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Unwelcome Companions: Loneliness Associates with the Cluster of Pain, Fatigue, and Depression in Older Adults

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Abstract

Objective: Pain, fatigue, and depression commonly co-occur as a symptom cluster in pathological inflammatory states. Psychosocial stressors such as loneliness may lead to similar states through shared mechanisms. We investigated the association of loneliness with pain, fatigue, and depression in older adults. **Methods:** Using Health and Retirement Study data ($N = 11{,}766$), we measured cross-sectional prevalence of frequent, moderate to severe pain; severe fatigue; depressive symptoms; and co-occurrence of symptoms surpassing threshold levels (i.e., symptom cluster). Logistic regression models evaluated associations with loneliness. **Results:** Pain, fatigue, and depression were reported in 19.2%, 20.0%, and 15.3% of the total sample, respectively. The symptom cluster was seen in 4.9% overall; prevalence in lonely individuals was significantly increased (11.6% vs. 2.3%, $p < .0001$). After adjusting for demographic variables, loneliness associated with the symptom cluster (adjusted OR = 3.39, 95% CI = 2.91, 3.95) and each symptom (pain adjusted OR = 1.61, 95% CI = 1.48, 1.76; fatigue adjusted OR = 2.02, 95% CI = 1.85, 2.20; depression adjusted OR = 4.34, 95% CI = 3.93, 4.79). **Discussion:** Loneliness strongly associates with the symptom cluster of pain, fatigue, and depression. Further research should examine causal relationships and investigate whether interventions targeting loneliness mitigate pain, fatigue, and depression.

Keywords

loneliness, pain, fatigue, depression, symptom clusters, psychosocial stressors

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Introduction

Symptom clusters are groups of co-occurring and related symptoms posited to have a common underlying mechanism (Miaskowski et al., 2004). Pain, fatigue, and depression have been noted to occur together in a variety of disease states, including cancer (Gaston-Johansson et al., 1999; Reyes-Gibby et al., 2006; Thornton et al., 2010), multiple sclerosis (Forbes et al., 2006), and systemic lupus erythematosus (Margiotta et al., 2019). The cluster of symptoms has been noted to co-occur more frequently than expected by chance alone (Laird et al., 2011), prompting investigation into whether a shared mechanism may explain the development of co-occurring pain, fatigue, and depression. Prevalence estimates of the symptom cluster have varied from 5.7% in a general sample of older adults (Reyes-Gibby et al., 2006) to as high as 17.2% in adults with cancer (Bjerkeset et al., 2020; Lin et al., 2013). The symptom cluster is associated with poor quality of life and impaired function (Cleeland & Reyes-Gibby, 2002; Gaston-Johansson et al., 1999).

Certain aspects of pathological inflammation or immune system dysregulation may drive the clustering of these symptoms. Aberrant activation of pro-inflammatory cytokines and abnormal hypothalamic-pituitary-adrenal (HPA) axis activity correlate with malaise, fatigue, pain, and depressed mood (Thornton et al.,

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2010; Vollmer-Conna et al., 2004). However, these processes have been unable to completely explain the connection between pain, fatigue, and depression. These symptoms have been found together in the absence of identifiable inflammatory states (Jaremka et al., 2014), and they have persisted or even emerged after cancer treatment is completed (National Institutes of Health, 2003). We believe that there may be psychosocial processes at play. In this study, we explored the possibility that loneliness may drive the cluster. Prior small studies have found that loneliness associates with pain, fatigue, and depression in certain specialized populations, including those with complex pain disorders (Jacobs et al., 2006; Jaremka et al., 2014; Stout et al., 2018; Wolf & Davis, 2014). This relationship has yet to be confirmed in a general population of older adults.

