Received: 27 October 2021 | Revised: 10 February 2022 | Accepted: 11 March 2022

DOI: 10.1111/jgs.17796

CLINICAL INVESTIGATIONS

Journal of the
American Geriatrics Society

Bad company: Loneliness longitudinally predicts the symptom cluster of pain, fatigue, and depression in older adults

Victoria D. Powell MD[1,2] | **Navasuja Kumar MBBS, MPH**[1] | **Andrzej T. Galecki MD, PhD**[1,3] | **Mohammed Kabeto MS**[1] | **Daniel J. Clauw MD**[4] | **David A. Williams PhD**[4] | **Afton Hassett PsyD**[4] | **Maria J. Silveira MD, MA, MPH**[1,2]

[1]Division of Geriatric and Palliative Medicine, University of Michigan, Ann Arbor, Michigan, USA

[2]Geriatric Research, Education, and Clinical Center, LTC Charles S. Kettles VA Medical Center, Ann Arbor, Michigan, USA

[3]Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA

[4]Department of Anesthesiology, University of Michigan Medical School, Ann Arbor, Michigan, USA

Correspondence
Victoria D. Powell, Division of Geriatric and Palliative Medicine, University of Michigan, 300 N Ingalls, Room 912, Ann Arbor, MI 48109-2007, USA.
Email: powellvd@med.umich.edu

Funding information
This work was supported by the National Institute on Aging at the National Institutes of Health (grant numbers T32 AG062043 (V.P.), P30 AG024824 (M.K, N.K., A.G.) and the Pilot and Exploratory Projects in Palliative Care grant from the University of Michigan Division of Geriatric and Palliative Medicine. The HRS is sponsored by the National Institute on Aging at the National

Abstract

Background: Pain, fatigue, and depression frequently co-occur as a symptom cluster. While commonly occurring in those with cancer and autoimmune disease, the cluster is also found in the absence of systemic illness or inflammation. Loneliness is a common psychosocial stressor associated with the cluster cross-sectionally. We investigated whether loneliness predicted the development of pain, fatigue, depression, and the symptom cluster over time.

Methods: Data from the Health and Retirement Study were used. We included self-respondents ≥50 year-old who had at least two measurements of loneliness and the symptom cluster from 2006–2016 ($n = 5974$). Time-varying loneliness was used to predict pain, fatigue, depression, and the symptom cluster in the subsequent wave(s) using generalized estimating equations (GEE) and adjusting for sociodemographic covariates, living arrangement, and the presence of the symptom(s) at baseline.

Results: Loneliness increased the odds of subsequently reporting pain (aOR 1.22, 95% CI 1.08, 1.37), fatigue (aOR 1.47, 95% CI 1.32, 1.65), depression (aOR 2.33, 95% CI 2.02, 2.68), as well as the symptom cluster (aOR 2.15, 95% CI 1.74, 2.67). The median time between the baseline and final follow-up measurement was 7.6 years (IQR 4.1, 8.2).

Conclusions: Loneliness strongly predicts the development of pain, fatigue, and depression as well as the cluster of all three symptoms several years later in a large, nonclinical sample of older American adults. Future studies should examine the multiple pathways through which loneliness may produce this cluster, as well as examine whether other psychosocial stressors also increase

Gerontological Society of America (GSA) 2021 Annual Scientific Meeting.

See related article by Kotwal et al. in this issue.

Institutes of Health (grant number U01 AG009740) and is conducted by the University of Michigan.

risk. It is possible that interventions which address loneliness in older adults may prevent or mitigate the cluster of pain, fatigue, and depression.

KEYWORDS

complex pain, psychosocial stress, quality of life, social support

INTRODUCTION

Pain, fatigue, and depression co-occur more frequently than expected by chance alone,[1] resulting in poor quality of life and impaired functional status.[2] Together, these symptoms form a cluster which may have shared underlying mechanisms.[3] This cluster is best characterized in patients with cancer, where 8%–13% of survivors[4,5] and 10%–76% of those with active cancer[6–8] report the co-existence of pain, fatigue, and depression. The presence of this cluster shows no apparent relationship with a specific malignancy; it has been reported in those with lung,[6,7,9] breast,[5] prostate,[4] and gastrointestinal cancers.[8] These symptoms are quite common in other clinical populations with prevalence estimates of 66% of patients with systemic lupus erythematosus,[10] 16% of patients with multiple sclerosis,[11] and 11% of patients with end-stage renal disease.[8] In the general population, prevalence appears to be somewhat lower, around 5%–6%.[12,13] That the cluster is found in multiple unrelated conditions suggests that its etiology may be distinct from a specific condition but perhaps shared with several. One factor that appears to be associated with the emergence of this symptom cluster is the subjective experience of social isolation even when other people are present, which defines the phenomenon of loneliness.[14] Loneliness is only modestly correlated with objective social isolation, and feeling lonely may predict poor outcomes better than objective social isolation.[15,16]

Loneliness can induce emotional states (e.g., anxiety disrupting sleep) and physiological changes (e.g., alterations in gene expression and immune function) that activate a general stress response and promote behaviors that increase the likelihood of short-term survival.[17] However, when loneliness persists, the same responses that are adaptive in the short-term can cause adverse long-term health consequences.[18] Indeed, loneliness has been associated with many poor outcomes, including a 26% increased risk of premature mortality.[18] Moreover, the negative impact of loneliness may be increasing due to social distancing measures necessary for controlling the coronavirus disease 2019 (COVID-19) pandemic.[19,20]

Several studies have demonstrated strong cross-sectional relationships between loneliness and pain, fatigue, and depression,[12,21] but the directionality of the relationship remains unclear. Longitudinal studies examining the temporal relationship to date have included only a single component of the cluster (i.e., pain)[22,23] or were limited by small sample sizes and examination of select populations.[24] Findings have been mixed, with loneliness preceding pain[25] or the symptom cluster,[24] pain preceding loneliness,[22] and bidirectional relationships[23] all reported. Notably, "pain" is frequently captured broadly as either present or not, with no information on pain's severity and/or functional impact.[13,22,23] These factors are important because they influence decisions to seek treatment.[26] It remains unclear to what extent loneliness predicts development of clinically significant pain along with fatigue and depression.

