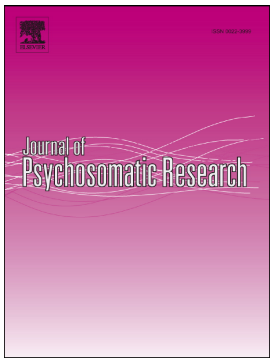

Respiratory dysfunction in persistent somatic symptoms: A systematic review of observational studies

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Respiratory dysfunction in persistent somatic symptoms: A systematic review of observational studies.

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Abstract

Objective: This systematic review aims to analyze the existing literature investigating respiratory functioning in people with Persistent Somatic Symptoms (PSS) compared to healthy controls, to identify patterns of respiratory disturbances by symptom or syndrome, and describe any respiratory outcomes consistent across diagnoses.

Methods: A systematic review following PRISMA guidelines was conducted. A comprehensive search was carried out across five databases (PubMed (NCBI), PsycArticles (Ovid), Web of Science (Core Collection), Embase, and Scopus) using two customised search strings for persistent somatic symptoms and objective respiratory parameters. Title/abstract screening and data extraction were carried out independently by two reviewers. The modified Newcastle-Ottawa Scale was used for quality assessment of the studies. Studies investigating baseline respiratory functioning in adult patients with PSS compared to healthy controls, using at least one objective respiratory were included.

Results: 18 studies met the inclusion criteria for the review, with a pooled sample size of n=3,245. Chronic pain conditions were found to be the most prevalent subset of diagnoses of interest, comprising six of the studies. 10 studies included measures of lung capacity, flow and/or volume, nine studies reported measures of ventilation, and four studies investigated respiratory muscle functioning. 13 of the included studies reported significant differences in at least one objective respiratory measure between groups (at rest). Scores on self-reported measures of dysnpea and breathlessness were higher in patients compared to healthy controls, while objective respiratory outcomes were varied.

Conclusion: The current systematic review is consistent with previous literature suggesting more pronounced experiences of breathlessness in patients with PSS, and significant disparities between reported dyspnea and objective respiratory outcomes. Research investigating the uncoupling between subjective and objective respiratory outcomes is needed to understand the mechanisms behind breathing disturbances in PSS.

Keywords:
Persistent somatic symptoms, Respiration, Psychophysiology, Stress, Hyperventilation

Introduction

Persistent Somatic Symptoms (PSS) is a term used to describe a broad range of distressing somatic complaints that cannot be wholly explained by underlying organic disease or pathology [1]. PSS affect approximately 10% of the general population, with a 12-month prevalence rate of an estimated 6.3% in Europe [2]. In adult clinical settings, 20-50% of patients presenting to primary care and up to 50% of new referrals to secondary care experience PSS [3]. PSS can be seen in most medical specialities and are often associated with functional impairment, comorbid mental health conditions, and reduced quality of life [4]. In addition to the chronic disability and distress associated with these symptoms on an individual level, there are also high associated costs for social and healthcare services worldwide [4, 5]. Although effective diagnostic and treatment options for PSS exist [6], there is a myriad of barriers that prevents patients from accessing suitable care, and subsequently prolong illness [7]. Within recent years, there has been a push towards increasingly multidisciplinary options for diagnosing and treating PSS, departing from reductionist and dualistic disease-based models of medicine [8]. While patients with PSS can present with a range of heterogenous symptoms, current explanatory models emphasize the likelihood of common underlying mechanisms across different symptoms and syndromes, and thereafter the importance of trans-diagnostic treatment options [4]. Current understandings of the mechanisms underlying the generation and maintenance of PSS emphasize the interplay between biological, psychological, and social factors [9].

The autonomic nervous system (ANS) is essential for regulating physiological responses to stress. While dysregulation in stress physiology is thought to play a large part in the aetiology and maintenance of functional symptoms and disorders, the respiratory system has been widely overlooked in research. A review by Martínez-Martínez and colleagues in 2014 found that in 196 case-control studies investigating sympathetic nervous system performance in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis,

most studies utilised HRV analysis or sympathetic skin response to assess sympathetic function [10]. Respiratory variables in the included studies were only assessed in a few tilt table tests and were often secondary to measures of blood pressure and heart rate. Nevertheless, the respiratory system, as measured by respiratory rate, volume, and variability, is one of the most responsive physiological systems to both internal and external demands [11]. Reduced respiratory variability has been linked to chronic stress and poor ANS functioning [12] and individuals with reduced parasympathetic activity tend to demonstrate lower respiratory sinus arrhythmia (RSA) and decreased variability in both respiratory and heart rates (HRV) when compared to individuals with heightened parasympathetic activity [13]. Studies have indicated the significance of dysfunctional breathing in the context of predisposing, precipitating, and perpetuating factors in PSS [14–17], while breathing dysfunction has been observed clinically in patients with a range of functional disorders, including irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS), fibromyalgia, and functional neurological symptom disorder (FNSD) [17–21]. Abnormal breathing patterns, such as hyperventilation, cause changes in the function of the central nervous system (CNS) resulting in somatic experiences commonly seen in PSS (i.e., brain fog/ lightheadedness, dizziness, chest pain, palpitations, and breathing difficulties). This may suggest a bidirectional relationship between the biomechanical, biochemical, and psychophysiological aspects of dysfunctional breathing and PSS.

Although biomedical factors, such as dysregulation in the immune, endocrine, and autonomic nervous systems have been observed in patients with PSS [22], existing research indicates these biological and pathophysiological factors do not act alone in generating and perpetuating these symptoms [23]. Instead, a complex interplay between these factors and various cognitive-perceptual, emotional, behavioural, and social mechanisms may shape individuals' perceptions and experiences of their symptoms. This interplay may also account in part for discrepancies between measurable physiological outcomes and subjective experiences, in which sensations of dypnea and symptoms of breathlessness may be disproportionate to measurable changes [17]. This phenomenon may be especially prominent in domains related to respiration and breath perception, wherein the mere cognitive anticipation of breathlessness could elicit these sensations [24].

