions. Orthostatic symptom burden was higher in POTS than other LTCs. Serum activity against adrenergic α1 receptors, physical functioning, depression, catastrophizing, prolonged cognitive stress testing and anxiety were significantly associated with symptom burden in medium-high quality studies. Preliminary medium-high quality evidence from predominantly proof-of-concept (n = 11) studies and one 3-month × 2 factorial design trial suggest that compression garments, propranolol, pyridostigmine, desmopresin, and bisoprolol may hold promise in reducing symptom burden. Directions for future research include investigating associated factors over time, the development of complex interventions which address both biological and psychosocial factors associated with symptom burden, and effectiveness trials of these interventions.

Significance: POTS symptom burden is high, particularly in relation to orthostatic intolerance when compared to other long-term conditions (LTCs). Despite this burden, there are no effectiveness randomized controlled trials of treatment to reduce symptoms in POTS. This review provides a starting point to understanding researched biological and psychosocial factors associated with this burden. There was however inconsistency in the measurement of symptom burden, lowering the confidence of cross-study inferences. A coherent definition of POTS symptom range, severity and impact along with a validated and reliable POTS-specific instrument is currently lacking. A standardized questionnaire to assess POTS symptom burden as a core outcome measure will help clarify future research and clinical practice.

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1. Introduction

Postural orthostatic tachycardia syndrome (POTS) is an autonomic nervous system disorder, characterized by an excessive increase in heart rate of >30 bpm upon standing without a drop in blood pressure, accompanied by symptoms (Lei et al., 2019). The etiology is considered multifactorial but is poorly understood. Hypothesized putative pathophysiological mechanisms include the presence of an autoimmune disorder and auto-inflammation (Fedorowski, 2019), small fiber peripheral and autonomic neuropathy, hyperadrenergic states, and hypovolemia (Garland et al., 2015; Raj, 2006; Fouad et al., 1986; Raj and Robertson, 2007; Jones et al., 2016). Reported precipitating factors include a range of biological, psychological, and social factors including viral infection (Raj et al., 2021), vaccination, pregnancy, surgery, trauma, and/or psychosocial stress (Fedorowski, 2019; Raj et al., 2021). Around 87% of people living with POTS experience mild-moderate depression (Anderson et al., 2014), over half experience sleep disturbances (Xu et al., 2016; Pederson and Blettner, 2017; Pengo et al., 2015; Bagai et al., 2014; Bagai et al., 2011; Raj et al., 2011) and many have mild to moderate anxiety symptoms (Raj et al., 2009a; Raj et al., 2018; Wagner et al., 2012), all of which may exacerbate POTS symptoms (Raj et al., 2018). In developed countries, the prevalence of POTS has been estimated between 0.2%–1.0% (Fedorowski, 2019; Zadourian et al., 2018; Zhao and Tran, 2020). Patients are predominantly female (5:1 ratio female/male), and misdiagnosis and diagnostic delays are common (Shaw et al., 2019; Knoop and Dunoody, 2022).

A key feature of POTS is a high symptom burden, defined as the range, severity and/or impact of symptoms (Gapstur, 2007). According to 2015 consensus criteria (Sheldon et al., 2015), POTS is primarily characterized by orthostatic intolerance (OI) or symptoms from being upright. What is considered symptoms of OI varies, but tends to include light-headedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue (Sheldon et al., 2015). POTS is also associated with a wide range of other autonomic dysfunction symptoms, including digestive (Mehr et al., 2018) and bladder symptoms (Grubb, 2008; Walker et al., 2021), pupillomotor symptoms (such as light sensitivity (Cortez et al., 2020)), secretomotor symptoms (such as dry eyes and mouth), sleep dysfunction, and vasomotor symptoms (e.g. skin color changes). Finally, patients report miscellaneous symptoms, in upright or other positions, such as respiratory (Loughnan et al., 2021; Stewart et al., 2018; Taneja et al., 2011) and cognitive dysfunction (Anderson et al., 2014), headaches (Ray et al., 2022), vestibular symptoms (Bogle et al., 2022) and disturbances in thermoregulation and sweating. Although it is clear that POTS symptoms can severely affect quality of life (Lei et al., 2019), comparable to individuals who have COPD or congestive heart failure (Grubb, 2008), it is less clear which are the distinguishing symptoms of POTS when compared to other long term conditions. The high incidence of multimorbidity in POTS, may further complicate the severity and range of symptoms reported (Vermino et al., 2021).

Although a comprehensive review of quality of life in syncopal conditions including POTS has been published since the start of the current review (Hockin et al., 2022), it did not include symptom burden as a defined outcome measure. As the etiology of POTS is poorly understood, managing symptoms is the focus of current treatments. However, none of these treatments are currently approved or licensed for POTS (Zadourian et al., 2018). A systematic review of factors associated with symptom burden in POTS and efficacy of interventions to reduce symptom burden, may lead to clearer treatment recommendations and future research into existing and novel treatments. As the literature on symptom burden in POTS is relatively sparse, the aims of this review are broadly focused to (1) review studies which compare proposed POTS measures of symptom burden in patients with POTS and other long term conditions to ascertain if POTS symptoms are distinguishing features of the condition, (2) synthesize evidence on factors associated with symptom burden in POTS, (3) synthesize evidence on the efficacy of interventions for symptom burden in POTS, (4) evaluate the methodological quality of evidence reviewed, and (5) propose specific areas for future research in this area.

2. Literature search methods

The protocol for this review was registered on Prospero (ID CRD42021251780). Reporting was done in line with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidance (Page et al., 2021).

2.1. Eligibility criteria

Eligibility criteria are summarized in Table 1. Studies were eligible if they included patients clinically diagnosed with POTS of any severity using published criteria from the 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of POTS, which are as follows (Sheldon et al., 2015): (1) frequent symptoms that occur with standing such as lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue; (2) an increase in heart rate of ≥30 bpm when moving from a recumbent to a standing position held for >30 s (or ≥40 bpm in individuals 12 to 19 years of age); and (3) the absence of orthostatic hypotension (<20 mmHg drop in systolic blood pressure) (Sheldon et al., 2015).

Studies with 70% or more adult participants (over 16 years of age) were eligible if they examined the association between POTS symptom burden and at least one biomedical, psychological, or social factor by assessing bivariate relationships, multivariable relationships or group comparisons.

Study designs including cross-sectional (including baseline analysis of RCT data), prospective cohort, retrospective cohort, and case-control studies were included. Randomized controlled experimental and intervention trials of any intervention type where self-reported POTS symptom burden was a primary or secondary outcome measure were eligible and no restrictions were imposed on the type of control/comparator. Any type of control condition was deemed eligible.

Non-empirical, general discussion, or theoretical papers, case reports, case series, systematic reviews and qualitative studies were excluded. Studies not published in English, and studies using mixed samples where specific POTS data could not be extracted were also excluded.

2.1.1. Specific requirements regarding POTS symptom burden measures

POTS symptom burden was defined as symptoms reported directly by the patient (Rothrock et al., 2011; Speight and Barendse, 2010) as a
sum of scores from a standardized instrument which may measure the severity, range or impact of POTS-specific symptoms that limit normal activities or cause physical and psychological suffering (Gill et al., 2012). Questionnaires commonly used for quantifying self-reported symptom burden in POTS could be broadly divided into two types; those that measure autonomic symptoms, and those that measure orthostatic symptoms. Although POTS is characterized by orthostatic symptoms, as a syndrome, symptoms often extend beyond orthostatic intolerance and may include a range of non-orthostatic contributions to symptom burden (Garland et al., 2015; Rea et al., 2017). Therefore, both orthostatic and autonomic measures were included for the purpose of systematically reviewing characteristic features, associated factors and interventions related to symptom burden in POTS. Non-standardized measures were included for the purpose of symptom burden (Garland et al., 2015; Rea et al., 2017). Therefore, both orthostatic and autonomic measures were included for the purpose of systematically reviewing characteristic features, associated factors and interventions related to symptom burden in POTS. Non-standardized lists of symptom questions or ratings were excluded. More generic questionnaires that measured impact or health-related quality of life (QoL) (such as SF-36) as opposed to POTS specific symptoms were also excluded (except as correlates of symptom burden). A table summarizing the symptom burden measures included can be found below (Table 2).

2.2. Search strategy and study selection

A comprehensive literature search was initially run on 30 November 2020 and then rerun on 18 January 2022. Studies were identified by conducting systematic online searches of APA PsycINFO (Ovid); MEDLINE(R) (Ovid) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (Ovid); Embase (Ovid); CINAHL; CENTRAL; Web of Science Core Collection; and APA PsycArticles for quantitative studies using relevant keywords, including Postural Orthostatic Tachycardia Syndrome, Postural Tachycardia Syndrome and POTS as search terms. A detailed search strategy is provided in Table 1. Symptom questionnaires varied widely from between 5 and 169 items (Schrezenmaier et al., 2005; Kaufmann et al., 2012; Suarez et al., 1999). Therefore, a range of instruments and questionnaires were used.