In this study, we examined the longitudinal relationship between loneliness and the symptom cluster of pain, fatigue, and depression in a large cohort of older Americans, hypothesizing that loneliness would predict the subsequent development of each symptom and the cluster. For the reasons above, we chose to focus only on pain reported as moderate to severe in intensity that interferes

Key points

- More severe loneliness independently predicts pain, fatigue, depression, and the cluster of all three symptoms years later, even when controlling for baseline pain, fatigue, and depression, as well as other potential confounders.
- While all effects were significant, we observed the largest effect size for loneliness as a predictor of depression and the symptom cluster.

Why does this paper matter?

Loneliness is a common psychosocial distress state that increases risk of developing pain, fatigue, and depression even in absence of a specific diagnosis or inflammatory state; interventions which address feelings of loneliness may mitigate or prevent these symptoms.

with daily activities. Understanding the directionality of the relationship is a critical step in the development and refinement of interventions for those with co-occurring pain, fatigue, and depression. Should loneliness play a causal role in symptom cluster development, interventions aimed at palliating feelings of loneliness might have a role in its treatment or prevention.

METHODS

Data source and study design

Data were obtained from the Health and Retirement Study (HRS), a large longitudinal panel survey, which collects biennial data from Americans ≥50 years-old assessing multidimensional aspects of aging. The HRS has been ongoing since 1992, and new birth-year cohorts are enrolled every 6 years and followed until death. The HRS is administered by the Institute for Social Research at the University of Michigan and sponsored by the National Institute on Aging; detailed information regarding study design is available at (http://hrsonline.isr.umich.edu). Core information, which includes assessment of pain and depression, is collected every wave (i.e., every 2 years). Fatigue information is collected every other wave (i.e., every 4 years). Starting in 2006, an additional "Leave-Behind" questionnaire, intended to be completed after the Core interview, has assessed psychosocial and lifestyle factors related to aging, including loneliness.[27] A random 50% of participants are given the opportunity to complete the Leave-Behind survey every other wave (i.e., every 4 years), with the remaining 50% having the opportunity the following wave. Completion rates range from 72.7%–87.7% of eligible participants.[27] This study utilized six HRS waves from 2006–2016.

We examined the longitudinal relationship between loneliness (primary predictor), each symptom (pain, fatigue, and depression), and the symptom cluster (primary outcome). We defined the baseline measurement as the first time a self-responding HRS participant, age ≥50 years-old, provided nonmissing data for loneliness, the symptom cluster, and relevant sociodemographic covariates of interest (described in the following section). Follow-up measurements were defined as the subsequent time(s) an individual provided a complete set of loneliness and symptom cluster data. As we were interested in the longitudinal relationship, individuals who provided only a baseline measurement (i.e., with zero follow-up visits) were excluded. Depending on when participants provided baseline data, the number of follow-up measurements available for longitudinal analysis was one or two, occurring up to 8 years after baseline (as each participant was given the opportunity to complete the Leave-Behind questionnaire every other wave). Because fatigue is assessed at HRS entry and every other wave, while the Leave-Behind survey is administered to a random 50% of participants every other wave, the most recent year for which any participants who previously provided baseline data had complete sets of follow-up data were 2016. This study was exempt from IRB review as it involved only deidentified, publicly available data.

Measures

Symptom cluster

The primary outcome of interest was the dichotomous (yes/no) presence of all three symptoms (pain, fatigue, and depression) at or exceeding threshold levels as described below. Those not meeting criteria for the symptom cluster were used as the comparison group. Individual symptoms of pain, fatigue, and depression were also examined separately, using those not reporting the symptom as comparators.

We utilized a multistep process to determine the presence of pain, which was assessed in each core survey wave. Subjects were asked if they are "often troubled" with pain. Those answering "yes" were then asked follow-up questions regarding pain severity (mild, moderate, or severe) and pain interference with usual activities (yes/no). We defined pain as frequent, moderate, or severe intensity pain that interfered with functioning. While these criteria have been used in some previous studies using HRS data to examine pain,[12] they are stricter than others.[13,22]

The presence of fatigue was assessed in the initial HRS interview and every other wave. Participants were asked whether they have "persistent, severe fatigue or exhaustion." Those answering "yes" met criteria for fatigue, similar to other studies using the HRS and related longitudinal panel surveys.[13,28]

Depressive symptoms were ascertained every core survey wave using the 8-item Center for Epidemiologic Studies Depression Scale (CES-D), a reliable and valid tool for identifying clinically significant affective symptoms with a range from 0 to 8.[29] We defined those with CES-D scores ≥4 as surpassing the threshold for identifying depression. This cut point, which corresponds with a sensitivity of 72% and specificity of 86%,[30] has been used previously in HRS studies of depressive symptoms.[12,13]

Loneliness

Loneliness was assessed every other wave in the Leave-Behind survey using the 3-item version of the University of California, Los Angeles (UCLA) Loneliness Scale

(Cronbach's alpha = 0.72).[31] Individuals were asked how often they felt or experienced the following: (1) they lacked companionship, (2) left out, and (3) isolated from others. Participants could answer "often," "some of the time," or "hardly ever or never" for each question. A mean loneliness index was created by reverse-scoring the items and taking the mean (range 1–3) as recommended by HRS documentation.[27,32] Mean loneliness index scores of "1" indicated all items were answered as "hardly ever or never" (i.e., loneliness absent), while a score of "3" indicated that all three symptoms were experienced often (i.e., most severe loneliness). The mean loneliness index was used as the primary predictor in the models.

