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Bad Company: Loneliness Longitudinally Predicts the Symptom Cluster of Pain, Fatigue, and Depression in Older Adults

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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.

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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 years-old who had at least two measurements of loneliness and the symptom cluster from 2006-2016 (n=5,974). 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 risk. It is possible that interventions

which address loneliness in older adults may prevent or mitigate the cluster of pain, fatigue, and depression.

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

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 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 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 was 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 six 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 two years). Fatigue information is collected every other wave (i.e., every four 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 four 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 non-missing 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 eight 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 was 2016. This study was exempt from IRB review as it involved only de-identified, 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 multi-step 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 – 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 years-old who provided at least two complete sets of loneliness and symptom cluster data and had non-missing covariates at the baseline measurement (n=5,974). 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 non-normally 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 "don't 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 have 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).

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 5,997. When restricted to those who had non-missing baseline covariate data, the final analytical sample contained 5,974 unique individuals (Figure 1). Of these individuals, 3,269 (54.7%) and 2,705 (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 Supplemental Table 1. 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=1,059), 17.2% (n=1,025), 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 (Supplemental Table 2). 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, 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 eight years is twice as 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) 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 towards 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.

Acknowledgements:

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.

Authors' Contributions:

Conception and design (VP, MS, DC), acquisition of data and data analysis (NK, MK, AG), interpretation of data (all authors), drafting the article (VP), critical revisions (DW, AH, DC, MS). The final version was approved by all authors.

Sponsors' Role:

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

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Table 1. Participant characteristics at baseline

Age in Years, Mean (SD)	65.5 (9.2)
Sex, n (%)	
Male	2,381 (39.9%)
Female	3,593 (60.1%)
Race/Ethnicity, n (%)	
Non-Hispanic White	4,372 (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	3,224 (54.0%)
Some College/2 - 4 year Degree	1,207 (20.2%)
Masters/Professional Degree	614 (10.3%)
Living Arrangement, n (%)	
Living with partner/spouse	4,074 (68.2%)
Not living with partner/spouse but living with someone	692 (11.6%)
Living alone	1,208 (20.2%)
Total Wealth in Quartiles, n (%)	
First quartile (<$44,300)	1,493 (25.0%)
Second quartile ($44,300- $196,000)	1,495 (25.0%)
Third quartile ($196,001-$558,000)	1,493 (25.0%)
Fourth quartile (>$558,000)	1,493 (25.0%)
Comorbidities, n (%)	
Hypertension	3,382 (56.6%)
Diabetes	1,168 (19.6%)
Cancer	802 (13.4%)
Chronic Lung Disease	573 (9.6%)
Heart Disease	1,290 (21.6%)
Stroke	324 (5.42%)

Psychiatric problems	1,033 (17.3%)
Arthritis	3,533 (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 (%)	1,059 (17.7%)
Fatigue, n (%)	1,025 (17.2%)
Depression, n (%)	748 (12.5%)
Symptom Cluster, n (%)	226 (3.8%)

[a] Notes: Data source: Health and Retirement Study, 2006-2016, n = 5,974. Range 1 – 3.

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

Outcome	OR (95% CI)	*p*	QIC	OR (95% CI)	*p*	QIC
	Model 1[a]			**Model 2[b]**		
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

Notes: Data source: Health and Retirement Study, 2006-2016, n=5,974. 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.

[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.

