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Lisa M. Jaremka, Rebecca R. Andridge, Christopher P. Fagundes, Catherine M. Alfano, Stephen P. Povoski, Adele M. Lipari, Doreen M. Agnese, Mark W. Arnold, William B. Farrar, Lisa D. Yee, William E. Carson, III, Tanios Bekaii-Saab, Edward W. Martin, Jr., Carl R. Schmidt, and Janice K. Kiecolt-Glaser

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Pain, Depression, and Fatigue: Loneliness as a Longitudinal Risk Factor

Lisa M. Jaremka, Rebecca R. Andridge,
and Christopher P. Fagundes
The Ohio State University College of Medicine

Catherine M. Alfano
National Cancer Institute, Bethesda, Maryland

Stephen P. Povoski, Adele M. Lipari, Doreen M. Agnese, Mark W. Arnold, William B. Farrar, Lisa D. Yee,
William E. Carson, III, Tanios Bekaii-Saab, Edward W. Martin, Jr., Carl R. Schmidt,
and Janice K. Kiecolt-Glaser
The Ohio State University College of Medicine

Objective: Pain, depression, and fatigue function as a symptom cluster and thus may share common risk factors. Interpersonal relationships clearly influence health, suggesting that loneliness may promote the development of the pain, depression, and fatigue symptom cluster. We hypothesized that loneliness would be related to concurrent symptom cluster levels and increases in symptom cluster levels over time.

Method: We utilized two observational studies with distinct longitudinal samples. Study 1 was a sample of cancer survivors and benign controls ($N = 115$) assessed annually for 2 years. Study 2 was a sample of older adults caring for a spouse with dementia (caregivers) and noncaregiver controls ($N = 229$) assessed annually for 4 years. Participants completed annual measures assessing loneliness, pain, depression, and fatigue. **Results:** Across both samples, lonelier participants experienced more concurrent pain, depression, and fatigue and larger increases in symptom cluster levels from one year to the next than less lonely participants. Sleep quality did not mediate the results in either study. All analyses were adjusted for relevant demographic and health variables. **Conclusions:** Two longitudinal studies with different populations demonstrated that loneliness was a risk factor for the development of the pain, depression, and fatigue symptom cluster over time. The current research helps identify people most at risk for pain, depression, and fatigue, and lays the groundwork for research about their diagnosis and treatment. These data also highlight the health risks of loneliness; pain, depression, and fatigue often accompany serious illness and place people at risk for poor health and mortality.

Keywords: pain, depression, fatigue, loneliness, aging

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Close and caring relationships clearly influence physical health and longevity (Burman & Margolin, 1992; Holt-Lunstad, Smith, & Layton, 2010). For example, loneliness, the experience of perceived social isolation, enhances risk for a wide range of health problems; people who were lonelier reported worse physical health, experienced more chronic diseases, and were more likely to develop coronary heart disease than those who felt more socially connected (Sugisawa, Li-

ang, & Liu, 1994; Thurston & Kubzansky, 2009). Indeed, the odds of survival are 45% lower among lonely compared with nonlonely people, an effect that is on par with the negative health effects of obesity and inactivity (Holt-Lunstad et al., 2010). Importantly, the link between loneliness and mortality remains after accounting for health-relevant risk factors (Luo, Hawkey, Waite, & Cacioppo, 2012; Perissinotto, Stijacic Cenzer, & Covinsky, 2012).

Lisa M. Jaremka, Institute for Behavioral Medicine Research, The Ohio State University College of Medicine; Rebecca R. Andridge, College of Public Health, The Ohio State University College of Medicine; Christopher P. Fagundes, Institute for Behavioral Medicine Research, The Ohio State University College of Medicine; Catherine M. Alfano, National Cancer Institute, Bethesda, Maryland; Stephen P. Povoski, Adele M. Lipari, Doreen M. Agnese, Mark W. Arnold, William B. Farrar, Lisa D. Yee, and William E. Carson, III, Comprehensive Cancer Center and Department of Surgery, The Ohio State University College of Medicine; Tanios Bekaii-Saab, Comprehensive Cancer Center and Department of Internal Medicine, The Ohio State University College of Medicine; Edward W. Martin, Jr., and Carl R. Schmidt, Comprehensive Cancer Center and Department of Surgery, The Ohio

State University College of Medicine; Janice K. Kiecolt-Glaser, Institute for Behavioral Medicine Research, Comprehensive Cancer Center, and Department of Psychiatry, The Ohio State University College of Medicine.