Covariates

Sociodemographic covariates were defined at baseline. We chose covariates known to associate with loneliness including age, gender, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and other), education level (no degree, GED/high school diploma, some college to four-year degree, and Master's degree and above), and living arrangement (living with partner/spouse, not living with partner/spouse but living with someone, or living alone).[33,34] Medical and psychiatric comorbidities were obtained from the baseline core survey. Participants were asked if "a doctor has ever told you that you have" any of the following medical conditions: hypertension, diabetes, cancer, chronic lung disease, heart disease, stroke, arthritis, or psychiatric problems in general. The number of comorbidities was summed and analyzed as a composite variable (range 0–8). Total wealth information was divided into quartiles. The time in years between measurements was included as an additional covariate.

Study sample

The analytical sample consisted of American adult participants ≥50 year-old who provided at least two complete sets of loneliness and symptom cluster data and had nonmissing covariates at the baseline measurement ($n = 5974$). Because we were interested in changes over time, only those with at least two complete sets of loneliness and symptom cluster data were included.

Primary analysis

Participant characteristics were described by summarizing means and standard deviations for normally distributed continuous variables, medians, and interquartile range for nonnormally distributed continuous variables, and tabulations of categorical variables. All variables were examined for missing data. We coded a lack of response, refusal to respond, or responses of "do not know" as missing and excluded these data from analysis. We treated missing values of the dependent variables as missing completely at random.

To test whether loneliness was associated with the subsequent development of the symptom cluster over time, we developed logistic regression models using the generalized estimating equations (GEE) approach with an autoregressive correlation structure to account for correlation between individuals' measurements over time.[35] Similar models were fitted for individual symptoms (pain, fatigue, and depression). Time-varying loneliness at earlier wave(s) (i.e., baseline and/or first follow-up) was used to predict the presence of the symptom cluster in subsequent wave(s) (i.e., first and/or second follow-up). All models were adjusted for the presence of the outcome of interest at baseline and time between measurement(s) in years. Additional models adjusted for sociodemographic covariates. For all models, the comparator was the absence of the outcome (symptom cluster, pain, fatigue, or depression). As participants' baseline measurements were drawn from multiple waves depending on when they provided the first complete dataset, we did not apply year-specific weights or adjust for complex sampling design. Model fit was assessed using quasi-likelihood under the independence model criterion (QIC).[36] Finally, we applied adjusted models to two hypothetical populations who did not have the symptoms or cluster at baseline. These two populations were otherwise identical except for loneliness; the first was modeled as having the most severe loneliness (mean loneliness index = 3), while the second modeled as having the lowest (mean loneliness index = 1). This method allowed assessment of loneliness' effect on the predicted probability of reporting each symptom and the cluster over time, while holding other factors constant.

Sensitivity analysis

As one of the CES-D items directly asks whether individuals felt lonely, a sensitivity analysis was conducted excluding this item. Logistic regression using GEE was conducted examining the effect of time-varying loneliness at previous wave(s) on reporting depression and the symptom cluster in subsequent wave(s), excluding the loneliness question. We used the same cut-point of CES-D scores ≥4 to define depression. Otherwise, the sensitivity analyses were conducted identically to the primary analysis. All analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

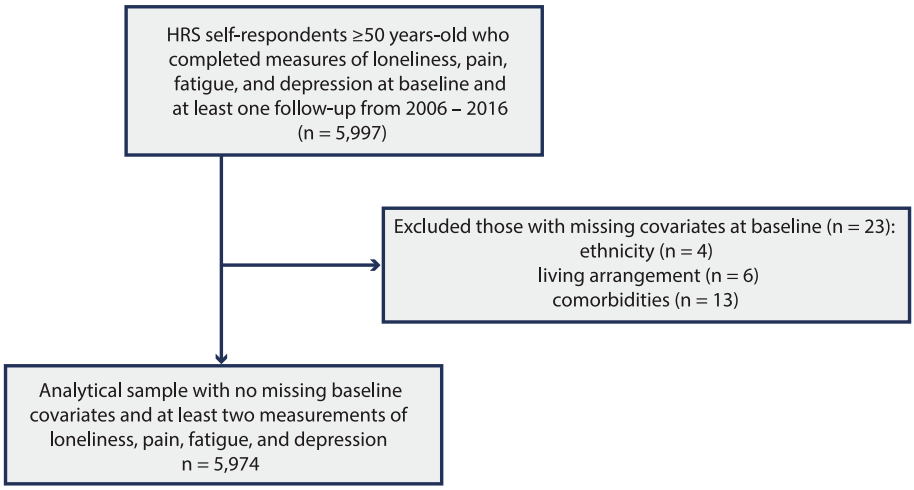

FIGURE 1 STROBE flowchart for cohort selection. The study flowchart following the STROBE (strengthening the reporting of observational studies in epidemiology) statement (http://www.strobestatement.org)

RESULTS

Descriptive statistics

The total number of HRS participants age ≥50 years who provided responses regarding loneliness and symptom cluster data in at least two waves from 2006–2016 was 5997. When restricted to those who had nonmissing baseline covariate data, the final analytical sample contained 5974 unique individuals (Figure 1). Of these individuals, 3269 (54.7%) and 2705 (45.3%) provided one and two complete sets of follow-up data, respectively (i.e., two and three total measurements). The median time between baseline and final follow-up was 7.6 years (IQR 4.1, 8.2). Details regarding HRS waves providing baseline and follow-up data available in Table S1. The cluster was present in 3.8% ($n = 226$) at baseline. The proportion of individuals meeting threshold criteria for pain, fatigue, and depression at baseline were 17.7% ($n = 1059$), 17.2% ($n = 1025$), and 12.5% ($n = 748$), respectively. The mean loneliness index had a median value of 1.3 (IQR 1.0–2.0). Participant baseline characteristics are reported in Table 1.