While a small number of systematic reviews have explored respiratory outcomes and interventions in single patient groups such as fibromyalgia and chronic pain syndromes [25–28], the current systematic review aims to build upon previous reviews by including studies

across diagnoses. The current systematic review will therefore analyse the available literature investigating respiratory functioning in PSS and related disorders in comparison to healthy controls, and describe syndrome or diagnosis-specific respiratory features, as well as trans-diagnostic respiratory patterns.

2. Methods and Materials

The current study is part of the innovative training network ETUDE (Encompassing Training in fUnctional Disorders across Europe; https://etude-itn.eu/), ultimately aiming to improve the understanding of mechanisms, diagnosis, treatment, and stigmatization of Functional Disorders [29]

2.1 Protocol and Pre-registration

The systematic review protocol was pre-registered on PROSPERO (ID: CRD42022354761) and the Open Science Framework (https://osf.io/tx38w). The 'Preferred Reporting Items for Systematic Review and Meta-Analysis' (PRISMA) checklist and protocol [30] were followed in this review.

2.2 Search

Five databases were searched for relevant studies: PubMed (NCBI), PsycArticles (Ovid), Web of Science (Core Collection), Embase, and Scopus on December 11th, 2022. There were no specified search dates, restrictions, or filters applied to the searches. Search alerts were created and monitored to identify any studies published after the initial search was conducted. A customised search strategy and terms were created for each database with the support of an expert research librarian, and pilot searches were conducted prior to the final search to finalise search terms and strategy. Reference lists of included studies were used to identify any further studies not identified during the initial search. Two sets of search terms were created (see supplemental materials):

1) Terms encompassing the main functional syndromes, disorders, and symptoms. The search term list was based on a recent and relevant systematic review [31]. Search terms for less commonly known functional disorders and symptoms (i.e., idiopathic environmental intolerance) in which respiratory functioning was known to be studied were also included, with the support of experts in the field.

2) Terms related to respiratory functioning, including specific respiratory measures and variables, developed with the help of experts in the field of respiratory research (EV and OVdB)

2.3 Eligibility Criteria

The PICOS (participants, intervention, comparison, outcome, and study design) framework was utilized in this systematic review to determine studies eligible for inclusion, and was as follows:

Participants: adults (18 years or above) with a diagnosis of, or suspected, functional symptom, syndrome, or disorder.

Comparison: healthy controls

Outcome: at least one objective respiratory measure/parameter

Study design: observational studies (case-control, cohort, cross-sectional)

Studies were excluded if they did not meet the above criteria, or met any of the points in the exclusion criteria below:

- Long-COVID/COVID-19 studies without focus on functional symptoms.
- Letters, editorials, book chapters (with no relevant study cited).
- Only self-report respiratory measure used.
- Studies investigating (only) lactulose breath test, hydrogen breath test, and/or methane breath test, with no other objective respiratory measure.
- Respiration measured during or after (only) tilt-up test.
- Respiration measured during or after (only) stress tests or maximal cardiopulmonary stress tests when respiratory functioning/mechanisms was not the primary focus of study.
- Respiration/ respiratory functioning not primary focus of study.

2.4 Study Selection

Title and abstract screening were conducted by SN and KFW based on the predefined inclusion and exclusion criteria above, on the Rayyan reference management software [32]. Full texts of eligible studies and studies in which there was uncertainty regarding eligibility were thereafter screened. Studies with conflicting eligibility decisions were discussed by SN and KFW, and there was no event in which there was further disagreement needing a third-

party to arbitrate. The inter-rater reliability, as measured by Cohen's Kappa coefficient, was calculated to be 0.73, signifying a substantial level of agreement between SN and KFW.

2.5 Data Extraction

Data extracted from the eligible studies (see table 1 included: author name, publication year, country of publication, symptom(s) or syndrome(s) investigated, condition in which respiratory outcomes were measured, respiratory function measures, additional measures, and the main results and conclusions drawn. Data was extracted independently by reviewers SN and KFW.

2.6 Quality Analysis

Included studies were assessed for risk of bias and quality using the Newcastle-Ottawa Scale (NOS) [33] for observational studies (see table 1). The modified NOS is a tool used to assess risk of bias in non-randomised observational studies based on an overall score given for patient selection, comparability, and outcome (for cohort and cross-sectional studies) or exposure (for case-control studies). Scoring for case-control studies and cross-sectional studies differed slightly, with three overall scores of 'Good' (6-8 for case-control studies; 7-9 for cross-sectional studies), 'Fair' (3-5 for case-control studies; 4-6 for cross-sectional studies), and 'Poor' (0-2 for case-control studies; 0-3 for cross-sectional studies).

2.7 Data Synthesis

Studies included in the review were synthesised narratively and included: sample size, study design, population of interest, respiratory measures used, additional environment/conditions, main findings, and additional measurements. Meta-analyses were not appropriate for the current systematic review due to the heterogeneity of the study populations and respiratory measures used.

3. Results

3.1 Search results

Database searches retrieved a total of 2509 articles. After the removal of duplicate articles (986) and screening of the remaining 1523 articles, 75 full-text articles were assessed for eligibility and 16 articles were determined to be appropriate for inclusion in the review [34–51]. Reference lists from the full-text articles screened for eligibility were checked, through which a further 2 eligible articles were identified (n=18).

