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Examining the cross-sectional and longitudinal effects of anxiety sensitivity on indicators of disease severity among patients with inflammatory arthritis

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ABSTRACT

Few studies have investigated anxiety sensitivity (AS) in the context of inflammatory arthritis (IA), despite evidence of a relationship between AS and pain. This study examined cross-sectional and longitudinal relationships between AS and indicators of IA severity in 148 participants with IA. AS and its factors (social, physical, cognitive) were self-reported. Arthritis severity was physician-assessed (disease activity scales) and self-reported (physical function; pain and fatigue). Cross-sectional correlations assessed the association between AS and arthritis severity outcomes. Longitudinal multivariable mixed-effect regressions assessed the association of AS total and AS factors at each visit with disease severity outcomes. All AS factors were significantly and positively correlated (at the same visit) with function, pain, and fatigue. AS total significantly predicted pain, fatigue, and function. Cognitive AS significantly predicted fatigue, and physical AS significantly predicted pain and fatigue. Social AS significantly predicted pain, fatigue, function and weighted joint count (articular burden). AS is associated with several indicators of disease severity among those with IA; unique findings emerged across factors with the broadest disease impact by social AS. The AS factors, especially social AS, may contribute to the development and severity of IA symptoms, which may have implications for interventions.

1. Introduction

Rheumatoid arthritis (RA) is a debilitating chronic disease, characterized by joint inflammation and damage associated with pain and functional disability. RA affects up to 1% of the general population and is one of the most studied inflammatory arthritides (Alamanos, Voulgari, & Drosos, 2006; Cross et al., 2014; Hitchon, Khan, Elias, Lix, & Peschken, 2019). People with RA and other inflammatory arthropathies (termed inflammatory arthritis (IA) throughout) have higher rates of mental health problems, including anxiety and depression, compared to the general population (Covic et al., 2012; Lin et al., 2015; Lu et al., 2016; McDonough et al., 2014). Nearly 40% of people with RA report moderate or extreme anxiety/depression (Peterson, Li, Blackburn, & Kielar, 2016). Some suggest a bi-directional relationship between IA and mental health conditions (Kessler & Bromet, 2013; Lu et al., 2016; Murphy, Sacks, Brady, Hootman, & Chapman, 2012; Remes, Brayne, van der Linde, & Lafortune, 2016). In Manitoba, for example, people with RA have an increased lifetime risk of being diagnosed with anxiety (prevalence rate ratio 1.2 fold higher) or depression (prevalence rate ratio 1.4 fold higher) compared to the general population as well as an increased risk of developing a new diagnosis of anxiety or depression after an RA diagnosis (incidence = 1.24 for anxiety; Marrie et al., 2018). A related psychological construct, anxiety sensitivity (AS), has garnered significant recent attention in pain research (Asmundson, Wright, & Hadjistavropoulos, 2000); however, has been largely unexplored in the context of IA. Anxiety Sensitivity (AS) was first introduced by Reiss and McNally (1985) and refers to the tendency to fear body sensations associated with anxiety because of their perceived negative physical, psychological, or social consequences (Taylor et al., 2007). Interpreting the experience of physical symptoms

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as negative or dangerous can lead to a constant fear of these sensations, which may negatively impact emotional and physical well-being (Olatunji & Wolitzky-Taylor, 2009). The current study aims to investigate the cross-sectional and longitudinal relationship between AS and indicators of disease severity among those with IA.

There are a number of indicators of disease severity among those with IA including pain, fatigue, physical functioning, markers of inflammation, and joint deterioration. A significant body of IA literature has focused on the impact of psychological factors on pain, and to a lesser extent, fatigue. Pain is the most important predictor of mental health among people with RA, after controlling for other disease indicators (Courvoisier et al., 2012). In an early arthritis cohort from the Netherlands, depression and anxiety were found to be associated with more pain (Boer, Huizinga, & van der Helm-van Mil, 2018). These findings support a potential bidirectional association between pain and mental health. In a systematic review, authors found depression led to heightened pain among individuals with RA (Dickens, McGowan, Clark-Carter, & Creed, 2002), and depression in RA increases work disability (Lowe et al., 2004) and social withdrawal (Katz & Yelin, 2001), emphasizing the negative impact of mental health comorbidity. With respect to fatigue, in a sample of patients with arthritis, those with an anxiety disorder had higher levels of fatigue compared to those without an anxiety disorder (Fifield et al., 2001). In addition to poorer pain and fatigue, RA patients with comorbid anxiety/depression have poorer functioning, greater work impairment, lower health-related quality of life, and are more dissatisfied with treatment than those without anxiety and/or depression (Enns et al., 2018; Masood, Salim, Nasim, Khalid, & Afzal, 2017; Peterson et al., 2016). At the extreme, depression has also been found to be an independent risk factor for mortality in patients with RA (Ang, Choi, Kroenke, & Wolfe, 2005).

