Understanding the symptom experience in chronic conditions

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UNDERSTANDING THE SYMPTOM EXPERIENCE IN CHRONIC CONDITIONS

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There is no path to happiness,

happiness is the path.

[Buddha]

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Declaration of Authorship and Sources

This thesis contains no material that has been extracted in whole or in part from a thesis that I have submitted towards the award of any other degree or diploma in any other tertiary institution, except for the award of the joint PhD degree at my primary institution (i.e., University of Rome Tor Vergata, Italy).

No other person's work has been used without due acknowledgment in the main text of the thesis.

All research procedures reported in the thesis received the approval of the relevant Ethical Committee (where required).

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Abstract of the PhD thesis

Background: The World Health Organization defines chronic conditions as those having long duration, slow progression, and requiring some level of healthcare management across time. In 2019, on average, more than 30% of adults across *Organisation for Economic Co-operation and Development* countries had a chronic condition. Due to population aging, this number is projected to continuously increase and cause disability and premature death, making it an important global health concern. Chronically ill people are burdened by several symptoms, which often occur simultaneously. High symptom burden is associated with higher healthcare utilization and hospitalization rates, higher health-care costs, and lower quality of life. People with chronic conditions may improve their clinical outcomes, including symptoms, if they perform adequate self-care to maintain their health, monitor, and manage their symptoms. However, patients often find it difficult to perform self-care and, in these cases, caregivers could help. Moreover, accumulating evidence suggests that people with a chronic condition experience difficulties in perceiving their symptoms, which, in turn, is associated with distorted or exaggerated symptom burden. This might be related to illness-induced interoceptive impairments. Interoception refers to the processes through which the brain detects, elaborates, and responds to signals originating from within the body, including symptoms. In chronic conditions, some brain structures, such as the insular cortex, tend to be damaged and this leads to interoceptive alterations, which, in turn, results in symptom-processing deficits.

Objectives: This PhD project aimed to a) cluster patients based on their physical and psychological symptoms and predict symptom cluster membership based on variables other than symptoms; b) assess the influence of caregiver contribution to self-care on symptom burden and the mediating role of patient self-care; c) explore the role of interoception in the symptom experience of people with a chronic condition.

Methods: In the first study, we clustered 510 Italian patients with heart failure based on their symptoms. The cluster analysis was performed using two scores of the Hospital Anxiety-Depression

scale and two scores of the Heart-Failure Somatic Perception Scale. ANOVA and chi-square test were used to compare patients' characteristics among clusters. For the predictive analysis, we split the data into a training set and a test set and trained three classification models on the former to predict patients' symptom-cluster membership based on 11 clinical/sociodemographic variables. Permutation analysis investigated which variables best predicted cluster-membership. In the second study, we performed multigroup confirmatory factor analysis to test measurement invariance, and autoregressive longitudinal path analysis with contemporaneous mediation to test the study hypotheses. In the third study, we conducted a systematic review. We searched five databases and included all primary research published between 2013-2021 in which at least one dimension of interoception was measured. Any chronic condition and any symptom were included. Only the adult population was considered.

Results: In the first study we identified four clusters of HF patients based on the intensity and combination of psychological and physical symptoms: mixed distress (high psychological, low physical symptoms), high distress, low distress, moderate distress. NYHA-class and sleep quality were the most important variables in predicting symptom cluster membership. In the second study, we found that higher caregiver contribution to self-care maintenance was associated with higher patient self-care maintenance (β=0.280, $p<0.001$), which, in turn, was associated with lower symptom burden (β=-0.280, $p<0.001$). Patient self-care maintenance mediated the effect of caregiver contribution to self-care maintenance on symptom burden (β=-0.06, 95% BC bootstrapped CI: -0.13; -0.03). In the third study, we included 18 quantitative studies investigating the relationship between three interoceptive dimensions (i.e., accuracy, sensibility, awareness) and condition-specific symptoms in eight chronic conditions. We found that people with chronic conditions had lower interoceptive accuracy than healthy controls. Higher interoceptive sensibility was associated with lower symptom severity/frequency. Only one study explored interoceptive awareness.

Conclusion: This PhD project offers new insights into the science of symptoms experienced by adults with a chronic condition, emphasizes the underling the role of caregivers on symptom burden, and promotes further understanding of the role of interoceptive mechanisms in symptom perception. By doing so, this PhD project can better support clinicians and researchers in identifying tailored symptom-management strategies and in investigating the effect of clusters of symptoms on patient outcomes, even when direct access to symptoms-related data is absent.

Keywords: Symptoms; Chronic Conditions; Interoception; Self Care; Heart Failure; Caregivers.

CHAPTER 1: Introduction and Overview

Epidemiology of chronic conditions

The World Health Organization defines chronic conditions as those having a long duration, generally slow progression, and requiring some level of health care management across time.[1,2] Such a definition includes persistent communicable conditions (e.g., HIV), noncommunicable conditions (e.g., heart failure, diabetes), long-term mental disorders (e.g., schizophrenia), and ongoing physical/structural impairments (e.g., blindness, amputation).[2,3] In 2019, on average, more than 30% of adults across the 26 OECD (Organization for Economic Cooperation and Development) countries was affected by a chronic condition.[4] Common risk factors of chronic conditions include tobacco and alcohol consumption, physical inactivity, unhealthy diets, genetic predisposition, environmental exposures, and socioeconomic factors.[5] Due to the prevalence of such risk factors and the aging of the population, the incidence of chronic conditions around the world is continuously increasing and causing disability and premature death, making chronic illness an important global health concern.[4] Chronic conditions are a significant economic burden on healthcare systems and individuals worldwide. Over the period 2011-2030, non-communicable chronic conditions alone (e.g., cardiovascular diseases, cancers, chronic respiratory diseases, diabetes) will cost the global economy more than 30 trillion US $, representing 48% of global GDP (Gross Domestic Product) in 2010.[6]

Overall, studying chronic conditions is crucial for improving the understanding of the causes, consequences, and mechanisms of chronic conditions; to inform prevention plans and interventions to reduce the burden of the diseases; to identify effective strategies for managing symptoms and improving outcomes; to help identify and address health disparities; and to inform policy decisions and resource allocation.[5,7]

Symptom burden in chronic conditions

Chronically ill people are burdened by several physical symptoms that contribute to lowered quality of life[8-11], high hospitalization[12,13] and mortality rates.[8,14] In addition, patients with a chronic condition often experience psychological symptoms, such as anxiety and depression,[15] that can further intensify physical symptoms.[16] It is extremely important to monitor and manage symptoms so that illness exacerbations are prevented and/or addressed in a timely fashion.

Symptoms are subjective physical or mental experiences, appraised and defined by the patient, and reflective of an altered health state or change therein.[17] Many theories aim to describe the symptom experience and processing of symptoms, such as the Theory of Unpleasant Symptoms [18], the Dynamic Symptoms Model [19], the Model of Pathways to Treatment [20], the Illness Action Model [21], the Symptoms Experience in Time Model [22], the Situational Adaption Model [23], Self-Regulation Theory [24], the Symptom Interpretation Model [25], the Cognitive Perceptual Model of Symptom Perception [26], Kolk's Symptom Perception Model [27], and the Middle-Range Theory of Self-Care of Chronic Illness integrated with symptoms[17]. All these theories identify common steps consisting of detecting, interpreting, and responding to bodily changes (i.e., symptoms).

Detection of a symptom may indicate that a normal sensation is different in its severity and/or frequency so that the patient identifies it as a bodily change (i.e., a symptom).[20,28] As symptoms are detected, they can be interpreted. Symptom interpretation refers to the process of characterizing a bodily change (e.g., its intensity, frequency, distress, quality),[18,29] applying meaning to it (e.g., depending on the cultural background, cognitive resources, knowledge, attention, expectation)[27,28] and, eventually, labeling it as a symptom.[17] Finally, once a symptom has been detected and interpreted, symptom response may occur.

Symptom can be influenced by physiologic factors (e.g., energy, diseases), psychological factors (e.g., mood), and situational factors (e.g., family status, social support, lifestyle behaviours). These factors interact with each other and influence symptoms synergically.[18] In turn, symptoms

influence functional performance (e.g., physical and social activities)[30,31] and cognitive performance (e.g., problem solving).[30,32] These variables (i.e., influencing factors, symptoms, performance) interact with each other in a complex system, moderating and mediating the effects of each other.[18,33-35]

Symptom clusters

In people with a chronic condition, multiple physical and psychological symptoms often occur simultaneously,[18,36-39] and their co-existence in clusters may increase the perceived severity of each symptom.[40,41] A symptom cluster consists of two or more co-occurring symptoms,[42] and increasing evidence suggests that symptom clusters may be more predictive of clinical outcomes than single symptoms.[37,43,44] Cluster analysis can be useful to identify clusters of symptoms (i.e., different symptoms occurring together forming a cluster e.g., gastrointestinal cluster or fatigue cluster)[36,45,46] but also to identify clusters of patients based on different levels of the same subset of symptoms[47] (i.e., different distributions of the same number/type of symptoms forming different clusters e.g., high physical + low psychological symptoms cluster; low physical + high psychological symptoms cluster). The first approach, clustering symptoms, allows understanding of how symptoms are grouped into mutually exclusive clusters, while the second one, clustering patients based on their symptoms, allows understanding of how the same symptoms are differently distributed in a population and how burdensome they are in different combinations.

Identifying symptom clusters could allow healthcare professionals to better understand the symptom experience of chronically ill patients[37] and deliver tailored care. Second, it could make patients aware of symptom clusters, help them to recognize impending exacerbations[40] and adopt timely symptom management strategies.[48] Third, it could foster future investigations assessing the effect of clusters of symptoms on patient outcomes.[49]

Most studies implementing cluster analyses adopted the first clustering technique (i.e., clustering symptoms), recruited hospital patients only, focused on symptoms having diverse impact on clinical outcomes, or considered either physical or psychological symptoms. For these reasons, we aimed to address these gaps by conducting the first study of this PhD thesis entitled "*Cluster analysis of heart failure patients based on their psychological and physical symptoms and predictive analysis of cluster membership*".

The role of self-care in the symptom experience

Symptoms can be alleviated by adequate self-care behaviours but, at the same time, symptoms can also influence the self-care process itself.[17] In the Middle-Range Theory of Self-Care of Chronic Illness[50] self-care is defined as the process of maintaining health and managing illness. Specifically, self-care behaviours include self-care maintenance (e.g., taking medication as prescribed, to maintain health and prevent symptoms exacerbations), self-care monitoring (e.g., routine testing to recognize early changes), and self-care management (e.g., changing the diet or medication dose based on emerging symptoms to effectively address them). However, patients often find it difficult to perform self-care and, in these cases, caregivers may help.

The situation-specific theory of caregiver contribution to patient self-care defines caregiver contribution to self-care[51] as the process through which caregivers support patients in maintaining illness stability (i.e., caregiver contribution to self-care maintenance), in monitoring symptoms (i.e., caregiver contribution to symptom monitoring and perception), and in addressing symptoms (i.e., caregiver contribution to self-care management).[51] Caregiver contribution to self-care has been theorized to improve patient symptom burden, but this hypothesis has not been tested yet. In addition, the potential mediating role of patient self-care between caregiver contribution to self-care and symptom burden is also still unknown.

Symptom science and self-care science are intrinsically related,[17] as the processes of self-care monitoring and management imply perceiving and responding to symptoms. Self-care theory is

broader than symptom theory, but symptoms exert a strong influence on the self-care decision making process.[17] For instance, people may be more willing to engage in self-care behaviours if they have symptoms, but depressive symptoms and cognitive deficits can also decrease motivation to engage in self-care behaviors.[52,53] At the same time, self-care behaviours can also influence the symptom burden, and the symptom frequency and intensity.[54] To better understand the relationship between caregiver contribution to self-care, patient self-care, and symptom burden we conducted the second study of this PhD thesis entitled "*The influence of caregiver contribution to self-care on symptom burden in patients with heart failure and the mediating role of patient self-care: a longitudinal mediation analysis*".

The role of interoception in the symptom experience

Accumulating evidence suggests that people with a chronic condition experience difficulties in perceiving their symptoms,[17] which, in turn, is associated with distorted or exaggerated symptom burden.[55,56] One explanation to that might be related to illness-induced interoceptive impairments. Interoception is the ability of the organism to sense, interpret, and regulate signals originating from within the body (i.e., symptoms).[57] More specifically, interoception includes the processes through which the peripheral systems communicate to the central nervous system through afferent pathways, mainly including neural (e.g., the cranial/vagal and spinal pathways) and humoral (e.g., immune and endocrine) channels. When a signal reach the brain, interoceptors (i.e., specific receptors in neurons), detect and translate it into an electrical, hormonal, or other non-neural signal that are interpreted and integrated by the cortical regions of the brain.[57,58] Finally, the central nervous system responds to the signals by communicating to the peripheral nervous system through efferent pathways, producing physical sensations and feelings,[59] and influencing perceptions and behaviors.[59] As an example of interoceptive functioning, when a pain-signal originates in the periphery, it travels along pain-signaling pathways and reaches the central nervous system. There, the pain signal is processed, integrated with emotions and memories, and translated into a conscious feeling of pain. Eventually,

this process leads, for example, to the production of oxytocin and endorphins, as a chemical response to the pain-signal.[60,61]

Interoception is composed of three dimensions.[62] Interoceptive *accuracy* refers to how objectively accurate one is in detecting internal bodily signals (e.g., accurately detecting the heart rate) and can be measured with objective tests such as the heartbeat tracking task,[63] which requires individuals to count their heart beats during specified time periods. Interoceptive *sensibility* refers to the individual's belief in their interoceptive abilities as well as the degree to which individuals feel engaged in the processing of interoceptive signals[62] (e.g., perceived ability to notice when the heart rate changes). Interoceptive sensibility can be assessed using self-reported questionnaires such as the Multidimensional Assessment of Interoceptive Awareness,[64] and through confidence ratings (e.g., Visual Analogue Scale) on how well one rates their performance during an interoceptive accuracy task. Interoceptive sensibility measures the perceived ability to detect internal bodily changes but does not indicate whether this subjective interoceptive sensibility is accurate. Therefore, a strategy to address this is to combine an objective measure of interoceptive accuracy (e.g., the heartbeat tracking task) with a measure of interoceptive sensibility (e.g., subjective confidence in performing the task) to assess the association between subjective (perceived) and objective (actual) interoceptive ability. This third interoceptive construct is known as interoceptive *awareness*.[62,65] Interoceptive awareness can be assessed by computing the association between objective performance (interoceptive accuracy scores) and subjective awareness of performance (interoceptive sensibility scores, e.g., VAS) using a Receiver Operating Curve[66] mapping confidence onto accuracy, or a confidence–accuracy correlation[65] (i.e., Pearson's r).

Interoception can influence how individuals perceive, elaborate, and respond to symptoms.[67,68] Indeed, interoceptive processes can affect how aware one is about one's own symptoms, how accurately one perceives symptoms, and consequently how appropriately one processes and responds to symptoms.[62,68,69] The literature indicates that the insular cortex is the

primary site[70] for interoception. However, insular defects (i.e., neuronal and connectivity loss) have been found in some chronic conditions such as heart failure.[70-73] This suggests that people with a chronic condition may experience altered symptom perception and response due to insular and interoceptive defects.[71,74] Therefore, it is important to better understand the role that interoceptive processes play into the symptom experience of people with a chronic condition. This would allow to explore if common interoceptive patterns exist across chronic conditions, how they relate to symptom processing, and, eventually, develop interventions addressing interoceptive characteristics to improve clinical outcomes. This motivated us to conduct the third study of this PhD thesis entitled "*What is the role of interoception in the symptom experience of people with a chronic condition? A systematic review*".

PhD objectives

This PhD project aimed to advance science with further understanding of symptoms occurring across chronic conditions by addressing the gaps mentioned above. In particular, the aims of this PhD project were to:

a) cluster patients based on their physical and psychological symptoms, and predict symptom cluster membership based on variables other than symptoms;
b) assess the influence of caregiver contribution to self-care on symptom burden and the mediating role of patient self-care;
c) explore the role of interoception in the symptom experience of people with a chronic condition.

CHAPTER 2: Methodology

The first two studies (i.e., *Cluster analysis of heart failure patients based on their psychological and physical symptoms and predictive analysis of cluster membership*, and *The influence of caregiver contribution to self-care on symptom burden in patients with heart failure and the mediating role of patient self-care: a longitudinal mediation analysis*) represents secondary analyses that relied on data collected for the MOTIVATE-HF study.[75] The MOTIVATE-HF is a randomized controlled trial that enrolled 510 dyads of heart failure patients and their caregivers, and primarily aimed at improving patient self-care maintenance using a Motivation Interviewing (MI) intervention.[76] Motivational Interviewing is a counselling technique seeking to highlight the gaps between current behaviors and desirable behaviors to support the participants in reaching the latter.[77] In the MOTIVATE-HF trial the dyads were randomized into three arms: in arm 1 patients received the MI, in arm 2 both patients and caregivers received the MI, in arm 3 patients and caregivers only received the standard care (i.e., oral information on HF and its treatment, and medical follow-up appointments every 6-12 months). Standard care was also provided to those receiving the MI. A face-to-face Motivational Interview was delivered by specifically trained nurses followed by three telephone calls within two months to boost the MI intervention. Data were collected at baseline (prior the MI session) and after 3, 6, 9 and 12 months from enrollment. A large battery of instruments was adopted to collect data from the dyads.[76] Specifically, the Self-Care of Heart Failure Index v.6.2[78] was used to measure patient self-care, the Caregiver Contribution to Self-Care of Heart Failure Index[79] was used to measure caregivers' contribution to self-care, the HF Somatic Perception Scale[80] was used to assess the burden caused by physical symptoms of HF; the SF-12[81] was used to assess the generic physical and mental quality of life; the Kansas City Cardiomyopathy Questionnaire[82] was used to assess HF-specific quality of life; the Charlson Comorbidity Index was used to assess comorbidities, the Hospital Anxiety and Depression Scale[83,84] was used to assess symptoms of anxiety and depression; the Montreal Cognitive Assessment[85] was used to assess cognition; the Pittsburg Sleep Quality Index[86] was used to assess sleep quality; the Mutuality scale[87] was used to assess the

perceived relationship between patient and caregiver from both their perspectives, the Caregiver Preparedness Scale[88] was used to assess caregiver preparedness to assist the patient; the Multidimensional Scale of Perceived Social Support was used to assess the social support as perceived by caregivers.[89]

In the first study presented in this PhD thesis (i.e., *Cluster analysis of heart failure patients based on their psychological and physical symptoms and predictive analysis of cluster membership*) we only relied on baseline data of the MOTIVATE-HF trial. To understand how patients with heart failure experience their physical and psychological symptoms differently, we used the two scores of the Hospital and Anxiety Sale plus two scores of the Heart Failure Somatic Perception Scale (i.e., dyspnea, early and subtle symptoms) to group patients into mutually exclusive clusters based on different combinations and intensities of their physical and psychological symptoms (k-means nonhierarchical cluster analysis). Then, we trained a classification model to predict symptom cluster membership using 11 socio-demographic and clinical variables previously selected based on the existing literature suggesting their symptom-related relevance (e.g., illness duration, sleep quality, age, etc.). Detailed and extensive description of the methodology adopted in this study is reported in the *Methods* section of Chapter 3.

Since the results of this first study did not show any difference in the self-care management dimension among clusters but instead showed that patients with the lowest symptom burden had the highest level of self-care maintenance, this suggested that the association between symptoms and the different dimensions of self-care still needed further assessment. Thus, we explored it in the second study of this PhD thesis entitled *The influence of caregiver contribution to self-care on symptom burden in patients with heart failure and the mediating role of patient self-care: a longitudinal mediation analysis*). In this second study we relied on baseline and 3-months data of the MOTIVATE-HF trial. To understand the association between symptoms and the various dimensions of self-care (both from the patient and caregiver perspective) we performed an autoregressive longitudinal path

analysis with contemporaneous mediation. Specifically, we first assessed measurement invariance to control for the effect of the intervention across groups and over time. Then we tested our hypothesis: a) caregiver contribution to self-care influences patient self-care; b) patient self-care influences symptom burden; c) patient self-care mediates the relationship between caregiver contribution to self-care and symptom burden. Detailed and extensive description of the methodology adopted in this study is reported in the *Methods* section of Chapter 4.

The results of this second study better clarified how people with a chronic condition (such as heart failure) experience different levels of symptom burden and how they are differently associated with variables such as self-care behaviors. However, accumulating evidence suggests that people with a chronic condition may have impaired abilities in perceiving and recognizing their symptoms due to defects in some brain structures (e.g., insular cortex) and processes (i.e., interoception),[17] which contribute to lowering the ability to accurately perceive the frequency and severity of symptoms. While we know some about the different levels of interoceptive impairment in specific chronic conditions, nothing comparing different conditions is available in the literature. The absence of a synthesis of the evidence makes it challenging to identify potential common patterns among different chronic conditions. Thus, this motivated us to conduct the third study of this PhD thesis entitled "*What is the role of interoception in the symptom experience of people with a chronic condition? A systematic review*". In this last study we conducted a systematic review to synthesize the role of interoception (i.e., the ability of the brain to detect, elaborate and respond to bodily signals coming from within the body, such as increasing heartrate) in the symptom experience of adults with a chronic condition. To do that, we searched five databases, we included all primary research (all study designs) addressing our study aim published between 2013-2021 and measuring at least one dimension of interoception. Any chronic condition and any symptom were included, no language limits were applied, and only the adult population was considered. A thorough and extensive description of the methodology adopted in this study is reported in the *Methods* section of Chapter 5.

CHAPTER 3: Cluster analysis of heart failure patients based on their psychological and physical symptoms and predictive analysis of cluster membership.

This chapter is published in the following source:

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Abstract

Aim: Patients with heart failure experience multiple co-occurring symptoms that lower their quality of life and increase hospitalization and mortality rates. So far, no heart failure symptom cluster study recruited patients from community settings or focused on symptoms predicting most clinical outcomes. Considering physical and psychological symptoms together allows understanding how they burden patients in different combinations. Moreover, studies predicting symptom-cluster membership using variables other than symptoms are lacking. We aimed to a) cluster heart failure patients based on physical and psychological symptoms; b) predict symptom-cluster membership based on variables other than symptoms (i.e., sociodemographic/clinical variables).

Design: Secondary analysis of MOTIVATE-HF trial, which recruited 510 heart-failure patients from a hospital, an outpatient and a community in Italy. Data was collected between June 2014-October 2018.

Methods: Cluster analysis was performed based on the two scores of the Hospital Anxiety-Depression scale and two scores of the Heart-Failure Somatic Perception Scale predicting most clinical outcomes. ANOVA and chi-square test were used to compare patients' characteristics among clusters. For the predictive analysis, we split the data into a training set and a test set and trained three classification models on the former to predict patients' symptom-cluster membership based on 11clinical/sociodemographic variables. Permutation analysis investigated which variables best predicted cluster-membership.

Results: Four clusters were identified based on the intensity and combination of psychological and physical symptoms: mixed distress (high psychological, low physical symptoms), high distress, low distress, moderate distress. Clinical and sociodemographic differences were found among clusters. NYHA-class and sleep quality were the most important variables in predicting symptom cluster membership.

Conclusions: These results can support the development of tailored symptom-management intervention and the investigation of symptom-clusters' effect on patient outcomes. The promising results of the predictive analysis suggest that such benefits may be obtained even when direct access to symptoms-related data is absent.

Keywords*:* Heart failure; Symptom; Cluster analysis; Machine Learning.

Introduction

Heart failure (HF) is a global clinical syndrome affecting 1–2% of the adult population in developed countries,[90] and 26 million people worldwide.[36] Despite improvements in prevention, diagnosis, and treatments, outcomes in HF patients remain poor.[91] Indeed, HF patients experience multiple physical symptoms, such as dyspnoea and edema[12,92], which contribute to lowered quality of life[9,11], high hospitalization[12], and mortality rates[8,14]. Even after heart transplantation or implantation of ventricular assist devices, HF-symptoms often persist[93,94]. In addition, HF patients often experience psychological symptoms such as anxiety and depression,[15] which can intensify the perception of physical symptoms.[16] Ultimately, HF patients report levels of symptom burden as high as patients with advanced malignancies[91,95], which often increase as the disease progresses[96].

Symptoms are defined as "subjective physical or mental experiences, appraised and defined by the patient, and reflective of an altered health state or change therein" (p. 209).[97] In HF, multiple physical and psychological symptoms often occur simultaneously,[36-38] and their co-existence in clusters may increase the perceived severity of each symptom.[40] A symptom cluster consists of two or more co-occurring symptoms,[42] and increasing evidence suggests that symptom clusters may be more predictive of clinical outcomes than single symptoms.[37,44] Identifying symptom clusters could allow healthcare professionals to better understand the symptom experience of HF patients[37] and deliver tailored assistance. Second, it could make HF patients aware of symptom clusters, recognize impending exacerbations,[40] and adopt timely symptom management strategies.[48] Third, it could foster future investigations assessing the effect of symptom clusters on patient outcomes.[49]

Most studies performing cluster analysis, also within HF research, tended to cluster symptoms[36,37,40,45,46,48] (i.e., different symptoms occurring together forming a cluster e.g., gastrointestinal cluster, fatigue cluster), instead of patients based on different levels of the same subset of symptoms (i.e., different distributions of the same number/type of symptoms forming different clusters e.g., high physical-low psychological symptoms cluster; low physical-high psychological

symptoms cluster). The first approach, clustering symptoms, allows understanding how symptoms are grouped into mutually exclusive clusters, while the second one, clustering patients based on their symptoms, allows understanding how the same symptoms are differently distributed in a population and how burdensome they are in different combinations.