Loneliness as a predictor of the symptom cluster

Individuals reporting more severe loneliness had increased odds of reporting each individual symptom and the cluster over time. After adjusting for the presence of the outcome at baseline, time in years, and sociodemographic covariates, the odds of subsequently reporting pain, fatigue, and depression were 1.22 (95% CI 1.08–1.37), 1.47 (95% CI 1.32–1.65), and 2.33 (95% CI 2.02–2.68), respectively. The odds of reporting the cluster of symptoms were 2.15 (95% CI 1.74–2.67). A one-point increase in the lagged mean loneliness index, representing the difference in experiencing loneliness "hardly ever or never" to "some of the time" incurred a greater than two-fold increase in odds of reporting the symptom cluster at subsequent measurements (Table 2). When the model was applied to two hypothetical populations varying only in degree of loneliness, the predicted probability of reporting each symptom and the cluster was higher at all subsequent time points for those reporting more severe loneliness (Figure 2). Sensitivity analyses excluding the loneliness question from the CES-D did not change results (Table S2). All models which included sociodemographic covariates had better fit as assessed by lower QIC values.

Discussion

Pain, fatigue, and depression cluster together frequently, greatly impacting functional status and quality of life.[1–4,37] Because this cluster has been observed across many unrelated conditions,[4–11] a common vulnerability that is not specific to any one disease, such as loneliness, could potentially play a causal role. We found that loneliness independently predicts the development of the symptom cluster of pain, fatigue, and depression in a large sample of older American adults. Those who reported loneliness at least "some of the time" had more than two-fold odds of developing the symptom cluster compared with those who "hardly ever or never" felt lonely. This effect was present even after accounting for potential demographic, social, and clinical confounders. While loneliness and the symptom cluster have been found to strongly associate in other large cross-sectional studies,[12] to our knowledge, this is the first demonstration of the temporal association in a large, general sample of older Americans, and extends findings of smaller, longitudinal studies in specialized populations.[24]

This study provides several additional unique contributions. The follow-up period of up to 8 years is twice as

TABLE 1 Participant characteristics at baseline

Age in years, mean (SD)	**65.5 (9.2)**
Sex, *n* (%)	
Male	2381 (39.9%)
Female	3593 (60.1%)
Race/ethnicity, *n* (%)	
Non-Hispanic white	4372 (73.2%)
Non-Hispanic black	859 (14.4%)
Hispanic	590 (9.9%)
Other	153 (2.6%)
Education, *n* (%)	
No degree	929 (15.5%)
GED/HS	3224 (54.0%)
Some college/2–4 year degree	1207 (20.2%)
Masters/professional degree	614 (10.3%)
Living arrangement, *n* (%)	
Living with partner/spouse	4074 (68.2%)
Not living with partner/spouse but living with someone	692 (11.6%)
Living alone	1208 (20.2%)
Total wealth in quartiles, *n* (%)	
First quartile (<$44,300)	1493 (25.0%)
Second quartile ($44,300–$196,000)	1495 (25.0%)
Third quartile ($196,001–$558,000)	1493 (25.0%)
Fourth quartile (>$558,000)	1493 (25.0%)
Comorbidities, *n* (%)	
Hypertension	3382 (56.6%)
Diabetes	1168 (19.6%)
Cancer	802 (13.4%)
Chronic lung disease	573 (9.6%)
Heart disease	1290 (21.6%)
Stroke	324 (5.42%)
Psychiatric problems	1033 (17.3%)
Arthritis	3533 (59.1%)
Total comorbidities, Median (Q1, Q3)	2.0 (1.0, 3.0)
Mean loneliness index, median (Q1, Q3)[a]	1.3 (1.0, 2.0)
Pain, *n* (%)	1059 (17.7%)
Fatigue, *n* (%)	1025 (17.2%)
Depression, *n* (%)	748 (12.5%)
Symptom cluster, *n* (%)	226 (3.8%)

Note: Data source: Health and Retirement Study, 2006–2016, $n = 5974$.
[a]Range 1–3.

long as prior studies.[22–24] Notably, we chose to define "pain" as present only when it is frequent, moderate to severe in intensity, and interferes with functioning. These are characteristics that define "high-impact" pain, which is associated with increased healthcare utilization, cost, and opioid use.[26,38] Other studies investigating this relationship have simply defined pain as present or not, which may limit generalizability and clinical relevance.[13,22,23] Moreover, there is debate regarding the association's directionality. Some have posited that pain, fatigue, and depression in combination could cause activity and mobility restrictions, resulting in social isolation and, in turn, feelings of loneliness.[22] However, our findings suggest that loneliness precedes the symptom cluster. Indeed, others have observed the same directionality[24,39,40] supporting that loneliness may play a causal role in the development of these symptoms together.

Our findings add to a growing body of research supporting relationships between loneliness and a wide variety of adverse outcomes in older adults, including dementia[41] and cardiovascular disease.[42] Unfortunately, the prevalence of loneliness in older adults is increasing as the COVID-19 pandemic continues.[20] Thus, a comprehensive response to mitigate loneliness' myriad harms is more important than ever. One suggested approach that clinicians can immediately adopt is treating loneliness identically to other high-impact risk factors such as tobacco use and physical inactivity.[43] The first step in this approach is to routinely assess loneliness, ideally through a standardized, brief measure, such as the 3-item tool used in this study.[31] If a patient endorses significant loneliness, compassionately informing him or her of the risks for loss of independence and declining function can provide crucial motivation to address it.[43]

There are several possible explanations for how loneliness promotes poor outcomes which could inform ideal approach(es) to addressing loneliness clinically. Loneliness may cause a state of chronic, subclinical stress characterized by immune dysregulation and/or pathologic hypothalamic–pituitary–adrenal (HPA) axis activation.[17,44] Chronic overactivation of this stress response, as might occur when an individual appraises life as persistently and profoundly lacking support and connection (i.e., severe loneliness), may cause or intensify the experience of pain, fatigue, and/or depression. Another possible mechanism through which loneliness may promote the symptom cluster is via induction of maladaptive cognitions such as catastrophizing and self-criticism.[25,45] Feeling lonely may also inhibit health-promoting behaviors such as regular physical exercise.[46] The combination of chronic stress, maladaptive cognitions, and lack of health-promoting behavior could result in developing pain, fatigue, and depression over time, and should be examined in future longitudinal research.