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Correspondence concerning this article should be addressed to Lisa M. Jaremka, Ph.D., Institute for Behavioral Medicine Research, Ohio State University College of Medicine, 460 Medical Center Drive, Columbus, OH 43210. E-mail: lisa.jaremka@osumc.edu

Much less is known about the links between loneliness and somatic symptoms like pain, depression, and fatigue. Mounting evidence suggests that pain, depression, and fatigue function as a symptom cluster within a variety of populations, including multiple sclerosis patients, fibromyalgia patients, cancer survivors, and community dwelling adults (Bower et al., 2000; Forbes, White, Mathes, & Griffiths, 2006; Jaremka, Fagundes, Glaser, et al., 2013; Nicassio, Moxham, Schuman, & Gevirtz, 2002; Ohayon & Schatzberg, 2003; Thornton, Andersen, & Blakely, 2010; Walker, Katon, & Jemelka, 1993). For example, cancer survivors were two to four times more likely to simultaneously experience pain, depression, and fatigue than what would be expected by chance alone (Laird et al., 2011). The pain, depression, and fatigue symptom cluster was also more common among cancer survivors and community dwelling adults than the combination of any two of these symptoms on their own (Reyes-Gibby, Aday, Anderson, Mendoza, & Cleeland, 2006). Furthermore, researchers have used cluster analyses to demonstrate the co-occurrence of pain, depression, and fatigue (Motl & McAuley, 2009, 2010).

The pain, depression, and fatigue symptom cluster also affects peoples' quality of life and may share an underlying biological mechanism. Pain, depression, and fatigue often accompany serious illness and place people at risk for poor health and mortality (Becker et al., 1997; Hardy & Studenski, 2008; Schulz et al., 2000). Furthermore, pain, depression, and fatigue are a collective source of distress within a variety of populations, perhaps because they cluster together and mutually reinforce each other (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). For example, lung cancer survivors and multiple sclerosis patients with higher symptom cluster levels had poorer quality of life than those with lower symptom cluster levels (Fox & Lyon, 2006; Motl & McAuley, 2010). The administration of proinflammatory cytokines induces "sickness behaviors," behavioral changes that resemble depression and fatigue, like anhedonia and lethargy (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008), and the experience of pain is partially mediated by elevated inflammation (Marchand, Perretti, & McMahon, 2005).

Because pain, depression, and fatigue cluster together, are a collective form of distress, and share a common biological mechanism, it is useful to investigate them as a cluster. The identification of a common risk factor can promote interventions that simultaneously alleviate all three symptoms. Interpersonal relationships clearly affect health; thus, loneliness may be one common risk factor for the development of the symptom cluster. Initial research supports this possibility. For example, lonelier people reported more concurrent physical pain than those who felt more socially connected (Jaremka, Fagundes, Glaser, et al., 2013). Compared with their less lonely counterparts, lonelier people also experienced more concurrent depression and fatigue and became more depressed from one year to the next and more fatigued from one day to the next (Cacioppo, Hawkley, & Thisted, 2010; Cacioppo, Hughes, Waite, Hawkley, & Thisted, 2006; Hawkley, Preacher, & Cacioppo, 2010; Jaremka, Fagundes, Glaser, et al., 2013). Taken together, this research suggests that lonely people may develop pain, depression, and fatigue over time. Longitudinal studies that *simultaneously* examine all three symptoms are needed to help identify risk factors for the development of the symptom cluster over time.

The current research consisted of two longitudinal samples: (a) cancer survivors and benign (noncancer) controls, and (b) older adults caring for a spouse with Alzheimer's disease or a related dementia (caregivers) and noncaregiver controls. We chose these two samples because cancer survivors and people caring for a loved one with a serious medical condition are more distressed than community dwelling adults (Kiecolt-Glaser et al., 2003; Reyes-Gibby et al., 2006). In addition, older adults are highly vulnerable to the health problems resulting from pain, depression, and fatigue, including mortality (Hardy & Studenski, 2008; Moreh, Jacobs, & Stessman, 2010; Schulz et al., 2000). Thus, it is particularly important to understand the factors that promote pain, depression, and fatigue among these and other distressed and vulnerable groups. We hypothesized that loneliness would be related to concurrent symptom cluster levels and increases in the pain, depression, and fatigue symptom cluster over time. Although prior evidence suggests that cancer survivors and caregivers are more distressed than community dwelling adults (Kiecolt-Glaser et al., 2003; Reyes-Gibby et al., 2006), we expected the *relationship* between loneliness and the symptom cluster to be the same across these populations. We also explored sleep quality and aerobic exercise as two potential mechanisms linking loneliness and the symptom cluster, based on prior research connecting both to loneliness and/or somatic symptoms (Brown et al., 2012; Cacioppo et al., 2002; Landmark, Romundstad, Borchgrevink, Kaasa, & Dale, 2011; McMillan & Newhouse, 2011; Stepanski et al., 2009). Identification of common mediating pathways provided a second way to identify potential interventions that could simultaneously alleviate all three symptoms.