Some studies[38,47,98-100] clustered HF patients based on their symptoms: some of them only considered physical symptoms,[36,98] while others also included psychological ones.[38,47,100] However, the existing studies that included both physical and psychological symptoms had some limitations. First, they included several physical symptoms, not only those predicting most clinical outcomes. Second, few of them adopted the HF Somatic Perception Scale[80](HFSPS) to assess physical symptoms, as many adopted the Kansas City Cardiomyopathy Questionnaire[82] or the Minnesota Living with HF Questionnaire.[101] Compared to the HFSPS, the other two only include a narrow set of symptoms as they are not specifically intended to solely measure HF physical symptoms. Third, previous cluster analyses of HF-symptoms recruited patients from either hospital wards or outpatients, but not from community settings, which could have allowed a broader generalisation of results. Finally, previous studies have rarely given equal weight to physical and psychological symptoms when identifying the clusters.

Previous research showed that symptom clusters are associated with specific clinical and sociodemographic characteristics. For instance, higher psychological distress is associated with lower quality of life and younger age;[102,103] higher physical distress is associated with NYHA class III-IV and female gender.[103] Specific symptom data may not always be collected, contrary to other sociodemographic or basic clinical information such as NYHA-class. In cases where no data on symptoms are available, but other clinical and sociodemographic information is collected, it may be helpful to understand how the latter could still be used to predict symptom cluster membership. Indeed, this could facilitate addressing symptoms even when direct access to patients' symptoms is

impossible. In this study, we aimed to a) cluster HF patients based on their psychological and physical symptoms; and b) predict symptom cluster membership based on variables other than symptoms.

Methods

Design, study setting and sampling

This is a cross-sectional secondary analysis of baseline data from the MOTIVATE-HF RCT,[75] which aimed to improve self-care in HF patients through motivational interviewing. Adult patients (n = 510) were recruited from three Italian healthcare centers (hospital, outpatient, community). Inclusion criteria were a HF diagnosis with NYHA class II-III-IV; poor self-care (scored 0-2 on ≥2items of the Self-Care of HF Index v.6.2)[78]; willingness to participate in the study and sign the informed consent form. Exclusion criteria were severe cognitive impairment (scored 0-4 on the Six-item Screener[104]), myocardial infarction in the previous three months; living in residential facilities.

Data collection and data sources

After the study protocol[76] received ethical approval, patients were recruited. Research assistants screened them with the SCHFI v.6.2 and the Six-item Screener, and, if meeting the inclusion criteria, provided them with the questionnaires to complete. Data was collected between June 2014 and October 2018.

To identify the clusters, the HF Somatic Perception Scale (HFSPS) and the Hospital Anxiety and Depression Scale (HADS) were used. Both scales have been validated in an Italian population.[105,106] The HFSPS[80] is a valid and reliable instrument measuring HF physical symptom burden and consisting of 18 items grouped into four dimensions: chest discomfort, dyspnea, early and subtle, edema. Each item can be rated from 0 to 5. Higher scores indicate higher symptom burden. The HADS[83,84] is a valid and reliable instrument measuring anxiety and depression and consisting of two scales, one for anxiety and one for depression, with seven items each. Scores of both scales range between 0 and 21, with higher scores indicating higher anxiety or depression.

To describe patients' sociodemographic and clinical characteristics, the following instruments were adopted. The Montreal Cognitive Assessment[85] was used to measure cognitive function (scores 0-30, cut-off for normal cognition ≥26). The Mutuality Scale[87] was used to measure mutuality (scores 0-4, higher scores indicate greater mutuality). The 12-item Short Form was used to measure generic physical and mental quality of life[81] (standardized scores 0–100, higher scores indicate better quality of life). The Self-care of HF Index v.6.2[107] was used to measure self-care (composed of three scales measuring self-care maintenance, self-care management, self-care self-efficacy. Scores 0-100, cut-off for adequate self-care ≥70). The Pittsburgh Sleep Quality Index[86] was used to measure sleep quality (scores 0–21, cut-off for poor sleep quality ≥5). The Kansas City Cardiomyopathy Questionnaire[82] was used to measure the perceived HF-specific health status (scores 0-100, higher scores indicate higher health status). The Charlson Comorbidity Index[108] was used to measure the presence and severity of comorbidity and the related long-term mortality risk (scores 1-2: mild, 3-4: moderate, ≥5: severe risk).

Data analysis

Data analysis was performed with SPSS v.25[109] and SLEIPNER v.2.1[110] by implementing four sequential steps. First, we described patients' sociodemographic and clinical characteristics. Second, we conducted a missing-values analysis and tested for multivariate outliers using the SLEIPNER-RESIDUE module and confirmed if the Average Squared Euclidean Distance was <0.5. Third, we performed cluster analysis on the scores of the HADS subscales (anxiety, depression) and two HFSPS dimensions (dyspnea, early and subtle) and then derived the optimal number of clusters. We decided to include only Dyspnea and Early and Subtle symptoms because a) the inclusion of two psychological and two physical dimensions allows a more balanced cluster analysis, equally distributed between psychological and physical symptoms; and b) they have been shown to predict most clinical outcomes in HF patients.[80] Finally, we investigated differences among clusters with one-way analysis of variance (ANOVA).

For the cluster analysis,[111] we initially implemented Ward's hierarchical method (SLEIPNER-CLUSTER-module) to evaluate different cluster solutions based on the decrease of the explained error sum of squares.[111] Then, we further relocated individuals by k-means nonhierarchical analysis to increase cluster homogeneity[112] (SLEIPNER-RELOCATE-module). Finally, we evaluated the optimal number of clusters based on four indices: C-index,[113] G(+),[114] Gamma,[115] and Point-biserial correlation[116] (SLEIPNER-EVALUATE-module). ANOVA was conducted to investigate differences in patients' characteristics among clusters. Post-hoc tests were based on Bonferroni correction unless Levene's homogeneity test was not tenable; in this case, Games-Howell post hoc test was chosen. To compare frequency distributions, we implemented chi-square tests of independence.

The predictive analysis was performed in Python, using the scikit-learn library.[117] Three classification models were trained to predict the cluster membership of the patients based on 11 selected clinical and sociodemographic variables: age, gender, marital status, Charlson Comorbidity Index, Montreal Cognitive Assessment, NYHA class, HF duration, number of medications, SCHFI maintenance, SCHFI self-efficacy, Pittsburg Sleep Quality Index. We selected such variables based on the existing literature suggesting their symptom-related relevance. Plus, we excluded variables with numerous missing values (i.e., SCHFI self-care management n=156, hemoglobin n=50). The data was split into a training set (80%) and a test set (20%). The three classification models were: multinomial logistic regression with cross-validated regularization, support vector classification with cross-validated hyperparameter tuning, and random forest model with cross-validated hyperparameter tuning. The optimal set of hyperparameters for the models was found via nested cross-validation, and the models were trained on the training set. The models were subsequently evaluated on the test set based on three metrics (Accuracy, Balanced accuracy, and AUROC score). Finally, we investigated the importance of the 11 variables in predicting cluster membership by computing the decrease in accuracy of the classifier after randomly shuffling the values of a feature (permutation importance analysis).

Results

Characteristics of the sample

Patients (n=510) were typically older adults (72.4±12.3 years), predominantly men (58%), and partnered (62%). Most patients were in NYHA classes II-III (92.8%), with mild cognitive impairment (22.8±6.7), mild anxiety (7.8±4.4) and depression (7.9±4.4), poor physical (35.4±9.5) and mental (44.7±10.1) quality of life, and poor sleep (12.3±3.6). On average, self-care behaviors were inadequate (<70). No multivariate outliers and no missing values were detected neither in the HFSPS nor in the HADS (Table 1).

Sample characteristics	**M (SD) or n (%)**
Age (years)	72.37 (12.28)
Gender (female)	214 (42.0)
Marital Status	
Single/Never married	24 (4.7)
Married/Partnered	316 (62.0)
Divorced/Separated	20 (3.9)
Widowed	150 (29.4)
Occupation	
Unemployed/retired	428 (83.9)
Active worker	82 (16.1)
Education (≥ middle school)	168 (33.0)
Charlson Comorbidity Index	2.91 (1.98)
Hemoglobin (n=50 missing)	12.74 (2.25)
MoCA (n=7 missing)	22.84 (6.36)
NYHA class	
II	313 (61.4)
III	160 (31.4)
IV	33 (6.5)
Illness duration (months)	66.7 (76.66)
Number of medications	6.64 (2.90)
Mutuality scale (total score)	2.94 (0.62)
SF-12	
Physical component summary	35.46 (9.57)
Mental component summary	44.74 (10.17)
SCHFI	
Maintenance	45.44 (15.39)
Management (n=156 missing)	39.73 (17.64)
Self-efficacy	51.42 (21.59)
PSQI	
Total score	12.31 (3.68)

Duration	0.91 (0.99)
Disturbances	2.36 (0.61)
Latency	1.87 (0.80)
Daytime dysfunction	1.93 (0.81)
Efficiency	1.55 (1.26)
Quality	2.18 (062)
Medications	1.51 (0.78)
KCCQ	
Total score	57.09 (22.03)
Physical limitation	46.18 (24.26)
Symptom stability	67.55 (32.43)
Symptom frequency	47.04 (18.95)
Symptom burden	67.15 (28.90)
Self-efficacy	53.65 (22.72)
Quality of life	45.17 (25.55)
Social limitation	49.53 (29.21)
Clinical summary	51.64 (21.66)
HADS	
Anxiety	7.81 (4.40)
Depression	7.96 (4.42)
HFSPS	
Total score	27.78 (16.61)
Dyspnea	10.13 (7.60)
Chest discomfort	2.73 (2.35)
Early subtle	10.78 (6.11)
Edema	4.13 (3.54)

Table 1. Sociodemographic and clinical characteristics of the sample (N=510). **Note.** MoCA=Montreal Cognitive Assessment Scale; NYHA=New York Heart Association; HADS=Hospital Anxiety and Depression Scale; HFSPS=Heart Failure Somatic Perception Scale; SCHFI=Self-care of Heart Failure Index; PSQI=Pittsburgh Sleep Quality Index; KCCQ=Kansas City Cardiomyopathy Questionnaire.

Results of the cluster analysis

The 5, 4, and 3-cluster solutions were explored because of the steeper decline in the error sum of squares (Supplementary Table A). The G+ and Gamma indexes suggested the 5-cluster solution, C-index suggested the 3-cluster solution, and the point biserial correlation suggested the 4-cluster solution. However, the 5-cluster solution did not seem theoretically meaningful and, although having the highest ESS, it included one small cluster of 49 patients (9.61% of the total sample). The 3-cluster solution explained a relatively low variance. These considerations highlighted the 4-cluster solution as optimal.

Figure 1 and Table 2 show the mean scores of HADS (Anxiety and Depression subscales) and HFSPS (Dyspnea and Early and Subtle subscales) for each of the 4 clusters, which were labelled based on the intensity and combination of psychological and physical symptoms. Cluster 1 has high psychological symptoms scores and low physical symptoms scores, therefore it was labeled as "Mixed distress". Cluster 2 has high psychological and physical symptoms scores, therefore it was labelled as "High distress". Cluster 3 has low psychological and physical symptoms scores, therefore it was labeled as "Low distress". Cluster 4 has average psychological and physical symptoms scores, therefore it was labeled as "Moderate distress".

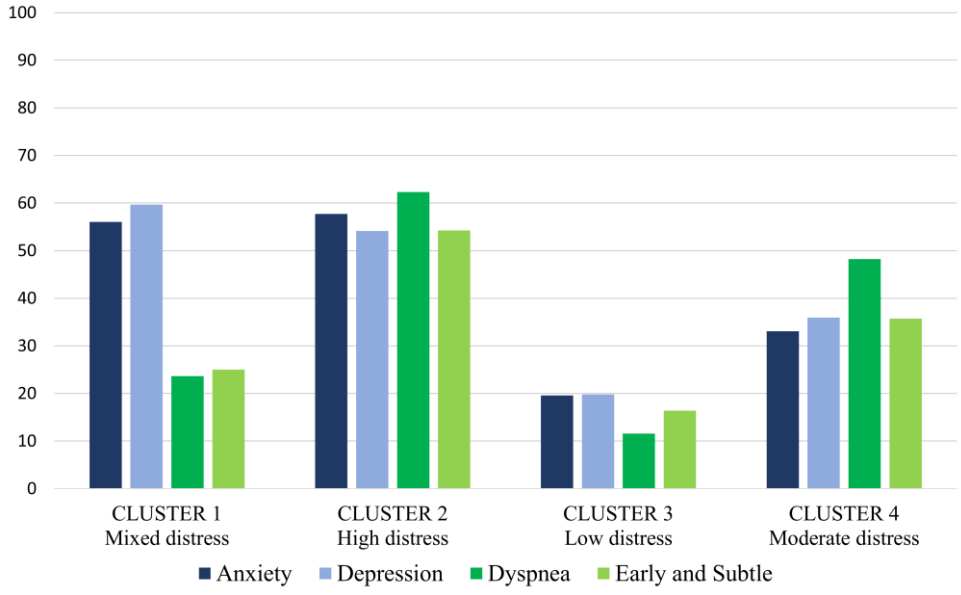

Figure 1. Graphical representation of the Heart Failure Somatic Perception subscales (Dyspnea, Early and Subtle) scores and the Hospital Anxiety and Depression subscales' (Anxiety and Depression) scores per each cluster. Each subscale has a standardized score from 0 to 100, with higher scores meaning higher physical symptom burden and higher anxiety and depression, respectively.

Clusters description and comparison

The ANOVA showed that the HADS and HFSPS subscales were statistically different across the clusters. The only exception was a non-significant difference in anxiety between clusters 1 and 2 ($p = 1.00$) (Table 2).

	Cluster 1 Mixed distress (n=86, 16.87%)	Cluster 2 High distress (n=106, 20.78%)	Cluster 3 Low distress (n=184, 36.08%)	Cluster 4 Moderate distress (n=134, 26.27%)	F or X^2	p	Post hoc test
Anxiety	11.77 (3.18)	12.12 (2.87)	4.11 (2.59)	6.95 (2.70)	207.03	< **0.001**	1 ≠ 3; 1 ≠ 4; 2 ≠ 3; 2 ≠ 4; 3 ≠ 4
Depression	12.53 (3.30)	11.37 (2.90)	4.16 (2.75)	7.55 (2.81)	227.08	< **0.001**	1 ≠ 2; 1 ≠ 3; 1 ≠ 4; 2 ≠ 3; 2 ≠ 4; 3 ≠ 4
Dyspnea	23.64 (16.12)	62.30 (16.77)	11.54 (12.03)	48.26 (16.18)	319.90	< **0.001**	1 ≠ 2; 1 ≠ 3; 1 ≠ 4; 2 ≠ 3; 2 ≠ 4; 3 ≠ 4**
Early and subtle	25.02 (11.02)	54.29 (9.25)	16.40 (9.77)	35.76 (10.77)	332.26	< **0.001**	1 ≠ 2; 1 ≠ 3; 1 ≠ 4; 2 ≠ 3; 2 ≠ 4; 3 ≠ 4

Table 2. Comparisons of the clusters according to the main scales' scores (n=510). Comparisons in the post-hoc test section refer to cluster numbers. Bonferroni post hoc test was performed unless otherwise specified. ** Games and Howell test; Significant p-values are in bold. Data are displayed as mean (SD). Anxiety and Depression scores are not standardized.

Individuals in cluster 1 (Mixed distress) had an equal distribution of gender, a mean age of 72.4 years, and were mainly in NYHA class II (Supplementary Table B). Patients in this cluster reported the lowest levels of mental quality of life (but not significantly different to cluster 2). Sleep quality (PSQI) and HF-related health status (KCCQ) scores reported by patients in this cluster laid in between those reported by patients in the other clusters, meaning they had more average PSQI and KCCQ scores compared to the other clusters (although not significantly different to cluster 4). Patients in this cluster reported the highest anxiety and depression levels compared to the other clusters (except cluster 2).

Patients in cluster 2 (high distress) were mostly female, with a mean age of 74.2 years, mainly in NYHA classes III-IV. Compared to the other clusters, they had less favorable sociodemographic and clinical characteristics. In fact, they exhibited the highest comorbidity, the lowest hemoglobin level, the poorest cognitive function, the poorest physical (together with cluster 4) and mental (together with cluster 1) quality of life, self-care self-efficacy, sleep quality, and HF-related health status. Patients in cluster 2 reported the highest levels of anxiety and depression (except compared to cluster 1).

Patients in cluster 3 (low distress) were mostly male, with a mean age of 69.2 years, mainly in NYHA classes I-II. Compared to the other clusters, they exhibited the most favorable sociodemographic and clinical characteristics: they were the youngest patients, they were the most partnered, had the lower comorbidity, the highest hemoglobin, cognitive function, physical and mental quality of life, self-care behaviors (especially self-care maintenance), sleep quality and HF-related health status. Patients in this cluster reported the lowest levels of both psychological and physical symptoms.

Patients in cluster 4 (moderate distress) were mostly male, with a mean age of 75.3, and equally distributed between NYHA classes. Compared to patients in the other clusters, they were the oldest and those with the poorest physical quality of life (not significantly different to cluster 2). Patients in this cluster reported mental quality of life scores laying in between those reported by patients in the other clusters. Sleep quality scores and HF-related health status of patients in this cluster laid in between those reported by patients in the other clusters (except to cluster 1), meaning this group of patients had average levels in the PSQI and KCCQ scales. Patients in this cluster also reported average levels of both psychological and physical symptoms, which fell between those reported by patients in all the other clusters.

Results of the predictive analysis

Three classifiers were trained to predict the symptom cluster membership based on 11 selected clinical and sociodemographic variables. When evaluating the classifiers on three metrics (Supplementary Table C), the Random Forest model with cross-validated hyperparameter tuning had the best performance, resulting in an accuracy=0.54, a balanced accuracy=0.49, and an AUROC=0.73.

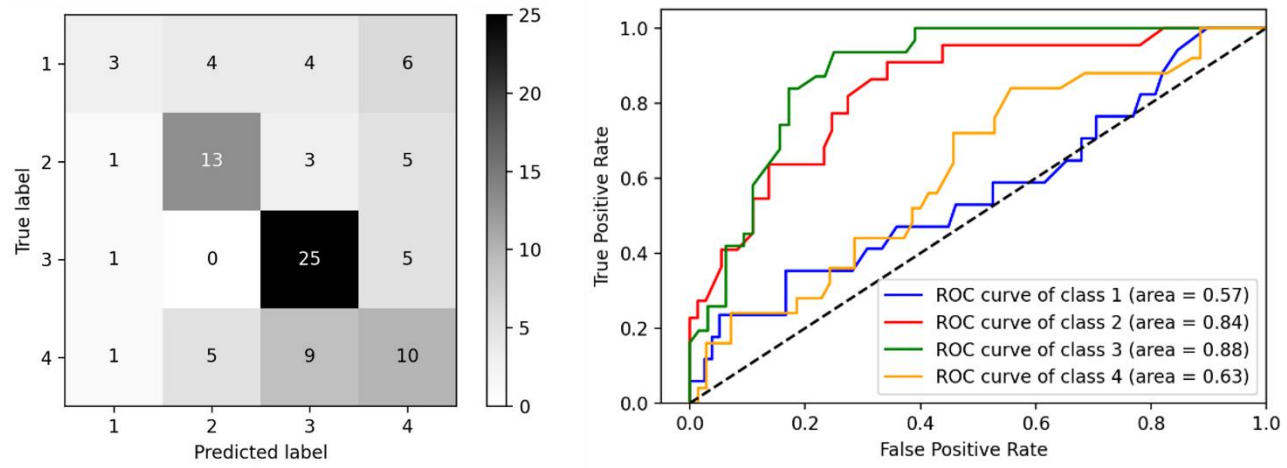

Figure 2. Performance of the Random Forest on test data. On the left, a confusion matrix shows the symptom cluster prediction (x-axis, "Predicted label") for the patients belonging to the four clusters (y-axis, "True label") (e.g., the model made a correct prediction for 25 out of the 31 patients actually belonging to cluster 3). On the right, a ROC plot illustrates the diagnostic ability of the classifier as its discrimination threshold varies. In this multiclass scenario, the individual classes are binarized (e.g., class 1 vs not class 1), and individual scores are computed for each cluster.

By inspecting the performance of the Random Forest model (Figure 2) it can be noted that the classifier has a greater ability to classify patients belonging to clusters 2 and 3 (AUROC=0.84, 0.88 respectively), than patients belonging to clusters 1 and 4 (AUROC=0.57, 0.63 respectively). The importance of the 11 clinical and sociodemographic variables was computed (Figure 3) and showed that NYHA class (Mean accuracy decrease=0.098, SD=0.029) and sleep quality (PSQI) (Mean accuracy decrease=0.089, SD=0.033) were the most important variables in predicting cluster membership.

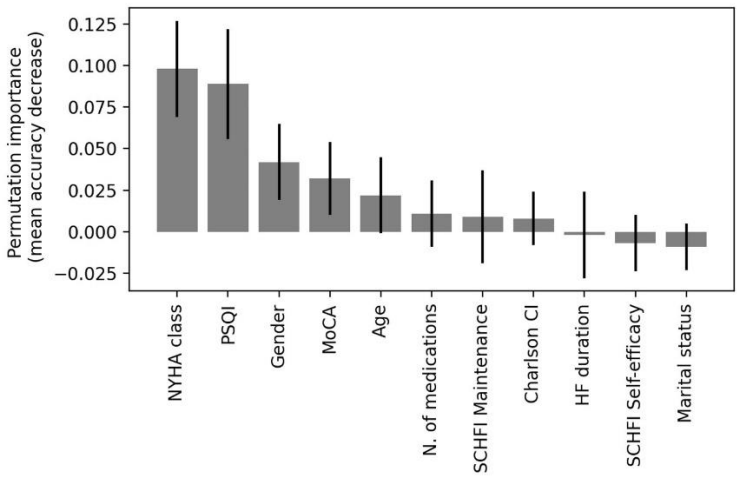

Figure 3. Importance of the 11 clinical and sociodemographic variables, measured as mean decrease in accuracy (±SD) when a specific variable is randomly shuffled. **Abbreviations.** NYHA=New York Heart Association; PSQI=Pittsburgh Sleep Quality Index; MoCA=Montreal Cognitive Assessment; SCHFI=Self-care of HF Index; CI = Comorbidity Index.

Discussion

The aim of this study was to cluster HF patients based on their psychological and physical symptoms. We found four clusters characterized by different levels and combinations of psychological and physical symptoms. We also found that NYHA class and sleep quality mostly predicted symptom cluster membership. These results may be particularly useful to clinicians, patients, as well as researchers within symptoms science. Indeed, they highlight the importance of addressing clusters of symptoms, instead of individual symptoms, to facilitate symptoms detection and to develop tailored strategies for symptom management.

We found four clusters characterized by either consistently high or consistently low psychological and physical symptoms (similarly to previous studies[38,47,100]), consistently moderate psychological and physical symptoms (similarly to Lee[38]), and high psychological combined with low physical symptoms (similarly to Denfeld[100] and Park[47]). We did not observe HF patients suffering from low psychological and high physical symptoms, as few other studies reported.[47,103] Increasing evidence highlights how somatic alterations can influence psychological functions and cognition,[118] suggesting that an increase in physical symptoms may lead to an increase in psychological symptoms. Our results support such assumption. Indeed, when physical symptoms were high also psychological symptoms were high too, and the opposite tendency did not occur in our clusters. This indicates that physical symptoms should be closely monitored as they seem to exert a leading role compared to the psychological ones. Some studies[16,119] found that psychological symptoms can also influence physical symptoms. However, consistent with prior research,[47,100] our 'mixed distress' cluster showed that psychological symptoms may be very high without affecting physical symptoms.

Similar to previous studies,[16,103,120] we found that women experienced higher symptom burden (cluster 'High distress') than men, and patients with higher psychological symptoms experienced lower quality of life.[102] Vongmany et al.[16] suggested that psychological symptoms (e.g., anxiety) may contribute to poorer self-management behaviors. However, we did not observe any significant difference in self-care management among clusters. Therefore, our results suggest that anxiety alone

may not be sufficient to reduce self-care management behaviors, as other variables like self-care self-efficacy or caregiver contribution may prevent worsening by counterbalancing its detrimental effect.