Figure 1: The PRISMA 2020 search strategy flow diagram [30]

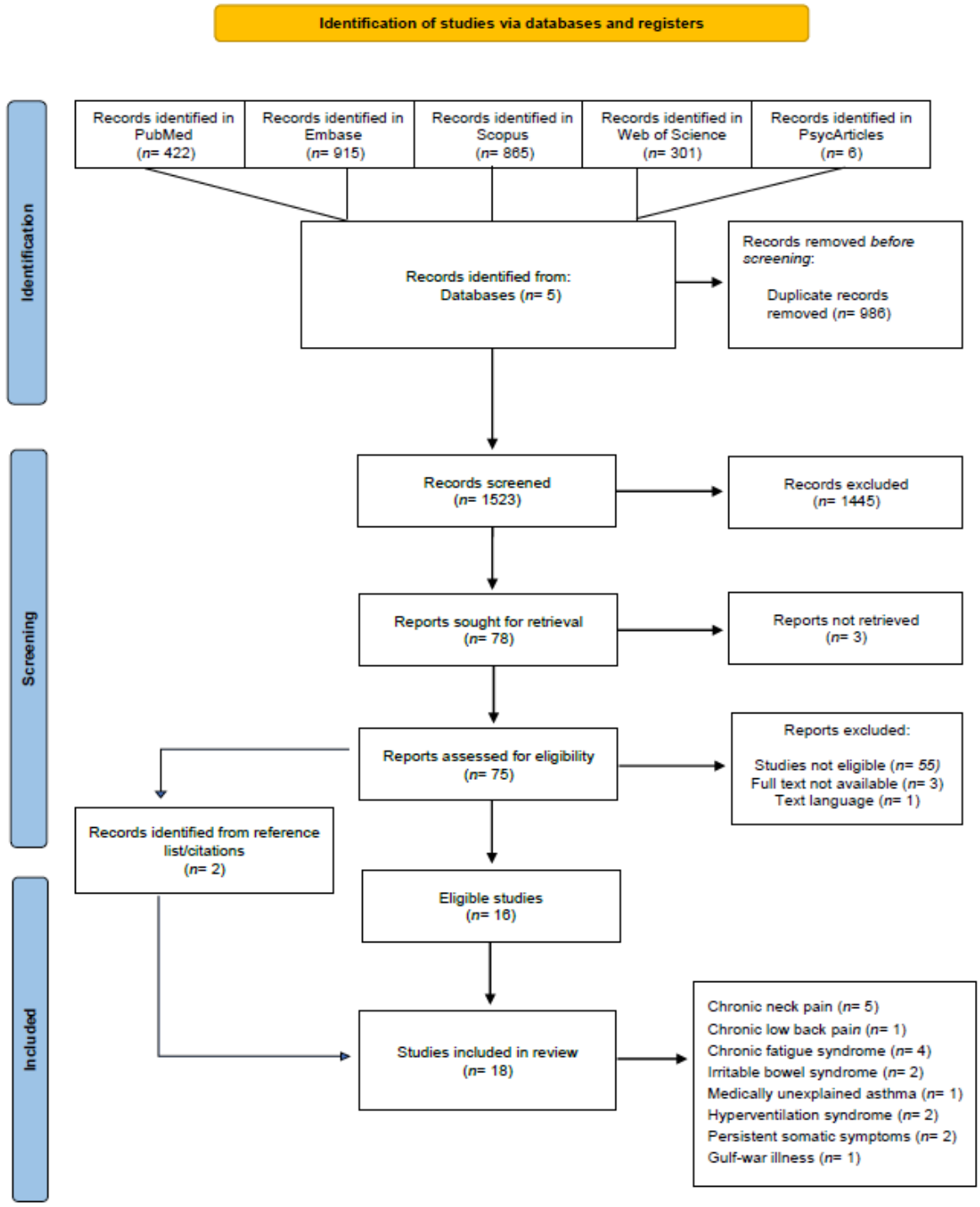

Table 1: Main data summarised from included studies.[1]

[1] **PetCO2**: End-Tidal Carbon Dioxide; **FetCO2**: Fractional End-Tidal Carbon Dioxide; **VC:** Vital Capacity; **IF**: Inspiratory Flow; **TI**: Inspiratory Time; **V1, Ti**: Mean Inspiratory Flow; **VE/VO2**: Ventilatory Equivalent for Oxygen; **VE/VCO2**: Ventilatory Equivalent for Carbon Dioxide; **FEV1**: Forced Expiratory Volume in 1 second; **PEF**: Peak Expiratory Flow; **FEF25-75%:** Forced Expiratory Flow between 25% and 75% of the FVC; **FEF25%/50%/75%**: Forced Expiratory Flow at 25%/50%/75% of the FVC; **R:** Airway Resistance; **MVV:** Maximum Voluntary Ventilation; **TLC**: Total Lung Capacity; **MIP** or **Pimax**: Maximal Inspiratory Pressure; **MEP** or **Pemax**: Maximal Expiratory Pressure