Few studies have examined mental health disorders in IA over time. Depression and anxiety symptoms were studied prospectively (at 0, 3, 6, 12 months) in a large study of patients with RA and psoriatic arthritis. Findings demonstrated that depression and anxiety were shown to reduce the likelihood of remission (Michelsen et al., 2017). Other longitudinal research determined that depression and/or anxiety symptoms were associated with increased arthritis disease activity and worse daily physical functioning among patients with RA when measured every 6 months for two years (Matcham, Norton, Scott, Steer, & Hotopf, 2016). The studies by Michelsen et al. (2017) and Matcham et al. (2016) are among the very few longitudinal investigations of the relationship between mental health and IA. Despite these robust relationships between anxiety/depressive disorders and physical and psychosocial outcomes, little research has examined AS (e.g., Mehta et al., 2016), which is a strong risk factor for anxiety and depression (Naragon-Gainey, 2010), and no studies have examined AS longitudinally in the context of IA.

AS is composed of three factors: social, cognitive, and physical. Previous research has found that each of these AS factors contribute differentially to the development of mental health issues. For instance, AS physical has been found to be most strongly related to fear-based disorders such as panic disorder (Allan, Macatee, Norr, Raines, & Schmidt, 2015), while AS cognitive has been more strongly linked to depression (Allan, Capron, Raines, & Schmidt, 2014). AS social appears to have associations with social anxiety, generalized anxiety, and depression (Allan et al., 2014). AS and its factors have been found to be significantly associated with chronic pain (Asmundson & Taylor, 1996; Asmundson, Norton, & Norton, 1999; Asmundson et al., 2000) and Asmundson and colleagues have developed a theoretical model to conceptualize this relationship, which posits that AS may lead to the exacerbation of pain and other physical health problems via fear of pain. The fear of pain inadvertently leads to a worse experience of pain (i.e., greater severity of pain), as a result of the associated negative sensations and cognitions, which ultimately leads to more behavioural avoidance and decreased physical functioning. Indeed, the fear of pain along with the fear of anxiety symptoms stresses the relationship of AS to chronic medical problems. For example, a meta-analysis found AS to be strongly associated with fearful appraisals of pain in both clinical and non-clinical populations (Ocañez, McHugh, & Otto, 2010). Further, AS has been found to influence pain-specific anxiety, and often leads to pain-specific avoidance behaviour, such as discontinuing an activity due to pain (Asmundson & Norton, 1995). This avoidance behaviour may result in lack of engagement in health promoting-activities thereby increasing pain-related functional impairment. In support, AS has been found to be indirectly associated with chronic pain-related functional impairment (Thibodeau, Fetzner, Carleton, Kachur, & Asmundson, 2013). Not only does AS in the context of a health problem lead to heightened suffering in terms of greater pain, disability, and distress (McCracken & Keogh, 2009), it is also associated with greater somatic symptoms beyond pain including gastrointestinal issues (Jakupcak et al., 2006), and increased cost to both patients and their employers (McCarberg & Billington, 2006). In sum, AS is associated with poor health outcomes, namely greater pain severity and disability, which may relate in part to its cognitive and behavioural features that result in poor symptom management in chronic health problems (Asmundson et al., 2000; Avallone, McLeish, Luberto, & Bernstein, 2012).

As indicated, the evidence on AS in the context of IA has been limited. To date, to the best of our knowledge only 3 studies exist, which were all carried out by the same research group in London, Ontario. Rice et al. (2016) found that RA patients with higher AS, worry, fear of pain, and perfectionism also indicated greater mood impairment, pain anxiety sensitivity (i.e., fear of the consequence of pain, see McCracken & Keogh, 2009), and pain catastrophizing (see also Mehta et al., 2016). More recently, this research group assessed fear of relaxation, AS, and pain catastrophizing in patients with RA compared to patients with chronic pain without RA (Rice et al., 2016). They found that the individuals in each group experience overlapping and unique factors that contribute to their perception of stress. When controlling for demographic variables and pain intensity, AS was similarly significantly associated with stress in both groups (Rice et al., 2016). However, AS was not specifically compared between groups. As indicated, these negative cognitions related to pain may actually perpetuate physical pain symptoms (Asmundson et al., 2000; Vlaeyen & Linton, 2000). This may also relate to greater distress and psychological inflexibility, which makes it more challenging to change behaviour towards healthier functioning (Hayes, Luoma, Bond, Masuda, & Lillis, 2006). Thus, when individuals fear their anxiety it can lead to greater pain and disability, and may transcend to other disease indicators in the context of IA such as increased joint involvement (suggesting greater progression of disease).