Loneliness is defined as an internal experience consisting of feelings of isolation, alienation, lack of connection with others or a greater purpose. Notably, loneliness is not determined by an objective lack of social interactions as commonly assumed (Coyle & Dugan, 2012; Perlman & Peplau, 1982). About half of older adults report feeling lonely some of the time (Gerst-Emerson & Jayawardhana, 2015; Perissinotto et al., 2012); about 20% have these feelings in a persistent and severe fashion (Steptoe et al., 2013). As a highly interdependent species, humans rely on social bonds for survival. Hawkley and Cacioppo (2010) posited that loneliness serves a vital function analogous to thirst or hunger; it is an internal sensation that motivates the individual to relieve the drive. According to this theory, when experienced transiently, loneliness may activate similar stress responses that motivate the individual to make biological resources available that move toward solving the problem of feeling alone or disconnected; therefore, feeling lonely may be highly adaptive (Hawkley & Cacioppo, 2010). However, when experienced chronically, it may pathologically induce a state of threat which may not serve an adaptive purpose, and may place the individual at risk of morbidity and mortality (Hawkley & Cacioppo, 2010). Loneliness is associated with a stunning variety of negative health outcomes; a recent meta-analysis found a 26% increased likelihood of premature mortality in lonely people (Holt-Lunstad et al., 2015). The relationship between loneliness and the symptom cluster of pain, fatigue, and depression in a general sample of older American adults has not been described.

The present study explored the prevalence of the cluster of pain, fatigue, and depression and its relationship with loneliness in a large cohort of older Americans at a single point in time. It was undertaken as an exploratory study to determine the value of research meant to investigate whether a causal pathway exists from chronic psychosocial stressors (i.e., loneliness) to the development of a complex signature constellation of physical and psychological disorders (i.e., the pain, fatigue, and depression symptom cluster). Should this pathway exist, it is possible that interventions which alleviate loneliness may treat or prevent the symptom cluster.

Methods

Data Source

We utilized six biennial waves of the Health and Retirement Study (HRS) from 2006 to 2016. The HRS is a large panel survey, administered by the Institute for Social Research at the University of Michigan and sponsored by the National Institute on Aging, which collects data every 2 years from older Americans to study the social, psychological, physical, and financial aspects of aging (Sonnega et al., 2014). The HRS follows respondents until death. New cohorts have been enrolled every 6 years beginning in 1998. Participation in the HRS is completely voluntary. At each wave, participants are provided with an informed consent document and give consent prior to the interview (Health and Retirement Study, 2018). Detailed information about the HRS may be found at (http://hrsonline.isr.umich.edu). Since 2006, a supplementary "Leave Behind" questionnaire has been administered to a random representative subset of 50% of participants every other wave (every 4 years) after the Core interview. The Leave Behind questionnaire assesses psychosocial aspects of aging such as loneliness and other potential life stressors (Clarke et al., 2008).

For purposes of this study, we examined the relationship between the outcome (the symptom cluster) and predictor of interest (loneliness) at a single point in time. This time point was the initial instance an individual provided complete data within the time period of interest (2006–2016). Thus, the sample was restricted to self-responding HRS participants from 2006 to 2016, age 50 years or more, who had non-missing data for variables as described below (Figure 1). Because it utilized publicly available de-identified data, the study was exempt from IRB review.

Measures

Symptom cluster (primary outcome). The primary outcome of interest was based on a composite score indicating the presence (yes/no) of pain, fatigue, and depression. Subjects who reported all three symptoms at threshold levels (Supplemental Figure 1) were considered to have the cluster. Subjects without all three symptoms were used as the comparison group. Those reporting only one symptom (as defined below) were examined separately and compared to those without that symptom. Individuals reporting only two symptoms were not considered to have the cluster and not examined separately as they were included in the individual symptom comparisons.

We determined the presence of pain using responses from three questions in HRS. In all waves of the Core

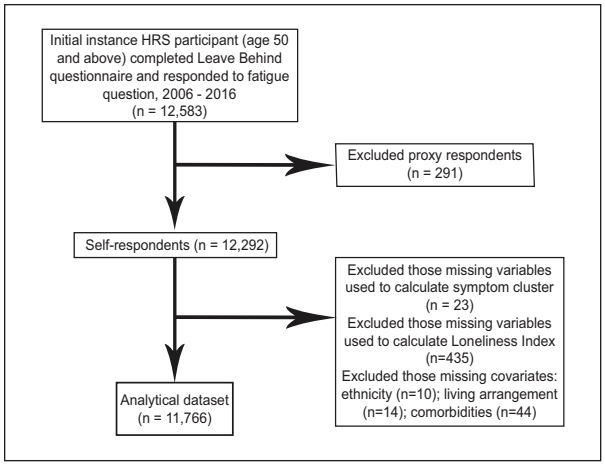

Figure 1. STROBE flow chart of cohort selection. The study flow chart following the STROBE (strengthening the reporting of observational studies in epidemiology) statement (http://www.strobestatement.org).