Study 1

Method

Setting and participants. Participants ($N = 115$) were recruited over several years as part of an ongoing prospective study of fatigue in cancer survivors. The 49 breast/colorectal cancer survivors and 66 noncancer controls were recruited from cancer clinics at The Ohio State University. Participants with an initial abnormal cancer test followed by a benign diagnosis served as noncancer controls. Individuals were ineligible if they had any prior history of cancer except basal or squamous cell carcinomas. Because cancer recurrence can affect distress levels, we also have a guideline in place that, with limited exceptions, we do not include people who have a high probability of cancer recurrence (e.g., Stage IV). Accordingly, recurrence was relatively infrequent in our sample ($n = 3$). Participants were primarily White (85%) and female (83%) and their average age was 56.77 years ($SD = 11.21$, range 30–88). Additional sample characteristics are listed in online supplementary eTable 1. The project was approved by the Ohio State University Institutional Review Board and all participants provided written informed consent before participating.

Design overview. Cancer survivors' first posttreatment appointment (T1) occurred 6 months after the completion of surgery, radiation, or chemotherapy, whichever came last. The second posttreatment visit (T2) was 12 months after T1. Benign controls were scheduled within a comparable time frame. Participants filled out the below questionnaires during both visits.

Outcomes and other measures. Loneliness was measured with the 8-item New York University Loneliness scale (NYUL; Rubenstein & Shaver, 1982). The NYUL assessed the extent to which participants felt chronically alone and socially isolated. Example items include “How often do you feel lonely?”, “Compared to other people your own age, how lonely do you think you are?”, and “I am a lonely person.” Individual NYUL items are measured on different metrics. Accordingly, each item was z-scored prior to creating the scale average (Rubenstein & Shaver, 1982). The NYUL scale demonstrates convergent validity with other loneliness measures and has good internal consistency (α s range from .88–.89; Rubenstein & Shaver, 1982; Russell, 1996).

The RAND-36 1.0 pain and vitality subscales have good psychometric properties and have been used extensively within cancer populations (Hays, Sherbourne, & Mazel, 1993; Vander Zee, Sanderman, Heyink, & de Haes, 1996). The 2-item pain subscale is not tied to any specific disease and the 4-item vitality subscale is a commonly used index of fatigue. Higher scores reflect *less* pain and fatigue within the past week. We used the RAND-36 vitality subscale as our primary fatigue measure because of its good psychometric properties, its frequent use in the cancer literature, and its availability in the second study.

The Multidimensional Fatigue Symptom Inventory–Short Form (MFSI–SF) is a 30-item measure with good psychometric properties (Stein, Jacobsen, Blanchard, & Thors, 2004). Higher numbers represent greater fatigue. The MFSI–SF was used as a secondary fatigue measure.

The Center for Epidemiological Studies Depression (CES-D) Scale is one of the most commonly used measures of depressive symptoms (Radloff, 1977). The CES-D has good discriminant validity, construct validity, and test–retest reliability. Three of the 20 items conceptually overlap with the loneliness measure (“I felt lonely,” “People were unfriendly,” and “I felt that people disliked me”) and were thus removed from the final composite.

The Charlson index is a widely utilized comorbidity measure which uses participants’ self-reported health information to assess 19 medical conditions (Charlson, Szatrowski, Peterson, & Gold, 1994); it has good concurrent validity, predictive validity, test–retest reliability, and interrater reliability (de Groot, Beckerman, Lankhorst, & Bouter, 2003). The Charlson was included to account for potential links between comorbidities and pain, depression, and fatigue.

The Pittsburgh Sleep Quality Index (PSQI) measures sleep quality over the past month (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). The PSQI can distinguish between people with and without sleep disturbances, indicating acceptable discriminant validity. Sleep quality was investigated as one potential link between loneliness and the symptom cluster.

The Godin Leisure–Time Exercise Questionnaire measures light, moderate, and vigorous activity over the past week and has good reliability and validity (Pereira et al., 1997; Godin & Shephard, 1985). Aerobic exercise is associated with low levels of fatigue, depression, and certain types of chronic pain (Brown et al., 2012; Landmark et al., 2011; McMillan & Newhouse, 2011). The moderate and vigorous activity items served as an index of aerobic

exercise. The measure was used to explore exercise as a second potential mediator linking loneliness and the symptom cluster.

Statistical analyses: Primary.