While there is information about the impact of mental disorders on the course of IA (e.g., Michelsen et al., 2017) and preliminary cross-sectional evidence linking AS to health indicators in RA patients (e.g., Mehta et al., 2016), no studies have longitudinally examined the impact of AS on disease activity or disease severity in IA. The range of disease activity indicators has also been limited in prior mental health research examining IA, which has largely focused on self-reported pain and fatigue. In this study, we examine the relationship between AS and a number of disease severity indicators including both self-reported and physician assessed disease activity assessments (see Supplemental table for IA definitions of disease severity indicators). The chosen physician reported (objective) IA activity indicators reduce the potential for confounding by non-inflammatory symptoms. Finally, existing studies in the context of IA have not differentiated between the cognitive, social, and physical aspects of AS. This is significant because, as discussed above, these AS factors have been found to differentially be associated with particular mental disorders, and different mental disorders have been found to be differentially associated with both the presence of IA (Marrie et al., 2018) and IA disease severity indicators (Sharma, Kudesia, Shi, & Gandhi, 2016). Further, Olthuis, Watt, Mackinnon, Potter, and Stewart (2015) found that physical and cognitive, but not social aspects of AS, had positive relationships with (increased) pain-

related anxiety in a sample of community adults. It is therefore important to explore whether these individual AS factors are differentially associated with various IA indicators.

The present study examines cross-sectional and longitudinal relationships between AS total and AS factors (cognitive, social, and physical) and patient-reported and physician-assessed indicators of IA severity in patients followed in a prospective early arthritis cohort. In light of prior research demonstrating the impact of mental disorders on IA disease indicators and preliminary research also demonstrating the impact of AS on chronic pain in particular, we hypothesize that (1A) AS will be associated with all IA disease severity indicators cross-sectionally and that (1B) Patient-reported outcomes will be affected longitudinally – pain, fatigue, and functionality as these are likely more greatly affected over the short-term (and likely variable across appointments) whereas the objective indicators would be associated with AS over the long term. These may be more greatly affected, as they are all patient reported outcomes and therefore, when AS is more severe, it would likely impact perception of increased severity. Considering prior research demonstrating a relationship between pain-related anxiety, a similar construct to AS physical and indicators of arthritic disease (Rice et al., 2016), we also hypothesize that (2A) AS physical will have the greatest impact (i.e., the broadest range of outcomes) on measures of disease severity in IA. Prior research has also found AS social to be strongly associated with anxiety disorders (Allan et al., 2015) and anxiety disorders have been shown to significantly impact IA disease (Sharma et al., 2016). Therefore, we also hypothesize that (2B) AS social will predict disease indicators. Finally, AS cognitive has been found to be most strongly related to depression (Naragon-Gainey, 2010), compared with other AS factors. Therefore, our final hypothesis (2C) is that AS cognitive will predict fatigue, which is a common symptom of depression (Demyttenaere, de Fruyt, & Stahl, 2005).

2. Method

2.1. Participants

The sample included longitudinal data on 148 adults with inflammatory arthritis (IA) drawn from a single centre prospective longitudinal Early Arthritis Cohort, which was established in 2000 by author CH. At cohort entry, eligible patients had recent onset of IA (joint pain and swelling) involving at least one joint with symptom duration of less than 12 months. Crystal arthropathies (i.e., accumulation of molecules in the form of crystals in one's joints such as gout), other connective tissue disorders, and infectious arthropathies (i.e., infected joints) were excluded. Patients were treated as per usual care following existing treatment guidelines and aiming for disease remission. Clinical data, routine laboratory studies and patient-reported outcome variables were collected. AS data were first included in the cohort data collection beginning in 2012, and have been subsequently collected on an annual basis. The other measures were assessed at every appointment, but only those that were assessed at the same appointment as the AS variables were included in the correlations and regressions. In this study, we analyzed data collected between 2012–2016. All participants provided informed consent and the study was approved by the University of Manitoba Health Research Ethics Board.

2.2. Measures

2.2.1. Sociodemographic variables

Sociodemographic variables included in the survey were gender, self-reported ethnicity, education, and work status. Ethnicity was categorized into White or other. Education was categorized into less than high school, high school, or more than high school.

2.2.2. Anxiety sensitivity

AS was measured using the 18-item Anxiety Sensitivity Index – 3 (ASI-3; Taylor et al., 2007). From the ASI-3, we derived three anxiety factors/subscales: physical, cognitive, and social, based on six items each. The physical factor involves the fear of the consequences of autonomic arousal and physical symptoms (e.g., fear of rapid heart beat). The cognitive factor involves the fear of the cognitive consequences of anxiety-related sensations (e.g., worrying thoughts are a marker of instability). The social factor involves the fear of social consequences of anxiety (e.g., worrying that others may notice one's anxiety). Items were rated from 0 (*very little*) to 4 (*very much*) so that total scores can range from 0 to 72; higher scores indicate greater anxiety sensitivity. This is considered to be the best existing measure of anxiety sensitivity and has been found to be both valid (i.e., convergent, discriminant, and criterion validities) and reliable (Taylor et al., 2007). We found the subscales of the ASI-3 to have Cronbach's alphas of .90 for physical, .87 for social, and .94 for cognitive, indicating good to excellent internal consistency (Cicchetti, Butcher, & Nelson, 1994).

