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## A Systematic Review of Biological Mechanisms of Fatigue in Chronic Illness


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# A Systematic Review of Biological Mechanisms of Fatigue in Chronic Illness

## Abstract

Fatigue, a commonly reported symptom, is defined as an overwhelming, debilitating, and sustained sense of exhaustion that decreases the ability to function and carry out daily activities. To date, cancer researchers have been in the forefront in investigating the possible biological mechanisms of fatigue, identifying inflammation, dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, and activation of the autonomic nervous system. The purpose of this systematic review is to describe fatigue and what is known about the biological mechanisms described in cancer in five chronic, noninfectious illnesses: heart failure, multiple sclerosis, chronic kidney disease, rheumatoid arthritis, and chronic obstructive pulmonary disease. We searched PubMed and EMBASE using *fatigue* as a major Medical subject headings (MeSH) heading with each individual disease added as a search term followed by each biological mechanism. We included only primary research articles published in English between 1996 and 2016 describing studies conducted in adult humans. We identified 26 relevant articles. While there is some evidence that the biological mechanisms causing fatigue in cancer are also associated with fatigue in other chronic illnesses, more research is needed to explore inflammation, the HPA axis, and the autonomic nervous system, and other mechanisms in relation to fatigue in a variety of chronic illnesses.

## Keywords

fatigue, inflammation, hypothalamic-pituitary-adrenal axis, autonomic nervous system, heart failure, multiple sclerosis, chronic kidney disease, rheumatoid arthritis, chronic obstructive pulmonary disease

## Disciplines

Cardiology | Cardiovascular Diseases | Circulatory and Respiratory Physiology | Endocrinology, Diabetes, and Metabolism | Medical Humanities | Medicine and Health Sciences | Neurology | Nursing | Sleep Medicine

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A Systematic Review of Biological Mechanisms of Fatigue in Chronic Illness

Abstract

Fatigue is a commonly reported symptom defined as an overwhelming, debilitating, and sustained sense of exhaustion that is unpleasant and decreases the ability to function and carry out daily activities. To date, cancer researchers have been in the forefront in investigating the possible biological mechanisms of fatigue. Investigators of cancer related fatigue have identified the biological mechanisms of inflammation, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, and activation of the autonomic nervous system. The purpose of this systematic review is to describe fatigue and what is known about these biological mechanisms of fatigue in five chronic, non-infectious illnesses: heart failure, multiple sclerosis, chronic kidney disease, rheumatoid arthritis, and chronic obstructive pulmonary disease. We searched PubMed and EMBASE using “fatigue” as a major MESH heading with each individual disease added as a search term followed by each biological mechanism. We included only primary research articles published between 1996 and 2016 that were conducted in adult humans and written in English. We identified 26 relevant articles. While there is some evidence that the biological mechanisms causing fatigue in cancer are also associated with fatigue in other chronic illnesses, more research is greatly needed to explore inflammation, the HPA axis, and the autonomic nervous system and other mechanisms in relation to fatigue in a variety of chronic illnesses.

Key words: fatigue, inflammation, hypothalamic-pituitary-adrenal axis, autonomic nervous system, heart failure, multiple sclerosis, chronic kidney disease, rheumatoid arthritis, chronic obstructive pulmonary disease.

Fatigue has been defined as an overwhelming, debilitating, and sustained sense of exhaustion that is unpleasant and

decreases the ability to function and carry out daily activities (Cella et al., 2007). Fatigue is reported by up to 45% of the US population and greatly reduces overall quality of life (Ricci, Chee, Lorandean, & Berger, 2007). Fatigue that is chronic and unresponsive to rest may be a sign of underlying pathology (Jorgensen, 2008) and chronic illness (Ricci et al., 2007). Much of the research on fatigue has been conducted in cancer patients, but fatigue is also known to occur commonly in persons with heart failure, multiple sclerosis, chronic kidney disease, rheumatoid arthritis, and chronic obstructive pulmonary disease (Junghaenel, Christodoulou, Lai, & Stone, 2011). Fatigue may also be a prodromal symptom for acute myocardial infarction (McSweeney et al., 2003) and major depression (Fava, Grandi, Canestrari, & Molnar, 1990). It may be a different entity in healthy and disease states but this is not fully understood at this point. In chronic illness, fatigue may be a protective factor signaling the body to rest.

Despite the prevalence of fatigue and its negative impact on the human experience, research exploring mechanisms of fatigue in different disease states is limited. Investigators of cancer have led the way in describing and exploring the underlying mechanisms of fatigue. As described below, cancer-related fatigue is thought to be caused by inflammation, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, and/or activation of the autonomic nervous system (Bower, 2014; Ryan et al., 2007; Saligan et al., 2015). Although many studies investigating biological mechanisms of fatigue have focused on only one possible mechanism (e.g. inflammation), these biological pathways can influence each other and activate other systems (Figure 1). For example, activation of the sympathetic nervous system, a branch of the autonomic nervous system, can produce a proinflammatory response (Pongratz & Straub, 2014). Perhaps it is the complexity of these

issues that has resulted in so little research in the area.

The purpose of this systematic review is to describe fatigue and what is known about the biological mechanisms of fatigue in five chronic, non-infectious illnesses: heart failure (HF), multiple sclerosis (MS), chronic kidney disease (CKD), rheumatoid arthritis (RA), and chronic obstructive pulmonary disease (COPD).