Loneliness predicting symptom cluster levels. Two sets of linear regressions were performed using SPSS 19.0 (IBM, New York). The first tested baseline (T1) relationships between loneliness and the pain, depression, and fatigue symptom cluster. The second examined the hypothesis that higher levels of loneliness are linked to increases in symptom cluster levels over time. To test changes over time, we investigated whether T1 loneliness predicted T2 symptom cluster levels controlling for T1 symptom cluster levels. Adjusting for T1 created a score reflecting residual change in the symptom cluster from T1 to T2.

The focus of our analyses was on symptom cluster composite scores, operationalized as the z-scored averages of pain, depression, and fatigue. The composite scores were created for conceptual, empirical, and statistical reasons. At the conceptual level, pain, depression, and fatigue share similar features that represent somatic/psychological distress. This perspective was based in part on the “middle-range theory of unpleasant symptoms,” which posits that symptoms jointly affect outcomes because they cluster together and mutually reinforce each other (Lenz et al., 1997). Furthermore, prior research has documented the existence of the pain, depression, and fatigue symptom cluster (Bower et al., 2000; Forbes et al., 2006; Jaremka, Fagundes, Glaser, et al., 2013; Nicassio et al., 2002; Ohayon & Schatzberg, 2003; Thornton et al., 2010; Walker et al., 1993); creating a composite score represented this conceptualization statistically (see also Jaremka, Fagundes, Glaser, et al., 2013). There were also statistical advantages to using a symptom cluster composite. Specifically, preliminary analyses indicated that the symptoms created reliable composites. Focusing on the symptom cluster avoided inflating Type I error with repeated tests of the same effects among highly related dependent variables.

We had two measures of fatigue and thus we created two symptom cluster composites. The primary composite used the RAND-36 fatigue subscale because of its frequent use in the cancer literature and its availability in the second study. The alternative composite used the MFSI–SF scale. In both cases, higher cluster scores reflected worse symptoms. Both T1 and T2 composites had good internal consistency (α > .80 in all cases).

We selected potential confounds based on their theoretical and empirical relationships to loneliness, pain, depression, and fatigue and kept the covariates the same within and across studies when possible. Every symptom cluster model adjusted for the following covariates: body mass index (BMI: kg/m²), age, gender, comorbidities, marital status (married = 1 vs. not married = 0), cancer status (cancer survivor = 1 vs. benign control = 0), cancer stage, and time since treatment. Cancer stage and time since treatment were only relevant to cancer survivors. Accordingly, cancer stage and time since treatment were included as covariates by adding the main effect of cancer status and the interactions between cancer status and either variable.¹

Loneliness predicting each individual symptom. We followed up on the symptom cluster analyses by testing the relation-

¹ Additional information about this analytic technique can be found in the online supplemental information.

ships between loneliness and each individual symptom. These analyses helped determine if a particular symptom was driving the symptom cluster effects. The covariates were the same as the symptom cluster analyses with the following differences. Pain-specific-comorbidities and non-pain-specific comorbidities were entered as separate covariates in the pain analyses. This covariate strategy was chosen because: (a) pain is a hallmark of certain diseases (e.g., rheumatoid arthritis); (b) the presence of pain-specific diseases was strongly related to pain reports in the current study; and (c) pain-specific diseases can limit mobility and, thus, potentially affect peoples' social connections (Albers et al., 1999), providing a potential confounding factor. We also added pain medication use to the pain analyses.

To test whether the relationships between loneliness and somatic symptoms were different for cancer survivors than benign controls, we investigated the interaction between cancer status and loneliness predicting the symptom cluster and each individual symptom. The interactions were nonsignificant, indicating that the strength of the association did not differ by cancer status and were thus dropped from the analyses.

Statistical analyses: Ancillary.

Testing for cyclicity. We tested whether the link between loneliness and the symptom cluster was unidirectional or cyclical. Specifically, we tested whether the symptom cluster at T1 predicted changes in loneliness over time using the same analytic strategy described above.

Exploring potential mechanisms. The final set of analyses explored sleep quality and aerobic exercise as mechanisms linking loneliness to changes in the symptom cluster over time. First, we simultaneously added T1 sleep and exercise to the longitudinal symptom cluster model to determine if the loneliness effect held when accounting for these variables. Next, we investigated whether (a) T1 loneliness predicted changes in sleep quality or aerobic exercise over time, and (b) T1 sleep quality or aerobic exercise predicted changes in the symptom cluster over time. This analytic strategy provided a strong test of mechanistic pathways because it examined changes in both the mediator and the outcome over time.

Results

All below analyses use the RAND-36 fatigue measure; unless otherwise noted, the patterns were replicated using the MFSI-SF fatigue measure. Reported beta coefficients are unstandardized. The means and standard deviations of loneliness, pain, depression, and fatigue broken down by cancer status are available in online supplementary eTable 2.

Primary analyses.