Study	Study aim/ primary outcome	Sample size	Patient group	Condition	Respiratory variable(s) measured	Main findings	Additional measures	Quality assessment (M-NOS)
Study	**Study design**	**Sample size**	**Patient group**	**Conditions**	**Respiratory measures**	**Main findings**	**Additional measures**	**Quality assessment**
Burton, 1993, UK [26]	Case-control	*n*=50 (20 patients, 30 healthy controls)	Recurrent functional symptoms	At rest, during the 20 breath test, during a 'think test'	PetCO2	80% of patients with two or more functional symptoms reported experiencing at least one of their symptoms during brief voluntary hyperventilation, and the remaining 20% of participants experienced non-specific symptoms which had occurred previously. While PCO2 did not significantly vary between patients and controls, 16/20 patients presented with	Score of breathlessness	Selection: 3 Comparability: 2 Exposure: 1 Quality score: Good

						possible psychogenic dyspnea.		
Laviettes et al. 1996, USA [27]	Case-control	*n*=19 (10 patients, 9 healthy controls)	Chronic fatigue syndrome	At rest, during psychological stressors: 1) Computational task, 2) Socioevaluative or speech task	VC, FEV1,IF, PetCO2, heart rate, tidal volume, breathing frequency, inspiratory time (TI), mean inspiratory flow (V1, Ti).	Patients with CFS were found to be hypocapnic as compared to healthy controls in all conditions. CFS patients presented with breathing patterns similar to those of patients with hyperventilation syndrome (hypocapnia during quiet breathing but show normal response to hypereapnia).	Modified Borg scale-perception of degree of dyspnea	Selection: 2 Comparability: 1 Exposure: 2 Quality score: Fair
Ringsberg & Akerlind, 1999, Sweden [28]	Case-control	*n*=30 (10 medically unexplained asthma patients, 10 asthm	Medically unexplained asthma	At rest, during the hyperventilation provocation test, during a mental stress test, and	PetCO2, respiratory rate	Patients with medically unexplained symptoms of asthma do not seem to experience persistent	Nijmegen questionnaire	Selection: 2 Comparability: 2 Exposure: 1 Quality score: Fair

		a patients, 10 healthy control)		the Word Color Conflict Test (WCCT)		chronic hyperventilation at rest, however present with slower recovery rate of PetCO2 following hyperventilation tests and stress tests. Patients presented with symptoms commonly associated with hypervenilation compared to healthy participants and patients with asthma. Mental stress was indicated to be a trigger for symptoms in patient with medicially unexplained asthma.		
Han et al., 2000, Belgium [30]	Cross-sectional	*n*=978 (819 patients, 159 healthy controls)	Somatoform disorders	At rest, during the hyperventilation provocation test	FetCO2	Symptoms of the central and peripheral nervous system during the hyperventilation provocation test result in spontaneou	Nijmegen questionnaire, STAI-trait	Selection: 4 Comparability: 2 Outcome: 1 Quality score: Good

						sly deeper ventilation, then enhancing more intense hyperventilation. Functional respiratory symptoms were found to lead to hypocapnia at rest and to a delayed recovery of etCO2 following HVPT		
Malmberg, Tamminen & Sovijarvi, 2000, Finland [29]	Cross-sectional	*n*=29 (16 patients, 13 healthy controls)	Hyperventilation syndrome	At rest, during orthostatic tolerance tests	FetCO2 and changes in ventilatory equivalents for oxygen (VE/VO2) and for CO2 (VE/VCO2)	Patients with HVS show an accenuated increase in ventilation in response to a change in body position from supine to standing, in comparison to healthy subjects. There was no difference in respiratory measures between groups at rest.	Hyperventilation symptom levels (i.e. dizziness etc).	Selection: 2 Comparability: 2 Outcome:2 Quality score: Fair

Yazar et al., 2001, Turkey [31]	Cross-sectional	*n*=270 (133 patients, 137 healthy controls)	Irritable bowel syndrome	At rest	FEV1, FVC, FEV1/FVC,PEF, FEF25-75%, FEF25%, FEF50%, FEF75%	The prevalence of asthma and respiratory symptoms were more common in the IBS group than in controls. Airway limitation/obstruction (FEV1, PEFR, and maximal mid-expiratory flow rate) was significantly higher in patients compared to healthy controls.	Respiratory symptoms questionnaire	Selection: 3 Comparability: 2 Outcome: 2 Quality score: Good
Amra, Emami, & Golshan, 2006, India [32]	Cross-sectional	*n*=194 (97 patients, 97 healthy controls)	Irritable bowel syndrome	At rest, during frequencies of pressure oscillations (airway resistance)	FVC, FEV1, R (airway resistence)	Dormant airway resistance was found in patients with IBS not presenting with respiratory complaints. Patients with IBS presented with lower FEV1, FVC and mean flow rates than healthy controls, as well as evidence of subclinical levels of airway resistence.		Selection: 2 Comparability: 2 Outcome: 2 Quality score: Fair

Ravindran et al., 2009, USA [33]	Cross-sectional	*n*=264 (135 patients, 129 healthy controls)	CFS	At rest	MVV, FEV1, PEF, FVC	Sensory hypersensitivity without any airflow obstruction may be responsible for the subjective perception of dyspnea in CFS. No significant differences in spirometry measures were found between groups, however patient with CFS reported considerably more respiratory effort during spirometry and chest discomfort intensity. Borg scale scores were higher in patients than healthy controls.	Dyspnea-12, Borg scale, STAI-Y1 and GAD-7	Selection: 3 Comparability: 2 Outcome: 3 Quality score: Good
Bazin et al., 2010, UK [34]	Case-control	*n*=10 (5 patients, 5 healthy controls)	Hyperventilation syndrome	At rest, during incremental CO2 inhalation	TLC, MVV, PetCO2	Patients with HVS may be more sensitive to changes in CO2 than controls. A borderline significant increase in PetCO2 at the limit of tolerance in	Visual Analogue Scale, Dyspnea-12	Selection: 2 Comparability: 2 Exposure: 1 Quality score: Fair