### Methods

With the support of a medical librarian we searched using PubMed and EMBASE using “fatigue” as a major MESH heading with each individual disease (e.g. “heart failure”) added as a search term followed by each mechanism (e.g. inflammation). We included only primary research articles from 1996-2016 that were conducted in adult humans and written in English. The initial search resulted in 970 articles (Figure 2). After removing duplicates, 656 article titles and abstracts were assessed for relevance. Thirty-eight full text articles were reviewed, with 12 more excluded because they did not investigate fatigue in an illness of interest (i.e., HF, MS, CKD, RA or COPD) with discussion of one of three specific mechanisms (i.e., inflammation, HPA axis, or autonomic nervous system). Electronic searches were supplemented by manual searching of reference lists and reviews. This process produced another 2 articles on RA. Twenty-six articles fulfilled the inclusion criteria and were independently reviewed by the four authors. All articles judged to be potentially relevant were discussed by the group before including them in this systematic review.

### Cancer-Related Fatigue



Prior literature reviews have focused on possible biological mechanisms or etiologies of cancer-related fatigue (Bower, 2014; Ryan et al., 2007; Saligan et al., 2015). Cancer-related fatigue is commonly reported in relation to cancer treatments; however, fatigue may be present before treatment and may increase during therapy. Fatigue may limit the receipt of optimal courses of treatment due to early discontinuation and fatigue may be a prognostic factor in cancer survival (Bower, 2007). Research on possible biological mechanisms of cancer-related fatigue has been robust because such understanding is believed to potentially lead to targeted interventions to improve fatigue and ultimately quality of life.

#### Mechanisms of fatigue in cancer

Possible biological mechanisms of cancer-related fatigue include inflammation, dysregulation of the HPA axis, and activation of the autonomic nervous system (Bower, 2014; Saligan et al., 2015). Inflammation related to the release of inflammatory cytokines such as interleukin (IL)-1 beta, IL-6 and tumor necrosis factor (TNF) alpha has been implicated in cancer-related fatigue prior to treatment, during treatment and after treatment (Bower, 2014). Dysregulation in the HPA axis has been implicated in cancer-related fatigue with alterations in cortisol levels (Saligan et al., 2015) or cytokine production (Saligan et al., 2015) and resulting increased inflammation. In addition, activation of the autonomic nervous system with increased sympathetic activity and reduced parasympathetic activity may contribute to cancer-related fatigue (Bower, 2014).

**Inflammation.** Inflammation is a component of immune function and patients with cancer have increased levels of inflammatory markers (e.g. TNF alpha, IL-6) that are associated with fatigue levels (Ryan et al., 2007; Saligan et al., 2015).

For example, prior to treatment, patients with acute myelogenous leukemia had elevated inflammatory markers, which were associated with fatigue levels (Meyers, Albitar, & Estey, 2005). Similarly, patients with ovarian cancer had elevated levels of IL-6 that were associated with fatigue prior to surgery (Lutgendorf et al., 2008).

Cancer treatments have also been found to increase fatigue and inflammation during treatment and after treatment (Bower, 2014). During radiation treatment for breast or prostate cancer, fatigue was found to be associated with C reactive protein (CRP) and IL-1 levels (Bower et al., 2009). A similar result was found in breast cancer patients undergoing chemotherapy, with fatigue associated with IL-6 levels (Liu et al., 2012). Patients with advanced colorectal, esophageal and non-small cell lung cancer who were receiving both radiation and chemotherapy had fatigue levels associated with increased inflammation (IL-6) (Bower, 2014; Wang et al., 2010). After treatment for cancer, fatigue can persist for 5-10 years or even longer (Bower et al., 2006). Both TNF receptor II (Bower et al., 2011) and CRP (Alexander, Minton, Andrews, & Stone, 2009) levels have been associated with fatigue one month after the completion of treatment in patients with breast cancer.

**HPA Axis.** Dysregulation of the HPA axis may be a mechanism in cancer-related fatigue or may cause inflammation that ultimately produces fatigue (Bower, 2014; Saligan et al., 2015). Anti-inflammatory properties may be affected by altering glucocorticoid production by the HPA axis and by regulating HPA axis cytokine production (McEwen et al., 1997). Cortisol levels were higher in breast cancer patients reporting fatigue compared to their counterparts without fatigue (Bower et al., 2005). Cortisol levels were also higher and cortisol variability was reduced in patients with ovarian cancer reporting fatigue

before cancer treatment (Weinrib et al., 2010).

**Autonomic Nervous System.** The autonomic nervous system, both the sympathetic and parasympathetic branches, is thought to play a role in cancer-related fatigue (Bower, 2014; Ryan et al., 2007) because an increased sympathetic response may increase inflammation. There may also be a vagal response from cancer treatments that induces “sickness behavior” (Ryan et al., 2007). In patients with breast cancer, fatigue was associated with elevated levels of norepinephrine (sympathetic response) and lower heart rate variability (parasympathetic response) (Fagundes et al., 2011).

Using cancer-related fatigue as the gold standard for comparison, the next sections explore five non-infectious illnesses to describe fatigue and explore the similarity between mechanisms. Table 1 outlines the measures used to study inflammation, the HPA axis and the autonomic nervous system for each disease. Table 2 includes the measures of fatigue used in each study.

### Fatigue of Heart Failure

Fatigue and dyspnea are the hallmark symptoms of chronic HF, but there is surprisingly little research on the fatigue of HF. In a qualitative study, HF fatigue was described as having both bodily and mental aspects (Falk, Granger, Swedberg, & Ekman, 2007). The bodily experience of fatigue was described by patients as a feeling of lacking strength and energy and feeling sleepy. The mental aspects of fatigue were described as demoralization and intellectual deficiency. Restorative activities (e.g., social interaction) alleviated fatigue in this small sample of patients with chronic HF.