2.2.3. Disease severity

2.2.3.1. Arthritis activity. Physicians recorded 68 tender and swollen joint counts (TJC, SJC), and reported a physician global assessment of disease activity (MD global). Joint counts were assessed as raw counts. The MD global was assessed by the question "How active is your patient's arthritis today" and recorded by the physician using a visual analogue scale (VAS; scored as not active 0 to very active 10). MD global was categorized into active (> 0) versus remission (0) categories. Systemic inflammation was measured using the Erythrocyte Sedimentation Rate (ESR) and/or C-Reactive Protein (CRP) in the hospital laboratory (see Supplementary Table for a description of these indicators). Arthritis disease activity was reported using the composite Disease Activity Score (DAS28(ESR)) score, which includes 28 TJC, 28 SJC, and ESR (Anderson, Zimmerman, Caplan, & Michaud, 2011). When ESR was not available, the DAS28(CRP) variable was substituted as both indices are correlated. The 28 joint count does not include ankles, feet, or hips. From here onward any Disease Activity Score variables will be abbreviated as DAS. The Lansbury Index evaluates 68 peripheral joints and weights each joint based on its relative surface area (Lansbury, 1956), thereby providing a more robust estimate of overall joint involvement. The Lansbury Index was categorized into active (> 0) versus remission (0) categories. Both Lansbury and standard joint count trajectories correlate with physical function as measured by the modified Health Assessment Questionnaire (HAQ; Cheung, Gossec, Mak, & March, 2014; Lim et al., 2017). Higher scores on the DAS and Lansbury Index indicate greater arthritis activity.

2.2.3.2. Functional status. Functional status was assessed using the Modified Health Assessment Questionnaire (mHAQ; Pincus et al., 1983). This instrument assesses eight domains of daily activity including dressing/grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. The eight items are rated on a 4-point rating scale ranging from 0 (*without difficulty*) to 3 (*unable to do*), and averaged so that higher scores indicate greater disability. The mHAQ is a widely used, validated measure of physical function (Linde, Sørensen, Ostergaard, Hørslev-Petersen, & Hetland, 2008).

2.2.3.3. Fatigue and pain. Patient reported fatigue and pain were assessed using patient reported visual analogue scales (VAS), which ranged from 0 to 100, and the following questions: "How much of a problem has unusual fatigue or tiredness been for you over the past 3 months" and "How much pain have you had because of your condition in the past week". This is a widely-utilized method to measure pain, and has been found to be reliable and valid (Hjermstad et al., 2011). Fatigue measured by VAS was initially found to be both valid and reliable by Lee, Hicks, and Nino-Murcia (1991), and more recently has been found to be valid for use among persons with RA (Hewlett, Hehir, & Kirwan,

2007). Higher scores on these scales indicate greater fatigue and pain.

2.3. Data analytic plan

Data were analyzed using SAS version 9.3 (SAS Institute, Cary NC). Proportions were calculated for the categories of the sociodemographic characteristics, while means (with standard deviations) were calculated for total AS, AS factors, and disease indicators. In order to test Hypothesis 1, cross-sectional Spearman correlations were calculated between the disease indicators and AS factors (social, cognitive, and physical).

Multivariable mixed-effects regression models were used to test Hypothesis 2. AS total and the AS factors were the independent variables and the dependent variables were IA disease indicators. These models examined how total AS and the various AS factors individually predicted each disease indicator, adjusting for disease duration, age, gender, education, and ethnicity. Random effects for each subject accounted for the statistical dependence between longitudinal measurements nested within individuals. Negative binomial mixed-effects models were used to predict SJC and TJC. Logistic mixed-effects models predicted the mHAQ, Lansbury weighted joint count, and MD Global, each of which was dichotomized at zero versus any positive non-zero value. Linear mixed-effects models predicted ESR, CRP, DAS, pain, and fatigue. Because of their skewed distributions, a log transformation was applied to ESR and CRP. Regression coefficients for these outcomes are therefore interpreted as percent change per unit increase in the covariate. Only patients with at least two mental health visits and known education level were included in the analyses. Linear mixed-effects models were estimated with SAS PROC MIXED. Logistic and negative binomial mixed-effects models were estimated with SAS PROC GLIMMIX.

3. Results

Table 1 displays the sample's demographic descriptive statistics and Table 2 displays the frequency of the number of assessments (visits). The mean age at first AS measurement was 49.7 (SD = *12.73*) years. The majority of participants were female (72.7%) and White (66.0%). Approximately one-third of the sample had a college education, while 42% had a high school education or less. The median duration of arthritis at first AS assessment was 82 months, (25%, 75%–36,115), 10% were assessed for AS within 1 year of IA diagnosis, and 76% met criteria for rheumatoid arthritis (according to the criteria outlined in Aletaha et al., 2010).