						HVS patient were found during free breathing.		
Ravindran et al., 2012, USA [35]	Cross-sectional	*n*=713 (257 patients, 456 healthy control)	Chronic fatigue syndrome	At rest	MVV, TLC	Sensory hypersensitivity without airflow limitation contributed to dyspnea in CFS. Correlates of dyspnea in controls were distinct from CFS suggesting different mechanisms.	MRC Chronic Dyspnea Scale, Borg Breathlessness Score,UCSD Shortness of Breath Questionnaire, Chronic Multiple Symptom Illness questionnaire, McGill short form Pain Score, Generalized Anxiety Diagnosis-7, Trait Anxiety Inventory.	Selection: 3 Comparability: 2 Outcome: 3 Quality score: Good
Dimitriadis, Kapreli, Strimpakos, & Oldham, 2013,	Cross-sectional	*n*=90 (45 patients, 45 healthy controls)	Chronic neck pain	At rest and during range of motion tests	MIP, MEP, Maximal voluntary isometric strength of neck flexors and extensors	Patients with chronic neck pain present with weakness of their respiratory muscles, resulting	Visual Analogue Scales, Neck Disability Index, Baecke Questionnaire, Hospital Anxiety	Selection: 3 Comparability: 2 Outcome: 2 Quality score: Good

Greece [36]					(manually measured)	from not only impaired global and local muscle systems, but also psychological factors such as pain catastrophizing and kinesiophobia.	and Depression Scale, Tampa Scale for Kinesiophobia, Pain Catastrophizing Scale	
Dimitriadis, Kapreli, Strimpakos, & Oldham, 2014, Greece [37]	Cross-sectional	*n*=90 (45 patients, 45 healthy controls)	Chronic neck pain	At rest	VC, FVC, MVV	Respiratory disturbances attributed to more restrictive rather than obstructive patterns. Respiratory dysfunction was associated mainly with cervical muscle dysfunction, pain intensity, and kinesiophobia. Spirometric outcomes in CNP patients presented similar patterns to pulmonary resrictive disorder, particularly in regards to neuromuscular weakness.	Hospital Anxiety and Depression Scale, Tampa Scale for Kinesiophobia, Pain Catastrophizing Scale, Visual Analog Scale, Neck Disability Index, Baecke Questionnaire of Habitual Physical Activity	Selection: 3 Comparability: 2 Outcome: 2 Quality score: Good

Wirth et al., 2014, Switzerland [38]	Case-control	*n*=38 (19 patients, 19 healthy controls)	Chronic neck pain	At rest and during neck range of motion tests	FVC, VC, PEF, FEV1, FVC FEF25%/50%/75%, MVV, Pimax, Pemax, thoracic spine mobility, chest expansion, neck function	In contrast to previous studies, respiratory function was only somewhat reduced in the patient group. Mechanical changes of the respiratory muscles may lead to chronic respiratory weakness due to plastic changes. Kinesiophobia was found to lead to poorer performance on pulmonary funtioning tests and reduced respiratory strength.	Baecke questionnaire	Selection: 2 Comparability: 2 Exposure: 1 Quality score: Fair
López-de-Uralde-Villanueva, Sollano-Vallez & Del Corral, 2018, Spain [39]	Cross-sectional	*n*=75 (44 patients, 31 healthy controls)	Chronic non-specific neck pain	At rest	Cervical Range of Motion test, MIP, MEP, FVC, FEV1, FEV1/FVC, PEF.	Patients with moderate-severe disability showed cervical motor function impairment and respiratory muscle weakness, compared to patients with mild disability and healthy controls.	Hospital Anxiety and Depression Scale, Pain Catastrophizing Scale, Neck Disibility Index	Selection: 3 Comparability: 2 Outcome: 2 Quality score: Good

Lindheimer et al., 2019, USA [40]	Cross-sectional	*n*=34 (20 patients, 14 healthy controls)	Gulf war illness	At rest and during cardiopulmonary exercise testing	MVV, tidal volume, respiratory frequency, VO2, VCO2, PetCO2, FEV1, FVC	Patients with GWI showed an excessive increase in tidal volume and respiratory frequency in response to exercise as a ventilatory strategy that is inefficient and contributes to poor performance and exertional symptoms. Ventilatory patterns among veterans with GWI can be characterised by an attenuated fR response to maximal exercise. There was no difference in respiratory functioning between groups at rest.	ECG, blood pressure, Kansas GWI Scale, Fatigue Severity Score	Selection: 2 Comparability: 1 Outcome: 2 Quality score: Fair
Yoon, 2019, South Korea [41]	Case-control	*n*=30 (15 patients, 15 healthy controls)	Chronic low back pain	At rest	EtCO2, RQ	Patients with CLBP had significantly lower EtCO2 at rest and shorter breathing hold time (BHT) than	Hi-Lo assessment, Nijmegen questionnaire, EMG, Tampa Scale for	Selection: 2 Comparability: 1 Exposure: 2 Quality score: Fair

						healthy controls. Patients with CLBP also exhibited significantly greater kinestiphobia, and less flexion relaxation phenomenon than healthy controls.	Kinesiophobia	
Awadallah et al., 2021, Egypt [42]	Prospective case-control	*n*=150 (75 patients, 75 healthy controls)	Chronic neck pain	At rest	Cervical active range of motion, FVC, FEV1, FEV1/FVC, FEF25%–75%, PEFR	Patients with chronic neck pain had significantly decreased pulmonary function parameters (FVC, FEV1, FEF 25–75, and PEFR) compared with age- and sex-matched healthy controls. This may be attributable to weakness in respiratory mucles, changes in thoracic cage mechanics, and hyperventilation secondary to pain.	Neck Disability Index, Visual Analog Scale.	Selection: 3 Comparability: 2 Exposure: 1 Quality score: Good