The fatigue of HF may reflect interacting peripheral and central factors (Witte & Clark, 2004). Peripheral or muscle fatigue is typically described as a deficiency in peripheral blood flow and skeletal muscle function leading to exercise-induced fatigue (Coats, 1998; Kränkel et al., 2003; Piepoli, Scott, Capucci, & Coats, 2001). Exercise training is proposed as the appropriate treatment for peripheral fatigue. Others speak about peripheral fatigue as a contributor to central fatigue of HF (Marzilli, 2014). The manner in which peripheral and central factors interact in HF needs further study, but for the purposes of this review we focused on central fatigue. In HF, greater fatigue is associated with worse clinical outcomes (Perez-Moreno et al., 2014). Smith and colleagues (Smith, Kupper, de Jonge, & Denollet, 2010) found that both severe exertional fatigue and severe general fatigue significantly predicted an increased mortality rate.

### Mechanisms of Fatigue of Heart Failure

Studies of mechanisms of fatigue in HF are limited and clearly more research is needed. Fatigue in HF has been attributed to illness severity (Jasiukeviciene et al., 2008) chronic hyponatremia, (Rai, Whaley-Connell, McFarlane, & Sowers, 2006) sleep apnea (Köhnlein, Klante, Elliott, & Welte, 2001), and depression (Fink et al., 2012; Jasiukiavichene & Vasiliauskas, 2006; Smith, Gidron, Kupper, Winter, & Denollet, 2009). Others discuss the fatigue of HF in terms of vital exhaustion, a psychological state characterized by unusual fatigue and depression, which has been linked to elevated levels of pro-inflammatory cytokines (Herrmann-Lingen et al., 2003).

**Inflammation.** Several investigative teams have studied the link between fatigue of HF and inflammation. Fink and colleagues found that fatigue was associated with HF severity as measured by the Seattle HF Model but cytokine levels were not associated with fatigue (Fink et al., 2012). Two teams have proposed dietary treatments to reduce inflammation. One team improved fatigue in HF patients by supplementing ubiquinol + L-carnitine to reduce pro-inflammatory cytokines (Kumar et al., 2007). Another team is currently studying the influence of supplemental lycopene and omega-3 fatty acids on fatigue in HF patients (Lennie et al., 2013). These nutritional approaches address components in the mitochondrial electron transport chain pathway, a deficiency that is rare except in liver disease (Paradies, Paradies, Ruggiero, & Petrosillo, 2014). Such dietary approaches to influencing the fatigue of HF represent a unique approach to a problem that is poorly understood.

**HPA Axis.** Few investigators have studied the influence of the HPA axis on the fatigue of HF. In a study of coronary artery disease patients (48 of 83 participants had HF), decreased thyroid hormone concentrations were independently associated with higher levels of physical fatigue and lower morning cortisol levels were independently associated with higher levels of mental fatigue (Bunevicius et al., 2012).

**Autonomic Nervous System.** The effect of the autonomic nervous system on the symptom of fatigue has not been studied in HF.

#### Fatigue in Multiple Sclerosis

Fatigue is common in people with MS and is similar to fatigue reported by individuals with other chronic illnesses and healthy individuals (Krupp, 2003). Fatigue of MS is disabling, as assessed by self-report and by performance-based measures of motor and cognitive function. Motor fatigue is significantly greater in MS than healthy individuals (Djaldetti, Ziv, Achiron, & Melamed, 1996). Memory and conceptual thinking are decreased in MS compared to healthy controls and both decline over the time course of the disease (Krupp & Elkins, 2000). Fatigue is associated with psychological distress and depressed mood along with neurological impairment; depressed mood influences the experience of fatigue in MS (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989). Patients who are distressed and depressed have higher levels of fatigue (Kroencke, Lynch, & Denney, 2000); (Krupp et al., 2002). Fatigue is a common feature that is associated with unemployment in patients with MS (Cadden & Arnett, 2015).

### Mechanisms of Fatigue in MS

Few studies have investigated possible mechanisms of fatigue in MS, perhaps believing that fatigue is a physiological adaptation to the pathology of MS (Krupp & Elkins, 2000). One possible explanation that may be unique to MS is involvement of the central nervous system. In MS there may be changes in the premotor, limbic, basal ganglia or brainstem area that decrease motivation or motor readiness resulting in fatigue (Krupp, 2003). Immune function, specifically inflammatory cytokines (Iriarte, Subirá, & de Castro, 2000), is implicated as a possible cause of fatigue in MS as are alterations in the neuroendocrine system (Powell, Moss-Morris, Liossi, & Schlotz, 2015).

**Inflammation.** One MS study focused solely on inflammation. Markers of systemic inflammation were not associated with self-report fatigue levels (Giovannoni, Thompson, Miller, & Thompson, 2001). Injection of interferon beta, a type of cytokine therapy used in MS to balance pro-and anti-inflammatory agents in the brain, can reduce the rate of MS relapses. However, 4 hours after injection of interferon beta, patients reported higher fatigue scores that were associated with the percentage of granulocytes relative to total leukocytes, suggesting an increased inflammatory response (Goebel et al., 2005). In another study, increased CD8+ T cells and cortisol levels were associated with fatigue in MS suggesting a possible contribution of both inflammation and HPA axis to fatigue (Gold et al., 2011). TNF alpha and interferon gamma were higher in patients with MS who reported fatigue (Heesen et al., 2006).