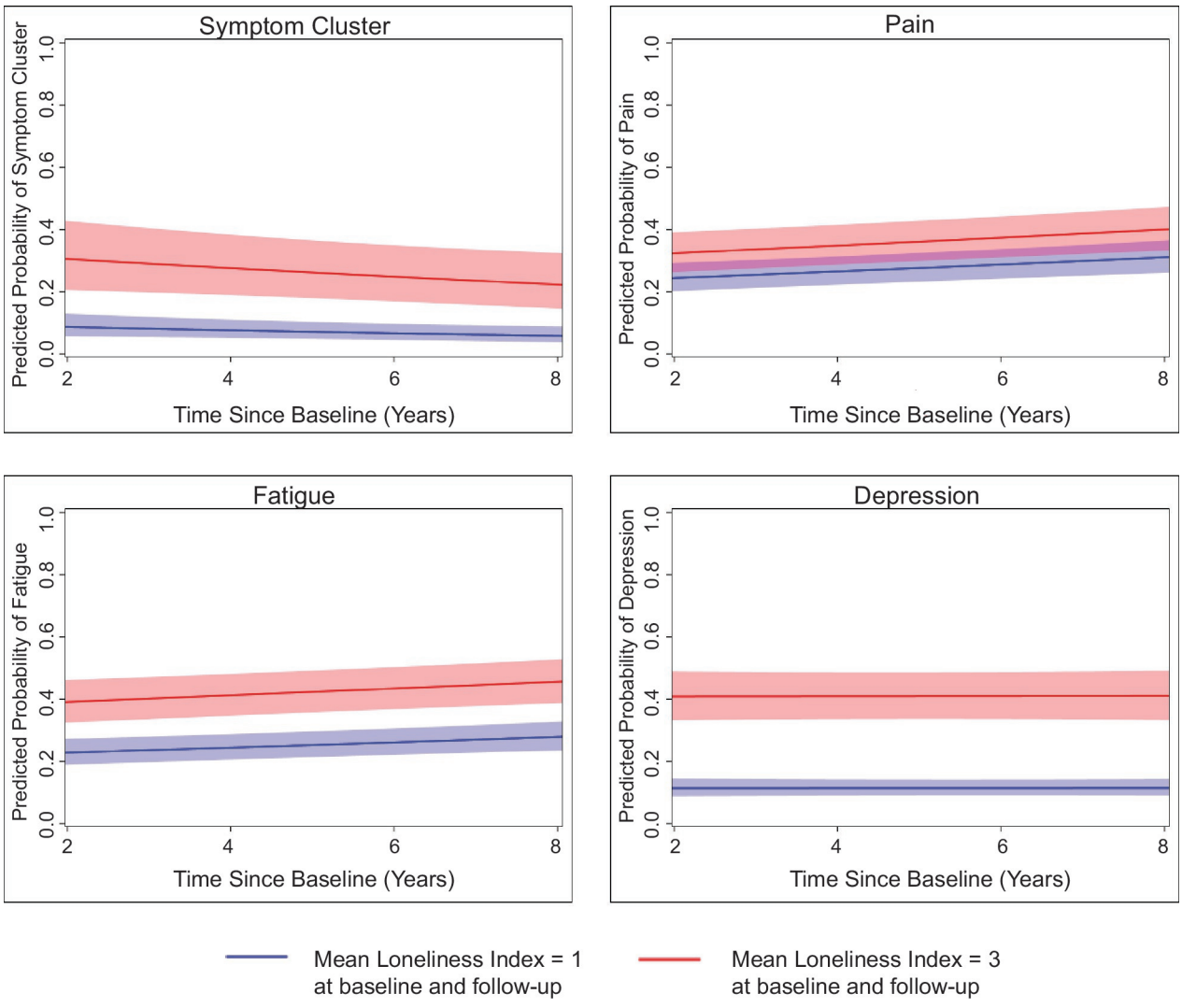
[b] Models 2, 4, 6, and 8 include time-varying loneliness at previous wave(s) as the primary predictor of the outcome, adjusting for follow-up time in years, the presence of the outcome at baseline, and baseline sociodemographic covariates (age, sex, race/ethnicity, education, total wealth in quartiles,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

**$p < .0001$

Legend

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

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.



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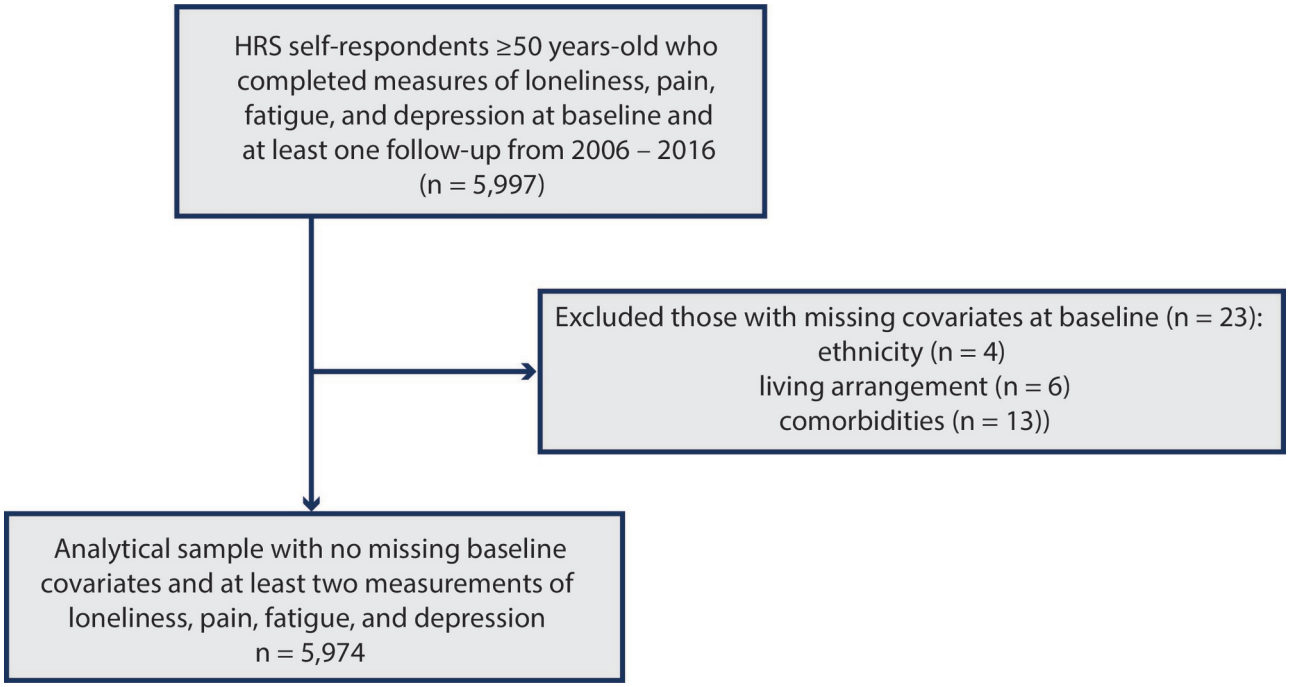

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