Previous studies in HF reported that younger patients experience either equal[98-100] or higher symptom burden,[121] especially psychological,[47,103] compared to older patients. Contrarily, we found that younger patients were less burdened from both physical and psychological symptoms. The authors of the above-mentioned studies argued that one possible reason for the lower symptom burden experienced by older patients could be due to declines in interoception (i.e., the ability to sense, elaborate and respond to symptoms), which, in the elderly, occur due to changes in adrenergic function.[122,123] However, we also know from the literature that older age is positively associated with an increased tendency to distract from body sensations, which, in turn, is negatively associated with interoceptive abilities and positively associated with symptom burden.[55,124-126] Thus, our results seem to confirm that older patients may suffer from greater interoceptive impairments, but in a way that such impairment might have led to distorted and exaggerated reported symptom patterns, resulting in a more burdensome experience of symptoms.

In HF patients, anxiety and depression are common comorbid conditions[127] that affect cardiovascular processes by altering neurohormonal function.[128] Thus, HF patients with anxiety or depression may exhibit a continued cycle of HF progression and increased anxiety and depression.[128] This seems to be confirmed by the consistence between the levels of physical and psychological symptoms in our clusters. However, our 'mixed distress' cluster represents an exception that could be due to impaired interoceptive levels discussed above. Since other studies[47,100] also reported clusters with mixed levels of physical and psychological symptoms in HF, it would be relevant to further investigate the reasons for such discordance.

Finally, to the best of our knowledge, this is the first study predicting symptom-cluster membership. We found that the Random Forest model had a greater ability to classify patients belonging to clusters 2 and 3. Indeed, patients belonging to these two clusters reported very high or very low symptom distress. Instead, patients in clusters 1 and 4 reported more average or mixed

distress, logically more difficult for a model to predict as being less 'extreme'. Future research should further replicate this type of predictive analysis on larger samples and considering even more variables that could potentially allow a more precise prediction of symptom-cluster membership. We also found that NYHA class and sleep quality, variables easily available in the clinic, were the most useful in predicting symptom cluster membership. These results are supported by the literature reporting significant association between sleep disturbances and physical symptom like dyspnoea and edema, as well as psychological symptoms of anxiety and depression.[129-131] NYHA class has been found associated with psychological symptoms, especially depressive symptoms,[132,133] and, as per definition, higher NYHA class implies higher physical symptom severity.[134] Relying on variables other than symptoms to predict symptom cluster membership has potential to allow healthcare professionals, as well as researchers, to know the symptom cluster membership of patients, without necessarily asking or having access to any symptom-specific information, and therefore facilitate the process of addressing and managing symptoms.

Strengths and limitations

Patients in our sample were mainly in NYHA class II–III, and had a rather long illness duration, which could have influenced the results and may reduce their generalizability. However, we innovatively recruited patients from three different settings, which may compensate for that limitation and enhance generalizability of results across different settings. Furthermore, it is desirable that predictive analyses performed by splitting the sample into test and training sets are computed on large samples to increase the validity of the results. Our sample size was moderately small, as we ended up with 102 patients in the test set. However, our predictive analysis represents a first attempt to predict symptom-cluster membership based on variables other than symptoms, and thus provide an exploratory starting point never done before.

Recommendations for future research

The results of this study further expand the existent literature investigating clusters of symptoms in patients with heart failure. Our results highlight the need to further investigate the effect

of clusters of symptoms, instead individual symptoms, on patient outcomes. The predictive analysis of symptom cluster membership should be further replicated on bigger samples and considering other potential clinical and sociodemographic variables.

Implications for policy and practice

The results of this study may assist clinicians and researchers in the development of tailored intervention to improve symptom detection and management. Furthermore, knowing which variables best predict symptom-cluster membership (i.e., NYHA class and sleep quality) can allow to address symptom-related issues even when direct access to symptoms-data is absent.

Conclusions

Our results indicate that, within an Italian HF population, it was possible to detect distinct clusters of HF patients based on different combinations and degree of physical and psychological symptoms. This may be particularly useful to support clinicians in providing interventions tailored to a specific symptom profile, to assist patients and caregivers in adopting appropriate symptom management strategies, and to spur future investigations assessing the effect of clusters of symptoms on patient outcomes. The promising results of the predictive analysis show that such benefits may be obtained even when access to symptoms-related data is absent.

Supplementary tables

	5-cluster solution	4-cluster solution	3-cluster solution
C-index	0.105	0.115	0.092
G(+) index	0.039	0.052	0.070
Gamma index	0.772	0.739	0.693
Point biserial correlation	0.418	0.474	0.445
ESS	67.250	62.340	55.246

Supplementary Table A. Fit indices of the cluster solutions identified with k-means clustering. **Note.** ESS=explained error sum of squares.

	Cluster 1 (n=86, 16.87%)	Cluster 2 (n=106, 20.78%)	Cluster 3 (n=184, 36.08%)	Cluster 4 (n=134, 26.27%)	*F or* X^2	p	Post hoc test
Age	72.37 (13.69)	74.20 (11.29)	69.21 (12.04)	75.32 (11.48)	7.68	< 0.001	2 ≠ 3; 4 ≠ 3**
Gender							
Female	44 (20.60)	68 (31.80) †	52 (24.30) †	50 (23.40)	39.79	< 0.001	
Male	42 (48.80)	38 (35.80) †	132 (44.60) †	84 (28.40)			
Marital status							
Partnered	48 (15.20)	52 (16.50) †	134 (42.40) †	82 (25.90)	18.12	0.001	
Not partnered	38 (19.60)	54 (27.80) †	50 (25.80) †	52 (26.80)			
Occupation							
Active worker	17 (20.70)	12 (14.60)	40 (48.80) †	13 (15.9) †	11.05	0.011	
Unoccupied/retired	69 (16.10)	94 (22.00)	144 (33.60) †	121 (28.30) †			
Education							
<= 8 yrs	57 (16.70)	78 (22.80)	112 (32.70)	95 (27.80)	6.15	0.100	
> 9 years	29 (17.30)	28 (16.70)	72 (42.90)	39 (23.20)			
Charlson Comorbidity Index	2.95 (2.34)	3.50 (2.29)	2.61 (1.70)	2.84 (1.74)	4.71	0.003	1 ≠ 3; 3 ≠ 2**
Hemoglobin	12.47 (1.77)	12.07 (2.14)	13.35 (2.57)	12.63 (1.98)	7.64	< 0.001	1 ≠ 3; 2 ≠ 3; 3 ≠ 4; 4 ≠ 1
MoCA	22.83 (6.81)	20.25 (7.43)	24.87 (5.04)	22.20 (5.92)	13.16	< 0.001	1 ≠ 2; 2 ≠ 3; 3 ≠ 4**
NYHA class							
II	61 (19.5)	31 (9.90) †	152 (48.60) †	69 (22.00) †	93.93	< 0.001	
III-IV	25 (13.00)	75 (38.90) †	29 (15.00) †	64 (33.20) †			
Illness duration (months)	64.52 (71.29)	62.31 (78.27)	67.66 (81.44)	68.66 (72.65)	0.17	0.917	
Number of medications	6.60 (3.28)	6.39 (2.39)	6.63 (3.00)	6.89 (2.88)	0.58	0.630	
Mutuality Scale (total)	2.88 (0.62)	2.83 (0.68)	3.00 (0.56)	2.95 (0.63)	1.97	0.117	
SF-12							
PCS	35.92 (10.01)	30.23 (6.88)	40.81 (9.16)	31.95 (7.73)	45.07	< 0.001	1 ≠ 2; 1 ≠ 3; 1 ≠ 4; 2 ≠ 3; 3≠ 4**
MCS	39.42 (8.71)	37.02 (7.49)	52.42 (7.67)	43.73 (8.58)	101.26	< 0.001	1 ≠ 3; 1 ≠ 4; 3 ≠ 2; 2 ≠ 4 3 ≠ 4**
SCHFI							
Maintenance	42.36 (18.83)	42.42 (14.61)	50.74 (13.41)	42.96 (14.35)	11.61	< 0.001	1 ≠ 3; 2 ≠ 3; 3 ≠ 4**
Management	36.32 (20.32)	39.68 (14.68)	41.39 (19.49)	40.04 (16.97)	0.938	0.423	
Self-efficacy	51.07 (24.79)	44.69 (22.33)	57.51 (18.93)	48.63 (20.20)	9.51	< 0.001	2 ≠ 3; 1 ≠ 4**
PSQI							
Total score	13.00 (3.82)	15.10 (3.78)	10.37 (3.12)	12.97 (3.21)	45.69	< 0.001	1 ≠ 2; 1 ≠ 3; 2 ≠ 3; 2 ≠ 4; 3 ≠ 4**

Duration	1.09 (1.20)	1.47 (1.29)	0.74 (1.05)	1.18 (1.28)	8.98	< 0.001	2 ≠ 3; 3 ≠ 4**
Disturbances	2.40 (0.60)	2.70 (0.60)	2.07 (5.23)	2.48 (0.57)	30.62	< 0.001	1 ≠ 2; 1 ≠ 3; 2 ≠ 3; 2 ≠ 4; 3 ≠ 4**
Latency	1.87 (0.80)	2.17 (0.78)	1.64 (0.76)	1.96 (0.78)	11.24	< 0.001	1 ≠ 2; 2 ≠ 3; 3 ≠ 4
Daytime dysfunction	2.05 (0.85)	2.58 (0.60)	1.42 (0.59)	2.04 (0.75)	68.20	< 0.001	1 ≠ 2; 1 ≠ 3; 2 ≠ 3; 3 ≠ 4; 4 ≠ 2**
Efficiency	1.67 (1.32)	1.77 (1.20)	1.33 (1.28)	1.59 (1.22)	3.34	0.019	2 ≠ 3
Quality	2.17 (0.71)	2.57 (0.55)	1.95 (0.53)	2.20 (0.57)	26.00	< 0.001	1 ≠ 2; 2 ≠ 3; 2 ≠ 4; 3 ≠ 4**
Medications	1.74 (0.86)	1.83 (0.89)	1.20 (0.56)	1.53 (0.74)	20.27	< 0.001	1 ≠ 3; 2 ≠ 3; 2 ≠ 4; 3 ≠ 4**
KCCQ							
Total score	45.04 (23.69)	29.95 (15.09)	68.65 (16.10)	42.19 (15.18)	131.62	< 0.001	1 ≠ 2; 1 ≠ 3; 2 ≠ 3; 2 ≠ 4; 3 ≠ 4**
Physical limitation	42.50 (24.53)	28.92 (18.20)	63.31 (20.22)	38.66 (18.26)	77.56	< 0.001	1 ≠ 2; 1 ≠ 3; 2 ≠ 3; 2 ≠ 4; 3 ≠ 4
Symptom stability	64.83 (32.85)	46.93 (28.60)	85.33 (24.00)	61.19 (32.81)	43.24	< 0.001	1 ≠ 2; 1 ≠ 3; 2 ≠ 3; 2 ≠ 4; 3 ≠ 4**
Symptom frequency	46.73 (20.88)	32.34 (12.43)	60.36 (15.18)	40.58 (14.04)	84.75	< 0.001	1 ≠ 2; 1 ≠ 3; 2 ≠ 3; 4 ≠ 2; 3 ≠ 4
Symptom burden	63.28 (29.33)	44.22 (22.56)	88.00 (17.84)	59.14 (26.69)	87.85	< 0.001	1 ≠ 2; 1 ≠ 3; 2 ≠ 3; 2 ≠ 4; 3 ≠ 4**
Self-efficacy	46.95 (24.55)	38.44 (17.40)	68.07 (18.14)	50.19 (19.63)	59.19	< 0.001	1 ≠ 2; 1 ≠ 3; 2 ≠ 3; 2 ≠ 4; 3 ≠ 4
Quality of life	39.00 (26.19)	24.21 (16.53)	64.90 (20.25)	38.62 (18.00)	104.59	< 0.001	1 ≠ 2; 1 ≠ 3; 2 ≠ 3; 2 ≠ 4; **
Social limitation	41.31 (28.99)	28.39 (21.47)	72.45 (22.43)	41.54 (22.16)	92.77	< 0.001	1 ≠ 2; 1 ≠ 3; 2 ≠ 3; 2 ≠ 4; 3 ≠ 4**
Clinical summary	48.75 (22.40)	33.60 (15.21)	68.75 (15.63)	44.26 (21.66)	114.16	< 0.001	1 ≠ 2; 1 ≠ 3; 2 ≠ 3; 2 ≠ 4; 3 ≠ 4**

Supplementary Table B. Differences between the four clusters on sociodemographic and clinical variables (total sample n=510). **Abbreviations.** MoCA: Montreal Cognitive Assessment Scale; NYHA: New York Heart Association; HADS: Hospital Anxiety and Depression Scale; SF-12 PCS: Short-Form 12 Physical Component Summary; SF-12 MCS: Short-Form 12 Mental Component Summary; HFSPS: Heart Failure Somatic Perception Scale; SCHFI: Self-care of Heart Failure Index; PSQI: Pittsburgh Sleep Quality Index; KCCQ: Kansas City Cardiomyopathy Questionnaire. Bonferroni post hoc test; SCHFI, Self-care of Heart Failure Index; X^2, chi-square test. Comparisons in the post-hoc test section refer to cluster numbers. Bonferroni post hoc test was performed unless otherwise specified. ** Games and Howell test; † Significant standardized residual. Data are displayed as mean (SD) or n (%).

Classifier type	Accuracy	Balanced accuracy	AUROC score
Multinomial Logistic Regression	0.49	0.45	0.70
Support Vector Classification	0.44	0.40	0.67
Random Forest	0.54	0.49	0.73

Supplementary Table C. Comparison of three individual classifiers (Multinomial Logistic Regression, Support Vector Classification, and Random Forest) based on three performance metrics (accuracy, balanced accuracy, AUROC score) computed on test data.

How this study led to the following one

Previous research[16] suggested that symptoms may influence self-management behaviors. The results of this study did not show any significant difference in self-care management among clusters, but instead showed that patients with the lowest symptom burden had the highest level of self-care maintenance. The results of this study suggested that the association between symptoms and the various dimensions of self-care still needed further assessment. Thus, we explored it in the second study of this PhD.

CHAPTER 4: The influence of caregiver contribution to self-care on symptom burden in patients with heart failure and the mediating role of patient self-care: a longitudinal mediation analysis.

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Abstract

Background: Patients with heart failure experience high symptom burden, which can be mitigated with adequate self-care. Caregiver contribution to self-care has been theorized to improve patient symptom burden. The mediating role of patient self-care in this relationship has not been tested yet.

Objectives: To assess the influence of caregiver contribution to self-care on symptom burden and the mediating role of patient self-care. Specifically, to test whether: a) caregiver contribution to self-care influences patient self-care; b) patient self-care influences symptom burden; c) patient self-care mediates the relationship between caregiver contribution to self-care and symptom burden.

Methods: Secondary analysis of the baseline and three-month data from the MOTIVATE-HF trial, which enrolled 510 dyads (patient with heart failure-caregiver) in Italy. Multigroup confirmatory factor analysis was used to test measurement invariance. Autoregressive longitudinal path analysis with contemporaneous mediation was used to test our hypotheses.

Results: On average, caregivers were 54 years old and mainly female, while patients were 72.4 years old and mainly male. Better caregiver contribution to self-care maintenance was associated with better patient self-care maintenance (β=0.280, $p<0.001$), which, in turn, was associated with lower symptom burden (β=-0.280, $p<0.001$). Patient self-care maintenance mediated the effect of caregiver contribution to self-care maintenance on symptom burden (β=-0.079, 95% BC bootstrapped CI: -0.130, -0.043). Better caregiver contribution to self-care management was associated with better patient self-care management (β=0.238, $p=0.006$). The model significantly accounted for 37% of the total variance in symptom burden scores ($p<0.001$).

Conclusions: This study expands the situation-specific theory of caregiver contribution to heart failure self-care, and provides new evidence on the role of caregiver contribution to self-care and patient self-care on symptom burden in heart failure.

Background

Heart failure is a chronic condition affecting 64.3 million people worldwide.[135] Moreover, its prevalence is progressively increasing due to the aging of the population and the improvement in treatment options.[136-138] Heart failure is associated with poor patient outcomes, such as cognitive impairments, sleep disorders, depression, dyspnea, and fatigue,[30,139-142] which all contribute to lower quality of life,[8-11] increased hospitalization[12,13] and mortality rates.[8,14] However, heart failure outcomes may improve if patients perform adequate self-care.[129,143] Although self-care behaviors are important, patients experience difficulties in performing them[144-146] due to multiple factors including older age, low self-efficacy, cognitive impairment, comorbidities, and depression.[147-150] In these cases, informal caregivers have a crucial role in contributing to patient self-care.[151]

The situation-specific theory of caregiver contribution to patient self-care defines caregiver contribution to self-care[51] as the process through which caregivers support patients in maintaining heart failure stability (caregiver contribution to self-care maintenance), monitoring symptoms (caregiver contribution to symptom monitoring and perception), and addressing symptoms (caregiver contribution to self-care management).[51] These three processes are sequential. Thus, caregiver contribution to self-care maintenance influences caregiver contribution to self-care monitoring and perceptions, which, in turn, influences caregiver contribution to self-care management. This theory identifies a) caregiver-related (e.g., skills), patient-related (e.g., duration of the illness) and dyadic-related factors (e.g., dyad relationship) that contribute to patient self-care, as well as b) caregiver and patient outcomes associated with caregiver contribution to patient self-care. The theory underlines that such outcomes may be both positive and negative.

The theory of caregiver contribution to heart failure self-care is still in its infancy and two aspects are still unknown. First, despite the fact that caregiver contribution to patient self-care implies supporting and influencing patients in self-care maintenance, symptom perception, and self-care management, only one study investigated patient self-care as a proximal outcome of the theory, which

found an association between caregiver contribution to self-care and patient self-care.[152] Second, since patient self-care is associated with various patient outcomes (e.g., reduction of mortality rates, and improved quality of life),[129,143] such outcomes could be considered as distal outcomes of the theory. However, these associations have never been tested. Among the distal outcomes of caregiver contribution to self-care, symptom burden is predominant. Indeed, patients with heart failure experience multiple symptoms that contribute to a decreased quality of life,[8-11] and high hospitalization[12,13] and mortality rates.[8,14] However, the association between caregiver contribution to patient self-care and patient symptom burden in heart failure remains unexplored.

The aim of this study was to investigate the influence of caregiver contribution to self-care on patient symptom burden and explore whether patient self-care mediates such a relationship. Knowing this would expand the situation specific theory of caregiver contribution to patient self-care and the existing knowledge on caregivers' influence on patient outcomes. Considering the theoretical propositions of the situation specific theories of caregiver contribution to self-care[51] and heart failure patient self-care,[153] we assessed the influence of caregiver contribution to self-care on symptom burden and the mediating role of patient self-care. Specifically, we tested whether a) caregiver contribution to self-care influences patient self-care; b) patient self-care influences symptom burden; c) patient self-care mediates the relationship between caregiver contribution to self-care and symptom burden.

Methods

Study design

We conducted a secondary analysis of the MOTIVATE-HF trial, based on the first two data collection time points (baseline and 3-month follow up, sometimes referred to as T0 and T1 respectively).[75] The MOTIVATE-HF study is a randomized controlled trial aimed at improving self-care in patients with heart failure[76] using Motivational Interviewing.[77] Participants were randomized

into three arms: Arm 1, where only patients received the intervention; Arm 2, where both patients and caregivers received the intervention, and Arm 3, where participants received standard care. The intervention in Arm 1 (only for patients) and 2 (both for patients and caregivers) consisted of a face-to-face Motivational Interviewing session followed by three telephone calls within two months to boost the initial intervention. After the intervention, follow-up data were collected at 3, 6, 9 and 12 months from enrollment. Previous analyses demonstrated that the intervention significantly improved patients' self-care,[75] physical symptoms,[154] heart failure specific quality of life,[155] and mortality rates,[156] and caregiver self-efficacy.[157] The study protocol was registered on Clinicaltrials.gov (NCT02894502) and the main results were published elsewhere.[75]

Participants and procedures

A total of 510 dyads of patient with heart failure and their caregivers were enrolled from June 2014 to October 2018 across three healthcare centers in Italy. Patients were eligible if they had a diagnosis of heart failure[158] (New York Heart Association functional class II-IV), poor self-care (score $\leq$ 2 on at least two items of the Self-Care of Heart Failure Index v.6.2[78]), and if they provided written informed consent. Patients were excluded if they had a myocardial infarction in the previous 3 months, lived in residential facilities, or suffered from severe cognitive impairment (score 0-4 on the Six-Item Screener[104]). Caregivers were enrolled whenever identified by their respective patients as those providing them with most of the informal care, and if they were willing to participate in the study.

Measurements

In the MOTIVATE-HF trial, multiple instruments were adopted, but here only those used in this analysis are reported. Caregiver contribution to self-care (maintenance and management) was measured with the Caregiver Contribution to Self-Care of heart failure Index,[79] which is a psychometrically sound questionnaire validated in an Italian heart failure population.[159] Such questionnaire is composed of 22 items divided into three scales: a) caregiver contribution to self-care

maintenance scale, measuring the extent to which caregivers support patients in adhering to pharmacological and behavioral prescriptions and monitoring symptoms; b) caregiver contribution to self-care management scale, measuring the extent to which caregivers help patients in responding to their symptoms; and c) caregiver confidence scale, measuring caregiver self-efficacy in contributing to self-care. Each item is scored on a 4-point Likert scale ranging from 1 (never) to 4 (always) and each scale score is standardized (0-100). Higher scores indicate better caregiver contribution to self-care, with a cut-off point $\geq$ 70 for caregiver contribution to self-care adequacy.[160] The reliability of the caregiver contribution to self-care maintenance and management in this study were satisfactory in this study, with factor score determinacy coefficients of 0.82 and 0.87, respectively.

Patients' self-care (maintenance and management) was measured with the Self-Care of heart failure Index v.6.2, which is a psychometrically sound questionnaire previously tested in an Italian heart failure population.[78] This questionnaire is composed of 22 items divided into three scales: a) self-care maintenance scale, measuring healthy behaviors, treatment adherence and symptom monitoring; and b) self-care management scale, measuring patients' ability to recognize and manage symptoms when they occur; c) self-care confidence scale, measuring patient perceived ability to engage in the self-care process. Each item of the Self-Care of heart failure Index can be scored on a 4-point Likert scale ranging from 1 (never) to 4 (always), and each scale score is standardized (0-100). Higher scores indicate better self-care, with a cut-off point $\geq$ 70 for self-care adequacy.[160] The factor score determinacy coefficients of the self-care maintenance and management scale were 0.72 and 0.78, respectively.

The burden of heart failure physical symptoms on patients was measured with the heart failure Somatic Perception Scale,[80] a psychometrically sound questionnaire [105] composed of 18 items divided into four dimensions: chest discomfort, dyspnea, early and subtle, and edema. Each item can be scored on a 6-point Likert scale ranging from 0 ("I did not have this symptom") to 5 ("Extremely bothersome symptom"). The total score ranges from 0 to 90, with higher scores indicating greater burden of

symptoms. In this study, reliability of the heart failure Somatic Perception Scale for the whole scale was satisfactory, with a factor score determinacy coefficient of 0.92.

Statistical analysis

Statistical analysis was conducted in three consequential steps. First, we described the sociodemographic characteristics of the sample. Means and standard deviation were calculated for continuous variables, and percentages and frequencies, for categorical variables. Second, we tested the measurement invariance of the scales. This was essential because we used data from an RCT and we needed to understand to what extent the intervention, performed on Arm 1 and 2 had influenced scale scores. The procedures used to measure invariance are detailed in the Appendix. Third, we tested the hypotheses guiding the study. The following variables were entered into the model: a) caregiver contribution to self-care maintenance and caregiver contribution to self-care management scores at baseline (autoregressive variables) and three months (independent variables); b) patient self-care maintenance and self-care management at three months (mediators); c) Heart Failure Somatic Perception Scale scores at three months (dependent variable); d) dummy variables of the intervention (covariates). We fitted an autoregressive longitudinal path analysis with contemporaneous mediation (i.e., mediation within the same time point).[161] We used path analysis because it can handle multiple dependent variables, mediating variables, and error terms. Contemporaneous mediation was specified because we assumed that the change in mediators (i.e., patient self-care maintenance and management at three months) began immediately after the first intervention session. To control for stability effects in constructs over time we specified the autoregressive effects of the scale scores administered at baseline on those at three months; with such effects, the stability variance at three months follow-up is accounted for, leaving variance that can authentically explain the relationships among the scales of interest (i.e., across the mediators and outcome).[162] We also used the latent factor scores of the scales instead of the observed scores to lower bias due to measurement error. Finally, we adjusted for the effect of the intervention using dummy variables.