2.3. Data extraction and synthesis

Two reviewers (I.K. and E.J.) independently extracted data using predefined data extraction criteria, based on the PICOS-PRISMA guidelines ( Liberati et al., 2009 ). Extracted information included (1) study design; (2) study aim; (3) the number of participants; (4) characteristics of patient sample (age, sex, ethnicity, co-morbidities, treatments, duration of symptoms); (5) how presence of POTS was defined by the authors; (6) comparator/control group (if applicable); (7) recruitment source and response rate; (8) predictor factors; (9) measure of symptom burden used; (10) key findings; (11) analysis conducted; (12) key quantitative data; and in addition for intervention studies (13) type of intervention and rationale, and (14) how participants were randomized.

Due to the wide variety of symptom measures used, and limited amount of data, meta-analyses were not possible and so a narrative review was conducted (McKenzie and Brennan, 2019). For comparisons of symptom burden in POTS and other chronic health conditions, a description of the synthesized findings and the certainty of the findings was provided (Campbell et al., 2020). For instrument domain and composite baseline scores, weighted pooled means and standard deviations were calculated based on sample size for POTS. Where possible, bivariate correlations between psychosocial factors and outcomes were reported and interpreted as small (0.10), medium (0.30) and large (0.50), using conventional psychology criteria to interpret correlation coefficients as a benchmark (Funder DC and Ozer, 2019), while acknowledging their limitations in that a statistically significant correlation does not necessarily mean a clinically relevant correlation (Schober et al., 2018). If correlation analyses were described but the data were not reported in the study, the authors were contacted to request the data.

2.4. Quality assessment

Eligible full-text articles were assessed for methodological quality according to the Downs & Black (Downs and Black, 1998) quality assessment, which was selected as it was adaptable to the broad range of methodological designs of included studies (Sanderson et al., 2007) (Table 3). The Downs & Black checklist assesses the quality of reporting, external validity, internal validity – bias, internal validity - confounding (selection bias), power, and a diagnostic validity question was added. For observational studies, the checklist was modified by removal of questions relevant to RCTs and scoring was adapted pro rata according to number of questions (15 was the maximum score; high- (12–15); medium- (9–11); and low-quality (8 or less)). Assessment of all studies yielded a low-, medium- or high-quality rating.

Studies were independently assessed by two reviewers (I.K. and E.J.). Any disagreement between reviewers was resolved through consensus and discussion. In cases where consensus could not be reached, the opinion of a third reviewer was sought.

3. Results

3.1. Overview of studies

The search yielded 5159 entries, detailed in the PRISMA diagram (Fig. 1). The 29 studies (17 observational; 12 interventional) eligible for inclusion were published between 2002 (Benrud-Larson et al., 2002) and 2021 (Johansson et al., 2021; Bourne et al., 2021). Results are summarised in Tables 2 (symptom burden measures), 3 (quality assessment), 4 (observational studies), 5a-c (mean symptom burden scores, including Fig. 2, which is a visual representation of COMPASS31 composite and domain scores per condition) & 6 (interventional studies).

The studies included a total of 1372 participants with POTS of a total sample size (including healthy controls and other conditions) of 2314 (range 10–464). The overall mean age of participants with POTS was 32 years (range of SD ±1.3–12.7). On average 81.4% of participants were female. For those studies that reported it (n = 5), the average duration of symptoms was 4.98 years (range of SD ±2.6–10).

Across the 29 studies, the 7 symptom burden instruments used summarized in Table 2 included autonomic symptom questionnaires COMPASS31 (Sletten et al., 2012) (n = 7); COMPASS (n = 1); Autonomic Symptom Profile (ASP (Suarez et al., 1999) n = 2); and orthostatic symptom questionnaires including Vanderbilt Orthostatic Symptom Score (VOSS (Raj et al., 2005) n = 11); Orthostatic Grading Scale (OGS, Schrezenmaier et al., 2005) n = 4); Orthostatic Hypotension Questionnaire (OHQ (Kaufmann et al., 2012) n = 3); and Orthostatic Intolerance Questionnaire (OIQ (Winker et al., 2003; Cai et al., 2020) n = 2). Symptom questionnaires varied widely from between 5 and 169 items assessing the range, severity and impact of symptoms. Domains and symptoms included orthostatic intolerance (OI) (although OI domain symptoms varied somewhat between questionnaires), vasomotor,
secretomotor, gastrointestinal, bladder, pupillomotor/vision, fatigue/sleep, mental clouding, head/neck/chest discomfort, perspiration, shortness of breath, tremulousness, nausea, palpitations, syncope and more (Table 2).

Overall, the methodological quality score, using the Downs and Black quality assessment tool (Downs and Black, 1998) was high in 17 studies (Cortez et al., 2020; Rea et al., 2017; Johansson et al., 2021; Raj et al., 2005; Barbic et al., 2020; Benrud-Larson et al., 2003; Kharraziha et al., 2020; Kimpinski et al., 2010; Lee et al., 2017; Coffin et al., 2012; Green et al., 2014; Green et al., 2013; Kpaeyeh et al., 2014; Moon et al., 2018; Raj et al., 2009b; Smith et al., 2020; Garland et al., 2021), medium in 12 studies (Benrud-Larson et al., 2002; Dipaola et al., 2020; Fisher et al., 2020; Kimpinski et al., 2012; Lewis et al., 2013; McDonald et al., 2014; Moon et al., 2016; Ruska et al., 2018; Wells et al., 2020; Bourne et al., 2021; Mar et al., 2014; Nardone et al., 2020), and low in 0 studies (Table 3).

The next part of the results is divided into two major sections. The first reviews the observational studies and the second the interventional ones.

3.2. Observational studies summary

Observational studies were conducted in the USA (n = 6), South Korea (n = 2), Italy (n = 2), UK (n = 2), Sweden (n = 2), Canada (n = 1), Australia, (n = 1) and Croatia (n = 1). The mean age of POTS participants was 31.1 (range of SD ± 1.3–12.5) in these observational studies. Observational studies included a total of n = 924 people with POTS and a total sample of n = 1853 (including healthy controls and other conditions). 6 observational studies were case-control, 8 were cross-sectional and 3 were longitudinal (including 2 prospective, 1 retrospective cohorts). Seven of the 17 observational studies used COM-PASS31 to measure symptom burden, two used the Autonomic Symptom Profile (of which one only used the 9-item OI subscale of the ASP), one used COMPASS, four used the Orthostatic Grading Scale (OGS), one used the Orthostatic Intolerance Questionnaire (OIQ) and three used the Orthostatic Hypotension Questionnaire (OHQ) (Table 4). For observational studies, key weaknesses across studies were in adjustment for confounding, power and external validity.

3.2.1. Time course and comparisons of symptom burden in POTS and other groups

Medium-high quality longitudinal evaluation of POTS found a reduction of symptom burden over time (Dipaola et al., 2020; Kimpinski et al., 2012). Experiencing pregnancy was not associated with significant changes in symptom burden (Kimpinski et al., 2010). The range of percentages of total symptom burden scale scores for POTS was 34.5%.
Table 2
Symptom burden questionnaires table.

| Reference                  | Name of the questionnaire | Origin/condition | Description                                                                                                                                                                                                 | Number of items/questions | Domains included | Measuring range/severity/impact of symptoms? | Cronbach’s alpha Scoring | Other comments                                                                                                                                                                                                 |
|----------------------------|----------------------------|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------|------------------------------------------------|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Suarez et al., 1999        | ASP - Autonomic Symptom Profile | Autonomic disorders | This questionnaire contains 169 items concerning different aspects of autonomic symptoms. ASP is a questionnaire designed to comprehensively evaluate the severity and distribution of symptoms and the autonomic functional capacity of patients with autonomic disorders. | 169                      | 11 domains:     | Severity, distribution of symptoms and autonomic functional capacity of patients | α (continued on next page) | Higher scores indicate worse symptoms. Selected questions from the ASP questionnaire were used to create COMPASS as a scoring instrument.                                                                 |
|                           |                            |                  |                                                                                                                                                                                                            |                           |                  |                                                |                          |                                                                                                                                                                                                             |
| Suarez et al., 1999        | COMPASS - Composite Autonomic Symptom Score | Autonomic disorders | This questionnaire was made up of a limited set of 84 clinically selected questions from the ASP (see above).                                                                                                                                                     | 84                       | 11 domains:     | Severity, distribution of symptoms and autonomic functional capacity of patients | α of old, new scoring algorithm (1) = α | The Composite Autonomic Symptom Scale (COMPASS) with item-weighting was established from the ASP; higher scores indicate more or worse symptoms.                                                                                   |
|                           |                            |                  |                                                                                                                                                                                                            |                           |                  |                                                |                          |                                                                                                                                                                                                             |
| Sletten et al., 2012       | COMPASS 31                  | Autonomic disorders | The abbreviated 31-item COMPASS-31 was developed through expert review and exploratory factor analysis, as a self-assessment instrument of autonomic symptoms and function. It provides clinically relevant scores of autonomic symptom severity based on the well- | 31                       | 6 domains:      | Global autonomic symptom severity, and domain scores | α = Orthostatic Intolerance: 0.92 | Autonomic function tests were performed to generate the Composite Autonomic Scoring Scale (CASS) and to quantify autonomic deficits. Results of the COMPASS were compared with the CASS derived from the Autonomic Reflex Screen to evaluate validity. For the overall total CASS score and COMPASS score, the rank correlation was 0.67. Scores of symptoms of orthostatic intolerance and secretomotor dysfunction best predicted the CASS on multiple stepwise regression analysis. Score out of a total of 100. Following appropriate weighting, COMPASS 31 is a refined, internally consistent, and markedly abbreviated quantitative measure of                                                                 |
|                           |                            |                  |                                                                                                                                                                                                            |                           |                  |                                                |                          |                                                                                                                                                                                                             |
Table 2 (continued)