Loneliness predicting symptom cluster levels. As expected, lonelier people had concurrently higher symptom cluster levels than less lonely people, $b = .60$, $t(103) = 6.91$, $p < .001$, $R^2 = .25$. Furthermore, loneliness predicted changes in the symptom cluster over a 1-year period; participants who were lonelier at T1 had significantly larger symptom cluster increases from T1 to T2 than those who were less lonely, $b = .22$, $t(101) = 2.93$, $p = .004$, $R^2 = .02$.

Loneliness predicting each individual symptom. Consistent with the symptom cluster analyses, lonelier participants experienced significantly more concurrent pain: $b = -11.94$, $t(101) =$

-4.38 , $p < 0.001$, $R^2 = .12$; depression: $b = 7.45$, $t(103) = 7.44$, $p < 0.001$, $R^2 = .27$; and fatigue: $b = -13.82$, $t(103) = 5.12$, $p < 0.000$, $R^2 = .17$ than less lonely participants. Importantly, participants who were lonelier at T1 also had significantly larger increases in pain: $b = -4.32$, $t(99) = -2.06$, $p = 0.042$, $R^2 = .02$; depression: $b = 4.82$, $t(101) = 4.51$, $p < 0.001$, $R^2 = .07$; and fatigue: $b = -7.07$, $t(101) = -2.74$, $p = 0.007$, $R^2 = .03$ over time than less lonely participants.

Ancillary analyses.

Testing for cyclicity. Ancillary analyses tested whether the symptom cluster was linked to changes in loneliness over time. The T1 symptom cluster was unrelated to changes in loneliness from T1 to T2, $b = 0.10$, $t(101) = 1.60$, $p = .112$, $R^2 = .01$.²

Exploring potential mechanisms. The relationship between loneliness and changes in symptom cluster levels over time held when we added both sleep quality and aerobic exercise as additional covariates, $b = .23$, $t(99) = 3.04$, $p = .003$, $R^2 = .02$, suggesting that the loneliness effect was not fully explained by either sleep quality or exercise. Complete statistics for both the longitudinal and concurrent regression models (including all previously described covariates plus sleep and exercise) are available in Table 1 and online supplementary eTable 3, respectively.

Loneliness at T1 was unrelated to changes in sleep quality over the following year, $b = .66$, $t(98) = 1.48$, $p = .142$, $R^2 = .01$. In addition, T1 sleep quality was unrelated to changes in symptom cluster levels, $b = .01$, $t(98) = .33$, $p = .740$, $R^2 = .00$. Similarly, loneliness at T1 was unrelated to changes in exercise levels over time, $b = 7.82$, $t(100) = .38$, $p = .702$, $R^2 = .00$. Contrary to expectations, more exercise at T1 was marginally related to larger symptom increases from T1 to T2, $b = .01$, $t(100) = 1.85$, $p = .067$, $R^2 = .01$. Thus, sleep and exercise did not explain the link between loneliness and increases in symptom cluster levels over time.

Study 2

Method

Setting and participants. Participants ($N = 229$) were part of a longitudinal study about older adults caring for a spouse with Alzheimer's disease or a related dementia; four sequential years assessed the key study variables. The 125 caregivers and 104 noncaregiver controls were recruited through local newspapers and community groups. Caregivers were also recruited through diagnostic clinics, the local Alzheimer's disease association, and caregiver support programs. People who were not caring for a chronically ill or disabled spouse served as noncaregiver controls. Participants were primarily White (86%) and female (72%) and their average age was 69.68 years ($SD = 9.55$, range 35–91). Additional sample characteristics are listed in online supplemental eTable 4. The project was approved by the Ohio State University Institutional Review Board and all participants provided written informed consent before participating.

² The symptom cluster composite using the MFSI-SF marginally predicted increases in loneliness from T1 to T2, $b = 0.11$, $t(101) = 1.82$, $p = 0.072$, $R^2 = .01$.

Table 1
Fully Adjusted Study 1 Regression Analyses: T1 Loneliness Predicting T2 Symptom Cluster Levels

Predictor	Outcome: T2 symptom cluster levels				
	Unstandardized beta coefficient (<i>b</i>)	Standard Error	<i>t</i>	*Partial R ²	<i>p</i>
T1 symptom cluster	.64	.08	7.85	.69	<.001
T2 body mass index	.01	.01	0.72	.00	.472
T2 age	.01	.00	1.92	.00	.058
T1/T2 gender	.11	.13	0.89	.00	.377
T2 comorbidities	.07	.03	2.16	.01	.033
T2 marital status	-.07	.10	-0.66	.01	.510
T1/T2 cancer status	-1.03	.43	-2.39	.00	.019
T1/T2 cancer stage (interaction with cancer status)	.01	.08	0.98	.00	.331
T2 days since tx ended (interaction with cancer status)	.00	.00	2.00	.01	.049
T1 exercise	.00	.00	1.28	.01	.202
T1 sleep quality	.01	.02	0.71	.00	.480
T1 loneliness	.24	.08	3.04	.02	.003

Note. Higher numbers reflect higher symptom cluster levels. These analyses reflect the models reported in the ancillary analyses that include both potential mediators, sleep and exercise.