**HPA axis.** Cortisol, a common marker of stress, regulates the immune system and energy metabolism. Fatigue is associated with lower waking cortisol levels and larger awakening cortisol responses in MS (Powell et al., 2015). MS patients with fatigue had higher levels of adrenocorticotrophic hormone, a compound that can increase cortisol production and release, than those who did not report fatigue.

**Autonomic Nervous System.** In one study, hand grip (one test of autonomic function) was associated with self-reported fatigue scores (Merkelbach, Dillmann, Kölmel, Holz, & Müller, 2001). Increased vagal activity occurred in younger patients with MS (less than 45 years old) who reported fatigue (Keselbrener et al., 2000).

#### Fatigue in Chronic Obstructive Pulmonary Disease

Fatigue is common, often severe and disabling in COPD (Baltzan et al., 2011). Although dyspnea is the primary symptom that interferes with patients' lives, fatigue is the next most common symptom (Paddison, Effing, Quinn, & Frith, 2013). Dyspnea and fatigue scores are associated with impaired physical functioning (Woo, 2000) and reduced ability to perform daily activities (Kapella, Larson, Patel, Covey, & Berry, 2006). Fatigue can increase COPD progression, negatively affect health status and quality of life, and lead to disability in these patients (Paddison et al., 2013); (Baghai-Ravary et al., 2009). Increasing fatigue levels also predict future hospitalizations (Paddison et al., 2013).

### Mechanisms of Fatigue in COPD

Although fatigue is known to be common in COPD, there is little research on mechanisms of the fatigue. There may be an association between fatigue and inflammation (Al-Shair et al., 2011) and between fatigue and the HPA axis in patients with COPD (Schuetz et al., 2015). Research studying the association between fatigue and the autonomic nervous system is needed in patients with COPD.

**Inflammation.** Only one study of patients with COPD assessed the association between fatigue and inflammatory markers of TNF alpha, CRP and IL-6 (Al-Shair et al., 2011). Only higher levels of TNF alpha were associated with fatigue in patients with COPD.

**HPA axis.** Only one study investigated the association between fatigue and adrenal function in COPD. These investigators did not find an association between fatigue and cortisol levels (Schuetz et al., 2015).



**Autonomic Nervous System.** We did not find any studies investigating the association of the autonomic nervous system and fatigue in COPD.

### Fatigue in Chronic Kidney Disease

Fatigue is one of the most common symptoms reported by people living with chronic kidney disease (CKD), with an average prevalence of 71% (Murtagh, Addington-Hall, & Higginson, 2007). Patients with CKD have described fatigue as a constant lack of energy (A. E. Horigan, 2012) that investigators have attributed to both physical and mental domains. Fatigue is especially prevalent in those with end-stage renal disease receiving hemodialysis (CKD5) (Caplin, Kumar, & Davenport, 2011; Jablonski, 2007; Weisbord et al., 2005). One study found that 14.7% of the patients with CKD5 had fatigue scores higher than twice the standard deviation of the mean for healthy volunteers (Koyama et al., 2010). Fatigue in these patients is associated with reduced quality of life, increased the risk of cardiovascular events, and reduced survival (Bossola, Vulpio, & Tazza, 2011; A. Horigan, Rocchiccioli, & Trimm, 2012; A. E. Horigan, 2012; Koyama et al., 2010). Fatigue predicts cardiovascular events in CKD5, independent of accepted risk factors of age, diabetes, malnutrition, and a history of cardiovascular disease (Koyama et al., 2010).

### Mechanisms of Fatigue in Chronic Kidney Disease

Mechanisms of fatigue in chronic kidney disease are largely understudied. However, existing studies suggest that inflammation and the autonomic nervous system may be associated with the fatigue of CKD (Bossola, Di Stasio, Giungi, Rosa, & Tazza, 2015; Cruz, Mahnensmith, & Perazella, 1997; Fujii et al., 2013).

**Inflammation.** CKD is thought to be a pro-inflammatory state; however, little is known regarding the inflammatory pathways involving fatigue. One study revealed that fatigue in CKD5 was significantly associated with increased levels of IL-6 (Bossola et al., 2015). No other studies exploring inflammatory pathways in relation to the fatigue of CKD were found.

**HPA Axis.** No studies investigating the relationship between the HPA axis and fatigue in CKD were found.

**Autonomic Nervous System.** One study compared autonomic function in CKD5 to that of healthy people (Fujii et al., 2013; Fukuda et al., 2008). In CKD5 patients there was a positive association between impaired autonomic function and fatigue.

### Fatigue in Rheumatoid Arthritis

RA is an autoimmune disease characterized by joint pain, tenderness and inflammation. It is accompanied by several factors impacting quality of life, including sleep disturbances, pain, depression, and fatigue (Jump, Fifield, Tennen, Reisine, & Giuliano, 2004; Pollard, Choy, Gonzalez, Khoshaba, & Scott, 2006). Fatigue has been reported in about 80% of persons with RA and was rated as severe by 50% (Pollard et al., 2006). Individuals with RA describe fatigue as a loss of physical and mental energy, or weariness and lack of motivation, that is overwhelming (Hewlett et al., 2005). While patients consider

management of their fatigue a treatment priority, it is infrequently addressed by health care providers and rarely considered a primary outcome in RA research (Hewlett et al., 2005; Hewlett, Nicklin, & Treharne, 2008).