These symptoms have been identified in pain conditions characterized by central nervous system (CNS)

TABLE 2 Lagged association of loneliness as a time-varying predictor of pain, fatigue, depression, and cluster of symptoms

Outcome	OR (95% CI) Model 1[a]	*p*	QIC	OR (95% CI) Model 2[b]	*p*	QIC
Symptom cluster	2.58 (2.12, 3.14)	**	2205.11	2.15 (1.74, 2.67)	**	2046.93
	Model 3[a]			**Model 4**[b]		
Pain	1.41 (1.26, 1.57)	**	6833.21	1.22 (1.08, 1.37)	**	6549.57
	Model 5[a]			**Model 6**[b]		
Fatigue	1.61 (1.45, 1.78	**	7445.86	1.47 (1.32, 1.65)	**	7136.07
	Model 7[a]			**Model 8**[b]		
Depression	2.51 (2.20, 2.86)	**	5310.83	2.33 (2.02, 2.68)	**	5058.63

Note: Data source: Health and Retirement Study, 2006–2016, $n = 5974$. Generalized estimating equations (GEE) logistic regression was used for all models. The absence of the outcome (pain, fatigue, depression, or symptom cluster) was used as the reference group for all models. QIC: quasi-likelihood under the independence model criterion.

**$p < 0.0001$.

[a]Models 1, 3, 5, and 7 include time-varying loneliness at previous wave(s) as the primary predictor of the outcome, adjusting for follow-up time in years and the presence of the outcome at baseline.

[b]Models 2, 4, 6, and 8 include time-varying loneliness at previous wave(s) as the primary predictor of the outcome, adjusting for follow-up time in years, the presence of the outcome at baseline, and baseline sociodemographic covariates (age, sex, race/ethnicity, education, total wealth in quartiles, living arrangement and total number of comorbidities).

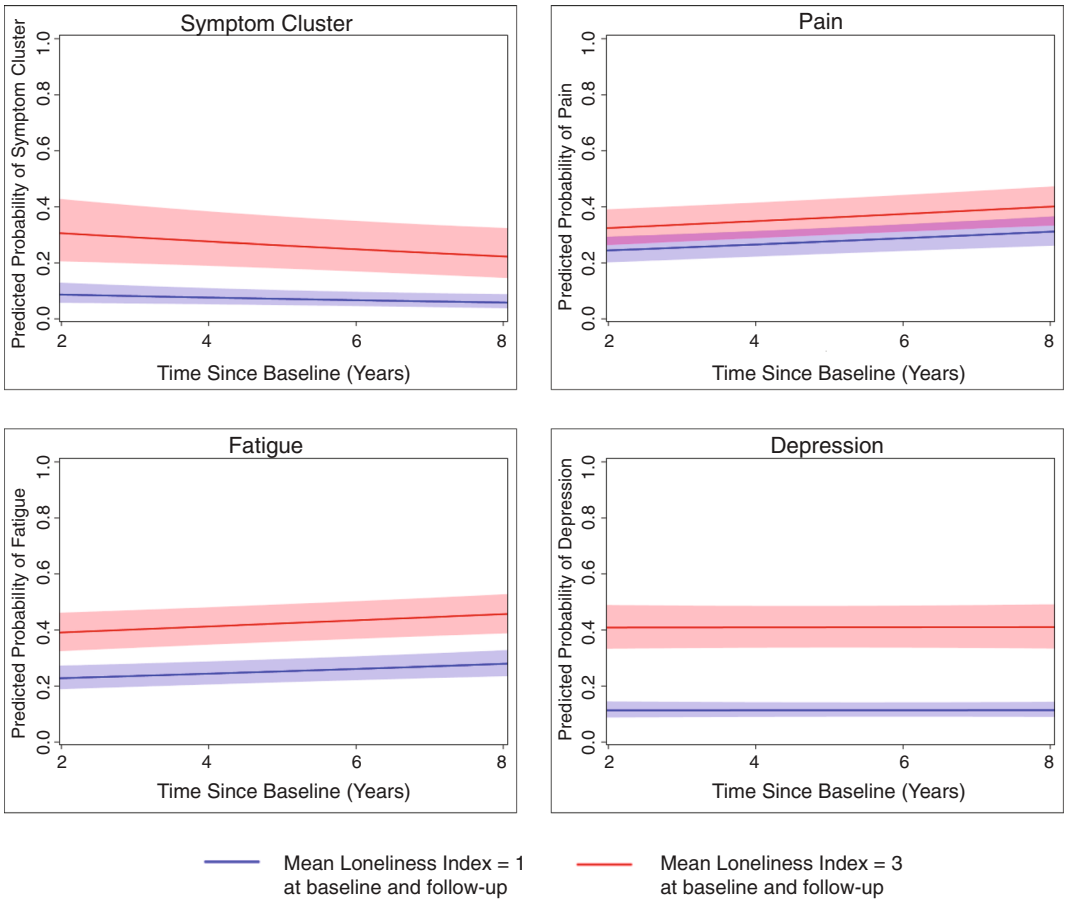

FIGURE 2 Model-based predicted probabilities of reporting the symptom cluster and individual symptoms (pain, fatigue, and depression) over time for two hypothetical identical populations which vary only in mean loneliness index. The first hypothetical population (in blue) was assigned a mean loneliness index of 1 (indicating lowest level of loneliness) for baseline and follow - up measurements. The second hypothetical population (in red) was assigned a mean loneliness index of 3 (indicating highest level of loneliness) for baseline and follow-up measurements. Other characteristics were held constant for the two hypothetical populations and included age 62 years, white/non-Hispanic ethnicity, female sex, high school/GED education level, living with spouse or partner, lowest quartile of total wealth, four comorbidities, and absence of the symptom(s) or symptom cluster at baseline. Solid lines indicate predicted probabilities, with shaded regions indicating 95% confidence interval