* Partial R² refers to the percent of variance in symptom cluster levels explained by each predictor.

Design overview. Participants attended four study appointments at 1-year intervals. They filled out the below questionnaires during each visit.

Outcomes and other measures. Three of the questionnaires were the same as Study 1. Specifically, participants completed an abbreviated 3-item version of the NYUL scale (Cacioppo et al., 2000) and the RAND-36 pain and vitality subscales. The Beck Depression Inventory (BDI) –Short form consists of 13-items measuring depressive symptomology (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). The BDI has good internal consistency and demonstrates convergent validity with other measures of depression (Reynolds & Gould, 1981). Health questions from the Older Americans Resources and Services (OARS) questionnaire assessed 17 types of health problems (Fillenbaum & Smyer, 1981). Following prior research, we summed the total number of health problems (Kiecolt-Glaser et al., 2003). Participants were asked to compare the amount of sleep they had in the last 3 days with the amount they felt they optimally needed. They also reported how many hours they spent doing vigorous physical activity within the past week.

Statistical analyses: Primary. We used generalized estimating equations (GEE), an extension of generalized linear models, to account for repeated measurements of the same individual over time (Diggle, Heagerty, Liang, & Zeger, 2002). We used robust standard error estimates (the “sandwich estimator”) with an independent “working” correlation matrix to perform inference; specifying a “working” correlation matrix is necessary to obtain parameter estimates and the robust variance estimator is valid even if this structure is misspecified. In addition, using GEE allowed us to include participants with partially missing data.

Loneliness predicting symptom cluster levels. Mirroring Study 1, two sets of GEE analyses were conducted using SPSS 19.0 (IBM, New York). The first investigated loneliness and concurrent symptom cluster levels and tested all concurrent relationships simultaneously (Years 1–4). The second predicted current symptom cluster levels controlling for the prior years’ symptom cluster levels; all combinations of sequential years were analyzed simultaneously. Similar to Study 1, we computed the

z-scored average of pain, depression, and fatigue, which had acceptable internal consistency across all years ($\alpha > .76$ in all cases except year 3, $\alpha = .71$).

The covariates were identical to Study 1 except the cancer-specific covariates were replaced by caregiving status (caregiver = 1 vs. noncaregiver control = 0). In addition, because we only had marital status data available for two of the four years of data collection and marital status changed over time for many women (e.g., some became widowed during the course of the study), we excluded marital status from the final analyses. This allowed us to retain the maximum sample size and number of repeated assessments in our analyses.³ We did not include year in the study as a covariate because age was conceptually more relevant to each outcome, and each change in age reflected an additional year in the study. Time-varying covariates were used for all analyses.

Loneliness predicting each individual symptom. As in Study 1, we expanded upon the symptom cluster analyses by testing the relationship between loneliness and each somatic symptom. The covariates were the same as the symptom cluster analyses except the pain analyses were modified as described in Study 1.

We separately tested the caregiving status by loneliness and age by loneliness interactions predicting changes in the symptom cluster and each individual symptom. The interactions were nonsignificant, indicating that the relationships between loneliness and changes in the symptom cluster did not differ by caregiving status or age, and were thus dropped from the analyses.

Statistical analyses: Ancillary. The ancillary analyses were identical to Study 1. We first tested whether the link between loneliness and the symptom cluster was unidirectional or cyclical. We also explored sleep quality and exercise as mediators linking loneliness and symptom cluster changes over time.

³ We explored all primary analyses with marital status included in the models; with one exception noted in the results, all results remained unchanged.

Results

The means and standard deviations of loneliness, pain, depression, and fatigue broken down by caregiving status are available in online supplementary eTable 5.

Primary analyses.

Loneliness predicting the symptom cluster. As expected, lonelier participants experienced significantly higher concurrent symptom cluster levels than less lonely participants, $b = 0.40$, $\chi^2(1, N = 223) = 107.87$, $p < 0.001$. Furthermore, loneliness was related to changes in the symptom cluster over time. Specifically, participants who were lonelier had significantly larger increases in the pain, depression, and fatigue symptom cluster from one year to the next than those who were less lonely, $b = 0.06$, $\chi^2(1, N = 200) = 3.91$, $p = .048$.