| Reference            | Name of the questionnaire                  | Origin/condition                  | Description                                                                                                                                                                                                 | Number of items/questions | Domains included                                                                 | Measuring range/severity/impact of symptoms? | Cronbach’s alpha | Scoring, Other comments                                                                 |
|----------------------|--------------------------------------------|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------|-------------------|----------------------------------------------------------------------------------------|
| Winker et al., 2003  | OIQ - Orthostatic Intolerance Questionnaire | Orthostatic Intolerance           | A symptom score that measures the frequency of nausea, tremor in hands, dizziness, palpitation, headache, profuse perspiration, blurred vision, chest discomfort, light-headedness, and concentration difficulties. | 8                          | Symptoms when the individual stands up from a sitting or supine position or remains prolonged standing; | Frequency of a range of symptoms            | $\alpha = 0.888$ | Score between 0 and 4 for each symptom. The total symptom score is the sum of the single item scores (sometimes averaged for all 10 symptoms to aggregate the global symptom strain). The symptom score has some predictive value in head-up tilt test results, which can be used as a preliminary assessment instrument. The median score in POTS was highest among 272 5–18 year-olds with OI symptoms (including POTS and vasovagal syncope according to HUT). |
| Kaufmann et al., 2012 | OHQ - Orthostatic Hypotension Questionnaire | Neurogenic Orthostatic Hypotension | A validated 10-item scale to assess the comprehensive symptom burden and severity of neurogenic orthostatic hypotension (NOH).                                                                                       | 10                         | Two components: the six-item OH symptoms assessment scale 0–10 severity (OHSAS): | Severity of symptoms, functional impact     | $\alpha \geq 0.8$ | The composite OHQ score is calculated by averaging the OHSAS and the OHDAS, with higher being more severe symptoms. Validation analyses were performed on the two scales and a composite score of the OHQ. The OHQ can evaluate the severity of symptoms and the functional impact of NOH as well as assess the efficacy of treatment. (continued on next page) |
| Reference                  | Name of the questionnaire | Origin/condition | Description                                                                 | Number of items/questions | Domains included                                                                 | Measuring range/severity/impact of symptoms? | Cronbach’s alpha | Scoring, Other comments                                                                 |
|---------------------------|----------------------------|------------------|------------------------------------------------------------------------------|---------------------------|---------------------------------------------------------------------------------|-----------------------------------------------|-----------------|----------------------------------------------------------------------------------------|
| Schrezenmaier et al., 2005 | OGS – Orthostatic Grading Scale | Orthostatic Hypotension | A reliable and valid measure of the severity of symptoms of orthostatic hypotension. | 5                         | Severity, frequency, and interference with daily activities                      | a ~ 0.91                                      |                 | Each item is rated on a scale of 0 to 4. Adding the scores for the individual items creates a total score. Strong internal consistency. The scale items correlated significantly with each of the CASS sub-scores (total: $r = 0.41$), mostly with the CASS adrenergic sub-score ($r < 0.40$). Sum of scores indicates severity, with higher being more severe. VOSS had different naming conventions over time. (Vanderbilt POTS symptom score). |
| Raj et al., 2005           | VOSS - Vanderbilt Orthostatic Symptom Score, previously Vanderbilt POTS symptom score | POTS, Orthostatic Hypotension | Self-rate of the severity of 9 symptoms on a 0 to 10 scale (with 0 reflecting an absence of symptoms). The sum of the scores at each time point is used as a measure of symptom burden. The symptoms were chosen because they reflect common complaints of patients with POTS. | 9                         | Rating 0-10 for these symptoms: 1. mental clouding 2. blurred vision 3. shortness of breath 4. rapid heartbeat 5. tremulousness 6. chest discomfort 7. headache 8. light-headedness 9. nausea | nr                                            |                 |                                                                                         |
(ASP) - 61.6% (OHQ) (Tables 5a–5c, Fig. 2). Medium-high quality studies found that people with POTS reported more orthostatic symptoms (mean ± SD OGS score 10.54 ± 3.83 out of 20 = 52.7%; OHQ 6.16 ± 1.78 out of 10 = 61.6%; OHQ 16.4 ± 3.2 out of 40 = 41%) than healthy controls (Rea et al., 2017; Johansson et al., 2021), people with orthostatic hypotension (Lee et al., 2017; Haldane et al., 2006). Antibodies against GPCRs have been linked to a number of conditions, including POTS (Luft, 2013; Vernino and Stiles, 2018), and one high quality study investigated serum activity against specific GPCRs (ADRA1, ADRB2, CHRM2, OPRL1) in POTS using a commercial cell-based assay (Kharrazia et al., 2020). Serum-mediated adrenergic α1 receptor activity had a strong association with orthostatic symptoms independent of the hemodynamic response. Activation of ADRB2, CHRM2, OPRL1 was not significantly associated with overall OHQ symptom scores. Results from this study indicated the presence of circulating proteins activating cardiovascular ADRA1 (adrenergic α1 receptor), ADRB2 (adrenergic β2 receptor), CHRM2 (cholinergic muscarinic type 2 receptor), and nociception-related OPRL1 (opioid receptor-like 1) in patients with POTS to a higher degree compared with controls. Confounders in terms of prevalent POTS co-morbidities (such as IBS or depression) which may have elicited their own bi-directional effects on immune responses (Canals et al., 2019; Grammatopoulos, 2017) were not controlled for in this study.

### 3.2.2. Factors associated with symptom burden in POTS

#### 3.2.2.1. Heart rate increase

Orthostatic heart rate increase is the primary diagnostic feature of POTS. One medium quality study observed no significant correlation between the degree of orthostatic heart rate increment and symptom burden (Moon et al., 2016).

#### 3.2.2.2. Serum activity against G protein–coupled receptors (GPCRs)

(G protein-coupled receptors (GPCRs) comprise a large class of proteins that regulate many physiological functions such as vision, smell, taste, neurotransmission, cardiac output, and pain perception (Vaidehi et al., 2002; Hudson et al., 2006). Antibodies against GPCRs have been linked to a number of conditions, including POTS (Luft, 2013; Vernino and Stiles, 2018), and one high quality study investigated serum activity against specific GPCRs (ADRA1, ADRB2, CHRM2, OPRL1) in POTS using a commercial cell-based assay (Kharrazia et al., 2020). Serum-mediated adrenergic α1 receptor activity had a strong association with orthostatic symptoms independent of the hemodynamic response. Activation of ADRB2, CHRM2, OPRL1 was not significantly associated with overall OHQ symptom scores. Results from this study indicated the presence of circulating proteins activating cardiovascular ADRA1 (adrenergic α1 receptor), ADRB2 (adrenergic β2 receptor), CHRM2 (cholinergic muscarinic type 2 receptor), and nociception-related OPRL1 (opioid receptor-like 1) in patients with POTS to a higher degree compared with controls. Confounders in terms of prevalent POTS co-morbidities (such as IBS or depression) which may have elicited their own bi-directional effects on immune responses (Canals et al., 2019; Grammatopoulos, 2017) were not controlled for in this study.

### 3.2.2.2. Serum activity against G protein–coupled receptors (GPCRs)

#### 3.2.2.3. Growth hormone

(G protein-coupled receptors (GPCRs) comprise a large class of proteins that regulate many physiological functions such as vision, smell, taste, neurotransmission, cardiac output, and pain perception (Vaidehi et al., 2002; Hudson et al., 2006). Antibodies against GPCRs have been linked to a number of conditions, including POTS (Luft, 2013; Vernino and Stiles, 2018), and one high quality study investigated serum activity against specific GPCRs (ADRA1, ADRB2, CHRM2, OPRL1) in POTS using a commercial cell-based assay (Kharrazia et al., 2020). Serum-mediated adrenergic α1 receptor activity had a strong association with orthostatic symptoms independent of the hemodynamic response. Activation of ADRB2, CHRM2, OPRL1 was not significantly associated with overall OHQ symptom scores. Results from this study indicated the presence of circulating proteins activating cardiovascular ADRA1 (adrenergic α1 receptor), ADRB2 (adrenergic β2 receptor), CHRM2 (cholinergic muscarinic type 2 receptor), and nociception-related OPRL1 (opioid receptor-like 1) in patients with POTS to a higher degree compared with controls. Confounders in terms of prevalent POTS co-morbidities (such as IBS or depression) which may have elicited their own bi-directional effects on immune responses (Canals et al., 2019; Grammatopoulos, 2017) were not controlled for in this study.)
### Table 4
Observational studies summary.