The model fit of the longitudinal path analysis was assessed with the Comparative Fit Index (CFI) and Tucker and Lewis Index (TLI) with acceptable fit ranges of 0.90 and 0.95, or > 0.95 indicating a good fit; Root Mean Square Error of Approximation (RMSEA) with values ≥ 0.10 indicating poor fit; Standardized Root Mean Square Residual (SRMR) with values ≤ 0.08 indicating good fit. We also report traditional chi-square statistics but did not use it to interpret model fit.[163] To test the hypothesis that patient self-care maintenance mediates the relationship between caregiver contribution to self-care maintenance and patient symptom burden (M1), and that patient self-care management mediates the relationship between caregiver contribution to self-care management and patient symptom burden (M2), we assessed indirect effects. Specifically, we tested the indirect effect from caregiver contribution to self-care maintenance to symptom burden through patient self-care maintenance and the indirect effect of caregiver contribution to self-care management to symptom burden through patient self-care management. To test these indirect effects we used the distribution of coefficients with 10,000 bias-corrected bootstrapped confidence intervals (CI).[164] We used SPSS v. 25[109] to conduct the descriptive data analysis and MPLUS 8.4[165] to do the measurement invariance analysis and the longitudinal path analysis.

Results

Characteristics of the participants

We enrolled 510 caregivers and 510 patients with heart failure. Caregivers had a mean age of 54 years, were mostly female (74.5%), partnered (70.8%), and working (73.5%). On average, their contribution to patient self-care was inadequate (<70) (Table 1). Patients had a mean age of 72.4 years, were mostly male (68%), partnered (62.0%), retired (83.9%), and in New York Heart Association class II (61.4%). On average, their self-care behaviors were inadequate (<70) and their symptom burden was low (Table 1).

	Patients (n=510)	**Caregivers (n=510)**
Baseline measures	Mean (SD) or n (%)	Mean (SD) or n (%)
Age	72.37 (12.28)	53.97 (15.46)
Gender (female)	214 (42)	380 (74.5)
Education (≥ middle school)	168 (33)	430 (85.9)
Marital Status		
Single/Never married	24 (4.7)	93 (18.2)
Married/Partnered	316 (62)	361 (70.8)
Divorced/Separated	20 (3.9)	36 (7.1)
Widowed	150 (29.4)	12 (2.4)
Occupation (retired)	428 (83.9)	135 (26.5)
Relationship with patient		
Spouse	-	189 (37.1)
Child	-	196 (38.4)
Sibling	-	17 (3.3)
Other	-	101 (19.8)
CCI	2.91 (1.98)	-
NYHA class		
II	313 (61.4)	-
III	160 (31.4)	-
IV	33 (6.5)	-
Illness duration (months)	66.7 (76.66)	-
HFSPS	27.78 (16.61)	
SCHFI maintenance	45.44 (15.39)	
SCHFI management	39.73 (17.64)	-
CC-SCHFI maintenance		51.48 (19.69)
CC-SCHFI management		51.24 (20.39)
T1 measures		
HFSPS *(n=146 missing)*	23.88 (15.95)	-
SCHFI maintenance *(n=179 missing)*	52.13 (20.42)	
SCHFI management *(n=179 missing)*	50.13 (20.42)	-
CC-SCHFI maintenance *(n=191 missing)*		54.52 (20.63)
CC-SCHFI management *(n=191 missing)*		58.59 (19.10)

Table 1. Descriptive statistics of the participants and instruments' scores at baseline and three-months' follow-up. **Abbreviations.** CCI, Charlson Comorbidity Index; CC-SCHFI: caregiver contribution to self-care of heart failure index; HFSPS: heart failure somatic perception scale; NYHA: New York Heart Association; SCHFI: self-care of heart failure index; SD: standard deviation. Note. T0, baseline; T1, 3-month follow-up. **Notes.** Missing values were handled with the FIML estimation. Percentages may not add up to 100% due to missing values.

Measurement of scale invariance

At baseline, all the scales were fully invariant, except for the caregiver contribution to self-care management scale, which only showed partial strict invariance. Regarding the scales at the three-month follow-up, the only fully invariant scale was the patient self-care management and the caregiver contribution to self-care maintenance scale. The caregiver contribution to self-care management scale reached partial metric invariance, whereas the Heart Failure Somatic Perception Scale and self-care maintenance scales did not even reach the configural step (Appendix).

In the longitudinal invariance models, the Heart Failure Somatic Perception Scale reached partial strict invariance, whereas patient self-care maintenance and management scales reached partial scalar invariance. The caregiver contribution to self-care maintenance scale was fully invariant, whereas the caregiver contribution to self-care management only reached partial metric invariance (Appendix: Table 1b). Considering the results of the invariance analysis, the mediation model was fitted with latent factor scores because the scales were not fully invariant across groups and time.

Hypothesis testing

The autoregressive longitudinal path analysis yielded adequate fit indices (X^2 (41) = 86.78, $p < 0.001$, RMSEA = 0.047, 90%CI: 0.33-0.06, p=0.63; CFI=0.93, TLI=0.92; SRMR=0.05). The model significantly accounted for 37% of the total variance in the Heart Failure Somatic Perception Scale scores ($p<0.001$). Table 2 summarizes the indirect effects of the hypotheses we tested. Figure 1 shows the results of testing the hypothesized associations.

	Estimate (β)	95% BC bootstrapped CI	
		Lower	Upper
Indirect effects			
CC to self-care maintenance (T0) → CC to self-care maintenance (T1) → SCHFI maintenance (T1) → symptom burden (T1)	**-0.038**	-0.063	-0.021
CC to self-care maintenance (T1) → SCHFI maintenance (T1) → symptom burden (T1)	**-0.079**	-0.130	-0.043
CC to self-care management (T0) → CC to self-care management (T1) → SCHFI management (T1) → symptom burden (T1)	0.009	-0.012	0.044
CC to self-care management (T1) → SCHFI management (T1) → symptom burden (T1)	0.013	-0.016	0.060

Table 2. Standardized specific indirect effects of the longitudinal mediation model. **Abbreviations.** BC, bias corrected; CI, confidence intervals; CC, caregiver contribution; β, standardized coefficient. T0 and T1 are the time points at baseline and three months' follow-up, respectively. **Note.** The significance of the effects was obtained by the bias-corrected bootstrap confidence intervals (based on 10,000 bootstrap replications). Significant estimates are indicated in bold.

Most of our hypotheses were confirmed (Table 1, Table 2, Figure 1). Most importantly, we found that caregiver contribution to self-care maintenance positively influenced patient self-care maintenance, which, in turn, negatively influenced symptom burden. Moreover, patient self-care maintenance negatively mediated the association between caregiver contribution to self-care maintenance and symptom burden (β=-0.079, 95% BC bootstrapped CI: -0.130, -0.043). That is, better caregiver contribution to self-care maintenance led to lower symptom burden via patient self-care maintenance.

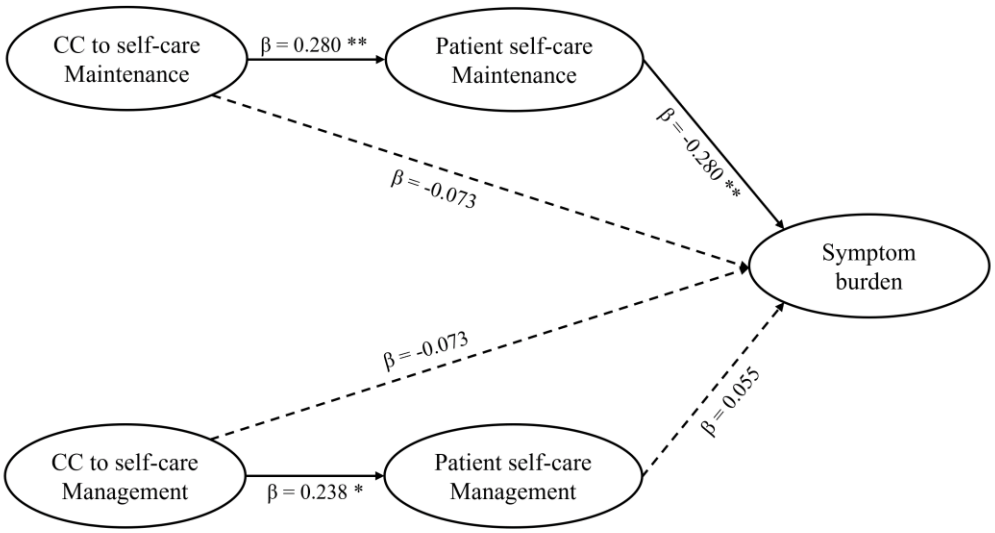

Figure 1. Results of the longitudinal path analysis. **Abbreviations.** CC: caregiver contribution, β: standardized coefficient, * $p < 0.01$; ** $p < 0.001$. **Note.** The relationship between CC to self-care maintenance and symptom burden is mediated by patient self-care maintenance (β=-0.079, 95% BC bootstrapped CI: -0.130, -0.043). The autoregressive longitudinal path analysis yielded adequate fit indices ($X2$ (41) = 86.78, $p < 0.001$, RMSEA = 0.047, 90%CI: 0.33-0.06, p=0.63; CFI=0.93, TLI=0.92; SRMR=0.05). The model significantly accounted for 37% of the total variance in the Heart Failure Somatic Perception Scale scores ($p<0.001$).

Discussion

The overall aim of this study was to investigate the influence of caregiver contribution to self-care on symptom burden in patients with heart failure, and to explore whether patient self-care mediates such a relationship. We found that caregiver contribution to self-care maintenance influenced patient symptom burden through the mediation of patient self-care maintenance. Although caregiver contribution to self-care management influenced patient self-care management, there was not a significant path between patient self-care management and symptom burden. These findings are particularly important because they a) expand the situation-specific theory of caregiver contribution to heart failure self-care, b) develop the existing knowledge about the role of caregivers in heart failure self-care and the impact of caregivers on patient outcomes.

The situation-specific theory of caregiver contribution to heart failure self-care specifies how caregiver contribution to self-care can have positive and negative outcomes on both patients and caregivers. Regarding the patient outcomes, better caregiver contribution to self-care maintenance

and management have been shown to be associated with higher patient quality of life[166] and lower mortality.[167] One study showed that caregiver contribution to self-care maintenance was positively associated with patient self-care management, and another study showed that caregiver contribution to self-care management mediated the relationship between caregiver preparedness and patient readmission at 3 months and length of hospital stay.[167] In the present study, we have shown that caregiver contribution to self-care maintenance and management influence patient self-care maintenance and management respectively, and that caregiver contribution to self-care maintenance influences patient symptom burden through the mediation of patient self-care maintenance. In practice, this means that if caregivers recommend behaviours such as physical activity, medication taking, or follow-up visits attendance, patients are better at performing such self-care behaviours and, eventually, experience lower symptom burden. Interestingly, we did not find a direct effect of caregiver contribution to self-care maintenance on symptom burden (β=-0.07, p=0.159) and this highlights that caregiver contribution to self-care maintenance improves symptom burden *only through* patient self-care. To our knowledge, this is the first study demonstrating an impact of caregiver contribution to self-care on patient symptom burden and the second one[152] demonstrating that patient self-care is a proximal outcome of caregiver contribution to heart failure self-care.

We were surprised to find that patient self-care management was not associated with symptom burden and, consequently, was not a mediator. The patient self-care management scale evaluates how quickly patients recognize heart failure symptoms (e.g., dyspnoea), how likely they implement strategies to address symptoms (e.g., reduce fluid intake), and how sure they are that the implemented remedy worked. The lack of association between patient self-care management and symptom burden could be explained by the fact that many different scenarios may occur among patients, making it difficult to find a clear and significant association. For example, in some cases, low symptom burden may be associated with low self-care management behaviours (as they would not be necessary in this scenario), while in others, high symptom burden may be associated with high self-care management behaviours[17] (as they would be implemented as a compensatory strategy in this scenario). In another

scenario, high and effective self-care management behaviours may lead to low symptom burden[168,169] (meaning that they succeeded in reducing the burden caused by the symptoms. Indeed, what is measured is the burden of symptoms, neither the mere incidence of symptoms nor the clinical signs). Therefore, the association between self-care management and symptom burden may vary over time, capturing different points of the self-care process.

In our study we also found that patient self-care maintenance influenced patient self-care management, as predicted by the theory.[170] However, we did not find any association between caregiver contribution to self-care maintenance and caregiver contribution to self-care management. So far, only two studies[171,172] found that caregiver contribution to self-care maintenance influenced caregiver contribution to self-care management. Therefore, more evidence is needed to support such a relationship.

Implications for clinical practice and research

Our study has important clinical implications in heart failure care. Although further studies are necessary to confirm what we observed, our findings suggest that interventions targeting caregiver contribution to self-care can improve patient self-care and patient symptom burden. Preventing and alleviating the burden of symptoms in patients with heart failure is essential since physical symptoms, such as dyspnoea and edema,[9,12,92,173] contribute to a lower quality of life,[8-11] and increase hospitalization[12,13] and mortality rates.[8,14]

Our results have several implications for research. First, they paved the way for further studies to confirm the association between caregiver contribution to self-care maintenance and physical symptom burden in patients with heart failure. If such a relationship is confirmed, it would be important to assess whether interventions aimed at improving caregiver contribution to self-care can also improve the burden of symptoms. Second, our findings underscore the importance of better investigating the association and the possible causality between caregiver contribution to self-care management, patient self-care management, and symptom burden. Indeed, caregiver contribution to

self-care management and patient self-care management may be associated with high symptom burden too (as in our results, although not significant). This could be explained in different ways. It could indicate that the burden caused by the symptoms was high enough to stimulate the caregiver and the patient to engage in more intense self-care management behaviours. However, it could also indicate that, despite intense self-care management behaviours, patients were still burdened by their symptoms, and therefore, these self-care management behaviours might be inadequate. Alternatively, self-care management and symptom burden may be negatively associated.

Strengths and limitations

A strength of this study is that it is one of the first contributions that shows how caregiver contribution to self-care can influence the burden of symptoms in patients with heart failure. Similarly, it is also the first to show the mediating role of patient self-care between caregiver contribution to self-care and symptom burden. Another strength is represented by the large sample size and the longitudinal nature of the data, which has allowed causal inference among the variables. Finally, invariance assessment, subsequent adjustment of the autoregressive model, and use of factorial scores represent additional strengths of the analysis because they limit threats to inference bias, which are typical of randomized controlled trials.

This study also has limitations. First, the patients were mostly in New York Heart Association class II; hence, we do not know whether the burden of symptoms experienced by patients in higher classes could have led to different results. Second, our sample purposefully recruited patients with low self-care; thus, the associations that we observed between patient self-care, caregiver contribution to self-care, and symptom burden may be specific to the group of patients with poorer self-care. Third, the measures available at the time of the study had the self-care monitoring elements embedded in the self-care maintenance scales. Consequently, it was not possible to assess whether symptom burden was differently associated to caregiver contribution to self-care maintenance or caregiver contribution to self-care monitoring. The same applies to the mediating role of patient self-care maintenance and

self-care monitoring. Finally, despite we included dummy variables for the intervention group vs the control group both for patients and caregivers to adjust the total scores, we do not know whether this has led to a complete control given that we used factor scores instead of the single items for each dimension.

Conclusions

In conclusion, the results of this study expanded the theory of caregiver contribution to heart failure self-care, showing patient self-care as an outcome of the theory. Moreover, this study showed that caregiver contribution to self-care maintenance and patients self-care maintenance can alleviate symptom burden in heart failure.

Appendix

Procedures for measurement invariance testing

For this study, we tested for both group and longitudinal invariance. Group invariance was tested across all scale administered at baseline in the three arms (e.g., caregiver contribution to self-care maintenance in Arms 1, 2 and 3) and across all scales administered at three-month follow-up. Specifically, regarding the Caregiver Contribution to Self-Care of Heart Failure Index scales, we tested group invariance between Arm 2 (in which caregivers had received the intervention) and Arm 1 plus Arms 3 (in which caregivers had not received the intervention). Regarding the Self-Care of heart failure Index 6.2 scales and the Heart Failure Somatic Perception Scale, we tested group invariance between Arm 1 and 2 (in which the patients had received the intervention) vs. Arm 3 (in which the patients had not received the intervention). Longitudinal invariance was tested for all the measures across the two time points (baseline and three-month follow-up).

Measurement invariance of all the scales was performed with multigroup confirmatory factor analysis (MGCFA)[174] using a stepwise framework,[175] in which the invariance assessment occurs at different hierarchical levels and in multiple groups or time points simultaneously. We used the robust

maximum likelihood estimator (MLR) on all invariance models, as many items in the scales were skewed (skewness and kurtosis > 1), and the Multivariate Normality Testing (MARDIA test) was significant ($p < 0.001$). For each invariance step (i.e., configural, metric, scalar, and strict), we compared the fit of the models with the differences in CFI (ΔCFI) and RMSEA (ΔRMSEA); invariance is established if ΔCFI is ≤0.01 and ΔRMSEA is < 0.015.[176] Chi square difference test was not used to judge invariance, since this method has high sensitivity to sample size.[163]

Results of group measurement invariance

The baseline starting models for the invariance testing were selected from the available literature.[78,159,177] The Heart Failure Somatic Perception Scale was specified with four factors according to Pucciarelli et al.[177] The fit was marginal due to the presence of a covariance among the residuals of items #14 and #11, and #6 and #7; $\chi 2$ (128, N = 510) = 405.79, P < 0.001; RMSEA = 0.065, P < 0.001; 90% CI, 0.06–0.07; CFI = 0.905; TLI = 0.89; and SRMR= 0.05. These covariances are reasonable because the first couple of items reflect fluid retention and the second reflect two symptoms that can coexist in heart failure. Consequently, we respecified the model with these covariances, after which the fit of the model improved: $\chi 2$ (127, N = 510) = 342.59, P < 0.001; RMSEA = 0.058, P < 0.001; 90% CI, 0.05–0.07; CFI = 0.93; TLI = 0.91; and SRMR= 0.05. The latter specification was used to test for group measurement invariance, by which we obtained full invariance at T0 (Table 1a). At T1 the starting model did not even obtain configural invariance: $\chi 2$ (258, N = 364) = 631.74, P < 0.001; RMSEA = 0.089, P < 0.001; 90% CI, 0.08–0.10; CFI = 0.86; TLI = 0.84; and SRMR= 0.08.

The self-care maintenance scale was specified on the full sample with the factor solution according to Vellone et al.[78] However, the fit of the model was unsatisfactory: $\chi 2$ (33, N = 510) = 256.69, P < 0.001; RMSEA = 0.115, P < 0.001; 90% CI, 0.10–0.13; CFI = 0.69; TLI = 0.58; and SRMR= 0.09. An exploratory factor analysis suggested the presence of two factors, which were composed of items #1, #4, #6, #7, and #9, and the other with items #2, #3, #5, #8, and #10. The first

factor was named health-promoting behaviors because all the items were related to preventive behaviors, whereas the second factor was named illness-related behaviors since all the items were related to actions to manage the disease. When we specified a new CFA with this solution, we obtained unsatisfactory fit indices due to the excessive covariances between the residuals of items #2 and #10, and #7 and #4. These covariances were reasonable because the first couple of items were related to monitoring practices that often co-occur in heart failure, and the second was related to physical activity. When we specified the CFA with these covariances we obtained marginal, although acceptable fit indices: $\chi 2$ (32, N = 510) = 104.45, P < 0.001; RMSEA = 0.067, P < 0.001; 90% CI, 0.05–0.08; CFI = 0.90; TLI = 0.86; and SRMR= 0.05. With this model, we obtained full group measurement invariance at T0. At T1 this starting model did not even obtain configural invariance: $\chi 2$ (71, N = 364) = 276.53, P < 0.001; RMSEA = 0.126, P < 0.001; 90% CI, 0.11–0.14; CFI = 0.82; TLI = 0.77; and SRMR= 0.12 (Table 1a).

The self-care management scale was specified with the factor structure according to Vellone et al.,[78] but the fit was unsatisfactory: $\chi 2$ (28, N = 298) = 55.98, P = 0.001; RMSEA = 0.082, P < 0.001; 90% CI, 0.05–0.11; CFI = 0.80; TLI = 0.79; and SRMR= 0.08. An inspection of the modification indices revealed an excessive covariance between items #13 and #15. These items were related to the consultation of a doctor or nurse for guidance and the reduction of fluid intake. After specification of this covariance, the fit of the model improved significantly: $\chi 2$ (7, N = 367) = 14.20, P = 0.048; RMSEA = 0.053, P < 0.001; 90% CI, 0.01–0.09; CFI = 0.96; TLI = 0.92; and SRMR= 0.03. The latter model was used as the baseline for testing the group measurement invariance. Table 1a indicates that with this scale we reached full invariance between the groups both at T0 and T1.

The caregiver contribution to self-care maintenance scale was specified according to Vellone et al.[79] The fit was marginal due to the presence of two correlated errors between items #8 and #5. This covariance is reasonable because these are items specifically related to adhering to the health care provider recommendations. After specification of this covariance, the fit of the model was satisfactory: $\chi 2$ (27, N = 510) = 70.82, P < 0.001; RMSEA = 0.057, P < 0.228; 90% CI, 0.04–0.07;

CFI = 0.96; TLI = 0.94; and SRMR= 0.03. This model was used to test for group measurement invariance. Table 1a shows the results of the group invariance; the scale achieved full invariance at both T0 and T1.

The caregiver contribution to self-care management scale was specified according to Vellone et al.[79] The fit of the initial model was marginal due to the presence of four correlated errors; that is, between items #14 and #13 and #13 and #12. These covariances are reasonable because the two pairs of items indicate the remedies used in case of fluid retention. After specification of these two covariances, the fit was good: $\chi 2$ (7, N = 365) = 18.96, P = 0.008; RMSEA = 0.068, P = 0.176; 90% CI, 0.03–0.11; CFI = 0.96; TLI = 0.92; and SRMR= 0.04. This model was used as a baseline to test group invariance. At baseline, the scale reached full scalar invariance, while at T1 it only achieved the configural step (Table 1a).

Results of longitudinal measurement invariance

All the models specified in this step were identical to those used to test group measurement invariance. The Heart Failure Somatic Perception Scale reached partial strict invariance (Table 1b). The self-care maintenance and management scales were partially scalar invariant, whereas the caregiver contribution to self-care management scale only reached partial metric invariance. The only fully invariant scale was the caregiver contribution to self-care maintenance scale (Table 1b).