sensitization.[47,48] This raises the possibility that certain clusters (pain, fatigue, and depression, but also sleep disturbance and cognitive dysfunction[48]) could be either risk factors or markers of central sensitization. In central sensitization, the CNS amplifies peripheral sensations and imbues them with emotional salience, resulting in the experience of chronic, widespread pain accompanied by other distressing symptoms.[49] Interestingly, studies of patients with fibromyalgia (the prototypical disorder of central sensitization[49]) suggest loneliness is particularly important. Patients with fibromyalgia report more frequent and more severe loneliness than those with painful conditions driven by peripheral inflammation (e.g., rheumatoid arthritis).[50] Second, on a day-to-day basis, feeling lonely precedes more severe pain episodes in fibromyalgia.[25] Taken together, these studies raise the possibility that loneliness could induce, maintain, or exacerbate changes in sensory processing, which could then be expressed as symptom clusters. Future studies should examine this hypothesis, including not only pain, fatigue, and depression, but sleep disturbance and subjective cognitive dysfunction as well.

The present study has several limitations. The first relates to measurement of the cluster. While validated tools exist for measuring each symptom, there is no gold standard measurement of the symptom cluster, making comparisons between studies challenging. We did not examine individuals with only two symptoms, which may limit the sensitivity of our findings. We dichotomized each symptom and the cluster; in reality, symptoms are likely to be present along a continuum. Our strict cut-point for pain could have reduced sensitivity to detect those with milder pain. Additionally, by requiring individuals to report all three symptoms at threshold levels to have the symptom cluster, we may have excluded those with only two symptoms and/or those with subthreshold symptom clusters. While these are limitations, they bias toward the null; the presence of strong associations with loneliness and the cluster despite these limitations increases the confidence in our findings. Second, while CNS sensitization may be at play in the symptom cluster, our study neither used a validated measure of CNS sensitization nor did we examine cognitive function, sleep, or obtain detailed descriptions of pain.

Our findings have implications for future research. Loneliness is but one psychosocial factor relating to this cluster. The impact of additional psychosocial factors should be examined. Also, future studies assessing symptom clusters should examine other symptoms, which may co-occur with pain, fatigue, and depression, especially subjective cognitive dysfunction and sleep disturbance.[47,48] Doing so will allow for better understanding of how the symptom cluster relates to CNS sensitization. Future research clarifying pathways should examine maladaptive cognitions, health-promoting behaviors, and biomarkers of immune response and HPA axis activity longitudinally.

Loneliness is unlikely to be the only psychosocial stressor that increases risk of developing the symptom cluster, but it is particularly intriguing as increasing evidence suggests that loneliness may be alleviated with intervention.[43] More work is needed to understand whether approaches that mitigate loneliness may have a role in the prevention or treatment of pain, fatigue, and depression.

CONCLUSION

Loneliness strongly predicts the development of pain, fatigue, and depression as well as the symptom cluster over time in a large, nonclinical sample of older American adults. This relationship persisted after adjusting for the presence of symptoms at baseline and sociodemographic covariates. Future studies should examine the multiple pathways through which loneliness and other psychosocial stressors may produce this cluster. This research both supports the routine clinical assessment of loneliness as a high-impact, potentially modifiable risk factor and continued interest in the development of interventions, which address loneliness in older adults. Such approaches may ultimately reduce the impact of loneliness on multiple outcomes, including the cluster of pain, fatigue, and depression.

AUTHOR CONTRIBUTIONS

Conception and design (Victoria D. Powell, Maria J. Silveira, Daniel J. Clauw), acquisition of data and data analysis (Navasuja Kumar, Mohammed Kabeto, Andrzej T. Galecki), interpretation of data (all authors), drafting the article (Victoria D. Powell), critical revisions (David A. Williams, Afton Hassett, Daniel J. Clauw, Maria J. Silveira). The final version was approved by all authors.

CONFLICT OF INTEREST

A.H. is a consultant to Happify Health. D.W. is a consultant to Swing Therapeutics, Inc. and to Community Health Focus. Inc. D.C. is a consultant to Pfizer, Tonix, Theravance, Zynerba, Samumed, Aptinyx, Daiichi Sankyo, Intec, Regeneron, Teva, and Lundbeck. D.C. receives research support from Pfizer, Cerephex, and Aptinyx. D.C. has been involved in litigation testifying against opioid manufacturers in the State of Oklahoma and Florida, and on behalf of Allergan regarding silicone breast implants.

SPONSORS' ROLE

The sponsor had no role in the design, methods, subject recruitment, data collections, analysis, and preparation of article.