| Reference                  | Design            | Location   | Aim of the study                                                                 | Sample size | Measure of symptom burden | Main results                                                                                                                                                                                                                                                   | Main analysis, correlation coefficients |
|----------------------------|-------------------|------------|----------------------------------------------------------------------------------|-------------|---------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| Barbic et al., 2020        | Case-control      | Italy      | 1. To evaluate the work ability of working POTS patients compared to a group of healthy controls.  
2. To evaluate the roles of the autonomic impairment of POTS patients and their individual cardiovascular autonomic responses to the orthostatic stimulus in work ability.  
To quantify quality of life and identify demographic and clinical correlates of functioning in a sample of patients with POTS. | 40: 22 POTS/18 Healthy Control | COMPASS-31 | WAI scores in POTS patients were inversely correlated to the intensity of autonomic symptoms and to the excessive cardiac sympathetic activation induced by gravitational stimulus. | Spearman correlation analysis  
Individual WAI and COMPASS31 scores $r = 0.46$ ($p = 0.03$)                                                                                                                                                                                            |                                       |
| Benrud-Larson et al., 2002 | Cross-sectional   | USA        |                                                                                   | 94          | Autonomic Symptom Profile (ASP) | Symptoms of orthostatic intolerance had the strongest correlation with the SF-36 physical component scale.                                                                                                                                                           | Spearman correlation analysis, Hierarchical regression analyses.  
ASP scales, SF-36 summary scales:  
Physical, Mental component correlation coefficients:  
Orthostatic intolerance $-0.45^*$,  
$-0.18$  
Vasomotor symptoms $-0.29^*$,  
$-0.11$  
Secretomotor dysfunction $-0.39^*$,  
$-0.04$  
Upper gastrointestinal tract symptoms $-0.28^*$, $-0.21$  
Diarrhea $-0.08$, $-0.17$  
Constipation $-0.27^*$, $-0.03$  
Bladder dysfunction $-0.32^*$, $-0.20$  
Pupillomotor symptoms $-0.33^*$, $-0.22$  
Sleep dysfunction $-0.27^*$, $-0.22$  
Total score $-0.49^*$, $-0.27^*$  
$^*P < 0.01$. $^*P < 0.05$  
(continued on next page)                                                                                                                                                                                                                                 |                                       |
| Benrud-Larson et al., 2003 | Cross-sectional   | USA        | To investigate correlates of disability in patients with POTS                     | 94          | 9-item OI subscale of the Autonomic Symptom Profile (ASP) | Orthostatic symptoms were significantly correlated with physical function, disability, depressive and anxiety symptoms and catastrophizing. Path analysis investigated associations between predictor variables and functional disability.  
Symptom severity (9 item ASP subscale for OI): Pearson correlation coefficients among the psychosocial predictor variables and outcome variables:  
Physical function $-0.46^*$  
Perceived disability $0.43^*$  
Depressive symptoms $0.30^*$  
Anxiety symptoms $0.27^*$  
(continued on next page)                                                                                                                                                                                                                                 |                                       |
### Table 4 (continued)

| Reference          | Design                     | Location     | Aim of the study                                                                 | Sample size | Measure of symptom burden | Main results                                                                                                                                                  | Main analysis, correlation coefficients |
|--------------------|----------------------------|--------------|----------------------------------------------------------------------------------|-------------|---------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| Cortez et al., 2020| Case-control               | USA          | To compare clinical characteristics and sensory thresholds between disease groups and controls, as well as in a subgroup analysis within the PoTS group, based on headache phenotype. | 80          | COMPASS-31                | COMPASS-31 scores were significantly higher in both PoTS and CM compared to controls as well as in PoTS-ALL compared to CM, the only domain where CM and PoTS significantly differed was that of orthostatic symptoms. | One-way ANOVA                          |
| Dipasola et al., 2020 | Longitudinal Prospective cohort | Italy       | To quantitatively and semi-quantitatively assess the burden of autonomic symptoms in a cohort of POTS patients followed over a period of 2 years. | 42, 25 had a 1-year follow-up and 12 had a 2-year follow-up | COMPASS-31                | Overall COMPASS 31 was significantly reduced compared to baseline at both 1-year and 2-year follow-up. A significant improvement in pupillomotor function at the 2-year follow-up was also observed. | One-way ANOVA                          |
| Fisher et al., 2020 | Cross-sectional (Baseline data for a larger intervention study) | USA          | To describe baseline psychological symptoms in patients with POTS, and examine associations between psychological and self-report autonomic symptoms. | 58          | COMPASS-31                | Depressive symptoms and pain catastrophizing were significantly associated with autonomic symptoms.                                                                 | Spearman correlation analysis          |
| Johansson et al., 2021 | Case-control               | Sweden       | To investigate circulating GH levels in PoTS versus age- and sex-matched healthy control group from the same geographical location by high-sensitivity chemiluminescence sandwich immunoassay for plasma GH detection. | 88; 46 with POTS, 42 healthy controls | Orthostatic Hypotension Questionnaire (OHQ) | Impairment of daily life activities subscale of the OHQ was inversely correlated with GH in POTS.                                                                 | Correlation coefficients between psychosocial measures, COMPASS-31 for each Measure: ASI total 0.16 GAD-7 total 0.26 PCS total 0.31a PHQ-8 total 0.48a PROMIS mental health T-score — 0.45a PROMIS physical health T-score — 0.60a a = statistically significant. Linear regression analysis, ANOVA Correlation between circulating growth hormone (GH) levels and OHQ: $r = -0.142$ ($p = 0.369$) OH daily activities score (OHDAQS): $r = -0.306$ ($p = 0.049$) OH symptoms assessment scale (OHSA): $r = -0.033$ ($p = 0.835$) Linear regression. A logistic model with all 4 GPCRs as POTS predictors: ADRA1 activation was associated with the OHQ composite score and OI symptoms during prolonged standing and walking for short or long periods. All 4 receptors were associated with a higher score for vision |                                      |
| Kharraziha et al., 2020 | Case-control               | Sweden       | To study serum antibody activity against G protein- coupled receptors in relation to symptoms in patients with POTS and controls using a commercial cell-based assay | 73, 48 patients with POTS and 25 healthy controls | Orthostatic Hypotension Questionnaire (OHQ) | ADRA1 activation was associated with the OHQ composite score and OI symptoms during prolonged standing and walking for short or long periods. All 4 receptors were associated with a higher score for vision | Activation association with the OHQ composite score ($\beta$ (per SD), $p$-value: ADRA1: $\beta = 0.768$, $p = 0.009$) (continued on next page) |
| Reference          | Design                  | Location       | Aim of the study                                                                 | Sample size | Measure of symptom burden                          | Main results                                                                                                                                                                                                 | Main analysis, correlation coefficients                                                                                     |
|--------------------|-------------------------|----------------|-----------------------------------------------------------------------------------|-------------|-----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| Kimpinski et al., 2012 | Longitudinal Prospective | Canada         | To prospectively evaluate patients who met standard criteria for postural tachycardia syndrome (POTS), at baseline and 1-year follow-up, using standard clinical and laboratory methods to assess autonomic function. | 58          | COMPASS (/ASP)                                      | Orthostatic symptoms, the major autonomic symptom reported by patients, improved in most patients.                                                                                                        | ADBR2: $\beta = 0.176, p = 0.599$  
CHRM2: $\beta = 0.290, p = 0.364$  
OPRL1: $\beta = 0.472, p = 0.118$  2 test and Spearman test                                                                                               |
| Kimpinski et al., 2010 | Longitudinal Retrospective cohort | USA          | To compare the clinical presentation, autonomic dysfunction, and pregnancy outcomes in parous and nulliparous women with postural tachycardia syndrome (POTS) and in women with POTS before and after pregnancy. | 112         | Orthostatic grading scale (OGS)                     | OI did not differ significantly between parous and nulliparous groups. OI symptoms did not differ statistically during any of the 3 trimesters. However, the general trend observed was worsening of OI in the first trimester and improvement in the second and third trimesters. | Mann-Whitney test. Data (parametric) paired t test. Repeated measures of analysis of variance                                                                 |
| Lee et al., 2017    | Cross-sectional         | South Korea   | To investigate the frequency and pattern of orthostatic symptoms during head-up tilt (HUT) in patients with orthostatic intolerance, and to assess the relationship between orthostatic symptoms during HUT and autonomic parameters. | 464         | Korean Orthostatic Grading Scale (KOGS)            | Patients with POTS had orthostatic symptoms more frequently during HUT compared to patients with OH.                                                                                                        | Independent-samples t-test, One-way ANOVA                                                                                     |
| Lewis et al., 2013  | Cross-sectional         | UK            | To characterise patients with CFS and POTS and differentiate them from CFS patients without POTS in terms of clinical and autonomic features. | 179         | Orthostatic grading scale (OGS)                     | CFS patients with POTS exhibited greater orthostatic intolerance, were younger, less fatigued, less depressed and had reduced day-time hypersonnenlce compared with patients without POTS. The POTS group had statistically significantly higher autonomic symptom burden (OGS) despite comparable levels of fatigue and sleepiness compared with a matched CFS cohort. | Fisher’s exact test and independent two-tailed Student’s t-test between continuous variables. Pearson R correlation for correlation between variables. Descriptive statistics |
| McDonald et al., 2014 | Cross-sectional         | UK            | To verify if POTS patients’ limitations are similar to patients with chronic fatigue syndrome (CFS) | 136         | Orthostatic Grading Scale (OGS)                     |                                                                                                                                                                                                            |                                                                                                                                                                                                 |
| Moon et al., 2016  | Cross-sectional         | Republic of Korea | To evaluate if the maximal heart rate (HR) increment after standing is associated with the clinical symptoms in patients with excessive orthostatic tachycardia (OT). Investigate the correlations among the symptoms of orthostatic intolerance (OI), depression, and health-related QOL, assess if patients with minimal OI symptoms suffer from depression or diminished QOL. | 107         | Orthostatic Intolerance Questionnaire (OIQ)       | The amount of the orthostatic HR increment was not associated with symptom burden. OI symptoms were significantly associated with depression and QOL. The total OIQ score revealed a positive linear relationship with the BDI-II scale and an inverse linear correlation with both PCS and MCS of the SF-36 scale.  | Spearman correlation                                                                                                                                                                           |