survey, subjects are initially asked "Are you often troubled with pain?" If participants answer yes, they are then directed to answer two additional questions. The first additional question concerns pain severity, phrased as "How bad is the pain most of the time: mild, moderate, or severe?" The final question ascertains pain interference; "Does the pain make it difficult for you to do your usual activities such as household chores or work? (yes/no)" Subjects were considered to have pain if they answered affirmatively that they were often troubled with pain; that their pain was moderate to severe in intensity; and that their pain interfered with normal function. Similar approaches have been used by other researchers studying pain using the HRS (Zimmer & Zajacova, 2018). We used a stricter definition of pain, namely "frequent, severe pain interfering with daily activities," in sensitivity analyses.

Fatigue was determined based on the answer to a single question "Have you had any of the following persistent or troublesome problems. . .Severe fatigue or exhaustion?" Starting in 1996, this question was administered to all participants on initial interview and every other wave thereafter. Participants were considered to have fatigue if they answered "yes." This approach is was used in other studies examining fatigue using the HRS and similar panel surveys (Parsons et al., 2011; Reyes-Gibby et al., 2006).

Depression or, more specifically, depressive symptoms were measured using the eight-item Center for Epidemiologic Studies Depression Scale (CES-D) (Steffick, 2000) which was administered to all subjects receiving the Core survey at each wave. A cutoff score of ≥4 was used as the threshold for depression, consistent with other studies investigating the symptom cluster using HRS data (Reyes-Gibby et al., 2006). Of note, one of the CES-D items directly asks about the presence of loneliness. To rule out co-linearity overlap between this item and our measure for loneliness, this item was excluded from the calculation of the CES-D in sensitivity analyses. The complete, validated version of the eight-item CES-D was used in the final analysis.

Loneliness (primary predictor). Loneliness was assessed using the University of California, Los Angeles (UCLA) Loneliness Scale which **yields** a Loneliness Index (Hughes et al., 2004; Smith et al., 2017). The three-item version of the UCLA Loneliness Scale has been validated (Cronbach's $\alpha = .72$) (Hughes et al., 2004) and includes the following items:

1) How often do you feel you lack companionship?
2) How often do you feel left out?
3) How often do you feel isolated from others?

For each question, participants can answer "often," "some of the time," or "hardly ever or never." The Loneliness Index is created by reverse-scoring these items and summing the total (range 3–9), with higher numbers indicating greater degrees of loneliness. We dichotomized based on the Loneliness Index (≥6 indicating significant loneliness present), as in prior research (Steptoe et al., 2013) for univariate and bivariate analysis. In all regression analyses, loneliness was maintained as a continuous variable (range 1–3) which was the mean of the three questions used to generate the Loneliness Index. A score of "1" indicates that a participant answered all questions "hardly ever or never," while scores of "2" or "3" indicates that all questions were answered as "some of the time" or "often," respectively.

Covariates. We examined individual characteristics known to associate with loneliness. These were obtained from the HRS Tracker file and included age, gender, race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, and other), education level (no degree, GED/high school diploma, some college/degree unknown, 2- and 4-year degree, and Master's degree and above), marital status, living alone, and comorbidities (Bruce et al., 2019; Cohen-Mansfield et al., 2016; Steptoe et al., 2013). We also examined wealth, which was obtained from RAND Corporation imputation of total wealth (RAND HRS Detailed Imputations File 2016 (V1), 2020) and divided into quartiles for analytical purposes. Medical and psychiatric comorbidities were ascertained via self-report regarding the presence of hypertension; diabetes mellitus; cancer; chronic lung disease; congestive heart failure; stroke; arthritis; and psychiatric problems in general (Fisher et al., 2005). We also examined the HRS wave from which the participants' data was obtained.