### Mechanisms of Fatigue in Rheumatoid Arthritis

Several treatments targeting improvement in RA disease activity have also reduced fatigue. For example, fatigue was reduced when pharmacologic agents were given to reduce inflammation caused by disease activity (Almeida et al., 2016; Chauffier, Salliot, Berenbaum, & Sellam, 2012), when physical activity was increased to limit physical deconditioning (Cramp et al., 2013), and when psychosocial interventions were used to improve coping strategies and promote behavior change (Cramp et al., 2013). Because these studies were not designed to focus on fatigue, no effort was given to elucidating the mechanisms underlying RA related fatigue. The success of these varied approaches in reducing RA related fatigue, albeit limited, suggests that multiple mechanisms lead to RA related fatigue (Cramp et al., 2013).

**Inflammation.** The inflammatory activity that characterizes RA as measured by swollen/tender joint counts, erythrocyte sedimentation rates (ESR), CRP, and the Disease Activity Score 28 (a composite score), has an inconsistent relationship with RA related reports of fatigue (Bergman et al., 2009; van Hoogmoed, Franssen, Bleijenberg, & van Riel, 2010). Patients reporting either the least or the greatest fatigue have minimal evidence of inflammation (low swollen joint counts and low CRP), whereas patients reporting moderate fatigue have high swollen joint counts and CRP (Lee et al., 2014). Few measures of inflammation have been associated with RA-related fatigue in cross-sectional (Bergman et al., 2009; van

Hoogmoed et al., 2010) or longitudinal studies (Druce, Jones, Macfarlane, Verstappen, & Basu, 2015; Feldthusen, Grimby-Ekman, Forsblad-d'Elia, Jacobsson, & Mannerkorpi, 2016; Repping-Wuts, Fransen, van Achterberg, Bleijenberg, & van Riel, 2007; Treharne et al., 2008). RA related fatigue has a mixed association with IL-6 in chronically stressed patients. In-vivo plasma levels of IL-6 have not been associated with RA-related fatigue, but increased in-vitro stimulated cellular production of IL-6 and reduced glucocorticoid inhibition of IL-6 have been associated with fatigue (Davis et al., 2008).

Capitalizing on the use of pharmacological interventions for RA that reduce joint inflammation and inhibit pro-inflammatory cytokines, several investigative teams sought to determine whether fatigue was reduced following commencement of these treatments. After beginning anti-TNF treatment, 70% of patients who were non-responsive to disease modifying anti-rheumatoid drugs reported reduced fatigue levels; effects were sustained in 80% of participants one year later (Druce, Jones, Macfarlane, & Basu, 2015b). Responders were more likely to be non-hypertensive, non-depressed, and non-steroid using seropositive females reporting good mental health and low disability levels (Druce, Jones, et al., 2015b). Changes in fatigue were not directly related to inflammation or disease activity but were related to reductions in pain, mental health, depression, and disability (Druce, Jones, Macfarlane, & Basu, 2015a). Evidence that RA related fatigue continues to be reported even after disease remission confounds our understanding of the possible role of inflammation in RA related fatigue (Druce, Bhattacharya, Jones, Macfarlane, & Basu, 2016). Collectively, this limited evidence is inconclusive regarding a precise role for inflammation in RA related fatigue.

**HPA Axis.** No studies investigating the relationship between the HPA axis and fatigue in RA were found.

**Autonomic Nervous System.** No studies investigating the relationship between the autonomic nervous system and fatigue in RA were found.

### Discussion

While investigators of cancer lead the way in defining possible mechanisms of fatigue, little research has been done investigating possible biological mechanisms of the common symptom of fatigue in other chronic illnesses. In this review we synthesized the current state of the literature describing inflammation, HPA axis and the autonomic nervous system as possible mechanisms of fatigue in patients with HF, MS, COPD, CKD and RA—common chronic conditions associated with persistent and disabling fatigue.

We found studies investigating the association between fatigue and inflammation in HF, MS, COPD, CKD and RA. However, there were conflicting reports in MS and RA where increased inflammation was not consistently associated with elevated levels of inflammatory markers. Possible reasons for this discrepancy could be related to the procurement and processing of the blood samples, disease severity, small sample sizes or other treatment effects. In addition, common inflammatory markers tested were IL-6, TNF alpha and CRP; perhaps there are other pro-inflammatory and anti-inflammatory markers associated with fatigue that have not been tested as yet.

Studies investigating fatigue and the HPA axis were only found in patients with HF, MS and COPD. Cortisol is a commonly used measure of the HPA axis. Cortisol levels were associated with mental fatigue in HF, fatigue levels in MS but

not in patients with COPD. However, in several illnesses these were only single studies, so few conclusions can be drawn. There may be other mechanisms that are unique to specific disease processes.

The autonomic nervous system and fatigue were studied in patients with HF, MS and CKD. The autonomic nervous system was implicated in peripheral fatigue in patients with HF; notably, only HF distinguished between peripheral or central fatigue. Impaired autonomic function was associated with fatigue in patients with MS and CKD. Typically, a battery of tests is used to evoke both sympathetic and parasympathetic responses. There was variability in the measurement of autonomic function across the HF, MS, and CKD studies. Without consistent measurements across disease states it is difficult to discern if these mechanisms of fatigue are the same among the diseases.

There are few studies testing the HPA axis or the autonomic nervous system as mechanisms for fatigue in the chronic diseases we examined. Even for studies of inflammation and fatigue, the methods used to collect specimens varied significantly (e.g. time of day when samples were collected). There is a circadian effect for inflammatory markers, the HPA axis, and the autonomic nervous system (Kalsbeek et al., 2012; Li et al., 2011). If this circadian effect was not accounted for in the studies, results may be suspect.