Table 1
Demographic and arthritis characteristics.

Socidemographic Variables	n (%) or Mean (SD)
Age (range: 20–76 years old)	49.7 (12.73)
Gender	
Female	109 (72.7%)
Male	41 (27.3%)
Ethnicity	
White	113 (75.3%)
Other	37 (24.7%)
Education level	
Less than high school	22 (14.7%)
High school	41 (27.3%)
More than high school	72 (48.0%)
Unknown	15 (10.0%)
Meet criteria for RA	112 (76%)
Disease duration at first assessment (months median 25%, 75%)	82 (36,115)

Note. $N = 148$.
"Other" ethnicity includes Black, Latin American/Hispanic, Filipino, Arab/West Asian, Southeast Asian, South Asian, Chinese, Korean, Japanese, and Indigenous (First Nations, Métis, Inuit).

Table 2
Frequency of the number of assessments (visits).

Visit number	n (%)
1	13 (8.7%)
2	27 (18.0%)
3	3 (12.0%)
4	29 (19.3%)
5	26 (17.3%)
6	15 (10.0%)
7	11 (7.3%)
8	10 (6.7%)
9	1 (.67%)

Note. $N = 150$.

Table 3
Disease indicator means and correlation coefficients.

Primary Variable	Mean (SD)	ASI social	ASI cognitive	ASI physical
		Spearman correlation (*r*)		
Swollen Joint Count	1.5 (3.77)	.087	.051	.068
Tender Joint Count	3.0 (5.92)	.098	.022	.031
Lansbury	14.8 (25.4)	.104	.014	−.003
ESR	21.8 (17.80)	.046	.068	.142*
CRP	8.8 (15.74)	.069	.045	.066
mHAQ	.36 (.44)	.266***	.230***	.247***
MD global	6.0 (10.92)	.128*	.091	.156**
Pain	31.3 (27.0)	.224***	.203***	.270***
Fatigue	38.5 (30.52)	.255***	.275***	.268***
DAS	2.9 (1.24)	.113	.043	.109

Note. *$p < .05$; **$p < .01$; ***$p < .001$. ESR = erythrocyte sedimentation rate; CRP = c-reactive protein; mHAQ = modified health assessment questionnaire; DAS = disease activity score 3 variable using ESR but excluding patient global. Spearman correlation coefficients are reported.

Several AS factors correlated with disease indicators (see Table 3). All AS factors were significantly positively associated with mHAQ ($r = .23–.27$, $p < .001$), pain ($r = .20–.27$, $p < .001$), and fatigue ($r = .26–.28$, $p < .001$), which partially confirms Hypothesis 1A that AS would be associated with all disease severity indicators cross-sectionally. There was a small but significant positive relationship between AS social and MD global ($r = .13$, $p < .05$), and between AS physical and ESR ($r = .14$, $p < .05$) and MD global ($r = .16$, $p < .01$).

Results of the longitudinal regression analyses are shown in Table 4. AS total significantly predicted greater pain (Estimate = .31, 95% CI = .003–.62, $p < .05$), fatigue (Estimate = .52, 95% CI = .20–.85, $p < .01$), and mHAQ (Estimate = 1.04, 95% CI = 1.00-1.08, $p < .05$). AS social significantly predicted poorer health according to the Lansbury Index (Estimate = .99, 95% CI = .98-.998, $p < .05$), mHAQ (Estimate = 1.12, 95% CI = 1.02–1.23, $p < .05$), pain (Estimate = .91, 95% CI = .12–.17, $p < .05$), and fatigue (Estimate = 1.19, 95% CI = .36–2.02, $p < .01$). AS physical significantly predicted greater pain (Estimate = .81, 95% CI = .03–1.58, $p < .05$) and fatigue (Estimate = 1.10, 95% CI = .28–1.92, $p < .01$). AS cognitive significantly predicted greater fatigue (Estimate = 1.29, 95% CI = .36–2.21, $p < .01$). This provides support for Hypothesis 1B that patient-reported outcomes will be affected longitudinally. As AS social and AS physical both predicted pain and fatigue, Hypothesis 2A was rejected, which stated that AS physical would have the greatest impact (i.e., the broadest range of outcomes) on measures of disease severity. Hypothesis 2B was confirmed, as AS social was related to patient-reported outcomes longitudinally. Finally, Hypothesis 2C was confirmed because AS cognitive significantly predicted fatigue.

4. Discussion

This study represents the first longitudinal investigation of AS on indicators of arthritis severity in IA. It is also the first study to differentiate between the cognitive, social, and physical aspects of AS over

Table 4
Regressions examining anxiety sensitivity indexes predicting various disease severity outcomes.