Statistical Analysis

Population characteristics were assessed by tabulating categorical variables and summarizing means and

standard deviation for continuous ones. In order to determine which covariates were significantly associated with loneliness, we performed Chi-square tests for categorical variables and Student's *t*-tests for continuous variables. We constructed logistic regression models to examine the relationship between the symptom cluster, individual symptoms, and loneliness. We chose to adjust for covariates that were both clinically meaningful and had statistically significant relationships with the cluster in bivariate analyses. The Hosmer-Lemeshow test was performed to assess goodness of fit of the model (Hosmer & Lemesbow, 1980).

All variables were examined individually for missing data. A lack of response (including refusal to respond) and a response of "don't know" were coded as missing. All missing data were excluded from analyses. Participants whose data were provided by proxies were excluded from analyses. Postestimation marginal effects were applied to adjusted logistic regression models to estimate the biological gradient or "dose-response" relationship of loneliness and the probability of having each individual symptom and the symptom cluster (Hill, 2015).

The dataset was constructed based on the initial time a participant provided complete data and thus included data from various years. As such, analyses were done without applying the year-specific weights and adjustment for complex sampling design. Analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC) and Stata version 15 (StataCorp, College Station, TX).

Results

From 2006 to 2016, the total number of HRS participants age ≥50 years who completed Leave Behind questionnaires and responded to fatigue questions during the same wave for the first time (as these were both administered every other wave) was $n=12,583$. After excluding participants whose data was provided by proxies ($n=291$, 2.3%) and those who had missing data ($n=526$, 4.2%), the final study population contained $n=11,766$ subjects available for complete case analysis (Figure 1).

Characteristics of participants are summarized in Table 1. Lonely subjects were significantly more likely to be female, non-White, less educated, and less wealthy. They were more likely live alone and have comorbid serious medical or psychiatric conditions (with the exception of cancer).

We observed pain, fatigue, and depression in 19.2% ($n=2,264$), 20.0% ($n=2,347$), and 15.3% ($n=1,805$) of the population respectively. 20.3% ($n=2,390$) of the population reported at least one of these symptom and 9.8% ($n=1,152$) reported two symptoms. Only 4.9% ($n=574$) of subjects had all three symptoms at threshold levels and were considered to have the symptom cluster. Sensitivity analyses utilizing a stricter definition of pain intensity (severe vs. moderate or severe) found a reduced prevalence of pain and the symptom cluster (5.9% and 2.1%, respectively) (Supplemental Table 1). Loneliness was present at threshold levels in 28.1% ($n=3,311$) of the total sample. Among individuals with the symptom cluster, however, loneliness occurred 66.7% ($n=383$) of the time. Loneliness was seen most often among those reporting depression (61.2%, $n=1,105$). It also more commonly occurred in pain (42.3%, $n=958$) and fatigue (45.5%, $n=1,069$). Loneliness prevalence fluctuated across HRS waves, with a nadir of 26.4% in 2006 to 2008 to a peak of 31.9% in 2010, then declining slightly to 28.8% by 2014 to 2016. As the analytical dataset included individuals in different cohorts (as determined by year of birth), with each participant contributing only once (and subsequent measurements of loneliness among individuals, if present, excluded by design), the HRS wave was not considered to be a valid measure of older Americans' loneliness prevalence and was not included in the final model. HRS wave was examined with a sensitivity analysis and found to not significantly affect odds of each symptom nor the symptom cluster (Supplemental Table 3).

Loneliness as a predictor of the symptom cluster. After adjusting for sociodemographic variables, lonelier individuals had higher odds of the symptom cluster (OR = 3.39, 95% CI = [2.91, 3.95]), as well as pain (OR = 1.61, 95% CI = [1.48, 1.76], fatigue (OR = 2.02, 95% CI = [1.85, 2.20]), and depression (OR = 4.34, 95% CI = [3.93, 4.79]) (see Table 2). A one-unit increase in the Loneliness Index mean corresponded to more than a three-fold increase in the odds of having the symptom cluster. We found a direct relationship between loneliness and the symptom cluster, with more severe levels of loneliness greatly increasing the probability of having each symptom individually as well as the symptom cluster (Figure 2). Of note, sensitivity analyses excluding the loneliness item from CES-D and utilizing a stricter definition of pain did not yield significantly different outcomes (Supplemental Tables 1 and 2). The Hosmer-Lemeshow test of goodness of fit of the final model (Table 2) had a *p*-value of .2034 for the symptom cluster.