Table 4 (continued)
| Reference | Design | Location | Aim of the study | Sample size | Measure of symptom burden | Main results | Main analysis, correlation coefficients |
|-----------|--------|----------|-----------------|-------------|---------------------------|--------------|----------------------------------------|
| Rea et al., 2017 | Case-control | USA | To quantitatively assess autonomic symptom burden in PoTS patients using the COMPASS-31, compared to that of autonomic failure/neuropathy and asymptomatic, healthy controls. | 111 PoTS (n = 32); autonomic failure/neuropathy (AF/N; n = 47) and asymptomatic, healthy controls (n = 32) | COMPASS-31 | Patients with PoTS diagnosis report greater symptom burden across all functional domains of autonomic function compared to controls, and with similar severity to AF/N. | Post-AIC Gamma Regression |
| Ruska et al., 2018 | Cross-sectional | Croatia | To investigate the performance of the COMPASS-31 questionnaire in a real-life setting in consecutive patients referred for objective testing of the autonomic nervous system (ANS), with the hypothesis that COMPASS-31 results differ depending on medications and findings of the tilt table test results. | 171. POTS: 6 patients (3.51 %) | Croatian version of the COMPASS-31 | Patients with postural orthostatic tachycardia had significantly higher orthostatic intolerance and vasomotor domains of COMPASS-31 (p = 0.048 and p = 0.022, respectively). | Spearman correlation analysis |
| Wells et al., 2020 | Case-control | Australia | To investigate the physiology underlying “brain fog” in the absence of orthostatic stress in POTS by assessing cognitive and haemodynamic responses in the middle cerebral artery at baseline, after initial cognitive testing, and after prolonged (30-min) cognitive stress test | 40; 22 with POTS, 18 healthy controls. | OHQ, COMPASS-31 | Prolonged cognitive stress test (PCST) resulted in greater symptom burden in POTS. | Mixed effect and random models |
than healthy controls, although levels were still within the normal range. The daily life activities subscale (OHDAS) of the OHQ symptom burden score had a medium inverse correlation with growth hormone in POTS, where higher impairment was associated with lower levels of growth hormone. The total overall OHQ symptom burden score was not significantly associated with growth hormone levels in POTS.

### 3.2.2.4. Anxiety.

The association between anxiety and symptom burden was explored in two medium-high quality studies (Benrud-Larson et al., 2003; Fisher et al., 2020). A small association was found in two studies between higher anxiety and greater autonomic/orthostatic symptom burden (Benrud-Larson et al., 2003; Fisher et al., 2020). The correlation was reported significant in one larger study (n = 94) (Benrud-Larson et al., 2003), but not the smaller one (n = 58) (Fisher et al., 2020). Anxiety sensitivity (fear of anxiety-related sensations due to a belief that these symptoms may be harmful (Reiss et al., 1986)) was not significantly correlated with autonomic symptoms in two studies (Benrud-Larson et al., 2003; Fisher et al., 2020), despite elevated levels of anxiety sensitivity in POTS patients in one study (Fisher et al., 2020).

### 3.2.2.5. Depression.

Three medium-high quality studies measured depression in relation to symptom burden (Benrud-Larson et al., 2003; Fisher et al., 2020; Moon et al., 2016). Two found medium correlations (Benrud-Larson et al., 2003; Fisher et al., 2020) and one large (Moon et al., 2016), where higher symptom burden scores were associated with higher depression scores. One medium quality study reported that some OI symptoms were more strongly associated with depression including chest discomfort and concentration difficulties (Moon et al., 2016).

### Table 5a

COMPASS-31 scores.

| Condition       | Reference, Method of reporting | Number of participants | total score out of 100 | Orthostatic domain score | Pupillomotor domain score | GI domain score | Bladder domain score | Vasomotor domain score | Secretomotor domain score |
|-----------------|--------------------------------|------------------------|------------------------|--------------------------|---------------------------|-----------------|----------------------|------------------------|--------------------------|
| POTS            | Barbic et al., 2020, Estimates from diagram Cortez et al., 2020, Median; IQR | 20                      | 51                     | 23                       | 2.5                       | 12.4            | 2.4                  | 2.6                    | 7.4                      |
|                 | Dipsa et al., 2020, Mean, SD  | 30                      | 52; 14                 | 28; 8                    | 3; 2                      | 10; 7           | 1; 2                 | 6; 4                   | 2; 3                     |
|                 | 1 yr follow up Dipsa et al., 2020, Mean, SD | (25)                    | 49.90 ± 14.33         | 27.52 ± 8.11             | 2.79 ± 1.16               | 9.37 ± 3.98     | 2.25 ± 1.86         | 2.20 ± 1.42             | 5.77 ± 4.50              |
|                 | (12)                           | 45.47 ± 14.54          | 22.88 ± 8.76           | 2.44 ± 1.01              | 9.57 ± 3.32              | 2.31 ± 1.50     | 2.27 ± 1.37         | 6.00 ± 3.39             |
|                 | 2 yr follow up Rea et al., 2017, Median, IQR | 32                      | 48.05, 33.91–61.98     | 20.00, 10.00–32.00       | 2.33, 1.58–3.67           | 9.82, 6.25–16.00 | 0.0–3.33             | 0.25, 0.0–0.46           | 4.00, 0.0–5.71           |
|                 | Dipsa et al., 2018, Median (min, max) | 7                      | 35.15 (12.17, 50.27)  | 24.00 (0.00, 28.00)      | 1.33 (0.00, 2.67)         | 5.36 (1.79, 9.83) | 0.00 (0.00, 3.33)  | 0.00 (0.00, 4.17)        | 2.14 (0.00, 4.29)        |
|                 | Wells et al., 2020              | 22                      | 46 ± 14                |                          |                           |                 |                      |                        |                          |
| POTS            | Mean ± SD                       |                         | Total / average, % of total score | 136                      | 48.69, 48.7 %             | 24.53           | 2.33                 | 9.95                   | 1.18                     | 2.59                     | 4.27                     |
| Chronic Migraine | Cortez et al., 2020, Median; IQR | 30                      | 34; 21                 | 20; 12                   | 3; 2                      | 7; 6            | 0; 1                 | 2; 6                   | 0; 2                     |
| Autonomic Failure/Neuropathy | Rea et al., 2017, Median, IQR | 47                      | 50.82, 39.38–61.97    | 7.00, 5.00–8.00          | 8.00                     | 12.00           | 2.00                 | 0.0–4.00               | 3.00, 1.00–4.00          |
| Vasovagal syncope | Ruska et al., 2018, Median (min, max) | 29                      | 20.89 (0.33, 45.11)   | 16.00 (0.00, 28.00)      | 1.00 (0.00, 3.00)         | 2.68 (0.00, 11.61) | 0.00 (0.00, 6.07)  | 0.00 (0.00, 2.50)        | 0.00 (0.00, 4.29)        |
| Orthostatic Hypotension | Ruska et al., 2018, Median (min, max) | 17                      | 22.67 (0.33, 49.25)   | 16.00 (0.00, 48.00)      | 1.33 (0.00, 2.33)         | 2.70 (0.00, 11.61) | 1.11 (0.00, 3.33)  | 0.00 (0.00, 4.17)        | 0.00 (0.00, 6.43)        |
| Orthostatic Intolerance | Ruska et al., 2018, Median (min, max) | 8                       | 27.57 (16.68, 33.43)  | 20.00 (8.00, 28.00)      | 1.17 (0.00, 3.67)         | 2.68 (0.00, 7.14) | 0.56 (0.00, 1.11)  | 0.00 (0.00, 2.50)        | 0.00 (0.00, 2.14)        |

3.2.2.6. Catastrophizing. Two medium-high quality studies explored catastrophizing (viewing or presenting a situation or future situation as considerably worse than it is) in relation to symptom burden and found small-medium correlations (Benrud-Larson et al., 2003; Fisher et al., 2020), where higher catastrophizing scores (from the pain catastrophizing scale and catastrophizing subscale of the coping strategies questionnaire) were associated with higher symptom burden. One medium quality study reported that the pain catastrophizing scale (helplessness, active rumination and excessive magnification of the experience of pain) had a medium significant association with greater autonomic symptoms (Fisher et al., 2020), whereas one high quality study found that a modified version of the catastrophizing subscale of the coping strategies questionnaire (assessing catastrophic thinking in response to autonomic symptoms) had a small significant correlation with greater symptom burden (Benrud-Larson et al., 2003).
3.2.2.8. Somatization. The association between self-reported somatization and symptom burden was explored in two medium-high quality studies (Benrud-Larson et al., 2003; Fisher et al., 2020) using the somatic vigilance questionnaire (assessing the attentional focus to internal bodily sensations) (Benrud-Larson et al., 2003; Schmidt et al., 1997) and the somatic symptoms subscale (PHQ-15) of the PHQ-SADS (Fisher et al., 2020; Kroenke et al., 2010). Severe somatization was reported in POTS participants in one study (Fisher et al., 2020) compared to the general population (Kocalevent et al., 2013), but no significant relationship with symptom burden was observed.