Another limitation is that self-reported fatigue was measured by a variety of different instruments. Some of the fatigue measures were subscales of more general instruments. For example, the Profile of Mood States measures vigor and depression along with fatigue (Curran, Andrykowski, & Studts, 1995). As investigators continue to study fatigue, a more uniform measure such as the Patient-Reported Outcomes Measurement Information System (PROMIS®) fatigue measure

would allow for comparisons across studies and diseases. Finally, there is the possibility that negative studies were not published. Absence of these findings impact our conclusions of possible mechanisms of fatigue.

Other factors that may contribute to fatigue in chronic illnesses include anemia, depression, sleep disorders (Ryan et al., 2007), and genetic risk factors (Bower, 2014) (e.g. *IL6* single nucleotide polymorphisms). These factors may be mechanisms of fatigue and need to be explored in future studies.

### Conclusions and Future Directions

While there is evidence of some underlying biological mechanisms of fatigue in cancer and the other chronic illnesses we explored, there are still gaps and areas of limited knowledge. Inflammation, the HPA axis, and the autonomic nervous system may interact to cause or accentuate fatigue, but more research is greatly needed to explore these mechanisms and others. Consistent measurements of self-reported fatigue and biological mechanisms are needed in order to compare and contrast different disease states. Because fatigue is a commonly reported symptom that can be debilitating, understanding biological mechanisms is essential in order to test targeted interventions.

The National Institutes of Health/National Institute of Nursing Research (NINR) recommends common data elements for measuring fatigue <https://cde.nlm.nih.gov/formView?tinyId=QktmQ9BqM>. At the time of this writing, NINR is seeking input from stakeholders regarding common data elements for measuring biomarkers such as cytokines (IL-1beta, IL-6, IL-10) for inflammation and free cortisol for HPA axis. Using standardized measurements of both patient-reported outcomes and

biomarkers should be considered when designing future research in order to facilitate comparisons across disease states and patient populations.

<b>Table 1. Inflammation, HPA axis, and Autonomic Nervous System Measures used in Chronic, Non-infectious Diseases</b>						
	<b>Cancer</b>	<b>Heart Failure</b>	<b>Multiple Sclerosis</b>	<b>COPD</b>	<b>Chronic Kidney Disease</b>	<b>Rheumatoid Arthritis</b>
<b>Inflammation</b>	<p><u>TNF-alpha:</u> (Saligan LN et al., 2015; Ryan JL , et al., 2007; Fink et al. 2012)</p> <p><u>IL-6:</u> (Saligan LN et al., 2015; Ryan JL , et al., 2007; Bower, 2014; Lutgendorf , 2008;</p>	<p><u>TNF-alpha:</u> (Fink et al., 2012; Kumar et al., 2007; Lennie et al., 2013)</p> <p><u>sTNFR1 and sTNFR2:</u> (Lennie et al., 2013)</p> <p><u>IL-6:</u> (Fink et al., 2012; Kumar et al., 2007)</p> <p><u>IL-10:</u> (Fink et al., 2012;</p>	<p><u>Urinary neopterin excretion:</u> (Giovannoni, 2001)</p> <p><u>CRP:</u> (Giovannoni, 2001)</p> <p><u>Soluble intercellular adhesion molecule-1:</u> (Giovannoni, 2001)</p> <p><u>IFN <math>\gamma</math>:</u> (Goebel,</p>	<p><u>TNF-alpha:</u> (Al-Shair, 2011)</p> <p><u>IL-6:</u> (Al-Shair, 2011)</p> <p><u>CRP:</u> (Al-Shair, 2011)</p>	<p><u>IL-6:</u> (Bassola et al., 2015)</p>	<p><u>IL-6:</u> (Davis et al., 2008)</p> <p><u>CRP:</u> (Lee at al., 2014; Druce, Jones, McFarlane, Basu, 2015a)</p> <p><u>Erythrocyte sedimentation rate:</u> (Treharne et al., 2008; Druce, Jones, McFarlane, Basu, 2015a)</p> <p><u>Disease Activity Score</u></p>



	<p>Liu, 2012; Wang 2010; Fink et al., 2012)</p> <p><u>IL-1 beta</u> (Bower, 2009; Alexander , 2009)</p> <p><u>CRP:</u> (Bower, 2009; Alexander , 2009) Fink et al., 2012</p> <p><u>TNF receptor II:</u> (Bower , 2011)</p>	<p>Kumar et al., 2007; Lennie et al. 2013F)</p> <p><u>CRP:</u> (Fink et al., 2012)</p>	<p>2005)</p> <p><u>TNF-alpha:</u> (Goebel, 2005)</p> <p><u>IL-10:</u> (Goebel, 2005)</p> <p><u>CD8+ T cells:</u> (Gold, 2011)</p>			<p><u>in 28 joints (DAS28):</u> (Bergman et al., 2009; Druce, Jones, Macfarlane, Verstappen, Basu, 2015; Druce, Jones, Macfarlane, Basu, 2015a; Druce, Jones, Macfarlane &amp; Basu, 2015b; Druce, Bhattacharya, Jones, Macfarlane, Basu 2016; Feldthusen et al., 2016; Repping-Wuts et al., 2007; van Hoogmoed et al., 2010)</p>
<b>HPA axis</b>	<p><u>Cortisol:</u> (Bower, 2005; Weinrib, 2010)</p>	<p><u>Cortisol:</u> (Bunevicius et al., 2012)</p>	<p><u>Cortisol:</u> (Gold, 2011, Powell, 2015)</p>	<p><u>Cortisol:</u> (Schuetz, 2015)</p>		
<b>Autonomic Nervous System</b>	<p><u>Norepinephrine:</u> (Fagundes, 2011)</p>		<p><u>Battery of tests:</u> (postural changes, pressure</p>		<p><u>Heart Rate Variability:</u> (Fujii et al., 2013)</p>	