Loneliness predicting each individual symptom. Lonelier participants concurrently experienced significantly more pain: $b = -6.60$, $\chi^2(1, N = 222) = 27.19$, $p < 0.001$; depression: $b = 2.01$, $\chi^2(1, N = 222) = 103.77$, $p < 0.001$; and fatigue: $b = -8.36$, $\chi^2(1, N = 222) = 85.73$, $p < .001$ than less lonely participants. Importantly, participants who were lonelier also had significantly larger increases in pain: $b = -2.37$, $\chi^2(1, N = 187) = 5.40$, $p = .020$, and fatigue: $b = -1.87$, $\chi^2(1, N = 187) = 7.43$, $p = .006^4$ and marginally larger increases in depression: $b = 0.28$, $\chi^2(1, N = 199) = 3.65$, $p = .056$ from one year to the next than less lonely participants.

Ancillary analyses.

Testing for cyclicity. Auxiliary analyses tested whether the symptom cluster was linked to changes in loneliness over time. The symptom cluster predicted marginal increases in loneliness from one year to the next, $b = 0.09$, $\chi^2(1, N = 200) = 3.59$, $p = .058$.

Exploring potential mechanisms. The relationship between loneliness and changes in the symptom cluster over time went from significant to marginal when we added sleep quality and exercise as additional covariates, $b = .06$, $\chi^2(1, N = 200) = 3.54$, $p = .060$, suggesting that the relationship between loneliness and changes in the symptom cluster over time *may* be partially explained by either sleep, exercise, or a combination of the two. Complete statistics for both the longitudinal and concurrent GEE models (including all previously described covariates plus sleep and exercise) are available in Table 2 and online supplementary eTable 6, respectively.

Lonelier participants experienced greater declines in sleep adequacy over time than less lonely participants, $b = -0.25$, $\chi^2(1, N = 201) = 4.74$, $p = .029$. However, sleep was unrelated to changes in symptom cluster levels over time, $b = -0.02$, $\chi^2(1, N = 200) = 1.19$, $p = .276$. Lonelier participants exercised marginally less over time than less lonely participants, $b = -0.37$, $\chi^2(1, N = 199) = 3.73$, $p = .054$. In addition, participants who exercised less experienced larger increases in symptom cluster levels over time than participants who exercised more, $b = -0.01$, $\chi^2(1, N = 200) = 3.98$, $p = .046$. Thus, in the current sample, reduced aerobic exercise may partially explain the link between loneliness and increases in symptom cluster levels over time.

Discussion

The current study demonstrated that loneliness is a risk factor for concurrent symptom cluster levels and the development of the

pain, depression, and fatigue symptom cluster over time. The results were also highly consistent across two longitudinal samples of older adults, cancer survivors and benign controls and caregivers and noncaregiver controls. Although caregivers were generally more distressed than noncaregivers, and perhaps more distressed than either the cancer survivors or benign controls, there was no evidence that cancer or caregiving status moderated the results. Accordingly loneliness is a risk factor for pain, depression, and fatigue across both medical and nonmedical populations.

Sleep quality and aerobic exercise were examined as two potential mediators linking loneliness to increased symptom cluster levels over time. Poorer sleep quality and less exercise were concurrently linked to higher symptom cluster levels in both studies. However, in Study 1, sleep and exercise did not mediate the longitudinal link between loneliness and the symptom cluster. In contrast, reduced exercise may partially explain the link between loneliness and increased symptom cluster levels in Study 2. Specifically, loneliness was marginally related to less exercise over time, and less exercise was linked to larger symptom cluster increases over time. Participants in the second study were an average of 15 years older than those in the first study. Physical activity declines with age, particularly over age 70 (Peel et al., 2005), one potential reason for the mechanistic differences across studies. The measurement of exercise also varied across studies; the measure used in the first study is well-validated whereas the second study utilized a single item index, one methodological limitation. Understanding the behavioral mechanisms linking loneliness to the symptom cluster is an important area for future research.

The current results replicate cross-sectional findings linking loneliness to symptom cluster levels using a different sample of cancer survivors (Jaremka, Fagundes, Glaser, et al., 2013). They also extend prior research in an important new direction by demonstrating that loneliness predicts *changes* in the symptom cluster over time, a first step in establishing a causal pathway. The present study provided the first piece of evidence that sleep quality and aerobic exercise do not consistently explain the relationship between loneliness and changes in symptom cluster levels over time. Furthermore, the two samples investigated in this article help generalize results from prior work to a sample of breast and colorectal cancer survivors, noncancer controls, people caring for a spouse with Alzheimer's disease, and noncaregiver controls.