3.2.2.9. Functional ability. Functioning and health-related quality of life (SF-36 and PROMIS Global Health questionnaires which measure functional health and well-being, comprising domains such as physical, mental, and social aspects of health, physical functioning, and bodily pain) was measured in relation to symptom burden in four medium-high quality studies (Benrud-Larson et al., 2002; Benrud-Larson et al., 2003; Fisher et al., 2020; Moon et al., 2016) (Table 4), of which two were conducted by the same team in the same cohort (Benrud-Larson et al., 2002; Benrud-Larson et al., 2003). All of these demonstrated significant medium-large correlations with self-reported symptom burden, where more severe symptoms were associated with increased impairment (Benrud-Larson et al., 2002; Benrud-Larson et al., 2003; Fisher et al., 2020; Moon et al., 2016). Both physical and mental component summary scales of SF-36 showed a negative linear relationship with total OIQ scores (Moon et al., 2016). Mental functioning components (PROMIS mental health T-score and SF-36 mental component) had small (Benrud-Larson et al., 2002) – medium (Fisher et al., 2020; Moon et al., 2016) correlations with symptom burden.

One high-quality study investigated the relationship between autonomic symptom burden and the ability to work (Barbic et al., 2020) in working POTS patients and controls, and found that a significant medium correlation was present between total autonomic symptom scores (COMPASS31) and Work Ability Index (WAI, an instrument which assesses the perceived ability to work) scores. The higher the total COMPASS31 score the lower the WAI score, and WAI scores were significantly lower in people with POTS compared to healthy controls (Barbic et al., 2020). One medium quality study examined pain disability index scores and found that higher pain disability scores had a significant medium correlation with higher symptom burden (Benrud-Larson et al., 2003).

3.2.2.10. Prolonged cognitive stress test. One medium quality study evaluated the effect of a prolonged cognitive stress test on symptom burden (OHQ and COMPASS31) (Wells et al., 2020). A significant increase in the OH symptoms assessment (OHSA) OHQ subscale was reported after the entire protocol, with a greater increase in people with POTS compared to the control group, although exact post-test symptom scores were not provided.

3.3. Randomized experimental and intervention studies summary

Randomized experimental and intervention studies were conducted in the USA (n = 9), Canada (n = 2), and South Korea (n = 1). The mean age of POTS participants was 34.1 (range of SD ± 2–12.7) in these studies. The 12 eligible studies had a total of n = 448 participants with POTS in a total sample of n = 461 (including healthy controls). Eleven of these studies measured symptom burden using the Voss (Vanderbilt Orthostatic Symptoms Score, previously Vanderbilt POTS symptom scores). One study measured symptom burden through the Orthostatic Intolerance Questionnaire (OIQ). 12 intervention studies assessed symptom burden as a primary or secondary outcome in randomized experimental trials (n = 11) and one 2 × 2 factorial design trial, of predominantly high quality using the Downs and Black rating (Table 6). For intervention studies, key weaknesses were the lack of reporting on distributions of principal confounders and adverse events, representativeness of participant samples and response rates among source populations, adjustment for confounding, and recruitment period according to the Downs & Black rating (Table 3). However, all 12 studies had limitations in terms of being experimental rather than treatment

Fig. 2. Breakdown of COMPASS-31 by conditions.
Note: For POTS, the weighted pooled average COMPASS-31 total score out of 100 is 48.69 (48.7%, range 35.15-52), range of SD ± 10.02-14.54 (n = 136), compared to VVS 20.98, OH 22.57, OI 27.57, CM 30 and AF/N 50.82, with orthostatic scores being the largest contributor (range 20-28).
trials with endpoints in hours \( (n = 10) \) or not having a placebo control group \( (n = 2) \) (Table 3), and compression conditions were not able to be blinded from participants, staff or assessors.

### 3.3.1. Pharmacological RCT and experimental studies

Eight medium-high quality trials investigated pharmacological treatments (Table 6). Medications were selected for reducing tachycardia (Propranolol, Bisoprolol) (Moon et al., 2018; Raj et al., 2009c), reducing the hyperadrenergic state (Melatonin) (Green et al., 2014), increasing parasympathetic nervous system activity (and therefore decreasing HR) and enhancing cardiovagal tone (Pyridostigmine) (Raj et al., 2005; Moon et al., 2018), increasing blood volume/pressure (Desmopressin, Sertraline) (Coffin et al., 2012; Mar et al., 2014), or demonstrating that certain medications may have negative effects on heart rate/hemodynamics and symptom burden in POTS (Modafinil, NRIs) (Green et al., 2013; Kpaeyeh et al., 2014).

In one high quality study, the only trial with longer term follow-up, 77 participants were randomized in a \( 2 \times 2 \) factorial design clinical trial of a 3-month medical treatment regimen, and symptom burden was assessed over 3 months (Moon et al., 2018) (Table 6). Group one trialed propranolol, group two bisoprolol, group three propranolol + pyridostigmine and group four bisoprolol + pyridostigmine. OIQ score improvements were consistent across treatment groups compared to baseline, although this study did not include a placebo group.

Seven medications were trialed in laboratory/tilt-based single dose crossover trials with endpoints measured in hours trials without further follow-up. Three of these experimental proof-of-concept trials, of Desmopressin, Pyridostigmine, and Propranolol (low dose more than high dose and high dose more than placebo) were effective in reducing symptom burden compared to placebo or high dose controls after 4 h tilt test. Two medications showed no impact on symptom burden at the tilt test: Melatonin reduced tachycardia but did not improve symptom burden compared to placebo (Green et al., 2014) and there was no significant difference between modafinil and placebo over the 4 h period with regard to POTS symptom burden scores (Kpaeyeh et al., 2014). Two pharmacological laboratory based randomized trials showed negative impacts of medications on symptom burden compared to placebo. POTS patients are often prescribed NRI medication for co-morbid conditions. Patients given Norepinephrine Reuptake Inhibition (NRI) atomoxetine reported increased symptom burden scores compared to placebo from baseline to 2 h after study drug administration. Sertraline, a selective serotonin reuptake inhibitor, also resulted in worse symptoms than placebo or high dose controls after 4 h tilt test. Two medications showed no impact on symptom burden at the tilt test: Melatonin reduced tachycardia but did not improve symptom burden compared to placebo (Green et al., 2014) and there was no significant difference between modafinil and placebo over the 4 h period with regard to POTS symptom burden scores (Kpaeyeh et al., 2014). Two pharmacological laboratory based randomized trials showed negative impacts of medications on symptom burden compared to placebo. POTS patients are often prescribed NRI medication for co-morbid conditions. Patients given Norepinephrine Reuptake Inhibition (NRI) atomoxetine reported increased symptom burden scores compared to placebo from baseline to 2 h after study drug administration. Sertraline, a selective serotonin reuptake inhibitor, also resulted in worse symptoms than placebo at 4 h, despite being hypothesized to target low blood pressure and reduce reflex tachycardia (Mar et al., 2014).

### 3.3.2. Dietary salt intake

One high quality proof-of-concept randomized two-armed crossover study (Garland et al., 2021) assessed the effect of high dietary sodium intake in POTS to counteract the hypovolemia and elevated plasma norepinephrine that can contribute to excessive orthostatic tachycardia. 14 patients with POTS and 13 healthy controls trialed 6 days of a low salt (10 mEq sodium/day) or high salt (300 mEq sodium/day) diet. There was a non-significant trend for lower symptom burden scores after upright posture in POTS on the high salt diet compared to the low salt diet, particularly for mental confusion, palpitations, light-headedness and headache (Garland et al., 2021).  

### 3.3.3. Compression garments

Compression garments are used to target blood flow, and reduce blood pooling and the associated exaggerated compensatory increase in heart rate. Neck compression, leg/abdominal compression, and splanchnic compression combined with propranolol were trialed in 3 randomized experimental crossover studies of short duration (5 min–2 h per condition) (Table 6). All three trials were associated with a significant treatment effect on symptom burden relative to the comparison conditions. The trials of a neck compression collar (Nardone et al., 2020)
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(5 min) and abdominal and lower body compression (10 min) (Bourne et al., 2021) both improved symptom burden during head-up-tilt. In the trial (2 h) combining splanchnic venous compression and propranolol, splanchnic venous compression alone did not improve symptom burden, but it did prevent the blood pressure decrease produced by propranolol, therefore the combination was more effective in improving symptoms than either alone (Smith et al., 2020).