Discussion

Loneliness, an individual's perception of alienation and isolation from others, is a complex psychosocial state associated with a number of negative health outcomes (Aziz & Steffens, 2013; Boss et al., 2015; Cacioppo et al., 2002, 2010; Holt-Lunstad et al., 2015; Luo et al., 2012; O'Luanaigh et al., 2012; Rapo-Pylkko et al., 2016; Steptoe et al., 2013). We have found that loneliness is strongly associated with the symptom cluster of pain, fatigue, and depression in older adults. The relationship exists in a dose-dependent fashion; higher levels of loneliness are associated with higher probability of each individual symptom as well as the cluster. The magnitude of the relationship remains high after

Table 1. Demographic variables of total sample and by presence of loneliness.

Variable	Total[a]	Loneliness present[b]	Loneliness absent[c]	*p*-Value[d]
Age mean (*SD*)	63.8 (10.4)	62.7 (10.4)	64.2 (10.4)	*
Sex *n* (%)				.0005
Male	4948 (42.1)	1309 (39.5)	3639 (43.0)	
Female	6818 (58.0)	2002 (60.5)	4816 (57.0)	
Race/ethnicity *n* (%)				*
Non-hispanic white	7612 (64.7)	2000 (60.4)	5612 (66.4)	
Non-hispanic black	2212 (18.8)	719 (21.7)	1493 (17.7)	
Hispanic	1508 (12.8)	440 (13.3)	1068 (12.6)	
Other	434 (3.7)	152 (4.6)	282 (3.3)	
Living arrangement *n* (%)				*
Lives with spouse/partner	7599 (64.6)	1643 (49.6)	5956 (70.4)	
Does not live with spouse/partner; but lives with another person	1693 (14.4)	689 (20.8)	1004 (11.9)	
Lives alone	2474 (21.0)	979 (29.6)	1495 (17.7)	
Education *n* (%)				*
No degree	2059 (17.5)	687 (20.8)	1372 (16.2)	
GED/HS diploma	5933 (50.4)	1679 (50.7)	4254 (50.3)	
Degree unknown/some college	233 (2.0)	74 (2.2)	159 (1.9)	
Two- or four-year college degree	2393 (20.3)	617 (18.6)	1776 (21.0)	
Masters/professional degree	1148 (9.8)	254 (7.7)	894 (10.6)	
Total wealth in quartiles *n* (%)				*
First quartile (up to $21,300)	2938 (25.0)	1165 (35.2)	1773 (21.0)	
Second quartile ($21,301–$138,500)	2935 (24.9)	880 (26.6)	2055 (24.3)	
Third quartile ($138,501–$447,500)	2949 (25.1)	717 (21.7)	2232 (26.4)	
Fourth quartile (above $447,500)	2944 (25.0)	549 (16.6)	2395 (28.3)	
Comorbidities *n* (%)				
Hypertension	6608 (56.2)	1974 (59.6)	4634 (54.8)	*
Diabetes	2499 (21.2)	837 (25.3)	1662 (19.7)	*
Cancer	1453 (12.4)	397 (12.0)	1053 (12.5)	.46
Chronic lung disease	1158 (9.8)	431 (13.0)	727 (8.6)	*
Heart disease	2479 (21.1)	771 (23.3)	1708 (20.2)	.0002
Stroke	740 (6.3)	273 (8.3)	467 (5.5)	*
Psychiatric problems	2114 (18.0)	1005 (30.4)	1109 (13.1)	*
Arthritis	6302 (53.6)	1894 (57.2)	4408 (52.1)	*
Number of comorbidities mean (*SD*)	2.0 (1.5)	2.3 (1.6)	1.9 (1.4)	*
HRS wave[e] *n* (%)				*
2006 and 2008	6498 (55.2)	1719 (51.9)	4779 (56.5)	
2010	1603 (13.6)	512 (15.5)	1091 (12.9)	
2012	2243 (19.1)	670 (20.2)	1573 (18.6)	
2014 and 2016	1422 (12.1)	410 (12.4)	1012 (12.0)	
Symptom cluster, *n* (%)	574 (4.9)	383 (11.6)	191 (2.3)	*
Pain, *n* (%)	2264 (19.2)	958 (28.9)	1306 (15.5)	*
Fatigue, *n* (%)	2347 (20.0)	1069 (32.3)	1278 (15.1)	*
Depression, *n* (%)	1805 (15.3)	1105 (33.4)	700 (8.3)	*