Outcome Variable	ASI Social		ASI Cognitive		ASI Physical		ASI total	
	Estimate	95% CI for Estimate	Estimate	95% CI for Estimate	Estimate	95% CI for Estimate	Estimate	95% CI for Estimate
Self-report								
Pain[a]	.91*	.12, .17	.34	−.55, 1.22	.81*	.03, 1.58	.31*	.003, .62
Fatigue[a]	1.19**	.36, 2.02	1.29**	.36, 2.21	1.10**	.28, 1.92	.52**	.20, .85
mHAQ[b]	1.12*	1.02, 1.23	1.08	.97, 1.20	1.10	.99, 1.22	1.04*	1.00, 1.08
Physician-assessed								
LogESR[a]	.02	−.01, .54	.01	−.02, .05	.02	−.02, .05	.01	−.01, .02
LogCRP[a]	.05	−.01, .12	−.005	−.04, .03	.001	−.03, .03	.001	−.01, .01
Swollen joint count[c]	.99	.93, 1.05	.97	.91, 1.04	−.02	−.08, .05	.99	.97, 1.02
Tender joint count[c,d]	.06	−.001, .11	–	–	–	–	1.02	.99, 1.04
Lansbury index[b]	.99*	.98, .998	.95	.87, 1.03	.96	.89, 1.04	.99	.96, 1.02
MD Global[b]	1.00	0.94, 1.06	.99	.92, 1.06	1.03	.97, 1.10	1.00	.98, 1.03
DAS[a]	.02	−.02, .06	−.005	−.05, .04	.01	−.03, .05	.01	−.01, .02

Note. $*p < .05$; $**p < .01$. mHAQ = modified Health Assessment Questionnaire; ESR = Erythrocyte Sedimentation Rate; CRP = C-Reactive Protein; DAS = Disease Activity Scale. Model is controlling for disease duration, gender, age, education, and ethnicity.
– = model not estimable due to missings.
[a] Linear mixed-effects model.
[b] Logistic mixed-effects model.
[c] Negative binomial mixed-effects model.
[d] Model not estimable for ASI cognitive and ASI physical.

time for IA disease indicators. Here, we have shown that in IA, self-reported pain, fatigue, daily functioning (assessed by self-reported mHAQ), and burden of joint activity as measured by the Lansbury index were longitudinally associated with one or more of the AS factors. Interestingly, AS social had the broadest impact with significant associations in pain, fatigue, mHAQ, and the Lansbury index over time. This is consistent and extends previous research that has found mental health issues to be associated with worse IA outcomes (Euesden et al., 2017). Indeed, among those with RA, depression has been found to lead to pain interference and functional limitations (Deb et al., 2018), increased fatigue (Matcham, Ali, Hotopf, & Chalder, 2015), and increase risk of stroke (Tsai et al., 2017). In terms of anxiety disorders and arthritis, anxiety has been found to be independently and longitudinally associated with pain (Odegard, Finset, Mowinckel, Kvien, & Uhlig, 2007) and panic has been found to be negatively associated with physical functioning (Piccinni et al., 2006). Given the previous work demonstrating the proinflammatory cytokine levels are increased among people with anxiety disorders (Hou et al., 2017), shared inflammatory pathways may contribute to a biological link between IA and anxiety or depression (Nerurkar, Siebert, McInnes, & Cavanagh, 2019). Elevations of AS in IA may relate to such shared inflammatory pathways (e.g., resulting in increased inflammatory processes such as proinflammatory cytokines), emotional adjustment reactions, or could precede IA. The findings in the present study are also consistent with existing research that has demonstrated that individuals with IA and high AS have greater disability (Mehta et al., 2016) and pain (McCracken & Keogh, 2009), the impact of AS on arthritis symptoms longitudinally has not been previously reported.

Results demonstrating a cross-sectional and longitudinal relationship between AS and disease severity indicators is in accordance with preliminary evidence (Mehta et al., 2016; Rice et al., 2016, 2016). However, these studies were cross-sectional and did not assess measures of inflammation or fatigue, only pain and functional status. With respect to mechanism, in a review, Horenstein, Potter, and Heimberg (2018) propose that AS increases the likelihood of developing chronic medical conditions (such as arthritis and other pain conditions) through increasing fear of physical symptoms, avoiding adaptive behaviours, engaging in maladaptive behaviours, and increased risk of altered physiological mechanisms. AS may not directly worsen chronic medical conditions, but rather indirectly by increasing one's vulnerability to fears of symptoms that are specific to physical health problems (such as fear of joint pain in the case of IA). It is also probable that IA can worsen mental health symptoms. Given the higher prevalence of mental health disorders among people with IA (Marrie et al., 2018), it is likely that sensitivity to bodily sensations as well as maladaptive cognitions and behavioural avoidance can worsen mental health outcomes. Therefore, it is reasonable to suggest that a mutual maintenance model (Asmundson & Taylor, 1996; Asmundson et al., 1999; Asmundson et al., 2000) is one plausible explanation for the relationship found in our study between AS and pain, fatigue, and function. This is supported by the significant correlations found in the present study between AS factors and several disease indicators, compared to the fewer significant longitudinal relationships. For example, pain and fatigue may be particularly related to psychological symptoms, as demonstrated in existing research (Kekow et al., 2011; Rice et al., 2016; Zyrianova et al., 2006).