Ramakers et al., 2022, Belgium [43]	Cross-sectional	*n*= 181 (151 patients; 36 patients with FM and/or CFS, 36 patients with panic disorder, 79 patients with stress-related disorders; 30 healthy controls).	Chronic fatigue syndrome and/or Fibromyalgia	At rest, mild respiratory challenge	PetCO2	Patients with more chronic and severe functional syndromes such as CFS and FM present a less active fight-flight response. Lower levels of PetCO2 were found following a mild respiratory challenge in patients with panic disorder and stress-related syndromes compared to healthy controls, but not in patients with CFS and FM.	Additional measures used, but not used in analyses or discussed in the paper.	Selection: 3 Comparability: 2 Outcome: 2 Quality score: Good

3.2 Study characteristics

3.2.1 General

The publication year of studies included in the review ranged from 1993 to 2022. Four studies were conducted within the same research groups: Ravindran et al., 2009 and Ravindran et al., 2012 [41, 43], and Dimitriadis et al., 2003 and Dimitriadis et al., 2014[44, 45]. Study sample size ranged from *n*=10 [42] to *n*= 978 [38, 42], and the pooled sample size was *n* =3,245.

3.2.2 Patient populations

The patient groups in the studies included in this review comprised of chronic neck pain (CNP; 5/18)[44–47, 50], chronic low back pain (CLBP; 1/18) [49], chronic fatigue syndrome (CFS; 4/18) [35, 41, 43, 51], irritable bowel syndrome (IBS; 2/18) [39, 40], medically unexplained asthma (MUA; 1/18) [36], hyperventilation syndrome (HVS; 2/18) [37, 42],

persistent somatic symptoms (not otherwise specified; 2/18) [34, 38], and gulf war illness (GWI; 1/18) [48].

Notably, studies in which chronic pain was the primary symptom [45–47, 49, 50] accounted for the largest subset of patient groups in the review. Studies investigating respiratory outcomes in patients with syndromes characterised by primary respiratory symptoms (i.e., MUA and HVS) only accounted for three of the 18 included studies [36, 37, 42]

3.2.3 Additional testing conditions

All included studies measured baseline levels of respiration at rest as necessitated by the inclusion criteria for the systematic review, however nine studies included a range of additional testing conditions. Three studies used the hyperventilation provocation test (HVPT) to induce voluntary hyperventilation and thereafter hypocapnia [34, 36, 38]. Ramakers and colleagues also conducted the HVPT with participants. However, because participants with acute hypocapnia (<30 mmHg) [52] during rest were excluded from the test and participants could voluntarily withdraw from the hyperventilation task, measures during the HVPT were not analysed in this study due to an unrepresentative sample. This study did, however, include a mild respiratory challenge (five consecutive sighs), with respiratory outcomes measured at baseline, during the respiratory challenge, and during recovery [51]. One study examined ventilatory patterns during cardiopulmonary exercise testing [48], and another during incremental CO_2 inhalation [42]. Three studies investigated respiration during psychological stress tests, including computational and socio-evaluative tasks [34–36]. Respiratory functioning during an orthostatic tolerance test (in response to standing) was measured in one study [37].

3.3 Objective respiratory measures and outcomes

Studies included a range of respiratory measures varying from biomechanical properties of lung function such as flow, volume, capacity, airway resistance, and cervical muscle strength, to biochemical measures including ventilation.

3.3.1 Lung capacity, flow, and volume

10 studies included measurements of spirometry [37, 39–41, 43, 45–48, 50]. Of these studies, only two studies did not find any significant differences in spirometry measures between patients and healthy controls [37, 46]. Significantly lower measures of lung capacity in patients compared to healthy controls were reported in six studies [39–41, 45, 47, 50]. Respiratory airflow (FEF, PEF, MEF50%) was significantly lower in patients in three studies [39, 43, 50], and measures of lung volume (FVC, VC, VT) were significantly reduced in four studies [40, 45, 48, 50].

3.3.2 Ventilation

Nine studies measured ventilation in patients[2]. *$FetCO_2$* was measured in two studies [37, 38]. Han and colleagues found significantly lower levels of $FetCO_2$ in patients with somatoform disorders at rest, and a delayed recovery of $FetCO_2$ following HVPT. Patients with respiratory symptoms were characterised by low $FetCO_2$ following HVPT whereas patients with dizziness, fainting, and or/ paresthesias exhibited higher $FetCO_2$ following HVPT [38]. Malmberg and colleagues found no difference between groups in $FetCO_2$ at rest, but reported significantly lower $FetCO_2$ in response to standing (orthostatic tolerance test) in patients with HVS [37, 38].

$EtCO_2$ (or $PetCO_2$) was measured in seven studies [34, 35, 42, 48, 49, 51]. Significant differences in $etCO_2$ levels between patient groups and healthy controls were found in three studies. Burton did not find any differences in $etCO_2$ between patients with recurrent functional symptoms and HC, however 80% of patients experienced >2 functional symptoms and 'excessive breathlessness' during the HVPT [34]. Patients with HVS in a study by Bazin and colleagues exhibited an increase in $etCO_2$ at the limit of CO_2 tolerance during free breathing, but not during a fixed breathing pattern [42]. Lavietes and colleagues reported significantly lower $etCO_2$ in CFS patients compared to healthy controls both at rest and during computational and social-evaluative tasks [35]. Significantly lower levels of PCO_2 were reported in patients with medically unexplained asthma, with longer periods of recovery following the HVPT [36]. Lindheimer et al. did not find any differences between ventilatory outcomes in patients with GWI compared to healthy controls at rest, but GWI patients did display a unique ventilatory pattern during exercise, characterised by greater depth (VT) and reduced breathing frequency [48]. Yoon and colleagues reported significantly lower levels of $etCO_2$ in patients with CLBP compared to healthy controls at rest [49]. $EtCO_2$ levels at rest, during a mild respiratory challenge, and in the proceeding recovery phase did not vary in a study comparing patients with FM and/or CFS and healthy controls [51].