	<u>Heart rate variability:</u> (Fagundes, 2011)		tests, the Valsalva maneuver, deep breathing and hyperventilation): (Merkelbach, 2001)  <u>Fluctuations in HR, BP, blood flow during supine and standing:</u> (Keselbrener, 2000)			
HR=heart rate, BP=blood pressure, TNF=tumor necrosis factor, IL=interleukin, CRP= C reactive protein, <u>sTNFR</u> =soluble tumor necrosis factor receptors, IFN $\gamma$ = interferon gamma, CD8= cluster of differentiation 8						

**Table 2. Measures Used in the Studies of Fatigue in Chronic, Non-infectious Diseases**

<b>Disease</b>	<b>Fatigue Measurement Used</b>	<b>Articles cited in this review</b>
Heart Failure	Profile of Mood States	Fink et al, 2012
	Visual analog scale	Kumar 2007
	Memorial Symptom Assessment Scale—Heart Failure	Lennie, et al, 2013
	Multidimensional Fatigue Inventory (MFI-20) and Dutch Exertion Fatigue Scale and Standardized cardiopulmonary exercise testing	Bunevicius, et al, 2012
Multiple Sclerosis	Fatigue Scale	Powell, Moss-Morries, Liossi, 2015
	Fatigue Questionnaire Scale	Giovannoni, Thompson, Miller, Thompson, 2001
	Krupp’s Fatigue Severity Scale	
	Profile of Mood States	Goebel et al. 2005
	Modified Fatigue Impact Scale	Gold et al. 2011
	Fatigue Severity Scale	
	Modified Fatigue Impact Scale	Heesen et al. 2006
	Revised Clinical Interview Schedule	
	Fatigue Severity Scale	Merkelbach, Dillmann, Kolmel, Holz, Muller, 2001
	Chronic Fatigue Scale	
COPD	Fatigue Severity Scale	Keselbrener et al. 2000
	Manchester COPD Fatigue Scale	Al-shair et al. 2011
	Modified Performance Score for COPD	Schuetz et al. 2015
Chronic Kidney Disease	Italian version of the Short Form (Short form [SF]-36®) vitality scale	Bossola et al., 2015
	Kuratsume and Yumaguti “New Fatigue Scale”	Fuji et al., 2013; Fukada et al., 2008

Rheumatoid Arthritis	SF-36 vitality scale	Druce, Jones, McFarlane, Basu, 2015a; Druce, Jones, McFarlane, Basu, 2015b, Druce et al., 2016
	Multidimensional Health Assessment Questionnaire (MDHAQ)	Lee et al., 2014
	Visual Analog Scale (unspecified)	Bergman et al., 2009
	Visual Analog Scale (0-100 mm)	Druce, Jones, Macfarlane, Verstappen, Basu, 2015; Treharne et al., 2008
	Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire	Feldthusen et al., 2016
	Numerical Rating Scale	Davis et al., 2008
	Fatigue severity subscale (Checklist Individual Strength (CIS)-fatigue) of the CIS (CIS20r)	Van Hoogmoed et al., 2010; Repping-Wuts et al., 2007