Scale	Model	$\chi 2$	p	df	RMSEA	RMSEA (CI)	CFI	ΔCFI	ΔRMSEA	Note
Heart Failure Somatic Perception Scale (T0)	Configural	485.002	<0.001	254	0.060	(0.052 – 0.068)	0.923	-	-	
	Metric	500.894	<0.001	269	0.058	(0.050 – 0.066)	0.923	0.000	-0.002	Specified covariances: #14 and #11, #6 and #7
	Scalar	518.195	<0.001	287	0.056	(0.048 – 0.064)	0.923	0.000	-0.002	
	Strict	531.421	<0.001	305	0.054	(0.046 – 0.062)	0.925	-0.002	-0.002	
	Strict with cov.	529.780	<0.001	307	0.053	(0.046 – 0.061)	0.926	-0.001	-0.001	
	Factorial	535.350	<0.001	313	0.053	(0.045 – 0.060)	0.926	0.000	0.000	
Self-care maintenance scale (T0)	Configural	140.945	<0.001	66	0.067	(0.051 – 0.082)	0.900	-	-	
	Metric	147.697	<0.001	76	0.061	(0.046 – 0.075)	0.903	0.003	-0.006	Specified covariances: #4 and #7, #2 and #10
	Scalar	157.384	<0.001	86	0.057	(0.043 – 0.071)	0.904	0.001	-0.004	
	Strict	165.883	<0.001	95	0.054	(0.040 – 0.068)	0.905	0.001	0.003	
	Strict cov.	166.184	<0,001	97	0.053	(0.039 – 0.066)	0.907	0.002	0.001	
	Factorial	170.342	<0.001	98	0.054	(0.040 – 0.067)	0.903	-0.004	0.001	
Caregiver Contribution to Self-care maintenance scale (T0)	Configural	102.929	<0.001	54	0.060	(0.042 – 0.077)	0.958	-	-	Specified covariances: #5 and #8
	Metric	106.517	<0.001	65	0.050	(0.032 – 0.067)	0.964	0.006	-0.010	
	Scalar	118.991	<0.001	75	0.048	(0.031 – 0.064)	0.962	-0.002	-0.002	
	Strict	128.736	<0.001	85	0.045	(0.028 – 0.060)	0.962	0.000	-0.003	
	Strict cov.	127.300	0.003	86	0.044	(0.026 – 0.059)	0.964	0.002	-0.001	
	Factorial	143.805	0.001	92	0.047	(0.032 – 0.062)	0.955	-0.011	0.003	
Caregiver Contribution to Self-care maintenance scale (T1)	Configural	96.115	<0.001	54	0.070	(0.046 – 0.092)	0.955	-	-	Specified covariances: #5 and #8
	Metric	108.941	0.001	65	0.065	(0.043 – 0.086)	0.954	-0.001	-0.005	
	Scalar	128.742	<0.001	75	0.067	(0.047 – 0.086)	0.943	-0.011	-0.002	
	Strict	142.088	<0.001	85	0.065	(0.046 – 0.083)	0.940	-0.002	-0.002	
	Strict cov.	140.232	<0.001	86	0.063	(0.043 – 0.081)	0.943	0.003	-0.002	
	Factorial	158.847	<0.001	92	0.067	(0.049 – 0.085)	0.929	-0.014	0.004	
Caregiver Contribution to Self-care management scale (T0)	Configural	37.745	<0.001	14	0.090	(0.060 – 0.134)	0.927	-	-	Specified covariances: #5 and #8
	Metric	46.984	<0.001	20	0.086	(0.054 – 0.118)	0.917	-0.010	-0.004	
	Scalar	53.850	0.001	26	0.077	(0.047 – 0.106)	0.914	-0.003	-0.009	
	Strict	67.590	<0.001	32	0.078	(0.052 – 0.104)	0.891	**-0.023**	0.001	
	Partial strict*	56.909	0.002	30	0.070	(0.041 – 0.098)	0.917	0.003	-0.007	
Caregiver Contribution to Self-care management scale (T1)	Configural	28.873	0.011	14	0.100	(0.048 – 0.157)	0.916	-	-	Specified covariances: #13 and #14 #13 and #12
	Metric	41.455	0.002	19	0.109	(0.064 – 0.155)	0.874	**-0.042**	-0.009	
	-	-	-	-	-	-	-	-	-	
Self-care management scale (T0)	Configural	29.643	0.029	17	0.064	(0.020 – 0.101)	0.938			Specified covariances: #15 and #13
	Metric	37.822	0.013	21	0.066	(0.030 – 0.099)	0.918	**-0.020**	0.002	
	Scalar	41.125	0.030	26	0.056	(0.018 – 0.088)	0.926	0.008	-0.010	
	Strict	45.326	0.059	32	0.048	(0.000 – 0.078)	0.935	0.009	-0.008	
	Strict cov.	46.303	0.062	33	0.047	(0.000 – 0.076)	0.935	0.000	-0.001	
	Factorial	46.271	0.078	34	0.044	(0.000 – 0.074)	0.940	0.005	-0.003	

Heart Failure Somatic Perception Scale (T1)	Configural	631.656	<0.001	258	0.089	(0.080 – 0.098)	0.860	-	-	Specified covariances: #14 and #11; #6 and #7
	-	-	-	-	-	-	-	-	-	
Self-care maintenance scale (T1)	Configural	285.637	<0,001	69	0.131	(0.116 – 0.147)	0.812	-	-	Specified covariances: #4 and #7, #2 and #10
	-	-	-	-	-	-	-	-	-	
Self-care management scale (T1)	Configural	24.876	0.098	17	0.062	(0.000 – 0.112)	0.969	-	-	Specified covariances: #15 and #13.
	Metric	28.136	0.136	21	0.053	(0.000 – 0.100)	0.972	0.003	-0.011	
	Scalar	36.692	0.101	27	0.055	(0.000 – 0.096)	0.962	-0.010	0.002	
	Strict	45.999	0.066	33	0.058	(0.000 – 0.094)	0.949	-0.013	0.003	
	Strict cov.	46.016	0.082	34	0.054	(0.000 – 0.091)	0.953	0.003	-0.004	
	Factorial	49.874	0.049	35	0.060	(0.003 – 0.095)	0.942	-0.011	0.006	

Table 1a. Group measurement invariance across the control and experimental groups at baseline (T0) and three-month follow-up (T1). **Abbreviations**. Df=degrees of freedom; CFI=comparative fit index; RMSEA, root mean square error of approximation; CI=90% confidence interval around RMSEA; $\chi 2$=chi-square; p=p-value of $\chi 2$; ΔCFI=change in the CFI relative to the preceding model; ΔRMSEA=change in the RMSEA relative to the preceding model. **Note.** *Release of variance of item #12.

Scale	Model	χ^2	p	df	RMSEA	RMSEA (CI)	CFI	ΔCFI	ΔRMSEA	Note
Heart Failure Somatic Perception Scale	Configural	1151.554	<0.001	544	0.047	(0.043 – 0.051)	0.910			Covariances: #14 and #11, #6 and #7
	Metric	1186.162	<0.001	562	0.047	(0.043 – 0.050)	0.908	-0.002	0.000	
	Scalar	1280.180	<0.001	580	0.049	(0.045 – 0.052)	0.897	-0.011	0.002	
	Strict	1451.870	<0.001	598	0.053	(0.049 – 0.056)	0.874	**-0.023**	0.004	
	Partial strict*	1379.702	<0.001	596	0.051	(0.047 – 0.054)	0.885	-0.012	-0.002	
Self-care maintenance scale	Configural	429.919	<0.001	146	0.062	(0.055 – 0.069)	0.892			Covariances: #7 and #4, #2 and #10
	Metric	467.923	<0.001	156	0.063	(0.056 – 0.069)	0.881	-0.011	0.001	
	Scalar	625.799	<0.001	166	0.074	(0.068 – 0.080)	0.825	**-0.056**	0.011	
	Partial scalar**	508.972	<0.001	160	0.065	(0.059 – 0.072)	0.867	-0.014	0.002	
Self-care management scale	Configural	77.831	0.001	41	0.046	(0.030 – 0.062)	0.939			Covariances: #15 and #13
	Metric	96.564	<0.001	47	0.050	(0.036 – 0.065)	0.918	0.021	0.004	
	Scalar	135.519	<0.001	53	0.061	(0.048 – 0.074)	0.863	**-0.050**	0009	
	Partial scalar***	104.007	<0.001	50	0.051	(0.037 – 0.065)	0.910	-0.008	-0.010	
Caregiver contribution to Self-care maintenance scale	Configural	230.915	<0.001	128	0.040	(0.032 – 0.048)	0.964			Covariances: #5 and #8
	Metric	259.329	<0.001	139	0.041	(0.034 – 0.049)	0.958	-0.006	0.001	
	Scalar	281.660	<0.001	149	0.042	(0.034 – 0.049)	0.954	-0.004	0.001	
	Strict	316.400	<0.001	159	0.044	(0.037 – 0.051)	0.946	-0.010	0.002	
	Strict cov	314.336	<0.001	160	0.044	(0.037 – 0.051)	0.947	0.000	0.001	
	Factorial	319.672	<0.001	166	0.043	(0.036 – 0.050)	0.947	0.000	-0.001	
Caregiver contribution to Self-care management scale	Configural	87.362	<0.001	39	0.057	(0.041 – 0.072)	0.934			Covariances: #13 and #14 #13 and #12
	Metric	106.977	<0.001	45	0.060	(0.045 – 0.074)	0.916	**-0.018**	0.003	
	Partial Metric****	102.606	<0.001	43	0.060	(0.045 – 0.075)	0.919	-0.015	0.000	

Table 1b. Longitudinal measurement invariance across baseline (T0) and three-month follow-up (T1). **Abbreviations.** Df=degrees of freedom; CFI=comparative fit index; RMSEA=root mean square error of approximation; 90% CI=90% confidence interval around RMSEA; χ2=chi-square; p=p-value of χ2; ΔCFI=change in the CFI relative to the preceding model; ΔRMSEA=change in the RMSEA relative to the preceding model. **Note.** * Release of variances of items #9 and 13. ** Release of intercepts of items #2, #5, #8, #10, #9. *** release of intercepts of items #13, #14, and #15. **** Release of loadings of items #15 and #16.

How this study led to the following one

Besides the evidence that people with a chronic condition experience different levels of symptom burden and that they are differently associated with variables such as self-care behaviors, accumulating evidence also suggests that people with a chronic condition may have impaired abilities in perceiving and recognizing their symptoms due to defects in some brain structures (e.g., insular cortex) and processes (i.e., interoception).[17] While we know some about the different levels of interoceptive impairment in specific chronic conditions, nothing comparing different conditions is available in the literature. The absence of a synthesis of the evidence makes it challenging to identify potential common patterns among different chronic conditions. This motivated us to conduct the third study of this PhD thesis.

CHAPTER 5: What is the role of interoception in the symptom experience of people with a chronic condition? A systematic review.

This chapter is published in the following source:

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Abstract

Background: Interoception, the ability of the organism to sense, interpret, and regulate signals originating from within the body, plays an important role in how individuals perceive and respond to symptoms. However, there is scarce evidence on the role of interoception in the symptom experience of people with chronic conditions.

Aim: To explore the role of interoception in the symptom experience of people with a chronic condition.

Methods: Systematic review. We searched PubMed, Psychinfo, Embase, CINAHL, and Science Citation Index-Expanded. We included primary research (all study designs) addressing our study aim, published between 2013-2021, and measuring at least one dimension of interoception. Any chronic condition and any symptom were included. No language limits were applied. Only the adult population was included.

Results: We included 18 quantitative studies investigating the relationship between three interoceptive dimensions (i.e., accuracy, sensibility, awareness) and condition-specific symptoms in 10 chronic conditions. People with chronic conditions had lower interoceptive accuracy than healthy controls. Higher interoceptive sensibility was associated with lower symptom severity/frequency. Higher interoceptive accuracy was associated with lower symptom severity/frequency in half of the studies, while the other half reported the opposite. Only one study explored interoceptive awareness.

Conclusion: Interoceptive abilities are lower in patients with chronic conditions. Higher interoceptive sensibility is associated with lower symptom severity/frequency, but this relationship is unclear when it comes to interoceptive accuracy and awareness.

Keywords: Chronic Conditions; Interoception; Symptoms; Systematic Review.

Introduction

Interoception refers to a set of processes through which an organism senses, interprets, integrates, and regulates signals originating from within the body.[57] Such signals may be biochemical, mechanical, thermal, or electromagnetic. Interoceptive functioning includes the processes through which the peripheral systems communicate to the central nervous system through afferent pathways, mainly including neural (e.g., the cranial/vagal and spinal pathways) and humoral (e.g., immune and endocrine) channels. When signals reach the brain, neurons in the brain and in the spinal cord encode them. In particular, interoceptors, which are specific receptors in neurons, detect internal signals and translate them into electrical, hormonal, or other non-neural signals that are interpreted and integrated by the hypothalamus, thalamus, insula, and other cortical regions of the brain.[57,58] Finally, the central nervous system responds to the signals by communicating to the peripheral nervous system through efferent pathways, including neural and non-neural efferent pathways,[57] producing physical sensations and feelings,[59] and influencing perceptions and behaviors.[59] Responses include activation of cardiovascular, gastrointestinal, endocrine and immune systems,[59,178] as well as reactions known as sickness behaviors.[179]

As an example of interoceptive functioning, when a pain-signal originates in the periphery, it travels along pain-signaling pathways (e.g., the spinothalamic tract) and reaches the central nervous system (e.g., the thalamus). There, the pain signal is processed, integrated with emotions and memories, and translated into a conscious feeling of pain. Eventually, this process leads, for example, to the production of oxytocin and endorphins, as a chemical response to the pain-signal.[60,61] In this systematic review, we aim to synthesize and better characterize the role of interoception in the symptom experience of adults with chronic conditions.

Current research on interoception has primarily addressed interoceptive accuracy. Interoceptive *accuracy* refers to how objectively accurate one is in detecting internal bodily signals (e.g., accurately detecting the heart rate). Interoceptive accuracy can be measured with objective tests

such as the heartbeat discrimination task,[180] which requires individuals to state whether an externally-provided stimulus (e.g., tones, lights) is synchronous or asynchronous with their own heartbeat, and the heartbeat tracking task,[63] which requires individuals to count their heart beats during specified time periods.

Interoceptive sensibility and awareness are measured far less frequently. Interoceptive *sensibility* refers to the individual's belief in their interoceptive abilities as well as the degree to which individuals feel engaged by the processing of interoceptive signals[62] (e.g., perceived ability to notice when the heart rate changes). High interoceptive sensibility entails, for example, being able to detect and regulate symptom-related distress by controlling bodily sensations and, thus, being less prone to worry about uncomfortable symptoms.[64,181] Interoceptive sensibility can be assessed using self-reported questionnaires such as the Multidimensional Assessment of Interoceptive Awareness,[64] which, despite its name, measures via self-report the conscious and subjective perception of interoception.[62,182] Interoceptive sensibility can also be assessed through confidence ratings (using a Visual Analogue Scale) on how well one rates their performance during an interoceptive accuracy task (for this reason Interoceptive sensibility is sometimes addressed as *confidence*).

Interoceptive sensibility measures individual differences in the perceived ability to detect internal bodily changes but does not indicate whether this subjective interoceptive sensibility is accurate. Therefore, a strategy to address this is to combine a measure of interoceptive accuracy (e.g., the heartbeat tracking task) with a measure of interoceptive sensibility (e.g., subjective confidence in performing the task) to assess the association between subjective (perceived) and objective (actual) interoceptive ability. This third interoceptive construct is known as interoceptive *awareness*. Interoceptive *awareness* occurs on a metacognitive level and refers to the awareness of one's level of accuracy in detecting internal body signals during an interoceptive accuracy test. A high level of interoceptive awareness reflects the ability to know when they are making good or bad interoceptive decisions on their interoceptive accuracy (i.e., do my true interoceptive abilities (interoceptive

accuracy scoring) and my perceived interoceptive abilities (interoceptive sensibility scoring) match?).[62,65] Interoceptive awareness can be evaluated by analyzing the relationship between objective performance and subjective awareness of performance, for instance using a Receiver Operating Curve[66] mapping confidence onto accuracy, or a confidence–accuracy correlation[65] (i.e., Pearson's r). All these interoceptive processes (Figure 1) facilitates the cerebral coordination of homeostatic reflexes and allostatic responses.[59] In other terms, the brain uses interoceptive signals to control bodily processes and eventually maintain a physiological homeostasis. When the organism fails to efficiently process and respond to bodily signals, including symptoms, diseases may progress. Indeed, accumulating research on interoception reports that accurately detecting and responding to internal bodily signals is important for both physical and mental well-being.[183]

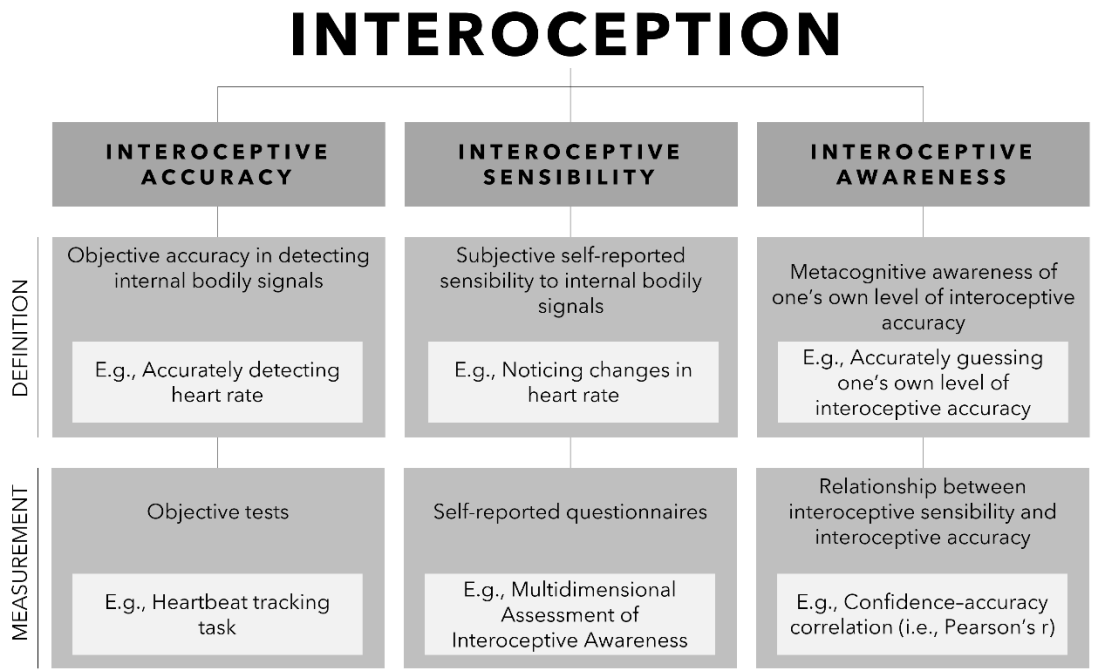

Figure 1. The three dimensions of interoception.

A symptom is a subjective physical or mental experience, appraised and defined by the person experiencing the symptom, and reflective of a bodily change.[17] Symptoms act as conscious signals to protect us from actual or potential bodily threat by stimulating action.[184] When the symptom gets to consciousness, it is 'perceived',[35] else it remains an un-detected sign. People with chronic conditions

may have symptoms that they ignore or deny (e.g., in hypoglycemia unawareness a person with diabetes person may experience hypoglycemia without noticing the signals such as sweating, irritability or tachycardia). Studying interoception is important as it can influence how individuals perceive, elaborate, and respond to symptoms.[67,68] Indeed, interoceptive processes can affect how aware one is about one's own symptoms, how accurately one perceives symptoms, and consequently how appropriately one processes and responds to symptoms.[62,68,69]

While we know some about the different levels of interoceptive impairment in specific chronic conditions and on the relationships between interoception and condition-related variables, it would be challenging, without a synthesis of the evidence, to identify the underlying commonalities among different chronic conditions. Indeed, some disease-specific and symptom-specific evidence is found in the literature, but nothing comparing different conditions is available. If there are common patterns in the relationship between interoceptive subdimensions and how symptoms are experienced by adults with different chronic conditions, this would allow investigators to draw more generalizable conclusions on the role of interoception in the symptom experience across chronic conditions. Understanding the role that interoception plays in the symptom experience may be particularly important for several reason. First, symptoms have a key role in the management of chronic illness.[17] Second, the insular cortex is the primary site for interoception, it is responsible for symptom perception, and insular defects (e.g., neuronal and connectivity loss) have been found in some chronic conditions such as heart failure.[70-73] This suggests that interoceptive characteristic can impact the symptom experience of people with a chronic condition.[71,74]

To address this gap, we synthesized and characterized the role of interoception in the symptom experience of adults with chronic conditions. Specifically, we explored a) interoceptive functioning in people with a chronic condition, and b) the association between interoceptive abilities and the symptom experience in people with a chronic condition. Eventually, such characterization may help to reveal common patterns among chronic conditions in terms of interoceptive functioning during the

symptom experience, spur the development of useful ways to incorporate interoception into established models of symptom experience, and support the development of interventions to address interoceptive characteristics to improve clinical outcomes in adults with chronic conditions.

Methods

Design

We originally aimed to synthesize both quantitative and qualitative evidence on the role of interoception in the symptom experience of adults with chronic conditions; however, only quantitative articles met our inclusion criteria. Therefore, we conducted a systematic review of quantitative studies using a narrative synthesis approach.[185,186]

Search strategies

Supported by a biomedical research librarian, we searched PubMed, Psychinfo, Embase, CINAHL, and Science Citation Index-Expanded. The main search terms included interoception, and chronic condition, or disease, or illness. We also included terms referring to the most prevalent chronic conditions (e.g., heart failure, diabetes, chronic obstructive pulmonary disease), as well as to the four sub-categories provided by the WHO's definition of chronic conditions (Table 1). MeSH terms related to the most prevalent chronic conditions were also used. We included articles published between 2013 – 2021 because the DSM-5 was published in 2013, thus previous diagnoses may be different than current diagnoses. Additionally, the MAIA instrument used to measure interoceptive sensibility was published in 2013. Finally, the three interoceptive components were considered interchangeable until 2013 when some authors in the field clarified their differences.[187,188] No language limits were applied. We only included adults ≥18 years old. The biomedical research librarian consulted in the adaptation of search terms, phrases, and strategies for each selected database. More details on the search strategies are reported in the Appendix I.

Inclusion and exclusion criteria

INCLUSION CRITERIA	• Primary research addressing the role of interoception in the symptom experience • Symptoms defined as "subjective physical or mental experiences, appraised and defined by the patient, and reflective of an altered health state or change therein"[17] and referring to the chronic condition of interest • Adults (≥ 18 years) with a chronic condition • Chronic conditions (per WHO definition: conditions with a long duration, generally slow progression, and requiring some level of health care management across time).[1,2] Such a definition includes persistent communicable conditions (e.g., HIV), noncommunicable conditions (e.g., cardiovascular diseases), long-term mental disorders (e.g., schizophrenia), and ongoing physical/structural impairments (e.g., blindness).[2,3]
EXCLUSION CRITERIA	• Non-primary research (e.g., literature reviews) • Studies exploring aspects of interoception other than its role in the symptom experience • Minors (< 18 years old) • Adults ≥ 18 years without a chronic condition as previously defined by the WHO

Table 1. Inclusion and exclusion criteria

Data extraction and synthesis

All identified citations were uploaded into EndNote X.9.3.3/2020[189] and then into the Rayyan web application for systematic reviews[190] to first remove duplicates and then conduct title and abstract screening. Two reviewers (GL and AM) independently screened the article titles and abstracts to identify those that preliminarily met inclusion criteria. Articles were flagged by each independent reviewer as "yes, keep", "no, discard" or "maybe keep the article". At the end of this first phase, the two reviewers discussed and resolved discrepancies. Afterwards, the same two reviewers proceeded to screen the full text of the chosen articles, adopting the same process (yes/no/maybe) as the first

phase. The data extraction process was documented using the PRISMA 2020 flow diagram[23] (Appendix II) and inter-rater reliability is reported below. The articles remaining after full-text review, were critically appraised and included in the review.

For each study included, we extracted data using the relevant standardized Joanna Briggs Institute (JBI) data extraction tools in JBI-SUMARI. Data extracted included characteristics of the population, geographical location, study setting, study aims, study design, type of intervention, outcomes measured and a description of the main outcomes. Any disagreement between the two reviewers on these details was resolved through discussion.

Quantitative data were synthesized using a narrative summary approach, which summarizes the quantitative evidence extracted from the included studies in words. This approach is recommended for studies with heterogeneous outcome measures where statistical pooling is not possible.[185] To provide transparency in the process, we clearly articulated the synthesis process throughout. While we aimed to create a homogeneous description of the role of interoception in the symptom experience of people with a chronic condition, we organized data creating subgroups based on the subdimensions of interoception (accuracy, sensibility, awareness) and their relationship with symptoms. Since the broader aim of this paper is to summarize the role of interoception in the symptom experience of people with a chronic condition, we organized results to highlight common patterns among chronic conditions. Therefore, we deliberately chose not to organize results based on the level of evidence to avoid segmentation. To help the reader understand the level of evidence, study designs are included in Table 2.

Quality appraisal

All studies selected for inclusion were uploaded into JBI SUMARI[191] and assessed for methodological validity using the standard JBI critical appraisal instruments, depending on the specific study type, by two independent reviewers (GL and AM). Disagreements were resolved

through discussion. Data quality was assessed independently by the same two reviewers. Regardless of data quality, all studies included underwent data extraction and synthesis. The outcomes of the quality assessment are described below.[192]

Results

The initial search identified 1360 records. After removing 534 duplicates, 826 records underwent title and abstract screening. A total of 28 remaining records underwent full-text screening. Finally, 18 remaining records were included in this review (Figure 2). Inter-rater reliability (consistency when including/excluding articles) during the title and abstract screening was 93%. During the full-text screening consistency was 91.3%.

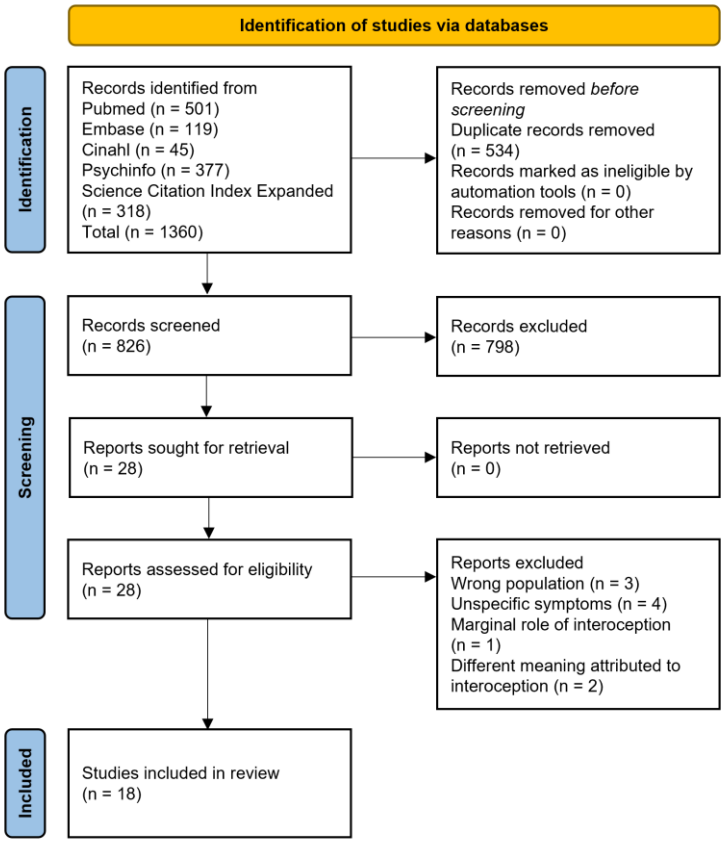

Figure 2. PRISMA Flow diagram

Quality appraisal

The results of the quality appraisal are reported in Appendix II. The two independent reviewers assessed the overall quality of the included studies as high (ranging between 75% to 100% for cross-sectional studies, 83% to 100% for quasi-experimental studies, and 69% to 85% for randomized controlled trials (RCTs)) with an inter-rater reliability of 87%.