ORCID

Victoria D. Powell https://orcid.org/0000-0002-7108-5449

TWITTER

Victoria D. Powell @victoriadpowell

REFERENCES

1. Laird BJA, Scott AC, Colvin LA, et al. Pain, depression, and fatigue as a symptom cluster in advanced cancer. *J Pain Symptom Manage*. 2011;42(1):1-11. doi:10.1016/j.jpainsymman.2010.10.261
2. Cleeland CS, Reyes-Gibby CC. When is it justified to treat symptoms? measuring symptom burden. *Oncology*. 2002;16(9 Suppl 10):64-70. http://www.ncbi.nlm.nih.gov/pubmed/12380956
3. Miaskowski C, Dodd M, Lee K. Symptom clusters: the new frontier in symptom management research. *J Natl Cancer Inst Monogr*. 2004;32:17-21. doi:10.1093/jncimonographs/lgh023
4. Baden M, Lu L, Drummond FJ, Gavin A, Sharp L. Pain, fatigue and depression symptom cluster in survivors of prostate cancer. *Support Care Cancer*. 2020;28(10):4813-4824. doi:10.1007/s00520-019-05268-0
5. Bjerkeset E, Röhrl K, Schou-Bredal I. Symptom cluster of pain, fatigue, and psychological distress in breast cancer survivors: prevalence and characteristics. *Breast Cancer Res Treat*. 2020;180(1):63-71. doi:10.1007/s10549-020-05522-8
6. Reyes-Gibby CC, Swartz MD, Yu X, et al. Symptom clusters of pain, depressed mood, and fatigue in lung cancer: assessing the role of cytokine genes. *Support Care Cancer*. 2013;21(11):3117-3125. doi:10.1007/s00520-013-1885-5
7. Lin S, Chen Y, Yang L, Zhou J. Pain, fatigue, disturbed sleep and distress comprised a symptom cluster that related to quality of life and functional status of lung cancer surgery patients. *J Clin Nurs*. 2013;22(9–10):1281-1290. doi:10.1111/jocn.12228
8. Jhamb M, Abdel-Kader K, Yabes J, et al. Comparison of fatigue, pain, and depression in patients with advanced kidney disease and cancer—symptom burden and clusters. *J Pain Symptom Manage*. 2019;57(3):566-575.e3. doi:10.1016/j.jpainsymman.2018.12.006
9. Wang SY, Tsai CM, Chen BC, Lin CH, Lin CC. Symptom clusters and relationships to symptom interference with daily life in Taiwanese lung cancer patients. *J Pain Symptom Manage*. 2008;35(3):258-266. doi:10.1016/j.jpainsymman.2007.03.017
10. Margiotta DPE, Fasano S, Basta F, et al. Clinical features of patients with systemic lupus erythematosus according to health-related quality of life, entity of pain, fatigue and depression: a cluster analysis. *Clin Exp Rheumatol*. 2019;37(4):535-539. http://www.ncbi.nlm.nih.gov/pubmed/31140392
11. Forbes A, While A, Mathes L, Griffiths P. Health problems and health-related quality of life in people with multiple sclerosis. *Clin Rehabil*. 2006;20(1):67-78. doi:10.1191/0269215506cr880oa
12. Powell VD, Abedini NC, Galecki AT, Kabeto M, Kumar N, Silveira MJ. Unwelcome companions: loneliness associates with the cluster of pain, fatigue, and depression in older adults. *Gerontol Geriatr Med*. 2021;7:233372142199762. doi:10.1177/2333721421997620
13. Reyes-Gibby CC, Aday LA, Anderson KO, Mendoza TR, Cleeland CS. Pain, depression, and fatigue in community-dwelling adults with and without a history of cancer. *J Pain Symptom Manage*. 2006;32(2):118-128. doi:10.1016/j.jpainsymman.2006.01.008
14. Perlman D, Peplau L. Theoretical approaches to loneliness. In: Perlman D, Peplau L, eds. *Loneliness: A Sourcebook of Current Theory, Research and Therapy*. Wiley; 1982:123-134.
15. Holwerda TJ, Deeg DJH, Beekman ATF, et al. Feelings of loneliness, but not social isolation, predict dementia onset: results from the Amsterdam Study of the Elderly (AMSTEL). *J Neurol Neurosurg Psychiatry*. 2014;85(2):135-142. doi:10.1136/jnnp-2012-302755
16. Ge L, Yap CW, Ong R, Heng BH. Social isolation, loneliness and their relationships with depressive symptoms: a population-based study. Khan HTA, *PLoS One*. 2017;12(8):e0182145. doi:10.1371/journal.pone.0182145
17. Cacioppo JT, Cacioppo S, Capitanio JP, Cole SW. The neuroendocrinology of social isolation. *Annu Rev Psychol*. 2015;66:733-767. doi:10.1146/annurev-psych-010814-015240
18. Holt-Lunstad J, Smith TB, Baker M, Harris T, Stephenson D. Loneliness and social isolation as risk factors for mortality: a meta-analytic review. *Perspect Psychol Sci*. 2015;10(2):227-237. doi:10.1177/1745691614568352
19. Smith BJ, Lim MH. How the COVID-19 pandemic is focusing attention on loneliness and social isolation. *Public Heal Res Pract*. 2020;30(2):e3022008. doi:10.17061/phrp3022008.
20. Kotwal AA, Holt-Lunstad J, Newmark RL, et al. Social isolation and loneliness among San Francisco Bay Area older adults during the COVID-19 shelter-in-place orders. *J Am Geriatr Soc*. 2021;69(1):20-29. doi:10.1111/jgs.16865
21. Rapo-Pylkko S, Haanpaa M, Liira H. Chronic pain among community-dwelling elderly: a population-based clinical study. *Scand J Prim Health Care*. 2016;34(2):159-164. doi:10.3109/02813432.2016.1160628
22. Emerson K, Boggero I, Ostir G, Jayawardhana J. Pain as a risk factor for loneliness among older adults. *J Aging Health*. 2018;30(9):1450-1461. doi:10.1177/0898264317721348
23. Loeffler A, Steptoe A. Bidirectional longitudinal associations between loneliness and pain, and the role of inflammation. *Pain*. 2021;162(3):930-937. doi:10.1097/j.pain.0000000000002082
24. Jaremka LM, Andridge RR, Fagundes CP, et al. Pain, depression, and fatigue: loneliness as a longitudinal risk factor. *Health Psychol*. 2014;33(9):948-957. doi:10.1037/a0034012
25. Wolf LD, Davis MC, Yeung EW, Tennen HA. The within-day relation between lonely episodes and subsequent clinical pain in individuals with fibromyalgia: mediating role of pain cognitions. *J Psychosom Res*. 2015;79(3):202-206. doi:10.1016/j.jpsychores.2014.12.018
26. Herman PM, Broten N, Lavelle TA, Sorbero ME, Coulter ID. Health care costs and opioid use associated with high-impact chronic spinal pain in the United States. *Spine (Phila Pa 1976)*. 2019;44(16):1154-1161. doi:10.1097/BRS.0000000000003033
27. Smith J, Ryan L, Fisher G, Sonnega A, Weir D. HRS Psychosocial and Lifestyle Questionnaire 2006–2016; 2017. https://hrs.isr.umich.edu/publications/biblio/9066
28. Parsons PL, Mezuk B, Ratliff S, Lapane KL. Subsidized housing not subsidized health: health status and fatigue among elders in public housing and other community settings. *Ethn Dis*. 2011;21(1):85-90. http://www.ncbi.nlm.nih.gov/pubmed/21462736
29. Steffick DE. Documentation of Affective Functioning Measures in the Health and Retirement Study. 2000. https://hrs.isr.umich.edu/sites/default/files/biblio/dr-005.pdf