4. Discussion

4.1. Observational studies

Synthesis of the evidence suggests a pattern of high burden of symptoms in POTS, particularly those of an orthostatic nature when compared to healthy controls and comparable conditions. Studies using the COMPASS31, showed people with POTS also report a wide range of autonomic symptoms of moderate to severe intensity (Barbic et al., 2020; Dipaola et al., 2020). The reported overall burden of autonomic symptoms was higher in people with POTS than a number of other LTCs, and comparable to patients with autonomic failure. Although COMPASS31 and OGS were the most commonly used measures, 6 different symptoms scales were used across the 17 observational studies reviewed, highlighting a lack of standardization or agreement regarding symptom assessment for POTS. The recent development of a POTS-specific symptom burden score (Spahic et al., n.d.), which reportedly strongly correlates with orthostatic heart rate increase in POTS, is therefore welcomed, although the instrument requires further external validation and replication in larger multi-center settings (Spahic et al., n.d.). In terms of correlates of symptom burden, there was high quality evidence from one study of a strong relationship between symptom burden and ADRA-1 activation. There was a larger volume of medium-high quality evidence of moderate to large associations between depression and physical functioning with symptom burden in POTS. Prolonged cognitive stress testing, anxiety and catastrophizing were also significantly associated with symptom burden, but there were fewer studies and sizes of the relationships were smaller. Heart rate increase, growth hormone, somatic vigilance and neuroticism showed no significant relationships to overall POTS symptom burden. Interestingly, despite the heterogeneity of measures, making it difficult to compare across studies, orthostatic symptom burden measures and autonomic symptom burden measures had fairly similar size correlation coefficients with factors in people with POTS.

Orthostatic intolerance (OI) is considered the hallmark feature of POTS (Herrera and Behm, 2021), but this review confirms people with POTS also report high levels of autonomic symptoms. However, a study which used an objective measurement of autonomic dysfunction in people with POTS (the Composite Autonomic Severity Score, CASS) reported only mild autonomic dysfunction (a score of 3 or less in 95 % of patients at baseline and 92 % at 1 year) (Kimpinski et al., 2012). Lee et al. concluded that autonomic symptom reports are a poor indicator of actual autonomic abnormalities (Lee et al., 2017), reiterating the difficulty in POTS in identifying biomedical measurements that corroborate symptoms as reported by the patient.

The current review also found little robust evidence of biomedical measurements that correlated with symptom burden. For example, the orthostatic heart rate increase, the main clinical and diagnostic feature of POTS (Barbic et al., 2020), was in one study found to have no significant association with symptom burden. People with POTS had a higher heart rate increment on head-up tilt (HUT) than healthy controls, people with CFS (Lewis et al., 2013; McDonald et al., 2014), chronic migraine (Cortez et al., 2020) and autonomic failure/neuropathy (Rea et al., 2017), but there was no significant relationship between the severity of symptom burden and HR increase. Whilst physical measurements such as orthostatic heart rate increase appears unrelated to symptom reports, orthostatic intolerance symptoms in children with POTS have shown significant positive associations with diastolic blood pressure variability (Sunwoo et al., 2017) and negative associations with 24-h sodium consumption/urinary excretion (Zhang et al., 2012) and serum resistin levels (Bai et al., 2017). These associations warrant further investigation in adult POTS populations.

The only biomedical factor associated with symptom burden in this review was serum activity against G protein–coupled receptor ADRA1. However, there is uncertainty around the usefulness of antibodies against GPCRs (Michel et al., 2009; Rhodes and Trimmer, 2006; Pradidarchee et al., 2009), and around the use of commercial ELISA (enzyme linked immunosorbent assay) tests (Hall et al., 2022). Although altered GPCR activity in people with POTS has been observed (Fedorowski et al., 2021).
### Table 6

| Author | Treatment target | Country of origin | Number of participants | Type of intervention | Study design | Type of control | Symptom burden questionnaire | Main result on symptom burden |
|--------|-------------------|-------------------|------------------------|----------------------|--------------|-----------------|-----------------------------|-------------------------------|
| Coffin et al., 2012 | Increase the circulating blood volume | USA | 30 | Desmopressin (DDAVP 0.2 mg orally) | Randomized crossover design on two separate mornings | Placebo | VOSS | Oral desmopressin significantly attenuated tachycardia and improved symptoms in POTS. |
| Garland et al., 2021 | Counteract the hypovolemia and elevated plasma norepinephrine that contribute to excessive orthostatic tachycardia | USA | 27: 14 POTS 13 HC | High Dietary Sodium Intake | Randomized 2-arm crossover study | Low-salt | VOSS | There was a nonsignificant trend for a lower symptom burden score in POTS on the HS diet than the LS diet. |
| Green et al., 2014 | Reduce the hyperadrenergic state, reduce tachycardia | USA | 78 | Melatonin | Randomized, crossover design on two separate mornings | Placebo | VOSS | Symptom burden was not improved with melatonin compared with placebo, there was a modest decrease in standing tachycardia. Placebo improved VOSS more than melatonin at 2 h (P = 0.031), the two interventions had comparable scores at 4 h. |
| Green et al., 2013 | Treating ADHD, peripheral vasoconstriction | USA | 27 | Atomoxetine 40 mg | Randomized, crossover design on two separate mornings | Placebo | VOSS | Symptom burden worsened with atomoxetine and standing HR acutely increased compared to placebo from baseline to 2 h after study drug administration. |
| Kpaeyeh et al., 2014 | Improving the cognitive symptoms of POTS | USA | 54 | Modafinil | Randomized crossover trial on separate days | Placebo | VOSS | No significant difference between modafinil and placebo over the 4 h period with regard to HR or symptom burden scores, increased standing/sitting BP. |
| Mar et al., 2014 | Increase blood pressure and attenuate reflex tachycardia induced by a presor response | USA | 39 | Sertraline | Randomized crossover trial on separate days | Placebo | VOSS | At 4 h, symptoms were worse with sertraline than placebo. No difference in HR. |
| Moon et al., 2018 | Reduce tachycardia, enhance cardiovagal tone | South Korea | 77 | Propranolol, Bisoprolol, and Pyridostigmine | 2 × 2 factorial design, randomized, clinical trial of a 3-month medical treatment regimen | Group 1: propranolol; Group 2: bisoprolol; Group 3: propranolol + pyridostigmine; Group 4: bisoprolol + pyridostigmine | OIQ (orthostatic intolerance questionnaire) | OIQ score improvements were consistent across every treatment group. |
| Raj et al., 2005 | Enhancing cardiovagal tone | USA | 17 | Pyridostigmine | Randomized crossover design on separate mornings | Placebo | VOSS | The decrease in symptom burden and HR within 4 h after study drug was significantly greater with pyridostigmine than placebo (continued on next page) |
| Author              | Treatment target                                                                 | Country of origin | Number of participants | Type of intervention | Study design                                      | Type of control | Symptom burden questionnaire | Main result on symptom burden                                                                 |
|--------------------|----------------------------------------------------------------------------------|-------------------|------------------------|----------------------|--------------------------------------------------|----------------|------------------------------|---------------------------------------------------------------------------------------------|
| Raj et al., 2009c  | Reducing tachycardia                                                             | USA               | 54 (protocol 1) 19 (protocol 2) | Propranolol, high and low dose. | Randomized crossover design on separate mornings | Placebo         | Vanderbilt POTS symptom score (VOSS)          | The symptom burden improvement from baseline to 2 h was greater with propranolol than placebo, the improvement in symptoms at 2 h was greater with low-dose propranolol than high-dose although HR was decreased more |
| Smith et al., 2020 | Reducing splanchnic venous pooling induced by upright posture                     | USA               | 18                     | Abdominal compression or propranolol | A placebo-controlled, randomized crossover study on separate days | Placebo         | VOSS                         | Neither propranolol nor compression improved symptoms compared with placebo. Splanchnic venous compression alone did not improve HR or symptoms but prevented the blood pressure decrease produced by propranolol. The combination was more effective in improving symptoms than either alone. |
| Bourne et al., 2021| Reducing splanchnic and lower extremity venous pooling                           | Canada            | 30                     | 4 compression conditions | Randomized crossover design with each participant completing 4 10 min HUTs. | 4 conditions: no compression, lower leg, abdominal/thigh, and full abdominal/ leg compression | VOSS                         | Abdominal and lower body compression reduced HR and improved symptoms during HUT. |
| Nardone et al., 2020| Increase brain blood flow, attenuate orthostatic symptoms and influence autonomic reflexes | Canada            | 10                     | Neck compression collar | Randomized crossover design (within participants) | Repeated measures | VOSS                         | The use of the collar reduced the orthostatic symptom score of participants during upright tilt, increased the HR response to deep breathing, and decreased resting ventilation. |
The findings of this review showed some self-reported psychosocial and disability factors significantly associated with symptom burden in POTS, which might indicate areas to target in intervention. Among these factors, self-reported physical functioning had the strongest association with symptom burden. Depression (measured with the BDI and PHQ8) was the strongest emotional factor associated with symptom burden in POTS. Depression may occur in response to the impact of POTS exceeding the individual’s ability to alleviate this impact (Beck and Bredemeier, 2016), although a small study in the wider literature suggests there may also be a biological link to depression in people with POTS; Volume reductions in the left insula observed in POTS correlated with, and predicted, depression (and trait anxiety) scores (Umeda et al., 2015). Studies not eligible for inclusion in the review found that nearly half of one POTS cohort were at risk of suicide (Pederson and Brook, 2017) and age, sleep disturbance and having POTS were reported as significant predictors of suicidal ideation (Pederson and Blettner, 2017). This suggests addressing sleep problems could reduce symptom burden as well as improve mood in people with POTS. The complex relationship between symptom burden and depression in people with POTS is an important one which merits further investigation.