All analytical cross-sectional studies reported inclusion and measurement criteria, and appropriate statistical analysis. Only 78% identified potential confounders and discussed strategies for dealing with them. All quasi-experimental studies clearly stated the causal relationships between variables, repeatedly measured outcomes during a complete follow-up, and adopted appropriate statistical analysis. Only 50% included a control group. All RCTs adopted a true randomization scheme and measured outcomes in a reliable way. Only 60% reported concealment to allocation group, of which 2/3 were double-blind (participant and assessors/interventionists), while 1/3 were single-blind (unblinded assessors/interventionists).

Participants

The total population size of the 18 included studies was 1347 participants. Patients' mean age ranged from 18 to 72.7 years. Most samples were predominately female (11 of 18 studies). Participants had different chronic conditions, including schizophrenia (n = 1 study), Giles de la Tourette syndrome (n = 2), Parkinson's disease (n = 1), somatoform disorders (n = 1), substance use disorder (n = 3), depressive disorder (n = 3), obsessive-compulsive disorder (n = 2), and chronic pain (n = 6). One study included patients with both depressive disorder and chronic pain.

Study	Country and setting	Study aim/s	Methods	Participants' characteristics	Main Results
Ardizzi M, et al. 2016 (Analytical Cross Sectional)	Italy (Outpatients at Perugia Mental Health Department)	• Explore interoceptive accuracy in schizophrenia patients vs. healthy controls • Explore association between interoceptive accuracy and patients' symptoms	• **Interoceptive accuracy:** Heart rate tracking task • **Positive and negative symptoms severity:** Positive and Negative Syndrome Scale for schizophrenia • **Psychopathological symptoms** in healthy controls: Symptom Checklist-90-Revised	**Patient group (schizophrenia, treated with atypical antipsychotic)** n = 23, 74% male, mean age 33.78±6.33, illness duration 9.22 ± 3.61 months. **Control group (healthy volunteers)** n = 23, 87% male, mean age 31.91±9.18	**Interoceptive Accuracy** Significantly ($p<0.05$, $r=0.483$) lower in schizophrenia patients than in healthy controls. In patients with schizophrenia: • It was positively correlated with positive symptoms severity ($p = 0.020$), especially grandiosity ($p = 0.009$)
Ateş Çöl I, et al. 2016 (Analytical Cross Sectional)	Turkey (Hospital inpatients and outpatients)	• Explore interoceptive accuracy in alcohol addicted patients • Explore association between interoceptive accuracy and alcohol craving	• **Interoceptive accuracy:** Heart rate tracking task • **Alcohol craving:** Penn Alcohol Craving Scale (PACS); Obsessive Compulsive Drinking Scale (OCDS)	**Patient group (alcohol addicted patients, sober for ≥ 2 weeks before admission)** n = 55, 90.9% male, mean age 43.38±10.8 **Control group (healthy volunteers)** n = 52, 90.4% male, mean age 41.34±11.50	**Interoceptive Accuracy** Significantly ($p<0.05$) lower in the alcohol-addicted patients (0.58±0.18) than the healthy controls (0.71±0.16). In alcohol-addicted patients: • it was ($p<0.05$) negatively correlated (correlation coefficient −0.330) with the levels of PACS

Study	Country and setting	Study aim/s	Methods	Participants' characteristics	Main Results
Di Lernia et al. 2020 (Analytical Cross Sectional)	Italy (Pain Center of the Humanitas San Pio X Clinic, Milan)	• Investigate three facets of interoception in patients with chronic pain vs. pain-free controls • Explore the association between interoception and pain severity	• **Interoceptive accuracy:** Heart rate tracking task • **Interoceptive confidence:** Visual Analogue Scale (VAS) • **Interoceptive sensibility**: Multidimensional assessment of interoceptive accuracy (MAIA) • **Pain:** Brief Pain Inventory – Short Form (BPI-SF) including a) Pain Severity Score (PSS) and b) Pain Interference Score (PIS) (we are only interested in PSS)	**Patient group (chronic primary pain OR chronic secondary musculoskeletal pain OR chronic neuropathic pain)** n = 60, 78.3% female, mean age 58.15±13.46, BMI 23.86±4.05 **Control group (healthy pain-free)** n = 20, 80% female, mean age 54±20.69, BMI24.11±4.51	**Interoceptive accuracy** • Lower in the patient group compared to controls (in particular, primary pain [0.31±0.35; p = 0.02] and neuropathic pain participants [0.35±0.27; p = 0.04] had significantly lower IAcc compared to controls [0.61±0.22]) **Interoceptive confidence** • Lower in the patient group compared to controls (in particular, primary pain [31.90±29.33; p = 0.02] and secondary musculoskeletal pain participants [32.67±29.03; p = 0.04] were less confident about their interoceptive perception compared to controls [59.05±16.43]) **Interoceptive sensibility** • No significant difference **Pain severity** • Positively predicted by interoceptive accuracy [$\beta = 0.35$, $p = 0.01$], and negatively by interoceptive confidence [$\beta = -0.287$, $p = 0.04$]. Both interaction terms were also significant IA × IC [$\beta = 0.40$, $p \leq 0.001$]
Duschek et al. 2017 (Analytical Cross Sectional)	Spain (Fibromyalgia Association of Jaén)	• Investigate interoceptive accuracy in patients with fibromyalgia vs healthy controls • Examine whether interoceptive accuracy was associated with fibromyalgia symptoms	• **Interoceptive awareness (actually, accuracy):** Heart rate tracking task • **Severity of fibromyalgia symptoms:** Fibromyalgia Impact Questionnaire (FIQ)	**Patient group (Fibromyalgia Syndrome)** n = 45, 100% female, mean age 49.93±8.81, BMI 26.98±3.70 **Control group (healthy women)** n = 31, 100%	**Interoceptive awareness (actually, Accuracy)** • Significantly lower in patients with fibromyalgia vs. controls ($p = 0.032$, $\eta^2=0.062$) • In patient with fibromyalgia, significantly negatively correlated with FIQ ($p<0.01$) → inverse relationship between

Study	Country and setting	Study aim/s	Methods	Participants' characteristics	Main Results
				female, mean age 47.13±9.38, BMI 25.41±4.41	interoceptive awareness and fibromyalgia symptom severity.
Eng et al. 2020 (Analytical Cross Sectional)	USA (Institutional Review Boards at the Icahn School of Medicine at Mount Sinai, Nathan Kline Institute for Psychiatric Research, New York University School of Medicine)	• Investigate interoceptive sensibility in patients with OCD vs. healthy controls • Evaluated the association between interoceptive sensibility and OCD symptoms	• **Interoceptive sensibility**: Multidimensional assessment of interoceptive awareness (MAIA) • **Obsessive-compulsive symptoms**: Dimensional obsessive-compulsive scale	**Patient group (obsessive-compulsive disorder)** n = 81, 65.4% female, mean age 34.1±12.6 **Control group (healthy controls)** n = 76, 51.3% female, mean age 31±10.1	Interoceptive sensibility subscales: In general: lower interoception was associated with greater OCD symptoms • Increased noticing, distracting, worrying, emotional awareness, listening, and decreased trusting of their body sensations ($p < .05$) in patients vs controls • Positive correlation between noticing subscale and symptoms related to symmetry, completeness, not-just-right experiences ($p = 0.014$, $r = 0.27$) and for concerns about responsibility for harm ($p = 0.030$, $r = 0.24$) in patients • Positive association between worrying subscale and a) concerns about responsibility for harm ($p = .004$, $r = 0.32$) and b) concerns about germs and contamination ($p = .043$, $r = -0.23$) in patients • Positive association between distracting subscale and symptoms related to unacceptable and taboo thoughts ($p = .027$, $r = -0.25$)

Study	Country and setting	Study aim/s	Methods	Participants' characteristics	Main Results
Ganos C, et al. 2015 (Analytical Cross Sectional)	UK (Non-listed)	• Examine the relationship between interoceptive accuracy and premonitory urges and tic expression	• **Premonitory urge to tic:** The Premonitory Urge for Tics Scale • **Tic severity:** Yale Global Tic Severity Scale • **Interoceptive awareness (actually, Accuracy):** heartbeat tracking task	**Patient group (Giles de la Tourette syndrome)** n = 19, 68.4% male, mean age 39.1.1±16.9 **Control group (healthy controls)** n = 25, 52% male, mean age 36±11	**Interoceptive awareness (actually, Accuracy)** • Lower in the patient group compared to controls (mean: patients 0.582±0.17; controls 0.674±0.16, p = 0.032) • Significant predictor of premonitory urges (p = 0.0076) → IA positively associated with premonitory urges (premonitory urges positively associated with severe tics, p = 0.049)
Ricciardi L, et al. 2016 (Analytical Cross Sectional)	United Kingdom (National Hospital for Neurology and Neurosurgery, London)	• Evaluate interoceptive accuracy in patients with Parkinson's disease vs healthy controls • Evaluate associations between interoceptive accuracy and symptoms in patients	• **Interoceptive sensitivity (actually, accuracy):** Heartbeat detection task • **Depression:** Hamilton Depression Score • **Anxiety:** Hamilton Anxiety Score • **Fatigue:** Fatigue Severity Scale	**Patients (Parkinson's Disease)** n=20, 65% male, mean age 61.4±9.8 years **Controls (healthy subjects)** n=20, 60% female, mean age 56.5±10.8	**Interoceptive sensitivity (actually, accuracy)** • Significantly lower in patients (0.58±0.22) versus controls (0.72±0.14) (p= 0.04) **Depressive symptoms**: higher in patients (8.7±5.8) versus controls (6.2±7.5) (p= 0.04) **Anxiety symptoms**: higher in patients (12.8±9.4) versus controls (7.9±9.5) (p= 0.05) No significant difference in **fatigue**. No significant correlations between interoceptive sensitivity and fatigue, depression, or anxiety.
Schmidt AF, et al. 2013 (Analytical Cross Sectional)	Germany (Substance Use Disorder treatment unit and outpatient centers)	• Explore the association between interoceptive accuracy and symptoms related to alcohol consumption	• **Interoceptive Awareness (actually, accuracy):** Modified heart rate tracking task • **Appetitive behaviour for alcohol**: German version of Obsessive-Compulsive Drinking Scale • **Tension Reduction Expectancy (TRE)**:	**Patients (substance use disorder)** n = 89, 56.2% male, mean age 47.49±9.19	• No direct associations between Interoceptive awareness (actually accuracy) with **drinking compulsions/obsessions** • Interoceptive awareness (actually accuracy) and TRE interacted as predictors of drinking compulsions and obsessions • Negative association between Interoceptive awareness (actually

Study	Country and setting	Study aim/s	Methods	Participants' characteristics	Main Results
			Subscale of Comprehensive Alcohol Expectancy Questionnaire		accuracy) and **self-reported compulsive drinking** ($p < 0.08$) (in substance abusers with higher TRE; but not in those with lower TRE)
de Jong M, et al. 2016 (RCT)	USA (Outpatient clinics of the Massachusetts General Hospital)	Investigate the effect of Mindfulness-Based Cognitive Therapy on interoceptive awareness and symptoms in patients with chronic pain and comorbid active depression	• **Interoceptive awareness (actually, sensibility):** Multidimensional Assessment of Interoceptive Awareness (MAIA) • **Depression symptom severity:** Quick Inventory of Depressive Symptomatology – Clinician rated (QIDS-C) • **Pain:** Pain Catastrophizing Scale (PCS)	**Intervention group (chronic pain + major depressive disorder OR Dysthymic Disorder OR Depressive disorder not otherwise specified ≥10 on the QIDS-C16)** n = 26, 76.5% female, mean age 50.06±11.68 Intervention: usual care + Mindfulness Based Cognitive Therapy (MBCT) **Control group (chronic pain + major depressive disorder OR Dysthymic Disorder OR Depressive disorder not otherwise specified ≥10 on the QIDS-C16)** n = 14, 66.7% female, mean age 51.67±10.08, receiving usual care	**Interoceptive awareness (actually, sensibility) subscales** • Emotional Awareness: increase ($p < 0.05$, $d = 0.573$) in the intervention group • Self-regulation: increase ($p = 0.001$, $d = 0.913$) in the intervention group **Depression** • In the intervention group, it decreased by the mediating effect of 'Not-Distracting' MAIA subscale ($a1 \times b1 = -3.584$, 95% CI -8.880 to -0.357) • Significant direct effect of the intervention on depression ($c' = 4.817$, $p = 0.048$) → MBCT reduced depression **Pain** • Decrease ($p = 0.041$, $d = -0.564$) of pain catastrophizing in the intervention group

Study	Country and setting	Study aim/s	Methods	Participants' characteristics	Main Results
Fissler M, et al. 2016 (RCT)	Germany (Non-clinical environment)	• Characterize deficits in interoceptive awareness in patients with depression • Investigate whether brief mindfulness training could reduce interoceptive deficits and depressive symptoms	• **Interoceptive awareness (actually, sensibility):** Multidimensional assessment of interoceptive awareness (MAIA) • **Depressive symptoms:** Beck Depression Inventory	**Intervention group (major depressive disorder)** n = 74, 56% female, mean age 42±12.5 Intervention: brief mindfulness training **Control group (healthy subjects)** n = 25, 60% female, mean age 36.4±12.5	**Interoceptive awareness (actually, sensibility)** • Improved in the intervention group compared to controls ($p < 0.005$) • In the intervention group, it was positively associated with the ability to decenter → the ability to decenter was negatively associated with depressive symptoms. **Depressive symptoms** • Significantly reduced in the intervention group ($p < 0.001$) compared to controls
Lauche R, et al., 2017 (RCT)	Germany (University hospital)	• Examine the association between interoceptive sensibility and pain in patients with chronic neck pain assigned to different training programs	• **Pain**: Visual analogue scale of 0-100 (from the German Pain Questionnaire) • **Interoceptive Awareness (actually, sensibility):** Multidimensional Assessment of Interoceptive Awareness instrument (MAIA) • **Postural Awareness**: Postural Awareness Scale	**Patient group (chronic non-specific neck pain)** n=75, 78.7% female Intervention: Tai Chi program or Neck Exercise Training	**Pain**: Reductions in pain intensity over time is positively associated with: • Pain intensity at baseline ($p < 0.001$, $r = 0.226$) • Decrease in anxiety ($p = 0.001$, $r = 0.102$) • Increase in the postural awareness ($p = 0.003$, $r = 0.078$) No other variables were associated with pain reduction.

Study	Country and setting	Study aim/s	Methods	Participants' characteristics	Main Results
Paolucci T, et al. 2017 (RCT)	Italy (Outpatient rehabilitation center)	• Determine the efficacy of the Feldenkrais method for relieving pain in patients with chronic low back pain and improve interoceptive sensibility	• **Pain:** VAS; McGill Pain Questionnaire • **Interoceptive sensibility:** Multidimensional Assessment of Interoceptive Awareness Questionnaire (MAIA)	**Patient group (chronic low back pain)** n = 26, 83% female, mean age 61.21±11.53, BMI 25.55±2.62 Intervention: Feldenkrais method **Control group (chronic low back pain)** n = 27, 81% female, mean age 60.70±11.72, BMI 26.18±2.62 Intervention: Back School group	**Pain**: Decreases ($p < 0.001$) in both groups without differences among the two groups **Interoceptive sensibility**: • All MAIA subscales significantly improved in both groups ($p < 0.001$) • In both groups, changes in pain (VAS) negatively correlated with changes in interoceptive sensibility (MAIA-N sub-score) after treatment ($p = 0.037$, $r = 0.296$)
Price CJ, et al. 2019 (RCT)	USA (Community Substance Use Disorder Outpatient Treatment Clinics)	• Examine the effects of the Mindful Awareness in Body-oriented Therapy intervention on substance use cravings and interoceptive sensibility	• **Interoceptive Awareness (actually, sensibility):** Multidimensional Assessment of Interoceptive Awareness (MAIA) • **Substance Use Craving:** 5-item Penn Alcohol Craving Scale (PACS), modified to address both alcohol and drugs.	**Patients (substance use disorder)** n = 187, 100% female, 75% white, median age 35 [22-61]. Among them: n = 74 received Mindful Awareness in Body-oriented Therapy (MABT) + Treatment as Usual; n = 67 received treatment as usual; n = 46 received Women's Health Education + Treatment as Usual.	**Interoceptive sensibility**: MABT group showed significant improvements in 6 of 8 MAIA sub-scales (Noticing: $\chi^2 = 13.51$, $p = .002$; Attention Regulation: $\chi^2 = 16.67$, $p < .001$; Emotional Awareness: $\chi^2 = 12.46$, $p = .002$; Self-regulation: $\chi^2 = 14.75$, $p < .001$; Body Listening: $\chi^2 = 17.99$, $p < .001$; and Trust: $\chi^2 = 13.18$, $p = .001$) **Substance use cravings**: Nearly significantly improved for those in MABT ($p = 0.053$)
Rae CL, et al. 2019 (RCT)	United Kingdom, London (non-listed)	• Investigate differences in interoceptive dimensions between patients with Giles de la Tourette	• **Tic Severity**: Yale Global Tic Severity Scale • **Premonitory Urge**: Premonitory Urge for Tics Scale	**Patients (Giles de la Tourette Syndrome)** n=21, 57% male, mean age 34 [18-51], mean education 15 years	**Interoceptive awareness** • No difference between patients and healthy controls • Negatively correlated with tic severity (impairment score) (measured with

Study	Country and setting	Study aim/s	Methods	Participants' characteristics	Main Results
		Syndrome vs health controls • Examine whether these differences predicted severity of premonitory sensations and tics	• **Attention Deficit Hyperactivity Disorder Symptoms**: Adult ADHD Self-Report Scale • **Obsessive Compulsive Disorder Symptoms**: Yale Brown Obsessive Compulsive Scale • **Anxiety**: State and trait versions of Spielberger Anxiety Inventory • **Interoceptive Accuracy**: Heartbeat Tracking Task; Heartbeat Discrimination Task • **Interoceptive Awareness**: Pearson correlation between heartbeat tracking task and reported confidence in Perception of Heartbeat • **Interoceptive Sensibility:** Awareness section of Body Perception Questionnaire (BPQ) • **Trait interoceptive prediction error (tIPE)**: Discrepancy between z-scored interoceptive accuracy and sensibility for both tracking and discrimination scores	**Controls (healthy subjects):** n=22, 45% female, mean age 34 [19-55], mean education 15 years	heartbeat tracking task) ($r = -0.371$, $p = 0.049$) **Interoceptive sensibility** • higher in patients (2.49) versus controls (1.97) (non-significant, $p = 0.072$) • significantly positively correlated with premonitory urge ($p = 0.003$, $r = 0.571$) • significantly positively correlated with tic severity (impairment score) ($p = 0.026$, $r = 0.431$) • significantly positively correlated with tic severity ($p = 0.008$, $r = 0.518$) **Interoceptive accuracy** • No difference between patients and healthy controls • Positively correlated with tic severity ($p = 0.049$, $r = 0.375$) **tIPE with heartbeat tracking task** significantly higher in patients (0.58) than controls (−0.53) ($p = 0.005$)

Study	Country and setting	Study aim/s	Methods	Participants' characteristics	Main Results
Berry M.P., et al., 2020 (Quasi Experimental)	USA (Pain clinics in Boston metropolitan area)	• Investigate the effects of a brief self-compassion training on pain-related brain processing	• **Interoceptive awareness (actually, sensibility):** Multidimensional Assessment of Interoceptive Awareness • **Pain:** Roland-Morris Low Back Pain and Disability Questionnaire (RMQ); and clinical low back pain intensity item of the Patient-Reported Outcomes Measurement Information System-29 (PROMIS-29)	**Patients (chronic low back pain):** n = 20, 65% female, mean age 40.15±12.56, receiving self-compassion training	The intervention: • Reduced **pain** intensity (PROMIS-29) ($p < 0.002$, $d = 0.55$) • Reduced **pain** intensity and disability (RMQ) ($p < 0.001$, $d = 0.63$) • Increased **interoceptive sensibility** ($p < 0.05$, $d = 0.46$)
Eggart M, Valdés-Stauber J. 2021. (Quasi Experimental)	Germany (Department of Psychiatry and Psychotherapy of Ulm University)	• Explore multidimensional self-reported interoception, somatic symptoms, and clinical improvements	• **Interoceptive sensibility:** MAIA • **Somatic symptom severity:** Symptom Checklist-90 SOMA • **Depression severity:** Beck Depressive Inventory	**Patients (major depressive disorder):** n = 87, 56.32% female, mean age 47.57±10.64, receiving treatment-as-usual	**Depression severity:** • Negatively associated with interoceptive sensibility, regarding the subscales of: Attention Regulation ($p < .001$), Trusting ($p < .01$), Not-Worrying ($p < .01$), and Self-Regulation ($p < .05$) **Somatic symptom severity**: • Negatively correlated with MAIA subscale 'Not-Worrying subscale' ($p < .001$) **Interoceptive sensibility**: • Negatively correlated with depression severity and somatic symptom severity (except for the Noticing and Not-Distracting subscales) • Partially mediated the effects of somatic symptom relief on treatment outcome (total indirect = 2.94 [95% BCa CI 0.99, 5.69])

Study	Country and setting	Study aim/s	Methods	Participants' characteristics	Main Results
					• Positively associated with treatment response ($p < .01$)
Schaefer M, et al. 2014 (Quasi experimental)	Germany (Outpatient Clinic for Psychotherapy)	• Test whether experimentally increasing interoceptive accuracy would decrease symptom severity	• **Interoceptive Accuracy:** Heartbeat Perception task/mental tracking task • **Depression:** Beck Depression Inventory-II • **Symptom severity:** Screening for Somatoform Disorders	**Patients (chronic unexplained physical symptoms – somatoform disorders)** n=29, 76% female, mean age 40.07±13.85 Intervention: interoceptive training **Control group** n=23, 70% female, mean age 45.26±13.57	**Interoceptive accuracy** increased over time in patients especially those with low anxiety ($p \leq 0.001$, $d = 0.596$). **Symptoms** significantly decreased over time in patients ($p \leq 0.001$, $d = 0.282$).
Schultchen D, 2019 (Quasi experimental)	Germany (Psychosomatic clinic)	• Investigate whether interoceptive accuracy is diminished in patients with OCD compared to healthy controls • Examine the effect of cognitive-behavioral therapy on interoceptive accuracy • Assess OCD, depressive and anxiety symptoms in patients	• **Severity and Symptoms of OCD:** Yale-Brown Obsessive-compulsive scale • **Depression symptoms:** Beck depression inventory • **Anxiety symptoms:** State-trait anxiety inventory • **Interoceptive Accuracy:** Heartbeat perception task	**Patients (obsessive compulsive disorder)** n=26, 54% male, mean age 28.6±7.2 years Intervention: Cognitive behavioral therapy **Controls (healthy subjects)** n=26, 26.5±5.6	**OCD symptoms:** • Reduction in patients over time ($p < 0.001$) **Interoceptive Accuracy:** • Lower in patients ($p = 0.002$, $\eta^2 = 0.17$) • Significantly negatively correlated with OCD symptoms ($r= -0.451$; $p<0.001$) • Negatively correlated with depression symptoms ($r= -0.213$; $p= 0.06$) • Negatively correlated with anxiety symptoms ($r= -0.211$; $p = 0.06$)

Table 2. Extracted data from included studies**. Abbreviations.** RCT=Randomized Controlled Trial; OCD=Obsessive Compulsive Disorder; MABT= Mindful Awareness in Body-oriented Therapy; MAIA=Multidimensional Assessment of Interoceptive Awareness; BMI=Body Mass Index; VAS=Visual Analogue Scale; MBCT=Mindfulness Based Cognitive Therapy.

Characteristics of included studies

We included 18 studies (Table 2), 15 of which were conducted in clinical settings, 1 in a non-clinical setting, and 2 did not specify the setting. Eight studies were cross-sectional, four were quasi-experimental, and six were RCTs. Interoception was operationalized as sensibility (n = 9, 50%), accuracy (n = 10, 56%), and/or awareness (n = 1, 6%) based on Garfinkel's definitions.[62] Some of the studies, however, attributed a different meaning to the three interoceptive constructs. Specifically, five studies[193-197] (28%) used "awareness" when they were actually measuring sensibility, three studies[198-200] (17%) used awareness to refer to accuracy, and one[201] (6%) used the term sensibility to refer to accuracy. For consistency, we homogenized all measurements to the Garfinkel definitions (e.g., when the Multidimensional Assessment of Interoceptive Awareness was used to measure interoceptive awareness, we coded it as measuring sensibility).

Measures

Interoception

Interoceptive sensibility was measured with the Multidimensional Assessment of Interoceptive Awareness[64] in all studies, except one[202] that used the Body Perception Questionnaire.[203,204] Interoceptive accuracy was measured with the heart beat perception task[63] (sometimes called 'heart rate tracking task' or 'heart rate detection task') by all studies, except one[202] that used the heart beat discrimination task.[205,206] Interoceptive awareness was assessed using the correlation between interoceptive accuracy and confidence.

Symptoms

Symptoms were measured differently in the various studies due to the different conditions considered. Details on the questionnaires used to assess symptoms in the included studies can be found in Table 2.