3.3.3 Respiratory muscle functioning

Four studies investigating chronic neck pain measured respiratory muscle functioning manually through range of motion (ROM) tests [44, 46, 47, 50]. Significant reduction in cervical motor range and muscle strength in patients with chronic neck pain was found in all four studies and respiratory outcomes on additional objective respiratory measures were

[2] *$FetCO_2$, $etCO_2$, and $PetCO_2$* are measures of the concentration of CO_2 at the end of the breath cycle. *$FetCO_2$* refers to the fractional concentration (percentage) of carbon dioxide at the end of expiration. *$EtCO_2$* (maximum concentration of CO_2) and *$PetCO_2$* (partial pressure of CO_2) are often used interchangeably and represent the concentration of carbon dioxide at the end of expiration.

found to be associated with levels of pain intensity, kinesiophobia, and cervical muscle dysfunction.

3.4 Additional measures

3.4.1 Self-report breathing measures

Three studies [36, 38, 49] included the Nijmegen questionnaire (NQ) [53], a self-report measure indicating the presence of hyperventilation syndrome and found higher scores on the NQ in patients with medically unexplained asthma and medically unexplained symptoms (respectively) than healthy controls. Interestingly, Han et al., 2000 and Yoon et al., 2019 found that the presence of respiratory symptoms was not significantly related to levels of $etCO_2$ [38, 49]. In contrast, Ringsberg and colleagues found significantly higher NQ scores in patients with medically unexplained asthma compared to patients with asthma and healthy controls[36]. Self-report scores of dyspnea were found to be higher in all four studies investigating breathlessness [35, 41–43], on measures including a modified Borg scale (a 0-4 ordinal dyspnea scale), the Dyspnea-12 [54], and the Medical Research Council chronic dyspnea scale (MRC) [55].

3.4.2 Pain measures

Five studies measured various aspects of pain. Higher pain severity and severity of disability in patients with chronic pain conditions was related to worse respiratory outcomes [43, 50]. Kinesiophobia and pain catastrophizing were found to play a part in restricting respiratory manoeuvres and was a predictor of poor MIP/MEP [44, 45, 47, 49].

3.4.3 Psychological measures

Self-report psychological measures were used in several studies, however only analysed in five studies [43–45, 47]. Measures of symptoms of depression and anxiety included the HADS [56], BDI [57], CES-D [58], GAD-7 [59], and STAI-YI/ STAI-Trait [60]. While all five studies found higher scores in depression and anxiety in respective patient groups, only one study investigated the possible mediating or moderating relationships between PSS, psychometric components, and respiratory outcomes, however found no significant interactions [43].

3.5 Quality assessment

Quality assessment for the included studies was established based on the NOS for case-control studies [33]. Ten studies were categorized as ‘good quality’, and eight studies were determined to be ‘fair quality’ (see table 1 and supplementary material).

4. Discussion

The studies included in the systematic review present evidence suggesting increased respiratory disturbances in patients with various functional disorders, as compared to healthy controls.

4.1 Psychophysiological respiratory factors in PSS

Studies including psychological stress tests, hyperventilation provocation tests, and incremental CO_2 inhalation conditions suggest that patients with PSS and FD have an increased stress-reactive physiological response, characterized by prolonged lower levels of $etCO_2$ and increased self-reported experiences of dyspnea and associated symptoms [34–36, 38, 42]. However, one study suggested patients with more chronic and severe FD may exhibit less respiratory sympathetic reactivity [51]. Psychophysiological factors have a pronounced influence on the development of dysregulated breathing and can affect both biomechanical and biochemical respiratory processes. Breathing is one of the few regulatory systems in our body that allows for both conscious and unconscious control, and is profoundly affected by both our external environments, and internal emotional and physiological states [61]. Acute and chronic stress can directly affect respiration, often leading to hyperventilation characterized by shallow and rapid breathing, which can occur sub-clinically or acute. This hyperventilation can subsequently result in hypocapnia and associated symptoms such as dizziness, tingling sensations, numbness, and heightened anxiety.

Stress can also impact respiration by triggering the activation of the sympathetic nervous system and the release of stress hormones like cortisol, which can contribute to additional respiratory changes. Breathing may be further impacted on a biomechanical level by psychophysiological factors such as negative affect, anxiety, and cognitive aspects of pain. Pain catastrophizing and the fear of exacerbation can result in adopting shallow breathing, muscle stiffness, and heightened levels of alertness [49]. These changes can heighten the likelihood of individuals avoiding deep breaths, refraining from exertion or movement, and assuming an inefficient posture for breathing which can result in limited lung capacity. Heightened perception and appraisal of breathlessness and dyspnea has also been reported in patients with PSS [62, 63] and may account for the more pronounced differences between physical parameters and sensory/symptom perception [64].

4.2 Biomechanical respiratory processes in PSS

Tests of respiratory muscle function measure the strength, efficiency, and endurance of muscles (such as the diaphragm and intercostal muscles) used for breathing.

The spirometry outcomes of the studies included in this review suggest that dysregulated respiratory patterns in flow (FEF, PEF, MEF50%), volume (FVC, VC, VT), and capacity (MVV, FEV1) may be present across PSS. Studies investigating biomechanical aspects of respiration in patients with PSS in this review found decreased respiratory functioning in patients with chronic pain conditions, and described more restrictive pattern linked to kinesiophobia and resulting muscle weakness. The results from these studies are in line with previous research indicating the presence of respiratory muscle deterioration and weakness in individuals with chronic pain [65]. Chronic pain has been associated with alterations in respiratory muscle strength and functioning, leading to dysregulated biochemical and biomechanical respiratory outcomes [26, 66]. One important feature related to pain is kinesiophobia, or the fear of movement, which has been linked to increased respiratory rate, shallow breathing patterns, and reduced oxygen saturation levels [67, 68]. Subsequent symptoms, including increased fatigue, decreased physical activity, dizziness, shortness of breath, and increased sensitivity to pain may further perpetuate the cycle of pain and fear of movement. While respiratory muscles themselves may not be intrinsic components of the ANS, the functioning of these muscles may interact bidirectionally with various factors associated with ANS-related mechanisms. Understanding the interplay between the ANS and biomechanical features of respiration may allow us to comprehend the broader physiological responses to stress, anxiety, or other emotional states.