Source. HRS, 2006 to 2016.
[a]Total $n = 11,766$.
[b]Loneliness present $n = 3,311$.
[c]Loneliness absent $n = 8,455$.
[d]*p*-Values $<.0001$ indicated with an asterisk (*). Statistical significance indicates significant differences between lonely and not lonely individuals.
[e]HRS wave 2006 and 2014 both contributed only 0.4% of the total sample and were combined with 2008 and 2016, respectively. Categorical variables analyzed via Chi-square test; continuous variables analyzed via Student's *t*-test.

adjusting for demographic factors including age, sex, race/ethnicity, living arrangement, education, wealth, and medical and psychiatric comorbidities. To our knowledge, this is the first demonstration of this association in a large sample of older Americans.

Of the three symptoms we examined, the relationship between loneliness and depression was strongest. This is not surprising as depression and loneliness are both entirely cognitive-psychosocial states, while pain and fatigue are defined by somatic symptoms. Loneliness

Table 2. Loneliness is associated with increased odds of pain, fatigue, depression, and the symptom cluster ($n = 11{,}766$).

	Odds ratio (95% confidence interval)			
Variable	Model 1		Model 2[a]	
Symptom cluster	4.90 (4.28, 5.61)	$p < .0001$	3.39 (2.91, 3.95)	$p < .0001$
Pain	2.16 (2.00, 2.34)	$p < .0001$	1.61 (1.48, 1.76)	$p < .0001$
Fatigue	2.55 (2.36, 2.76)	$p < .0001$	2.02 (1.85, 2.20)	$p < .0001$
Depression	5.36 (4.89, 5.87)	$p < .0001$	4.34 (3.93, 4.79)	$p < .0001$

Notes. Model 1 is unadjusted.
[a]Model 2 is adjusted for age, gender, race/ethnicity, living arrangement, education, total wealth, and number of comorbidities.