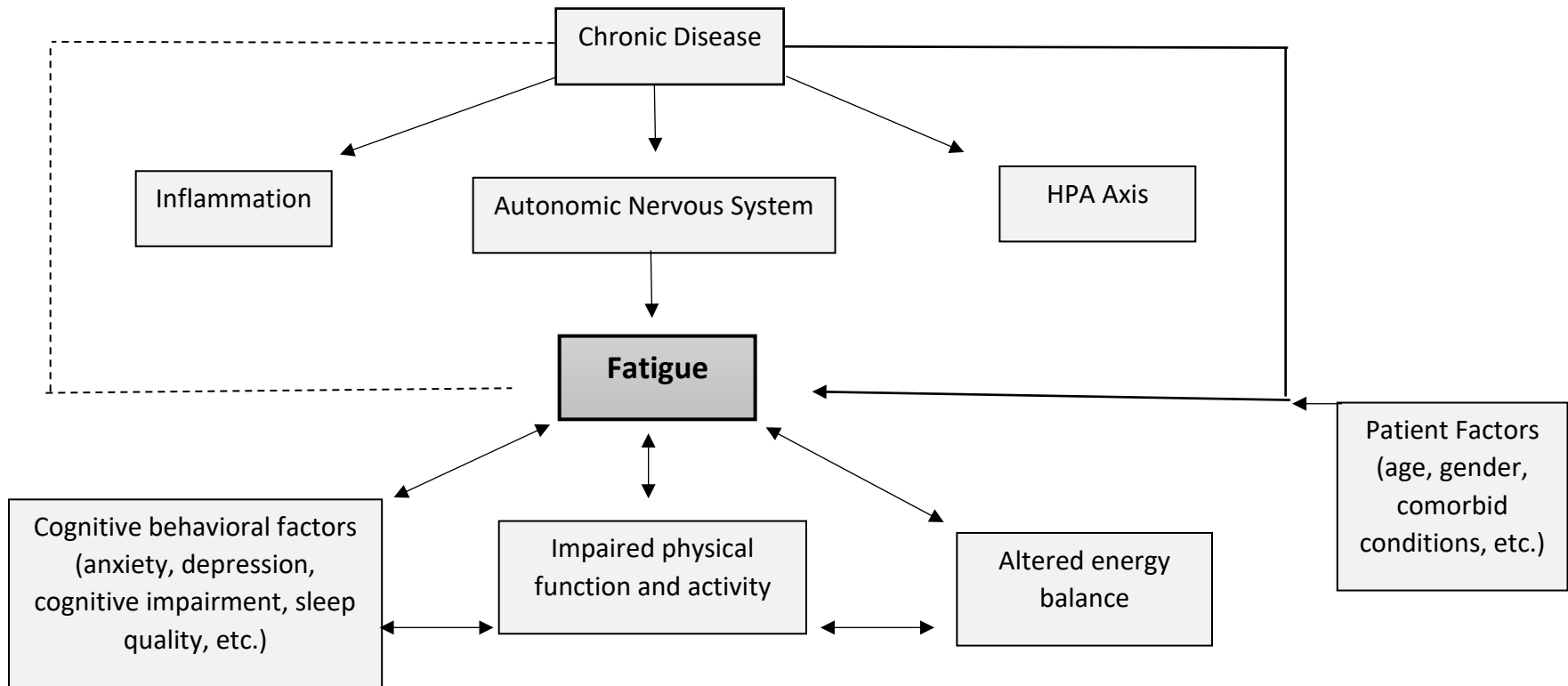


Figure 1. Chronic illnesses have underlying biological changes (inflammation, autonomic nervous system activation, HPA axis dysregulation) that appear to be associated with fatigue. The biological changes can be influenced by patient characteristics and modifiable factors. The cascade of events illustrated in this figure can impact cognitive behavioral factors, impair physical function, activity, and energy balance.



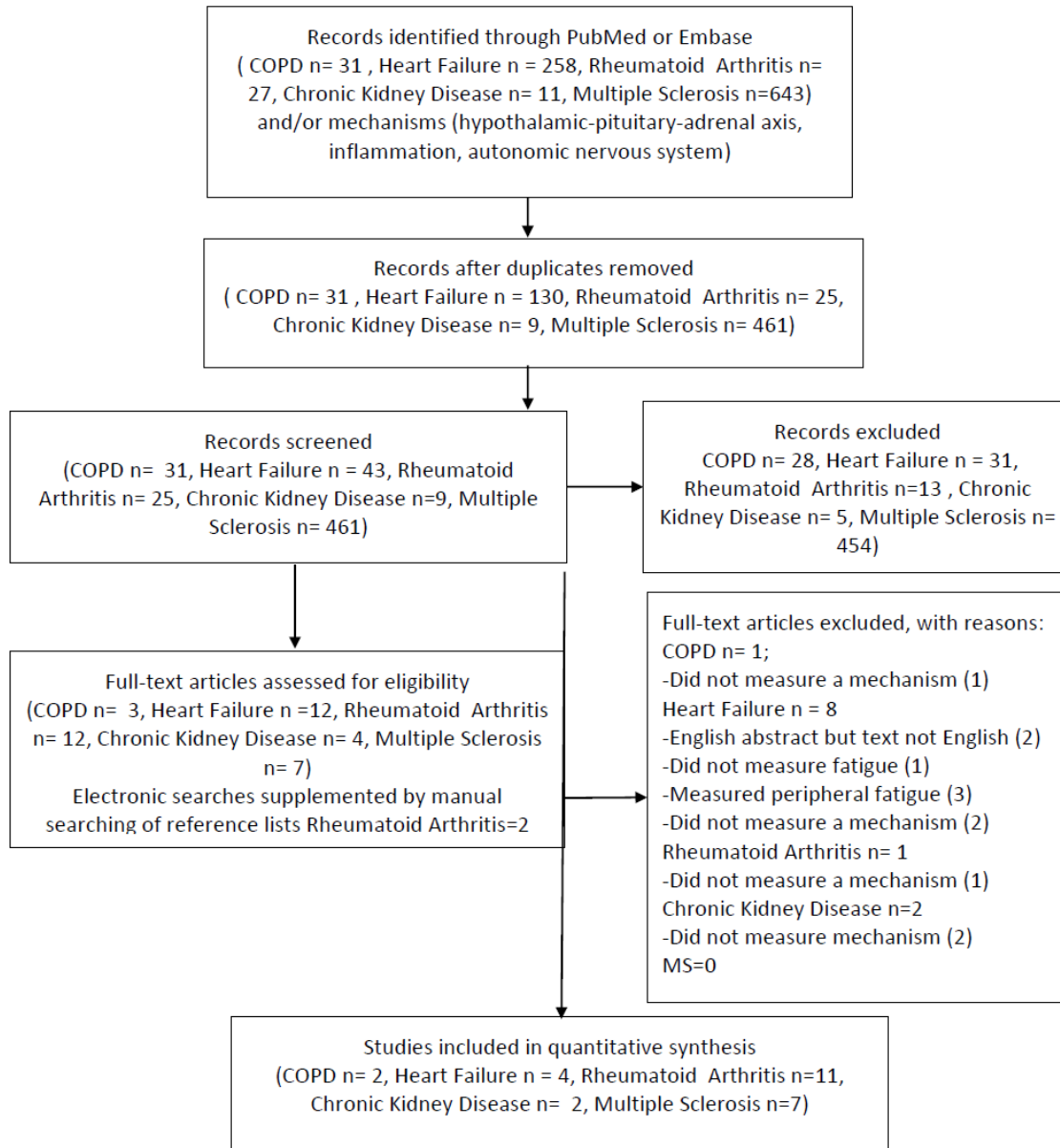


Figure 2 PRISMA Flow Diagram





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