Interoceptive accuracy and symptoms

Ten studies explored interoceptive accuracy. Among them, seven[198,199,201,207-210] (involving patients with Giles de la Tourette Syndrome, pain, schizophrenia, obsessive compulsive disorder (OCD), substance use disorders, or Parkinson's disease) found that patients had lower levels of interoceptive accuracy compared to healthy controls. One study (in Giles de la Tourette Syndrome[202]) did not find any significant difference in interoceptive accuracy in patients compared to controls, and two[200,211] did not compare interoceptive accuracy between patients and healthy controls.

Four studies (n = 2 in substance use disorder,[200,209] n = 1 in OCD,[210] n = 1 in chronic pain[198]) found that higher interoceptive accuracy was associated with lower symptom severity/frequency. One study[211] on patients with somatoform disorders delivered interoceptive training and found an increase in interoceptive accuracy over time together with a decrease in somatoform symptoms, suggesting a negative association between the two variables. Four studies (n = 2 in Giles de la Tourette syndrome,[199,202] n = 1 in chronic pain,[207] n = 1 in schizophrenia[208]) found that higher interoceptive accuracy was associated with higher symptom severity/frequency. A study[201] of patients with Parkinson's disease was the only one reporting no association between interoceptive accuracy and symptom severity/frequency.

In summary, most studies reported lower levels of interoceptive accuracy in patients with a chronic condition compared to healthy controls. However, it is unclear how interoceptive accuracy is associated with symptoms since half of the studies reported a negative association and the other half reported either a null or a positive association between interoceptive accuracy and symptoms severity/frequency.

Interoceptive sensibility and symptoms

Nine studies explored interoceptive sensibility. Among them, six reported no differences in interoceptive sensibility between patients and healthy controls, either because the two groups were

indeed similar with comparable levels of interoceptive sensibility,[193,202,212] or no control group was included.[195,196,213] One study[194] conducted on patients with a major depressive disorder found lower interoceptive sensibility in patients compared to healthy controls, while a study[181] conducted on patients with OCD found higher levels of interoceptive sensibility in patients than healthy controls. One study[207] involving patients with chronic pain measured interoceptive confidence, which can be considered as interoceptive sensibility,[62] and found that it was lower in patients compared to healthy controls.

Seven studies found that higher interoceptive sensibility was associated with lower symptom severity/frequency.[194,207,212,213] Three studies[193,196,197] in substance use disorder, chronic pain, and depressive disorder showed that meditation interventions increased interoceptive sensibility while decreasing symptoms severity/frequency, suggesting a negative association between these two variables. A study[195] in patients with chronic pain found no association between interoceptive sensibility and pain. Two studies[181,202] (one in Giles de la Tourette Syndrome and the other in OCD) found that higher interoceptive sensibility was associated with higher symptom severity/frequency.

In summary, most studies reported no significant differences in the levels of interoceptive sensibility between patients with a chronic condition and healthy controls. However, most studies reported that higher interoceptive sensibility was associated with lower symptoms severity and/or frequency.

Interoceptive awareness and symptoms

Only one study[202] conducted in patients with Giles de la Tourette syndrome measured interoceptive awareness. No difference was reported in the interoceptive awareness levels between patients and controls. However, the authors found that higher interoceptive awareness was associated with lower tic severity.

Discussion

This is the first systematic review examining the role that interoception plays in how people with a chronic condition experience symptoms. We found that people with a chronic condition have lower interoceptive accuracy than healthy controls; higher interoceptive sensibility is associated with lower symptom severity/frequency, but this association is unclear when it comes to interoceptive accuracy and awareness. Only one study explored interoceptive awareness. The included studies explored a diverse range of chronic conditions, most of which appeared associated with neurodivergence. Neurodivergence refers to ways of brain functioning that are different from what is considered 'typical' and includes psychiatric and neurodevelopmental conditions, such as autism spectrum disorders.[214-216]

We were surprised by the paucity of literature investigating the relationship between interoception and symptoms among non-communicable chronic conditions (e.g., diabetes or heart failure). It is important to understand interoceptive functioning not only in mental disorders and conditions in the neurodivergent spectrum (e.g., Giles de la Tourette syndrome), but also in non-communicable chronic diseases, which are predominantly physical, because it would facilitate further understanding about how to address symptom processing and response adults with chronic illness.[17,50] Indeed, previous research reported insular impairments in chronic diseases such as heart failure and diabetes.[70-73] As the insular cortex is responsible for interoceptive functioning and symptom processing, it would be relevant to further investigate common patterns in the insular structure, interoceptive functioning and symptom processing in people with chronic diseases.

We found little evidence on how the three subdimensions of interoception interrelate. Only one study[62] investigated the three dimensions together and found that interoceptive accuracy and sensibility were both positively associated with symptoms severity, while interoceptive awareness was negatively associated with symptom severity. In people with a chronic condition, it would be relevant to know if changes in one subdimension impact other subdimensions, and how such changes

relate to symptoms. We recommend that future studies investigating the association between interoceptive functioning and symptoms should explore at least two, but ideally all three interoceptive dimensions.

As interoceptive awareness is the combination of interoceptive accuracy and sensibility, one might expect that awareness is strictly dependent on the other two. However, a previous study on a normative sample found that the three interoceptive dimensions were significantly associated only in individuals with the highest interoceptive accuracy, and that interoceptive awareness did not predict interoceptive sensibility.[62] These findings suggest that interoceptive accuracy is the central construct underpinning other interoceptive measures.[62] Interoceptive accuracy may indicate higher accuracy in symptom perception. However, it may also be that people with higher interoceptive accuracy are able to perceive symptoms accurately and consciously when they are explicitly asked to do it, but they might not always be able to detect symptoms without an explicit nudge. Indeed, interoceptive accuracy tasks explicitly ask people to count heartbeats or report synchronicity between their heartbeats and external stimuli at specific time points; they do not simply ask people to report any bodily change detected within a time window. The two studies in our review that used the heartbeat discrimination task to assess interoceptive accuracy both reported it to be positively associated with symptom severity, contrary to most of the studies using the heartbeat tracking task. This finding is consistent with the suggested explanation that the two interoceptive accuracy tasks are not completely comparable.[202]

Previous studies reported how elderly experience changes in adrenergic function, which, in turn, leads to a decline in interoceptive abilities.[122,123] Consequently, such interoceptive declines in older patients have been suggested as responsible for the lowered symptom burden reported by the elderly.[121,123] However, some studies also found that older age is associated with higher tendency to distract from body sensations, which, in turn, is associated with lower interoceptive functioning and eventually higher symptom burden[125,126] potentially due to distorted and exaggerated symptom

perception. These results suggest that distracting from bodily sensations may be dysfunctional. Instead, focusing on bodily sensations while increasing interoceptive abilities could improve body awareness, accurate symptom perception, and lead to lower symptom burden.[193] Considering such mixed results, it would be relevant to further investigate the role of age in relation to interoception and the symptom experience.

Most studies found that participants with chronic conditions had lower interoceptive accuracy compared to healthy controls. Low interoceptive accuracy reflects an impairment in accurately detecting inner bodily signals. This finding may suggest a common pattern among chronic conditions, or at least among neurodivergent ones. Indeed, given the populations observed in our pool of studies, results may not be generalizable beyond neurodivergent chronic conditions. Future studies should investigate if this pattern also exists in physical non-communicable chronic conditions, such as heart failure and diabetes. Among the studies exploring interoceptive accuracy, half reported a negative association and half a positive association with symptom severity/frequency. It should be noted that no specific pattern by type of chronic condition was identified. This suggests that the relationship between interoceptive accuracy and symptoms might vary widely across chronic conditions. As interoceptive accuracy has been proposed as the central construct predicting the other interoceptive measures,[8] it would be relevant to explore its association with the other two interoceptive subdimensions, as well as its associations with symptom patterns and response.

Except for two studies conducted in patients with Giles de la Tourette syndrome or OCD, all studies reported a negative association between interoceptive sensibility and symptom severity and/or frequency. Overall, results suggest that there may be a common pattern across different chronic conditions indicating that interoceptive sensibility is generally negatively associated with the frequency and severity of perceived symptoms, regardless of the type of chronic condition. Therefore, when interoceptive sensibility is higher, symptoms may be distinguished from more 'benign' sensations and perceived as less severe and/or less frequent. We observed little evidence regarding

the relationship between interoceptive functioning and symptom management. Indeed, studies mainly addressed the relationship between interoception and aspects of symptom perception. The MAIA questionnaire, which measures interoceptive sensibility, has various subdimensions including 'self-regulation'. Most studies reporting improvements in interoceptive sensibility also found improvements in the 'self-regulation' subdimension. This may suggest a potential positive association between interoceptive sensibility and symptom management.[68]

Conclusion

In sum, our results show that all the interoceptive subdimensions examined can influence how people with a chronic condition experience their symptoms. Generally, patients with a chronic condition seem to have lower levels of interoceptive accuracy compared to healthy controls. Interoceptive sensibility is negatively associated with symptom frequency and severity, meaning that the higher the interoceptive sensibility, the less the symptoms are perceived as exaggerated and burdensome. The relationship between interoceptive accuracy and symptom frequency / severity is inconclusive and more studies are needed to explore this association in people with a chronic condition. Only one study investigated all three interoceptive subdimensions together. More studies doing so would be helpful to assess how the interoceptive subdimensions interrelate and how they are associated with symptom frequency and severity. Plus, most of the investigated conditions are associated with neurodivergence; studies investigating the relationship between interoception and symptoms in non-communicable chronic conditions are needed.

Limitations

This systematic review has some limitations. Most of the included conditions were associated with neurodivergence, and samples of the included studies were predominantly females. This might reduce the generalizability of the results. Additionally, the included RCTs were lower in quality than the other study types, and this might weaken the results of such studies. Finally, due to the

heterogeneity of study designs and outcomes being measured, we were unable to perform a meta-analysis.

Appendix I: Search strategies

PubMed

Search	Query	Records identified
#1	("Interoception"[Mesh] OR interoception[Title/Abstract] OR interoceptor*[Title/Abstract] OR interocept*[Title/Abstract]) AND ("Chronic Disease"[Mesh] OR "chronic disease*"[Title/Abstract] OR "chronic condition*"[Title/Abstract] OR "chronic illn*"[Title/Abstract] OR "chronically ill"[Title/Abstract] OR persistent communicable condition*[Title/Abstract] OR noncommunicable condition*[Title/Abstract] OR "non communicable disease*"[Title/Abstract] OR "noncommunicable disease*"[Title/Abstract] OR long-term mental disorder*[Title/Abstract] OR ongoing impairment*[Title/Abstract] OR "diabetes mellitus"[MeSH] OR "diabetes mellitus"[Title/Abstract] OR "diabetes mellitus type 2" [Title/Abstract] OR "insulin resistance"[MeSH] OR "insulin resistance"[Title/Abstract] OR DMII[Title/Abstract] OR DM2[Title/Abstract] OR IDDM[Title/Abstract] OR NIDDM[Title/Abstract] OR "noninsulin dependent"[Title/Abstract] OR "impaired glucose tolerance" [Title/Abstract] OR "impaired glucose tolerant" [Title/Abstract] OR "heart failure"[MeSH] OR "heart failure"[Title/Abstract] OR CHF[Title/Abstract] OR HF[Title/Abstract] OR "cardiac failure"[Title/Abstract] OR "heart decompensation"[Title/Abstract] OR "coronary artery disease"[MeSH] OR "coronary artery disease"[Title/Abstract] OR "coronary arteriosclerosis"[Title/Abstract] OR "coronary atherosclerosis"[Title/Abstract] OR "angina pectoris"[Title/Abstract] OR "CAD"[Title/Abstract] OR "heart disease"[Title/Abstract] OR "myocardial infarction"[Title/Abstract] OR "unstable angina"[Title/Abstract] OR "angor pectoris"[Title/Abstract] OR "coronary thrombosis"[Title/Abstract] OR "acute coronary syndrome"[Title/Abstract] OR "myocardial ischemia"[Title/Abstract] OR "myocardial ischaemia"[Title/Abstract] OR stroke[MeSH] OR stroke*[Title/Abstract] OR hemiplegia[MeSH] OR hemiplegia[Title/Abstract] OR hemiplegias[Title/Abstract] OR paresis[MeSH] OR paresis[Title/Abstract] OR "cerebrovascular trauma"[MeSH] OR "cerebrovascular trauma"[Title/Abstract] OR "cerebrovascular accident*"[Title/Abstract] OR CVA[Title/Abstract] OR apoplexy*[Title/Abstract] OR arthritis[MeSH] OR arthritis[Title/Abstract] OR rheuma*[Title/Abstract] OR osteoarthritis[MeSH] OR osteoarthritis[Title/Abstract] OR arthritides[Title/Abstract] OR polyarthritis[Title/Abstract] OR polyarthritides[Title/Abstract] OR asthma[MeSH] OR asthma[Title/Abstract] OR "status asthmaticus"[Title/Abstract] OR "bronchial hyper reactivity"[Title/Abstract] OR asthmatic[Title/Abstract] OR wheez*[Title/Abstract] OR bronchial*[Title/Abstract] OR "obstructive lung disease*"[Title/Abstract] OR "renal insufficiency, chronic"[MeSH] OR "chronic renal insufficiency"[Title/Abstract] OR "chronic kidney failure"[Title/Abstract] OR "chronic renal failure"[Title/Abstract] OR "chronic renal disease*"[Title/Abstract] OR "chronic kidney disease*"[Title/Abstract] OR "chronic kidney disorder*" [Title/Abstract] OR CKD[Title/Abstract] OR ESRD[Title/Abstract] OR CRD[Title/Abstract] OR "chronic kidney insufficiency"[Title/Abstract] OR "pulmonary disease, chronic obstructive"[MeSH] OR "chronic obstructive pulmonary disease*"[Title/Abstract] OR "chronic bronchitis"[Title/Abstract] OR COPD[Title/Abstract] OR "chronic obstructive airway disease"[Title/Abstract] OR "chronic airflow obstruction"[Title/Abstract] OR "chronic obstructive lung disease"[Title/Abstract] OR	501

	emphysema[Title/Abstract] OR essential hypertension[MeSH] OR hypertension[Title/Abstract] OR hypertensive[Title/Abstract] OR "high blood pressure*"[Title/Abstract] OR "Cardiovascular Diseases"[Mesh] OR "Neoplasms"[Mesh] OR "Respiratory Tract Diseases"[Mesh] OR "Endocrine System Diseases"[Mesh] OR "mental disorders"[Mesh] OR "peptic ulcer"[Mesh] OR "rheumatic diseases"[Mesh] OR epilepsy[Title/Abstract] OR diabetes[Title/Abstract] OR schizophrenia[Title/Abstract] OR depression[Title/Abstract] OR amputees[Title/Abstract] OR blindness[Title/Abstract] OR sexually transmitted diseases[Title/Abstract] OR "HIV infections"[Mesh] OR "HIV/AIDS"[Title/Abstract] OR cardiovascular disease[Title/Abstract] OR chronic obstructive pulmonary diseases[Title/Abstract] OR "neoplasms"[Mesh] OR cancer[Title/Abstract] OR carcinoma*[Title/Abstract] OR "Hematologic Diseases"[Mesh] OR "blood disorders"[Title/Abstract] OR anemia[Title/Abstract] OR "nervous system diseases"[Mesh] OR "sensation disorders"[Mesh] OR "hearing impair*"[Title/Abstract] OR deafness[Title/Abstract] OR ("Diseases Category"[Mesh] AND chronic*)) AND (alladult[Filter]) AND (2013:2021 [pdat])	

PsycINFO

Search	Query	Records identified

#1	("Interoception" OR interoception OR interoceptor* OR interoceptive OR interocept*) AND ("Chronic Disease" OR "chronic disease*" OR "chronic condition*" OR "chronic illn*" OR "chronically ill" OR persistent communicable condition* OR noncommunicable condition* OR "non communicable disease*" OR "noncommunicable disease*" OR ongoing impairment* OR "diabetes mellitus" OR "diabetes mellitus" OR "diabetes mellitus type 2" OR "insulin resistance" OR "insulin resistance" OR DMII OR DM2 OR IDDM OR NIDDM OR "noninsulin dependent" OR "impaired glucose tolerance" OR "impaired glucose tolerant" OR "heart failure" OR "heart failure" OR CHF OR HF OR "cardiac failure" OR "heart decompensation" OR "coronary artery disease" OR "coronary artery disease" OR "coronary arteriosclerosis" OR "coronary atherosclerosis" OR "angina pectoris" OR "CAD" OR "heart disease" OR "myocardial infarction" OR "unstable angina" OR "angor pectoris" OR "coronary thrombosis" OR "acute coronary syndrome" OR "myocardial ischemia" OR "myocardial ischaemia" OR stroke OR stroke* OR hemiplegia OR hemiplegia OR hemiplegias OR paresis OR paresis OR "cerebrovascular trauma" OR "cerebrovascular trauma" OR "cerebrovascular accident*" OR CVA OR apoplexy* OR arthritis OR arthritis OR rheuma* OR osteoarthritis OR osteoarthritis OR arthritides OR polyarthritis OR polyarthritides OR asthma OR asthma OR "status asthmaticus" OR "bronchial hyper reactivity" OR asthmatic OR wheez* OR bronchial* OR "obstructive lung disease*" OR "renal insufficiency, chronic" OR "chronic renal insufficiency" OR "chronic kidney failure" OR "chronic renal failure" OR "chronic renal disease*" OR "chronic kidney disease*" OR "chronic kidney disorder*" OR CKD OR ESRD OR CRD OR "chronic kidney insufficiency" OR "pulmonary disease, chronic obstructive" OR "chronic obstructive pulmonary disease*" OR "chronic bronchitis" OR COPD OR "chronic obstructive airway disease" OR "chronic airflow obstruction" OR "chronic obstructive lung disease" OR emphysema OR essential hypertension OR hypertension OR hypertensive OR "high blood pressure*" OR "Cardiovascular Diseases" OR "Neoplasms" OR "Respiratory Tract Diseases" OR "Endocrine System Diseases" OR "mental disorders" OR "peptic ulcer" OR "rheumatic diseases" OR epilepsy OR diabetes OR schizophrenia OR depression OR amputees OR blindness OR sexually transmitted diseases OR "HIV infections" OR "HIV/AIDS" OR cardiovascular disease OR chronic obstructive pulmonary diseases OR "neoplasms" OR cancer OR carcinoma* OR "Hematologic Diseases" OR "blood disorders" OR anemia OR "nervous system diseases" OR "sensation disorders" OR "hearing impair*" OR deafness OR "Chronic Disease" OR "chronic disease*" OR "chronic condition*" OR "chronic illn*" OR "chronically ill" OR persistent communicable condition* OR noncommunicable condition* OR long-term mental disorder* OR ongoing impairment* OR ("Diseases Category" AND chronic*) OR "chronic condition*" OR "non communicable disease*" OR "noncommunicable disease*") Filters: adults, years 2013-2021	377

EMBASE

Search	Query	Records identified

#1	('interoception' OR 'interoception'/exp OR interoception OR interoceptor* OR interoceptive OR interocept*) AND (noncommunicable AND condition* OR 'non communicable disease*' OR 'noncommunicable disease*' OR 'diabetes mellitus'/exp OR 'diabetes mellitus' OR 'diabetes mellitus type 2'/exp OR 'diabetes mellitus type 2' OR 'insulin resistance'/exp OR 'insulin resistance' OR dmii OR dm2 OR 'iddm' OR 'iddm'/exp OR iddm OR 'niddm' OR 'niddm'/exp OR niddm OR 'noninsulin dependent' OR 'impaired glucose tolerance'/exp OR 'impaired glucose tolerance' OR 'impaired glucose tolerant' OR 'heart failure'/exp OR 'heart failure' OR chf OR 'hf' OR 'hf'/exp OR hf OR 'cardiac failure'/exp OR 'cardiac failure' OR 'heart decompensation'/exp OR 'heart decompensation' OR 'coronary artery disease'/exp OR 'coronary artery disease' OR 'coronary arteriosclerosis'/exp OR 'coronary arteriosclerosis' OR 'coronary atherosclerosis'/exp OR 'coronary atherosclerosis' OR 'angina pectoris'/exp OR 'angina pectoris' OR 'cad' OR 'heart disease'/exp OR 'heart disease' OR 'myocardial infarction'/exp OR 'myocardial infarction' OR 'unstable angina'/exp OR 'unstable angina' OR 'angor pectoris' OR 'coronary thrombosis'/exp OR 'coronary thrombosis' OR 'acute coronary syndrome'/exp OR 'acute coronary syndrome' OR 'myocardial ischemia'/exp OR 'myocardial ischemia' OR 'myocardial ischaemia'/exp OR 'myocardial ischaemia' OR 'stroke' OR 'stroke'/exp OR stroke OR stroke* OR 'hemiplegia' OR 'hemiplegia'/exp OR hemiplegia OR hemiplegias OR 'paresis' OR 'paresis'/exp OR paresis OR 'cerebrovascular trauma'/exp OR 'cerebrovascular trauma' OR 'cerebrovascular accident*' OR 'cva' OR 'cva'/exp OR cva OR apoplexy* OR 'arthritis' OR 'arthritis'/exp OR arthritis OR rheuma* OR 'osteoarthritis' OR 'osteoarthritis'/exp OR osteoarthritis OR arthritides OR 'polyarthritis' OR 'polyarthritis'/exp OR polyarthritis OR polyarthritides OR 'asthma' OR 'asthma'/exp OR asthma OR 'status asthmaticus'/exp OR 'status asthmaticus' OR 'bronchial hyper reactivity' OR 'asthmatic' OR 'asthmatic'/exp OR asthmatic OR wheez* OR bronchial* OR 'obstructive lung disease*' OR 'renal insufficiency, chronic'/exp OR 'renal insufficiency, chronic' OR 'chronic renal insufficiency'/exp OR 'chronic renal insufficiency' OR 'chronic kidney failure'/exp OR 'chronic kidney failure' OR 'chronic renal failure'/exp OR 'chronic renal failure' OR 'chronic renal disease*' OR 'chronic kidney disease*' OR 'chronic kidney disorder*' OR ckd OR 'esrd' OR 'esrd'/exp OR esrd OR crd OR 'chronic kidney insufficiency'/exp OR 'chronic kidney insufficiency' OR 'pulmonary disease, chronic obstructive'/exp OR 'pulmonary disease, chronic obstructive' OR 'chronic obstructive pulmonary disease*' OR 'chronic bronchitis'/exp OR 'chronic bronchitis' OR 'copd' OR 'copd'/exp OR copd OR 'chronic obstructive airway disease' OR 'chronic airflow obstruction'/exp OR 'chronic airflow obstruction' OR 'chronic obstructive lung disease'/exp OR 'chronic obstructive lung disease' OR 'emphysema' OR 'emphysema'/exp OR emphysema OR 'essential hypertension'/exp OR 'essential hypertension' OR (('essential' OR 'essential'/exp OR essential) AND ('hypertension' OR 'hypertension'/exp OR hypertension)) OR 'hypertension' OR 'hypertension'/exp OR hypertension OR hypertensive OR 'high blood pressure*' OR 'cardiovascular diseases'/exp OR 'cardiovascular diseases' OR 'respiratory tract diseases'/exp OR 'respiratory tract diseases' OR 'endocrine system diseases'/exp OR 'endocrine system diseases' OR 'mental disorders'/exp OR 'mental disorders' OR 'peptic ulcer'/exp OR 'peptic ulcer' OR 'rheumatic diseases'/exp OR 'rheumatic diseases' OR 'epilepsy' OR 'epilepsy'/exp OR epilepsy OR 'diabetes' OR 'diabetes'/exp OR diabetes OR 'schizophrenia' OR 'schizophrenia'/exp OR schizophrenia OR 'depression' OR 'depression'/exp OR depression OR 'amputees' OR 'amputees'/exp OR amputees OR 'blindness' OR 'blindness'/exp OR blindness OR 'sexually transmitted diseases'/exp OR 'sexually transmitted diseases' OR (sexually AND transmitted AND ('diseases' OR 'diseases'/exp OR diseases)) OR 'hiv infections'/exp OR 'hiv infections' OR 'hiv/aids' OR 'cardiovascular disease'/exp OR 'cardiovascular disease' OR (('cardiovascular' OR 'cardiovascular'/exp OR cardiovascular) AND	119

	('disease' OR 'disease'/exp OR disease)) OR 'chronic obstructive pulmonary diseases' OR (chronic AND obstructive AND pulmonary AND ('diseases' OR 'diseases'/exp OR diseases)) OR 'neoplasms'/exp OR 'neoplasms' OR 'cancer' OR 'cancer'/exp OR cancer OR carcinoma* OR 'hematologic diseases'/exp OR 'hematologic diseases' OR 'blood disorders' OR 'anemia' OR 'anemia'/exp OR anemia OR 'nervous system diseases'/exp OR 'nervous system diseases' OR 'sensation disorders'/exp OR 'sensation disorders' OR 'hearing impair*' OR 'deafness' OR 'deafness'/exp OR deafness OR 'chronic disease'/exp OR 'chronic disease' OR 'chronic disease*' OR 'chronic illn*' OR 'chronically ill'/exp OR 'chronically ill' OR 'persistent communicable' OR (persistent AND communicable AND condition*) OR 'long-term mental' OR ('long term' AND mental AND disorder*) OR (ongoing AND impairment*) OR 'chronic condition*' OR (chronic AND ('non communicable disease*' OR 'noncommunicable disease*'))) AND ([adult]/lim OR [aged]/lim) AND [2013-2021]/py AND 'article'/it AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) Filters: adults, years 2013-2021	