30. Santor DA, Coyne JC. Shortening the CES-D to improve its ability to detect cases of depression. *Psychol Assess*. 1997;9(3):233-243. doi:10.1037/1040-3590.9.3.233
31. Hughes ME, Waite LJ, Hawkley LC, Cacioppo JT. A short scale for measuring loneliness in large surveys. *Res Aging*. 2004;26(6):655-672. doi:10.1177/0164027504268574
32. Clarke P, Fisher G, House J, Smith J, Weir D. Guide to Content of the HRS Psychosocial Leave-Behind Participant Lifestyle Questionnaires: 2004 &2006. Institute for Social Research. Published 2008. Accessed March 12, 2020. http://hrsonline.isr.umich.edu/sitedocs/userg/HRS2006LBQscale.pdf
33. Cohen-Mansfield J, Hazan H, Lerman Y, Shalom V. Correlates and predictors of loneliness in older-adults: a review of quantitative results informed by qualitative insights. *Int Psychogeriatrics*. 2016;28(4):557-576. doi:10.1017/S1041610215001532
34. Steptoe A, Shankar A, Demakakos P, Wardle J. Social isolation, loneliness, and all-cause mortality in older men and women. *Proc Natl Acad Sci U S A*. 2013;110(15):5797-5801. doi:10.1073/pnas.1219686110
35. Zeger SL, Liang K-Y. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986;42(1):121. doi:10.2307/2531248
36. Pan W. Akaike's information criterion in generalized estimating equations. *Biometrics*. 2001;57(1):120-125. doi:10.1111/j.0006-341X.2001.00120.x
37. Dodd MJ, Cho MH, Cooper BA, Miaskowski C. The effect of symptom clusters on functional status and quality of life in women with breast cancer. *Eur J Oncol Nurs*. 2010;14(2):101-110. doi:10.1016/j.ejon.2009.09.005
38. Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of chronic pain and high-impact chronic pain among adults — United States, 2016. *MMWR Morb Mortal Wkly Rep*. 2018;67(36):1001-1006. doi:10.15585/mmwr.mm6736a2
39. Cacioppo JT, Hawkley LC, Thisted RA. Perceived social isolation makes me sad: 5-year cross-lagged analyses of loneliness and depressive symptomatology in the Chicago Health, Aging, and Social Relations Study. *Psychol Aging*. 2010;25(2):453-463. doi:10.1037/a0017216
40. Hawkley LC, Preacher KJ, Cacioppo JT. Loneliness impairs daytime functioning but not sleep duration. *Health Psychol*. 2010;29(2):124-129. doi:10.1037/a0018646
41. Wilson RS, Krueger KR, Arnold SE, et al. Loneliness and risk of Alzheimer disease. *Arch Gen Psychiatry*. 2007;64(2):234. doi:10.1001/archpsyc.64.2.234
42. Valtorta NK, Kanaan M, Gilbody S, Ronzi S, Hanratty B. Loneliness and social isolation as risk factors for coronary heart disease and stroke: systematic review and meta-analysis of longitudinal observational studies. *Heart*. 2016;102(13):1009-1016. doi:10.1136/heartjnl-2015-308790
43. Perissinotto C, Holt-Lunstad J, Periyakoil VS, Covinsky K. A practical approach to assessing and mitigating loneliness and isolation in older adults. *J Am Geriatr Soc*. 2019;67(4):657-662. doi:10.1111/jgs.15746
44. Jaremka LM, Fagundes CP, Glaser R, Bennett JM, Malarkey WB, Kiecolt-Glaser JK. Loneliness predicts pain, depression, and fatigue: understanding the role of immune dysregulation. *Psychoneuroendocrinology*. 2013;38(8):1310-1317. doi:10.1016/j.psyneuen.2012.11.016
45. Wolf LD, Davis MC. Loneliness, daily pain, and perceptions of interpersonal events in adults with fibromyalgia. *Health Psychol*. 2014;33(9):929-937. doi:10.1037/hea0000059
46. Berkman LF, Krishna A. Social network epidemiology. In: Berkman L, Kawachi I, Glymour MM, eds. *Social Epidemiology*. Second Oxford University Press; 2014:234-289. doi:10.1093/med/9780195377903.003.0007
47. Schrepf A, Williams DA, Gallop R, et al. Sensory sensitivity and symptom severity represent unique dimensions of chronic pain: a MAPP Research Network study. *Pain*. 2018;159(10):2002-2011. doi:10.1097/j.pain.0000000000001299
48. Williams DA. Phenotypic features of central sensitization. *J Appl Biobehav Res*. 2018;23(2):e12135. doi:10.1111/jabr.12135
49. Clauw DJ. Fibromyalgia: a clinical review. *JAMAAssoc*. 2014;311:1547. doi:10.1001/jama.2014.3266
50. Kool MB, Geenen R. Loneliness in patients with rheumatic diseases: the significance of invalidation and lack of social support. *J Psychol Interdiscip Appl*. 2012;146(1–2):229-241. doi:10.1080/00223980.2011.606434

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Table S1 HRS wave serving as data source for baseline, first follow-up, and second follow-up.

Table S2. Lagged association of loneliness as a time-varying predictor of depression and the symptom cluster, excluding "lonely" question from CES-D as a sensitivity analysis ($n = 5969$)

How to cite this article: Powell VD, Kumar N, Galecki AT, et al. Bad company: Loneliness longitudinally predicts the symptom cluster of pain, fatigue, and depression in older adults. *J Am Geriatr Soc*. 2022;70(8):2225-2234. doi:10.1111/jgs.17796