Conclusions regarding the evidence for anxiety and cognitive stress were more uncertain. Seated prolonged cognitive stress testing was associated with both a reduced cerebral blood flow velocity in POTS, and an increase in orthostatic symptom burden after completion of the test (Wells et al., 2020). However, as cerebral blood flow reductions, orthostatic symptoms and cognitive impairment can occur during and after upright as well as seated positions in people with POTS (Anderson et al., 2014; Lewis et al., 2013; McDonald et al., 2014; Ross et al., 2013; Raj et al., 2018; Arnold et al., 2015; Campen et al., 2020; van Campen et al., 2020a; van Campen et al., 2021; van Campen et al., 2020b), the underlying mechanisms remain somewhat unclear and further studies to delineate these mechanisms are needed (Wells et al., 2020). Anxiety levels in POTS patients were reported as elevated in one study (Fisher et al., 2020), but most found there was only a small, mostly insignificant correlation between anxiety and symptom burden as measured with the GAD-7, State-Trait Anxiety Inventory, and ASI. Of note, previous studies have shown that although POTS patients scored high on a range of anxiety measures; when comparing anxiety questionnaire scores that included autonomic items (such as State-Trait Anxiety Inventory) with those that excluded autonomic items (such as ASI), POTS patients did not report symptoms of anxiety disorders more often than control groups (Raj et al., 2018; Wagner et al., 2012). This emphasizes the importance of careful questionnaire selection in the assessment of anxiety in POTS and its relationship with symptom burden to ensure that anxiety tools focus on psychological symptoms (such as fear, feeling nervous/depicted) rather than somatic symptoms of anxiety (such as tachypnoea, dizziness or palpitations) to minimize overlap with physical POTS symptoms (Raj et al., 2018; Khurana, 2006). None of the reviewed studies measured more illness-specific anxiety in relation to symptom burden and this should be a priority in future POTS research. Catastrophizing was shown to have a small but significant relationship with symptom burden in POTS, and modifying these cognitions and perceptions could be a potential target for intervention (Fisher et al., 2020; Masuki et al., 2007).

Finally, this review highlighted the paucity of studies exploring social factors in relation to POTS symptom burden, signifying a gap in the literature. Intervening is increasingly seen from a complex systems perspective, where the focus is on modifying cognitive, behavioral, and emotional responses to symptoms as well as the broader social and ecological determinants of these (Aunger and Curtis, 2016; Dolan et al., 2012; Hollands et al., 2017; Araujo-Saores et al., 2019). Further studies would benefit from investigating social factors/support in POTS more rigorously to determine whether this is a potentially important variable to target in treatment.

4.2. Interventional studies

This review identified and synthesized 12 randomized experimental and intervention studies. 11 of these were short-term experimental rather than treatment trials, designed to influence symptom burden in people with POTS over a matter of minutes or hours. Compression garments, desmopressin, propranolol, bisoprolol, and pyridostigmine showed promise in reducing acute symptom burden. Compression garments (n = 3; neck, abdominal and lower body) yielded positive preliminary results in reducing symptom burden in proof-of-concept studies with endpoints in minutes-hours (5 min-2 h). Propranolol, pyridostigmine, and desmopressin also showed short term reductions in a matter of hours (2-4) in symptom reports in the laboratory. However, only one 2 × 2 factorial design clinical trial assessed symptoms over three months, where a combination of propranolol, bisoprolol, and pyridostigmine showed positive results across treatment groups in reducing symptom burden (Moon et al., 2018). Some further trials (Taub et al., 2021; Batab and Baughan, 2022; Roeink et al., 2017) were not eligible for inclusion due to symptom burden not being measured, re-emphasizing the urgent need for more standardized reporting of symptom response in POTS (Wells et al., 2018). Most noteworthy is the absence of exercise and reconditioning trials in this review, which is currently considered a first line treatment (Kichloo et al., 2021), with evidence for effects on physiology (such as improved standing heart rate and blood volume) and quality of life (George et al., 2016; Fu et al., 2011; Armstrong et al., 2017; Gibbons and Freeman, 2010; Gibbons et al., 2021). The search criteria for this review did not return any of the existing studies in this domain due to symptom burden not being measured, or other inclusion criteria not being met, which led to the absence of this key POTS treatment intervention in the review. Quality of life and other patient-reported measures of disease burden as seen in recent studies of POTS therapies could potentially be considered as candidate standardized outcomes of interest in POTS, however review of these measures would be beyond the scope of the current review.

In the absence of longer-term randomized controlled trial data for POTS, Kichloo et al. (2021) synthesized current evidence on interventions for the treatment of POTS and attempted to classify treatments as first-, second-, and third-line therapies based on effectiveness and side-effect profile (Kichloo et al., 2021). There are no fully powered effectiveness studies of any of these interventions so to date this advice is largely speculative, and RCTs of the potentially promising medications are desperately needed.

There was a notable lack of psychological or behavioral interventions aimed at reducing symptom burden. There is extensive evidence in support of CBT, Acceptance and Commitment Therapy (ACT) and Autogenic Training for improving sleep, pain, fatigue, headache, immune function, heart rate variability and distress in other long-term conditions (Raj et al., 2018; Graham et al., 2016; Karekla et al., 2019; Bernard et al., 2018; Smith et al., 2014; Zabihiyeganah et al., 2019; Bowden et al., 2012; Miu et al., 2012; Ter Kuile et al., 1994; Seo and Kim, 2019; Setter and Kupper, 2002; Stojanovich and Marisavljevich, 2008; Chalder et al., 2021; McGregor et al., 2004; Duljic et al., 2012; Moss-Morris et al., 2012; Sweeney et al., 2021; Swai et al., 2019). Based on the findings reviewed in the observational studies section, it is likely that some of these therapies can be tailored (Skivington et al., 2021) to provide benefit in reducing symptom burden in people with POTS, either on their own or adjuvant to biomedical approaches, while ensuring that the burden of treatment does not exceed the individual’s ability to cope with this (Sav et al., 2015).
4.3. Limitations

There are several limitations that warrant consideration. Firstly, across the studies, symptom burden measures varied widely, and included questionnaires were primarily designed for autonomic disorders and orthostatic hypotension/intolerance, even though the presence of orthostatic hypotension rules out POTS in diagnostic criteria. The absence of a universally agreed POTS specific symptom questionnaire has led to the application of a wide range of symptom measures in POTS, making standardization and cross-study generalizations difficult. Second, the intentionally broad inclusion criteria resulted in high heterogeneity of study designs across the limited number of studies included. Considering this, findings from this review should be interpreted cautiously. Third, the short duration of most trials provided limited predictive value for long-term use of the interventions. Fourth, most of the study samples had limited participant numbers. Fifth, many studies did not base their rationale for selecting psychosocial variables on psychological theory, which made it difficult to derive a coherent picture of how constructs may be theoretically related, and which are most important, or to empirically test hypotheses. It is also important to note that psychological variables such as anxiety and depression were patient reported and not diagnoses. Sixth, many of the studies were cross-sectional, so the direction of the relationships among factors is unclear and causality cannot be assumed. Seventh, although an attempt was made to categorize the strength of correlation effect sizes, most studies did not base their rationale for selecting psychosocial variables on psychological theory, and may not reflect the true complexities of assessing their clinical significance. Finally, the observational studies’ quality was evaluated using a modified version of a reliable tool. While tailoring the quality assessment tool is recommended in the Cochrane handbook (Higgins et al., 2011), the modified tool did not undergo its own validation.

5. Conclusion

This is the first systematic review to explore symptom burden in POTS. Symptom burden was higher in POTS than many other LTCs, with orthostatic symptoms being the most discriminatory. Psychosocial factors, including depression, physical functioning, and catastrophizing were significantly associated with symptom burden, but neuroticism and somatization were not. This highlights some possible factors to address in future interventions. However, there are a number of other potentially relevant psychosocial factors which have not been explored in relation to symptom burden in POTS. Future work in this area should be grounded in a clearer theory base, allowing for the possible development of a more coherent theory-based intervention that then needs to be tested in an RCT. In terms of biological studies, preliminary evidence shows promise in addressing this, pending further validation (Spahic et al., 2011), the modified tool did not undergo its own validation.

CRediT authorship contribution statement

Iris Knoop: draft protocol, develop search strategy, obtain full-text reports, carry out and interpret findings and draft final review. Federica Picariello: draft protocol, develop search strategy, interpret analyses and draft final review; Nicholas Gall: draft protocol, develop search strategy, interpret analyses, editing of all drafts and final review; Claudia Chisari: interpret analyses and draft final review; Emma Jenkinson: obtain full-text reports, carry out and interpret analyses; All authors commented, discussed the results and commented on the manuscript.

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Declaration of competing interest

There are no conflicts of interests.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autneu.2022.103052.

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