It is noteworthy that AS social was overall the factor with the broadest impact in longitudinally predicting the different disease indicators including those relating to pain, fatigue, and function (mHAQ). This raises the question as to what it is about social concerns that is related to these aspects of disease that may be more broadly impactful than cognitive or physical aspects of AS. In the model outlined by Asmundson and Taylor (1996) AS is viewed as a predisposing factor leading to the development of fears, such as the fear of pain. The fear of pain inadvertently leads to a worse experience of pain (i.e., greater severity of pain), given the associated negative sensations and cognitions, which ultimately leads to more behavioural avoidance and decreased physical functioning. Following this model, it is probable that higher levels of AS social result in more isolation and social withdrawal (in line with behavioural avoidance). Specifically, it may be that individuals with IA who also fear the consequences of others noticing their anxiety may be more likely to avoid social interaction due to fear of negative evaluation. This avoidance may more broadly impact IA. Indeed, extensive research has documented the negative effects of social isolation on physical (i.e., cardiovascular disease) and mental health outcomes (Leigh-Hunt et al., 2017). This is supported by studies that found behavioural inhibition (i.e., withdrawing from situations interpreted as dangerous) predicts social anxiety (Panayiotou, Karekla, & Panayiotou, 2014), and prior research has found that found social anxiety is related to AS social (Deacon & Abramowitz, 2006; Naragon-Gainey, 2010). This can ultimately exacerbate their problems through avoidance of activities that could lead to improved health outcomes

such as exercise. Multiple studies have demonstrated the positive effect of physical activity in IA (see Cairns & McVeigh, 2009 for a review). This is particularly important in those with IA, as a lack of mobility is associated with greater disease activity (Grondal, Tengstrand, Nordmark, Wretenberg, & Stark, 2008). Thus, this leads to a possible connection between IA and social anxiety and the possibility that the negative cognitive and behavioural aspects of this psychological state may result in poorer health outcomes, which should be the subject of future research.

A second hypothesis is that AS social may be more strongly related to mental disorders, which may be mediating the effect between AS social and the indicators of disease severity. AS social has been found to be more strongly related to anxiety disorders (Allan et al., 2015), particularly social anxiety (Deacon & Abramowitz, 2006) compared to the other AS factors. Similarly, Naragon-Gainey's (2010) meta-analysis found that generalized anxiety disorder (GAD) symptoms were most strongly related to the social and cognitive components of AS. However, other research has found AS physical to be the strongest predictor of obsessive-compulsive disorder (OCD; Blakey, Abramowitz, Reuman, Leonard, & Riemann, 2017) and panic (Jurin & Biglbauer, 2018) symptoms, and AS cognitive to be most strongly related to depression and posttraumatic stress disorder (PTSD; Naragon-Gainey, 2010). Perhaps people with high AS social exhibit more social or generalized anxiety, and these mental disorders more greatly impact the relationship between AS social and disease severity indicators among IA. Indeed, while the research relating AS factors to physical health outcomes has been limited, one recent study found AS social to be the only significant predictor of dermatological diseases (Dixon et al., 2016). This research group also found AS social to moderate the association between stress and emotional and social functioning (Dixon, Witcraft, & Perry, 2019). There is likely a complex interplay between AS, psychological disorders and physical symptoms in the context of IA, which suggests the presence of a complex relationship and the need for further research in this area.

The finding that worsening joint burden (as indicated by the Lansbury Index) over time was predicted by AS social is noteworthy and novel. This is corroborated by previous research suggesting a positive relationship between anxiety and joint inflammation (Matcham et al., 2016; Peterson et al., 2016). In this study, joint counts were categorized to zero (i.e., remission) versus non-zero (i.e., any degree of joint activity). Only the Lansbury Index was significantly associated with AS. Other inflammatory markers that were not significantly associated with AS were SJC and TJC (which do not include the ankle and feet joints), and DAS (composed of TJC28, SJC28, and ESR or CRP). This suggests that the burden of joint involvement and potential joints involved are important contributors to AS. Thus, the larger the joint the greater the impact, such that larger inflamed joints such as knees and shoulders lead to greater restriction of mobility and function (Lim et al., 2017). This suggests that disability could be a mechanism or mediator through which AS social affects joint inflammation as measured by the Lansbury Index. Therefore, AS is likely perpetuated by the fact that people with IA feel less mobile or more pain, particularly due to limited mobility resulting from foot or ankle involvement. This greater joint involvement ultimately leads to increased fear of social consequences of anxiety. Social isolation may mediate the relationship between AS social and joint inflammation, which may further impact the opportunity for mobility and affect the number of large joints afflicted. Social isolation is common in both social anxiety (Teo, Lerrigo, & Rogers, 2013) and IA (Steptoe, Shankar, Demakakos, & Wardle, 2013), and is associated with less functionality (including inactivity; Leigh-Hunt et al., 2017).