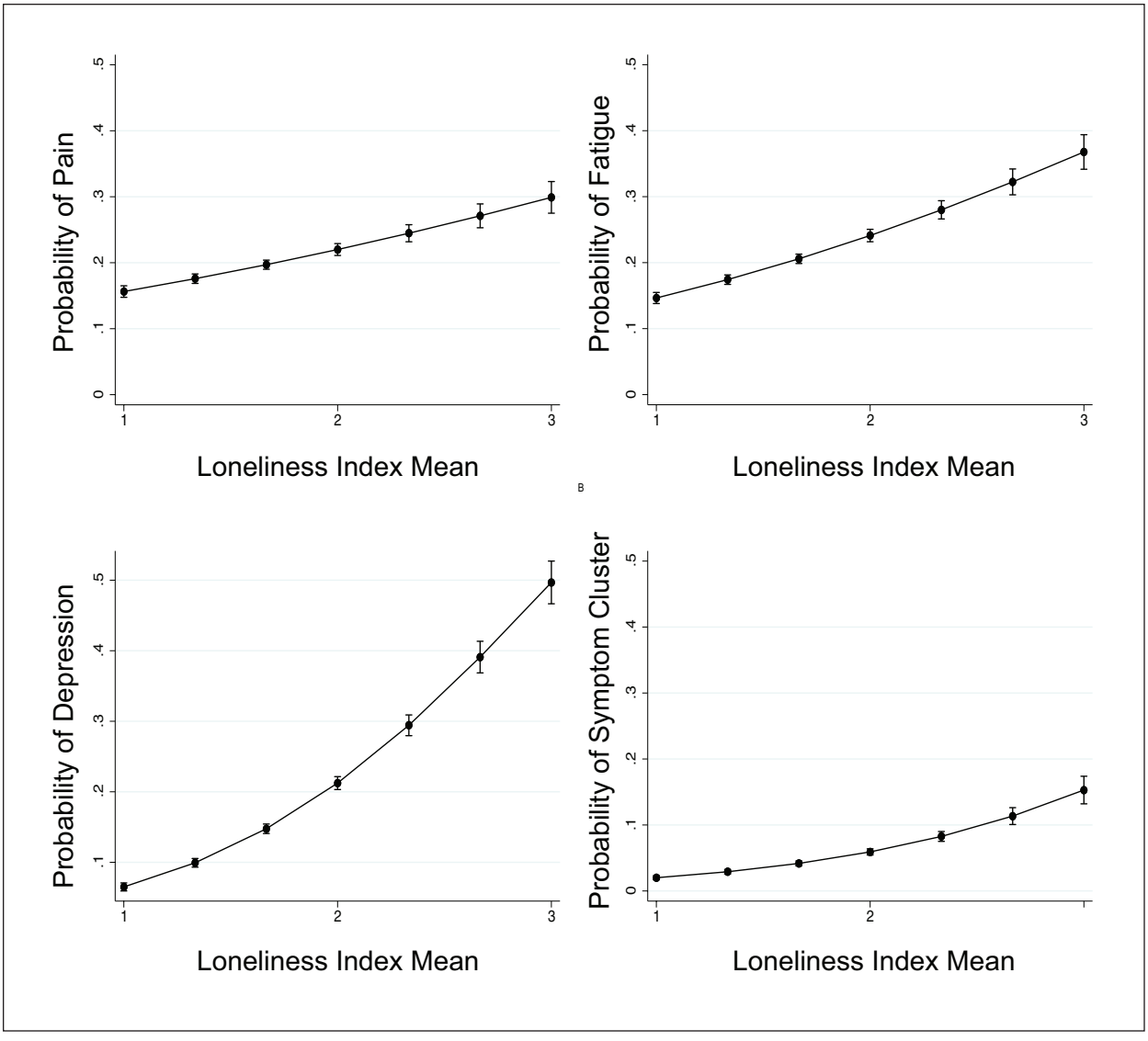

Figure 2. Increasing loneliness is associated with higher probability of pain, fatigue, depression, and the symptom cluster. Reporting higher average responses to loneliness questions was associated with higher probability of individual symptoms as well as the symptom cluster.

and depression have long been recognized as separate constructs that frequently co-occur (Weeks et al., 1980).

Strengths of our study relate to its design. The sample size was large, allowing us to have sufficient statistical power to test our hypotheses of interest and have confidence in point estimates of the strength of relationship with loneliness. We applied a simple, yet relatively rigorous definition of the symptom cluster, facilitating interpretability and replicability of our results. Accordingly, the prevalence of the cluster that

we observed (4.9%) was slightly lower than the 5.7% to 17.2% suggested by prior literature utilizing a variety of measures (Bjerkeset et al., 2020; Lin et al., 2013; Reyes-Gibby et al., 2006).

This study adds to a growing body of literature linking loneliness with negative health outcomes in older people. Lonely older adults face an increased risk of worsening cognitive function (Boss et al., 2015; O'Luanaigh et al., 2012), depression (Aziz & Steffens, 2013; Cacioppo et al., 2010), sleep disturbance(Cacioppo et al., 2002), and overall mortality (Holt-Lunstad et al., 2015; Luo et al., 2012; Steptoe et al., 2013). Older Americans may be particularly susceptible to loneliness through shrinking social networks (especially death of a spouse), changing social roles, and worsening health status (Dury, 2014; Jones et al., 1985; Luanaigh & Lawlor, 2008).