Similarly, dysfunctional breathing and associated respiratory discomfort has been shown to result in anticipatory stress which may further compromise breathing to become part of a positive feedback loop in which dysfunctional breathing and associated symptoms reinforce each other [69, 70]. Future clinical research may explore interventions aimed at retraining diaphragmatic and accessory respiratory muscles, in addition to challenging kinesiophobia and resulting avoidance behaviours.

4.3 Biochemical respiratory processes in PSS

While only three studies identified reduced resting $etCO_2$ levels in patients [27, 30, 41], an additional six studies revealed unique $etCO_2$ patterns, such as extended recovery times during psychophysiological tests, distinguishing them from the observed trends in healthy controls.

Patterns of airway obstruction and hyperresponsiveness were observed in studies with disorders associated with inflammation [35, 39–41], consistent with previous research

outlining associations between asthma and gastrointestinal conditions, including functional gastrointestinal disorders such as IBS [10]. A systematic review and meta-analysis found the risk of having asthma to be considerably higher in IBS patients, and indicated possible shared underlying mechanisms including inflammation, immune system dysregulation, and influence of the gut microbiome [71]. Common biological mechanisms underlying PSS and respiratory symptoms may include inflammatory processes and dysregulation in the ANS and stress response systems. Biomarkers of systematic inflammation, such as interleukin-6 and C-reactive protein, have been associated with functional disorders such as CFS/ME and IBS [39, 72, 73], and have also been found to be linked to airway inflammation and hyperresponsiveness [39]. Shared biological features of PSS and respiratory dysfunction may also include lowered cardiac vagal activity and hypocortisolism [23, 74, 75]. However, further multidisciplinary research into the underlying mechanisms behind the shared features observed between respiratory diseases and PSS and why certain individuals with respiratory diseases develop PSS (and vice versa) necessitates further investigation.

4.4 Symptoms of hyperventilation in the absence of hypocapnia

The persistence of symptoms of hyperventilation in the absence of actual hyperventilation (measured by hypocapnia) seen in several of the included studies and in the previous literature, requires a few potential explanations. Experimental studies have demonstrated that repeated hyperventilation can lead to perceptual-cognitive processes playing a prominent role in symptom generation, resulting a decoupling of the symptoms of hyperventilation and measurable hyperventilation [76, 77]. Recent research has also suggested the presence of a less active respiratory fight-flight response in more severe and chronic functional syndromes [51]. This phenomenon may be explained through a predictive processing framework, in which the brain functions as an inference engine, perpetually formulating hypotheses about sensory input and adjusting them based on subsequent perceptual feedback [78]. Using the example of repeated hyperventilation, there may be an initial mismatch between what the brain predicts or expects and the ensuing (often distressing) sensory experiences (i.e., light-headedness, racing heartbeat, tingling sensations), creating a prediction error. With repeated exposure to hyperventilation, the brain may adapt by adjusting its predictions to minimize these errors by generating symptoms and possibly establishing dysfunctional breathing patterns as a learned behavioural mechanism perpetuated by the body. Over time, this learned response may contribute to the persistence of symptoms. While breathing interventions to date have shown promise in areas such as stress management and pain reduction [28], future

research may benefit from incorporating interventions that also challenge beliefs and perceptions about breathlessness.

5. Strengths and Limitations

The main strength of this review is the investigation of objective respiratory outcomes across PSS. To our knowledge there are very few systematic reviews that have compiled and analysed the available literature investigating breathing dysfunction in PSS [25], and the current review is the first to do this across functional symptoms, disorders, and syndromes. Strengths of this systematic review also include that it was conducted in accordance with PRISMA guidelines, that search terms were created with support from experts in the field, and that several pilot tests were conducted with a search expert.

There are also some limitations to this review that are important to note. Due to the heterogeneity between included studies of patient populations, and the different respiratory measures and outcomes utilized, meta-analyses were not conducted. The review only included observational studies with baseline respiratory measures, and therefore may have excluded informative experimental studies investigating respiratory disturbances in patients with PSS. It is also important to consider that while studies only using self-report measures of breathing were not included in the study, studies utilizing both subjective and objective measures were included.

6. Conclusion

Respiratory disturbances are seen clinically and in the literature in a range of PSS and functional disorders, although existing research focuses largely on respiratory biomechanical changes in patients with chronic pain conditions. While there is evidence of certain syndrome or disorder-specific breathing patterns and disturbances, we propose that dysregulated breathing may be a trans-diagnostic mechanism both involved in and influenced by predisposing, precipitating, and perpetuating factors underlying PSS and functional disorders. The current systematic review is consistent with previous literature suggesting more pronounced experiences of breathlessness in patients with PSS, and more significant disparities between reported dyspnea and objective respiratory outcomes. Future research exploring both subjective and objective aspects of respiration in patients with PSS, along with interventions targeting breathing mechanics and addressing beliefs or perceptions about breathlessness, may contribute significantly to improving patient outcomes.

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Competing interest declaration

The authors have no competing interests to report.

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(References for studies included in this systematic review have been marked with an asterisk)

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