CINAHL

Search	Query	Records identified

#1	("Interoception" OR interoception OR interoceptor* OR interoceptive OR interocept*) AND ("Chronic Disease" OR "chronic disease*" OR "chronic condition*" OR "chronic illn*" OR "chronically ill" OR persistent communicable condition* OR noncommunicable condition* OR "non communicable disease*" OR "noncommunicable disease*" OR ongoing impairment* OR "diabetes mellitus" OR "diabetes mellitus" OR "diabetes mellitus type 2" OR "insulin resistance" OR "insulin resistance" OR DMII OR DM2 OR IDDM OR NIDDM OR "noninsulin dependent" OR "impaired glucose tolerance" OR "impaired glucose tolerant" OR "heart failure" OR "heart failure" OR CHF OR HF OR "cardiac failure" OR "heart decompensation" OR "coronary artery disease" OR "coronary artery disease" OR "coronary arteriosclerosis" OR "coronary atherosclerosis" OR "angina pectoris" OR "CAD" OR "heart disease" OR "myocardial infarction" OR "unstable angina" OR "angor pectoris" OR "coronary thrombosis" OR "acute coronary syndrome" OR "myocardial ischemia" OR "myocardial ischaemia" OR stroke OR stroke* OR hemiplegia OR hemiplegia OR hemiplegias OR paresis OR paresis OR "cerebrovascular trauma" OR "cerebrovascular trauma" OR "cerebrovascular accident*" OR CVA OR apoplexy* OR arthritis OR arthritis OR rheuma* OR osteoarthritis OR osteoarthritis OR arthritides OR polyarthritis OR polyarthritides OR asthma OR asthma OR "status asthmaticus" OR "bronchial hyper reactivity" OR asthmatic OR wheez* OR bronchial* OR "obstructive lung disease*" OR "renal insufficiency, chronic" OR "chronic renal insufficiency" OR "chronic kidney failure" OR "chronic renal failure" OR "chronic renal disease*" OR "chronic kidney disease*" OR "chronic kidney disorder*" OR CKD OR ESRD OR CRD OR "chronic kidney insufficiency" OR "pulmonary disease, chronic obstructive" OR "chronic obstructive pulmonary disease*" OR "chronic bronchitis" OR COPD OR "chronic obstructive airway disease" OR "chronic airflow obstruction" OR "chronic obstructive lung disease" OR emphysema OR essential hypertension OR hypertension OR hypertensive OR "high blood pressure*" OR "Cardiovascular Diseases" OR "Neoplasms" OR "Respiratory Tract Diseases" OR "Endocrine System Diseases" OR "mental disorders" OR "peptic ulcer" OR "rheumatic diseases" OR epilepsy OR diabetes OR schizophrenia OR depression OR amputees OR blindness OR sexually transmitted diseases OR "HIV infections" OR "HIV/AIDS" OR cardiovascular disease OR chronic obstructive pulmonary diseases OR "neoplasms" OR cancer OR carcinoma* OR "Hematologic Diseases" OR "blood disorders" OR anemia OR "nervous system diseases" OR "sensation disorders" OR "hearing impair*" OR deafness OR "Chronic Disease" OR "chronic disease*" OR "chronic condition*" OR "chronic illn*" OR "chronically ill" OR persistent communicable condition* OR noncommunicable condition* OR long-term mental disorder* OR ongoing impairment* OR ("Diseases Category" AND chronic*) OR "chronic condition*" OR "non communicable disease*" OR "noncommunicable disease*") Filter: adults, years 2013-2021	45

Science Citation Index - Expanded

Search	Query	Records identified
#1	(((((AB=(Interoception) OR AB=(interoception) OR AB=(interoceptor*) OR AB=(interoceptive) OR AB=(interocept*)) AND (AB=(Chronic Disease) OR AB=(chronic disease) OR AB=(chronic condition*) OR AB=(chronic illn*) OR AB=(chronically ill) OR AB=(persistent communicable condition) OR AB=(noncommunicable condition*) OR AB=(non communicable disease*) OR AB=(noncommunicable disease*) OR AB=(long-term mental disorder) OR AB=(ongoing impairment*) OR AB=(diabetes mellitus) OR AB=(diabetes mellitus) OR AB=(diabetes mellitus type 2) OR AB=(insulin resistance) OR AB=(insulin resistance) OR AB=(DMII) OR AB=(DM2) OR AB=(IDDM) OR AB=(NIDDM) OR AB=(noninsulin dependent) OR AB=(impaired glucose tolerance) OR AB=(impaired glucose tolerant) OR AB=(heart failure) OR AB=(heart failure) OR AB=(CHF) OR AB=(HF) OR AB=(cardiac failure) OR AB=(heart decompensation) OR AB=(coronary artery disease) OR AB=(coronary arteriosclerosis) OR AB=(coronary atherosclerosis) OR AB=(CAD) OR AB=(heart disease) OR AB=(myocardial ischemia) OR AB=(stroke) OR AB=(hemiplegia) OR AB=(paresis) OR AB=(cerebrovascular trauma) OR AB=(cerebrovascular accident) OR AB=(CVA) OR AB=(apoplexy) OR AB=(arthritis) OR AB=(rheuma*) OR AB=(osteoarthritis) OR AB=(arthritides) OR AB=(polyarthritis*) OR AB=(asthma) OR AB=(status asthmaticus) OR AB=(bronchial hyper reactivity) OR AB=(asthmatic) OR AB=(bronchial*) OR AB=(obstructive lung disease) OR AB=(chronic renal insufficiency) OR AB=(chronic kidney failure) OR AB=(chronic renal failure) OR AB=(chronic renal disease*) OR AB=(chronic kidney disease*) OR AB=(chronic kidney disorder*) OR AB=(CKD) OR AB=(ESRD) OR AB=(CRD) OR AB=(chronic kidney insufficiency) OR AB=(chronic obstructive pulmonary disease*) OR AB=(chronic bronchitis) OR AB=(COPD) OR AB=(chronic obstructive airway disease) OR AB=(chronic airflow obstruction) OR AB=(chronic obstructive lung disease) OR AB=(emphysema) OR AB=(hypertension) OR AB=(hypertensive) OR AB=(high blood pressure) OR AB=(Cardiovascular Disease) OR AB=(Neoplasm*) OR AB=(Respiratory Tract Diseases) OR AB=(Endocrine System Diseases) OR AB=(mental disorders) OR AB=(rheumatic diseases) OR AB=(epilepsy) OR AB=(diabetes) OR AB=(schizophrenia) OR AB=(depression) OR AB=(amputees) OR AB=(blindness) OR AB=(sexually transmitted diseases) OR AB=(HIV infection*) OR AB=(HIV/AIDS) OR AB=(cancer) OR AB=(carcinoma*) OR AB=(Hematologic Disease*) OR AB=(blood disorder*) OR AB=(anemia) OR AB=(nervous system diseases) OR AB=(sensation disorders) OR AB=(hearing impair*) OR AB=(deafness))) NOT AB=(child)) NOT AB=(children)) NOT AB=(pediatric)) NOT AB=(paediatric) Refined by publication years: 2013 or 2014 or 2015 or 2016 or 2017 or 2018 or 2019 or 2020 or 2021 Document Types: Article; NOT Web of Science Categories: Pediatrics	318

Appendix II – Critical appraisal

II.I JBI checklist for Analytical Cross-Sectional Studies

	Ardizzi M., et al., 2016	Ates Çöl I., et al., 2016	Di Lernia D., et al., 2020	Duschek S., et al., 2017	Eng GK., et al., 2020	Ganos C., et al., 2015	Rae CL., et al., 2019	Ricciardi L., et al., 2016	Schmidt AF., et al., 2016	Total
Were the criteria for inclusion in the sample clearly defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
Were the study subjects and the setting described in detail?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
Was the exposure measured in a valid and reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
Were objective, standard criteria used to measure the condition?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
Were confounding factors identified?	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	78%
Were strategies to deal with confounding factors stated?	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	78%
Were the outcomes measured in a valid and reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
Total	100%	75%	100%	100%	100%	100%	100%	75%	100%	

II.II JBI checklist for Quasi-Experimental Studies

	Berry M.P., et al., 2020	Eggart M., et al., 2021	Schaefer M, et al., 2014	Schultchen D., et al., 2019	Total
Is it clear in the study what is the cause and what is the effect?	Yes	Yes	Yes	Yes	100%
Were the participants included in any comparisons similar?	N/A	N/A	Yes	Yes	100%
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	N/A	N/A	Yes	Yes	100%
Was there a control group?	No	No	Yes	Yes	50%
Were there multiple measurements of the outcome both pre and post the intervention/exposure?	Yes	Yes	Yes	Yes	100%
Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	Yes	Yes	Yes	Yes	100%
Were the outcomes of participants included in any comparisons measured in the same way?	N/A	N/A	Yes	Yes	100%
Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes	100%
Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	100%
Total	83.3%	83.3%	100%	100%	

II.III JBI checklist for Randomized Controlled Trials

	De Jong M., et al., 2016	Fissler M., et al., 2016	Lauche R., et al., 2017	Paolucci T., et al., 2017	Price C.J., et al., 2019	Total
Was true randomization used for assignment of participants to treatment groups?	Yes	Yes	Yes	Yes	Yes	100%
Was allocation to treatment groups concealed?	Unclear	Yes	Yes	Yes	No	60%
Were treatment groups similar at the baseline?	Yes	Yes	Yes	Yes	Yes	100%
Were participants blind to treatment assignment?	No	Yes	No	No	No	20%
Were those delivering treatment blind to treatment assignment?	No	No	No	No	No	0%
Were outcomes assessors blind to treatment assignment?	No	Unclear	Yes	Yes	No	40%
Were treatments groups treated identically other than the intervention of interest?	Yes	Yes	Yes	Yes	Yes	100%
Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Yes	Yes	Yes	Yes	Yes	100%
Were participants analyzed in the groups where they were randomized?	Yes	Yes	Yes	Yes	Yes	100%
Were outcomes measured in the same way for treatment groups?	Yes	Yes	Yes	Yes	Yes	100%
Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes	Yes	100%
Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	100%
Was the trial design appropriate, and any deviations from the standard RCT decide accounted for in the conduct and analysis of the trial?	Yes	Yes	Yes	Yes	Yes	100%
Total %	69.23%	85%	85%	85%	69.23%	

CHAPTER 6: Discussion and conclusion

This PhD project aimed to advance the science of symptoms across chronic conditions by a) clustering patients based on their physical and psychological symptoms and predicting symptom cluster membership based on variables other than symptoms; b) assessing the influence of caregiver contribution to self-care on symptom burden and the mediating role of patient self-care; and c) exploring the role of interoception in the symptom experience of people with a chronic condition.

First, we identified clusters of patients based on different intensities and combinations of psychological and physical symptoms. We also found that symptom-cluster membership could be predicted by some clinical/sociodemographic variables. These results are relevant because they highlight the importance of addressing clusters of symptoms, instead of individual symptoms, to facilitate a comprehensive detection of symptoms and to develop tailored strategies for symptom management. Knowing to which symptom cluster a patient belongs to could facilitate the delivery of personalized symptom management strategies, with an efficient resource allocation. Indeed, knowing the existence of symptom clusters and the symptom cluster a patient belong to could allow healthcare professionals to deliver the specific care needed for the monitoring and management of symptoms depending on their intensity and combination. This would contribute to avoid the standardization of care and, instead, would promote patient-centered care, which focuses on maximizing patients' physical and emotional well-being[217] and have been shown to contribute to improved patient outcomes, better use of resources, decreased healthcare costs, and increased care satisfaction.[218]

In most cases, we observed that physical and psychological symptoms go together. However, we also found that psychological symptoms may be very high without affecting physical symptoms. This suggests that somatic alterations can influence psychological responses and cognition, as some investigators previously reported,[118] instead of the other way around. This indicates that physical symptoms should be closely monitored as they may exert a leading role and may trigger psychological symptoms. Similar to previous studies,[16,103,120] we also found that women experienced higher

symptom burden than men, and patients with higher psychological symptoms experienced lower quality of life.[102] Vongmany et al.[16] suggested that psychological symptoms in chronic ill patients may contribute to poorer self-management behaviors. We did not observe any significant difference in self-care management among clusters. However, we did observe that patients with the lowest symptom burden had the highest level of self-care maintenance. This suggested that the association between symptoms and the various dimensions of self-care needed further assessment, also considering potential mediation effects. Therefore, we explored that in the second study of this PhD project.

Furthermore, previous studies reported that younger patients experience either equal[98-100] or higher symptom burden,[121] compared to older patients. Contrarily, we found that younger patients were less burdened from both physical and psychological symptoms. The authors of the above-mentioned studies argued that one possible reason for the lower symptom burden experienced by older patients could be due to declines in interoception, which, in the elderly, occurs due to changes in adrenergic function.[122,123] However, the literature also report that older age is associated with an increased tendency to distract from bodily sensations, which, in turn, is associated with lower interoceptive abilities and higher symptom burden.[55,124-126] Thus, our results seem to confirm that older patients may suffer from greater interoceptive impairments, but in a way that such impairment might lead to a distorted and exaggerated perception of symptoms, resulting in a more burdensome symptom experience. These results highlighted the need to deepen the understanding of the role of interoception in the symptom experience of people with a chronic condition. Thus, we did that in the third study of this PhD project.

Innovatively, we also predicted symptom cluster membership using clinical and sociodemographic variables (See chapter 3 “Cluster analysis of heart failure patients based on their psychological and physical symptoms and predictive analysis of cluster membership”). Although future research should further replicate this type of predictive analysis on larger samples and

considering even more variables, this analysis revealed that variables easily available in the clinic (in our case, NYHA class and sleep quality) were particularly useful in predicting symptom cluster membership. These results are supported by the literature reporting significant association between sleep disturbances and physical symptoms like dyspnoea and edema, as well as psychological symptoms of anxiety and depression.[129-131] NYHA class has been found associated with psychological symptoms, especially depressive symptoms,[132,133] and, as per definition, higher NYHA class implies higher physical symptom severity.[134] Relying on variables other than symptoms to predict symptom cluster membership has potential to allow healthcare professionals, as well as researchers, to predict the symptom cluster membership of individual patients, without necessarily asking or having access to any symptom-specific information, and therefore facilitate the process of managing symptoms.

In the second study, we found that higher caregiver contribution to self-care maintenance was associated with higher patient self-care maintenance, which, in turn, was associated with lower symptom burden. We also found that patient self-care maintenance mediated the effect of caregiver contribution to self-care maintenance on symptom burden. In practice, this means that if caregivers recommend behaviors such as physical activity, medication taking, or follow-up visit attendance, patients are better at performing such self-care behaviors and, eventually, experience lower symptom burden. Interestingly, we did not find a direct effect of caregiver contribution to self-care maintenance on symptom burden ($\beta = -0.07$, $P = .159$), and this highlights that caregiver contribution to self-care maintenance improves symptom burden only through patient self-care. These findings are particularly relevant for the science of symptoms because they clarify the relationship among caregivers' contribution, self-care behaviors and symptom burden. These results expand the situation specific theory of caregiver contribution to self-care[51] and the current knowledge on caregiver contribution to self-care. Indeed, these results highlight that caregivers do play a role in patients care and their contribution to self-care can be helpful in reducing the symptom burden experienced by the patients.

Although further studies are necessary to confirm what we observed, these results suggest that targeting caregivers to increase their contribution to self-care may be a strategy to eventually improve patient self-care and patient symptom burden. Our findings also showed that caregiver contribution to self-care management positively influenced patient self-care management, as predicted by the theory,[170] but they did not reveal any association between caregiver contribution self-care management and symptom burden, or between patient self-care management and symptom burden. The lack of association between patient self-care management and symptom burden may be due to the fact that many different scenarios can potentially occur, making it difficult to find a strong and unique explanation of the relationship between these variables. For instance, in some cases, low symptom burden may be associated with low self-care management behaviours (as the latter would not be necessary), while in other cases high symptom burden may be associated with high self-care management[17] (as the latter would be implemented as a compensatory strategy). In another scenario, high and effective self-care management behaviours may lead to low symptom burden,[168,169] potentially indicating that they succeeded in reducing the burden caused by the symptoms. Therefore, the association between self-care management and symptom burden may vary over time, capturing different points of the self-care process.

Besides the findings that people with a chronic condition experience different levels of symptom burden and that they are differently associated with variables such as self-care behaviors, accumulating evidence also suggests that people with a chronic condition may have impaired abilities in perceiving and recognizing their symptoms due to defects in some brain structures (e.g., insular cortex) and processes (i.e., interoception).[17] While we know some about the different levels of interoceptive impairment in specific chronic conditions, nothing comparing different conditions is available in the literature. Without a synthesis of the evidence, it is challenging to identify potential common patterns among different chronic conditions. For this reason, we conducted the third study.

In the third study, we found that people with a chronic condition have lower interoceptive accuracy than healthy individuals (i.e., chronic ill patients are less accurate than healthy subjects in detecting internal bodily changes) and that higher interoceptive sensibility is associated with lower symptom severity/frequency (i.e., higher subjectively reported sensibility toward the perception of internal bodily changes is associated with lower self-reported symptom severity/frequency). These findings suggest that common patterns do exist among chronic conditions, indicating that chronically ill people struggle to accurately perceive their symptoms. Further, when ill people have higher levels of interoceptive sensibility they will be more able to a) distinguish symptoms from more 'benign' sensations and b) perceive them as less exaggerated and burdensome. These results are important because they show how interoceptive dimensions can influence how people with a chronic condition experience their symptoms. Thus, these results can support the development of future research and interventions targeting interoception to improve the symptom perception process in people with a chronic condition. This is inevitably pivotal for subsequently manage symptoms. Indeed, knowing that people with a chronic condition have lower interoceptive abilities and that higher interoceptive abilities are instead associated with lower perceived symptom burden, suggests that it may be beneficial to improve interoceptive abilities in people with a chronic condition. There are some evidence of interventions (e.g., meditations) that seem to be able to improve interoceptive abilities in some populations.[70,219] Thus, the synthesis provided in this systematic review highlights that it would be important to test interventions and implement strategies aiming to improve interoceptive abilities in adults with a chronic conditions.

Finally, we noticed that most of the studies exploring the role of interoception in the symptom experience addressed conditions associated with neurodivergence (i.e., ways of brain functioning that are different from what is considered 'typical' and includes psychiatric and neurodevelopmental conditions such as autism spectrum disorders).[214-216] Future studies should also explore interoceptive functioning in non-communicable chronic diseases (e.g., heart failure), which are predominantly physical.[17,50] This is even more important when considering that previous research reported insular

impairments in chronic diseases such as heart failure and diabetes.[70-73] As the insular cortex is responsible for interoceptive functioning and symptom processing, it would also be relevant to investigate the relationship among the insular structure, interoceptive functioning, and symptom processing in people with chronic diseases.

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Research Portfolio Appendix

Publications

- **Locatelli G.,** Iovino P., Pasta A., Jurgens C., Vellone E., Riegel B. (2023) A cluster analysis of heart failure patients based on their symptoms and a predictive analysis of symptom cluster membership. *Journal of Advanced Nursing* DOI:10.1111/jan.15890

- **Locatelli G.**, Iovino P., Jurgens C., Alvaro R., Rasero L., Riegel B., Vellone E. (2023). The influence of caregiver contribution to self-care on symptom burden in patients with heart failure and the mediating role of patient self-care: a longitudinal mediation analysis. Journal of Cardiovascular Nursing doi: 10.1097/JCN.0000000000001024 PMID: 37550831.

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- Piil K., **Locatelli G.,** Laegaard Skovhus S., Tolver A., Jarden M. (2022). Family-centred care in neuro-oncology: a longitudinal mixed-methods feasibility study. *Neuro-Oncology* (Vol. 24, Suppl. 2) https://doi.org/10.1093/neuonc/noac174.154

- **Locatelli G.**, Matus A., Ausili D., James R., Vellone E., Riegel B. (2022) What is the role of interception in the symptom experience of people with a chronic condition? A systematic review. *The 19th European Doctoral Conference Nursing Science – EDCNS. HBScience* (Vol. 13, Suppl. 1) https://doi.org/10.1007/s16024-022-00377-z

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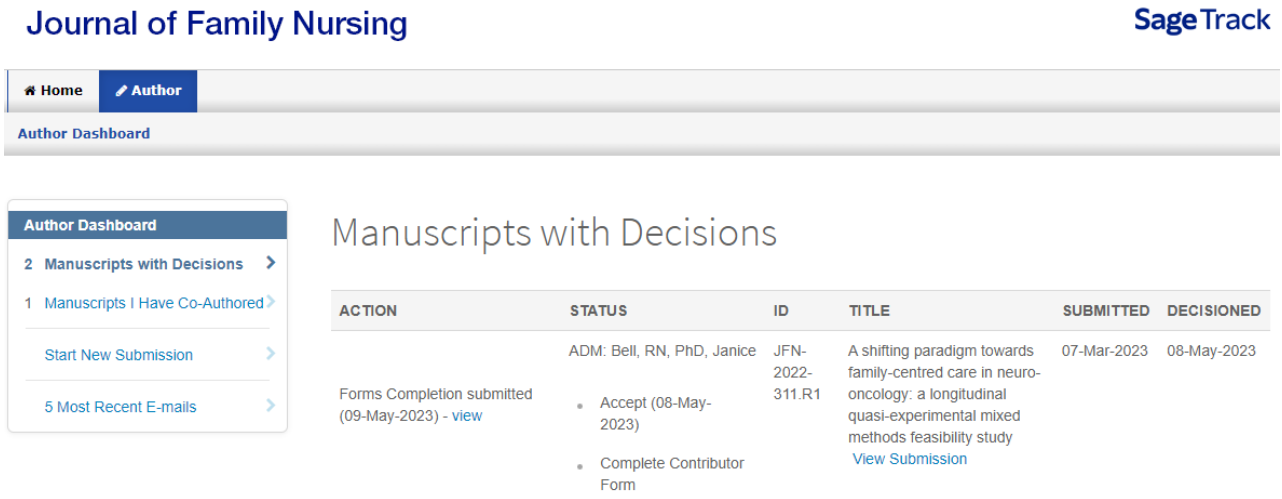
- Locatelli G., Iovino P., Jurgens Y. C., Alvaro R., Uchmanowicz I., Rasero L., Riegel B., Vellone E. (2023) Patient self-care mediates the relationship between caregiver contributions and symptom burden in heart failure. *This abstract will be published in November 2023 in the conference proceedings of the American Heart Association.*

Proof of articles accepted for publication and proof of refereeing

- Piil K., **Locatelli G**., Laegaard-Skovhus S., Tolver A., Jarden M. (2023). Family-centred care in neuro-oncology: a longitudinal quasi-experimental mixed methods feasibility study. *Journal of Family Nursing* (Accepted for publication).



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Cluster analysis of heart failure patients based on their psychological and physical symptoms and predictive analysis of cluster membership

Giulia Locatelli, Paolo Iovino, Alessandro Pasta, Corrine Y. Jurgens, Ercole Vellone, Barbara Riegel

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Abstract

Aim

Patients with heart failure experience multiple co-occurring symptoms that lower their quality of life and increase hospitalization and mortality rates. So far, no heart failure symptom cluster study recruited patients from community settings or focused on symptoms predicting most clinical outcomes. Considering physical and psychological symptoms together allows understanding how they burden patients in different

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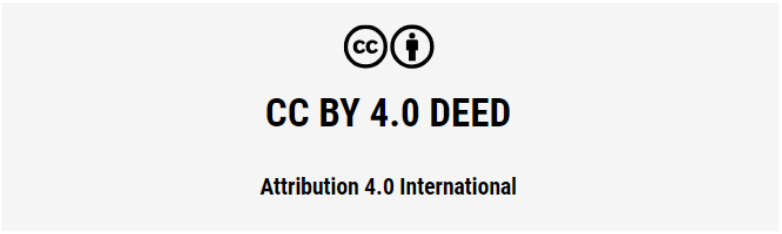

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PAPER	AUTHORS' STATEMENTS	SIGNATURE
Cluster analysis of heart failure patients based on their psychological and physical symptoms and predictive analysis of cluster membership.	LOCATELLI – I acknowledge that the extent of my contribution to this paper is 50%	
	IOVINO – I acknowledge that the extent of my contribution to this paper is 20%	
	PASTA – I acknowledge that the extent of my contribution to this paper is 8%	
	JURGENS – I acknowledge that the extent of my contribution to this paper is 5%	
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The influence of caregiver contribution to self-care on symptom burden in patients with heart failure and the mediating role of patient self-care: a longitudinal mediation analysis.	LOCATELLI – I acknowledge that the extent of my contribution to this paper is 50%	
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