What may underlie the relationship we observed? Loneliness may behave like other chronic stressors, converging on the same physiological responses that are seen in severe physical illness. Hawkley and Cacioppo's (2010) model proposes that the state of chronic threat caused by loneliness induces pathologic hypervigilance, which, in turn, imposes a substantial drain on executive function, attention/concentration, and self-regulation. This state may interfere with sleep quality, causing daytime fatigue (Friedman et al., 2005), and increased activation of the HPA axis and cortisol release (Steptoe et al., 2004). Increased cortisol has been linked to increased prevalence of the symptom cluster of pain, fatigue, and depression. (Thornton et al., 2010).

Immune system dysfunction (i.e., pathologic inflammatory signaling) that is induced or exacerbated by the chronically stressed state of loneliness may be the mechanism underlying the relationship. Indeed, lonely individuals have been found to have widespread genomic markers of immune activation and pro-inflammatory signaling along with reduction in mature B lymphocyte function and reduced innate immune response to viruses (Cole et al., 2007). An increase in inflammatory cytokines has been associated with depression (Dantzer, 2009) and fibromyalgia, a disease characterized by widespread pain and fatigue (Bazzichi et al., 2007). Several smaller studies in specialized populations have found associations with loneliness and the symptom cluster (Jaremka et al., 2013, 2014) alongside immune dysfunction. Future studies in large, general populations should examine this relationship longitudinally to better understand causality.

There is evidence that loneliness can be "treated"; several groups have had preliminary success reducing loneliness (Masi et al., 2011; Perissinotto et al., 2019). Methods include addressing maladaptive social cognitions (such as catastrophizing) (Masi et al., 2011). Maladaptive cognitions are almost always present in depression (Kovacs & Beck, 1978) and are frequently found in complex pain and fatigue disorders (Friedberg & Krupp, 1994; Keefe et al., 1989; Wolf et al., 2015). It is possible that maladaptive cognitions may be present in lonely individuals who also have the symptom cluster and represent a potentially targetable treatment strategy. Other novel approaches that show preliminary efficacy mitigating loneliness in special populations include group reminiscence therapy (Syed Elias et al., 2015) and meaning-centered psychotherapy (Breitbart, 2002; Breitbart et al., 2015). Interestingly, pharmacologic approaches for treating loneliness, such as allopregnanolone, have shown preliminary success in animal models and are currently under investigation (Cacioppo et al., 2015). Future studies should explore whether these or other interventions may be useful for more generalized populations experiencing loneliness.

Several important limitations of this study should be considered. First, this was an observational, cross-sectional study at a single point in time, thus not allowing us to determine the direction of the relationship between loneliness and the cluster. Second, as with any survey with a look-back design, we cannot exclude the possibility of recall bias. Future studies should examine this relationship longitudinally to better understand causality. Indeed, the population we studied could be followed longitudinally in forthcoming HRS waves to examine the directionality of the relationship between pain, the cluster, and loneliness. Third, by virtue of choosing strict criteria for our predictor and outcomes of interest, we may have underestimated the magnitude of the relationship between loneliness and pain. However, we believe the tradeoff increased the believability of our results. Lastly, some may disagree with how we identified the symptom cluster. However, the process was largely limited by how the HRS assessed pain, depression, fatigue, and loneliness. While the HRS used validated questions for assessing each symptom, it did not allow for assessing the symptom cluster using the same methodology as prior studies. Development and testing of a direct measure for the cluster is needed.

Conclusion

The symptom cluster of pain, fatigue, and depression is strongly associated with loneliness in large sample of older American adults. While prior research suggests multiple biological pathways for loneliness, a common psychosocial stressor, to play a causal role in development of this symptom cluster, this study did not examine these effects due to its exploratory nature. Future research should focus on elucidating the causal pathway as well as examining markers of inflammation, immune dysregulation, and changes in HPA axis activity. Depending upon the results, there may be an opportunity to prevent or mitigate pain, fatigue, and depression by addressing loneliness in older adults.

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Author Contributions

Conception and design: V.P., M.S. Statistical analysis: V.P., N.A., M.K., N.K., A.G. Interpretation of data: all authors. Drafting article: V.P. Critical intellectual revisions: all authors. Final approval: all authors.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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