Considering the relationship of AS with disease indicators, it is important to consider interventions targeting AS, as reducing AS in those with IA this could potentially improve disease symptoms. To date, cognitive behavioral therapy (CBT) has been found to be an effective intervention for targeting AS. A meta-analysis by Smits, Berry, Tart, and Powers (2008) examined 24 randomized controlled trials and found large effect sizes for the beneficial impact of CBT on AS. Tailoring CBT to restructuring patients' thoughts about how they are perceived by others and behavioural activation to re-engagement in valued activities will be particularly important given the AS social relationship with disease indicators. The AS social factor appears to correspond to distinct etiology and maintenance mechanisms of IA, so interventions specifically targeting AS social may be helpful for disease outcomes. CBT is also considered to be the most effective treatment for social anxiety disorder (Hofmann & Otto, 2017), and AS social is most strongly related to social anxiety disorder (Deacon & Abramowitz, 2006). AS social may also contribute to important information processing mechanisms that are present in social anxiety, such as self-focused attention (Heinrichs & Hofmann, 2001). There is also strong support for the use of CBT in patients with arthritis (Lumley et al., 2014; Sharpe, 2016; Zautra et al., 2008). This emphasizes the support for a mutual maintenance model between AS and pain/fatigue. Given that CBT is an intervention effective in both AS and pain, it would be particularly advantageous in those with IA. A recent review by Sharpe (2016) found CBT to be the most efficacious treatment for pain management in RA, especially when delivered early in disease course. Shigaki et al. (2013) tested the effectiveness of an online CBT intervention for individuals with IA. This intervention led to moderate and large effect sizes on quality of life and self-efficacy, respectively, that were maintained at 9-month follow-up. Such interventions, which can be engaged in from one's home, could be extremely beneficial in cases where individuals have severe IA that restricts or prevents them from leaving their homes and/or for rural populations.

CBT techniques that might be particularly relevant for this population are behavioural activation and interoceptive exposure. Behavioural activation can be an appropriate health promoting intervention to facilitate positive health behaviours. As alluded to, one specific focus of behavioural activation could be promoting exercise engagement, which has been shown to be an effective intervention for reducing AS and for conditions where AS might contribute to the pathology such as in persons with IA struggling with pain (Smits, Berry, Rosenfield et al., 2008). Interoceptive exposure is another behavioural intervention that may be particularly relevant for AS in the context of IA as it would allow for individuals with IA to learn how to be less fearful of the somatic sensations that they associate with their disease or AS. This could be accomplished by promoting engagement invivo (in session) activities such as tensing and relaxing muscles that would yield potentially anxiety-provoking sensations, leading to restructuring their interpretation of such sensations. Future research should specifically investigate the impact of reducing AS symptoms on both mental and physical health outcomes in IA.

This study has limitations. First, although longitudinal designs suggest possible causal effects, true causation cannot be confirmed through this self-report survey study and the potential bidirectional relationships between AS and IA disease indicators were not assessed. Second, we did not assess whether or not patients were seeking psychological or pharmacological treatment for mental health problems, which could be an important factor with respect to disease outcomes, and should be the subject of future research. Third, only the treating physician familiar with the patient's health history completed the physician-assessed measures. Thus, without multiple "raters" patient severity scores may be subject to provider bias. However, the physician caring for the patient was the only person appropriate for this type of assessment as they were most familiar with the patient's history. Finally, an assessment of mental health functioning was not specifically assessed, including anxiety and depression. Future research should aim to understand the relationship between AS and specific mental health profiles in IA, given the evidence that supports the use of CBT as a treatment for both mental health conditions and IA (Hofmann & Otto, 2017; Sharpe, 2016). This is especially important because of the higher prevalence of anxiety disorders among individuals with RA (Marrie et al., 2018) and given the indirect impact of AS on chronic medical

problems such as IA. As well, established interventions with strong empirical support exist for mental disorders and enhancing our understanding of how AS factors relate to mental disorders may help refine existing, effective interventions by making them more targeted.

4.1. Conclusion

AS is significantly associated with IA disease indicators, but the number of indicators affected differ across AS factors. Fatigue was strongly predicted by all three AS factors, suggesting that future research is needed to explore these relationships. AS social displayed the broadest impact on disease severity indicators among IA patients, suggesting that it might be an important intervention target. Mental health interventions such as CBT would likely benefit individuals with IA in coping with both their physical and mental health symptoms.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.janxdis.2019.102117.

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