Clinical Implications

Pain, depression, and fatigue affect a significant portion of the population; around 46% of adults report chronic pain, 13%–27% have depressive symptoms, and 30% are fatigued (Blazer, Hughes, & George, 1987; Elliott, Smith, Penny, Cairns Smith, & Alastair Chambers, 1999; Goldney, Fisher, Grande, & Taylor, 2004; Van't Leven, Zielhuis, van der Meer, Verbeek, & Bleijenberg, 2010).

⁴ The relationship between loneliness and changes in fatigue over time became nonsignificant when marital status was entered into the model, $b = -1.31$, $\chi^2(1, N = 155) = 1.28$, $p = 0.258$. Because we only had marital status data available for two of the four years of data collection, adding marital status to the models reduced our sample size and also limited the number of repeated assessments in our longitudinal analyses from four years to two years, which is the most likely explanation for the difference in fatigue results.

Table 2
Fully Adjusted Study 2 GEE Analyses: Prior Year's Loneliness Predicting Current Symptom Cluster Levels

Predictor	Outcome: Current year symptom cluster levels				
	Unstandardized beta coefficient (<i>b</i>)	Standard Error	χ^2	95% Wald CI	<i>p</i>
Body mass index (current year)	.02	.00	16.77	.01, .03	<.001
Age (current year)	.01	.00	6.57	.00, .01	.010
Gender	.09	.05	3.27	-.01, .18	.071
Caregiving status (current year)	-.01	.05	.02	-.10, .08	.898
Comorbidities (current year)	.05	.01	19.44	.03, .07	<.001
Exercise (prior year)	-.01	.00	4.29	-.02, -.00	.038
Sleep adequacy (prior year)	-.02	.01	1.28	-.04, .01	.258
Symptom cluster (prior year)	.59	.04	192.74	.51, .68	<.001
Loneliness (prior year)	.06	.03	3.54	-.00, .11	.060

Note. *N* = 229. Higher numbers reflect higher symptom cluster levels. These analyses reflect the models reported in the ancillary analysis section that includes both potential mediators, sleep and exercise.

Thus, mental health practitioners may encounter people experiencing pain, depression, or fatigue on a regular basis. Because pain, depression, and fatigue coexist, people often experience these symptoms simultaneously (Bower et al., 2000; Jaremka, Fagundes, Glaser, et al., 2013; Motl & McAuley, 2009; Nicassio et al., 2002; Ohayon & Schatzberg, 2003; Thornton et al., 2010; Walker et al., 1993). Accordingly, demonstrating that loneliness predicted increased symptom cluster levels over time helps identify people most at risk for these common symptoms and lays the groundwork for research about their diagnosis and treatment.

Most existing treatments for pain, depression, and fatigue focus on alleviating an individual symptom and are tailored to a specific medical population (e.g., cancer survivors; National Institute of Health, 2003). Although this approach has value, the current research demonstrated that loneliness is a common risk factor for all three symptoms, suggesting novel interventions for simultaneously treating pain, depression, and fatigue in both medical and nonmedical populations. For example, interventions aimed at decreasing loneliness may simultaneously reduce pain, depression, and fatigue. A recent review concluded that the most promising loneliness intervention is cognitive-behavioral therapy (Hawkley & Cacioppo, 2010).

Directions for Future Research and Limitations

Inflammation may be a common physiological correlate of loneliness, pain, depression, and fatigue and, thus, may partially explain the relationships evident in the current study. Data from naturalistic and laboratory studies suggest that loneliness enhances inflammation (Hackett, Hamer, Endrighi, Brydon, & Steptoe, 2012; Jaremka, Fagundes, Peng, et al., 2013). In addition, administration of proinflammatory cytokines induces "sickness behaviors," behavioral changes that resemble depression and fatigue (Dantzer et al., 2008), and the experience of pain is partially mediated by elevated inflammation (Marchand et al., 2005). Additional research is needed to delineate whether loneliness enhances risk for pain, depression, and fatigue because it elevates inflammation. Another possibility is that "sickness behaviors" may exacerbate or even cause feelings of social isolation. Furthermore, the inflammatory effects of loneliness may help explain the link between loneliness and poor health; chronic inflammation in-

creases risk for premature all-cause mortality and other age-related diseases (Ershler & Keller, 2000).

The current research highlights additional mental and physical health risks of loneliness; pain, depression, and fatigue often accompany serious illness and place people at risk for poor health and mortality (Becker et al., 1997; Hardy & Studenski, 2008; Schulz et al., 2000). Furthermore, untreated pain, depression, and fatigue are linked to immune alterations, particularly elevated inflammation (Bower et al., 2011; Marchand et al., 2005). Accordingly, loneliness may start a negative cascade by promoting inflammation and pain, depression, and fatigue. These somatic symptoms may further elevate inflammation and ultimately result in serious health problems. The present study further suggests that intervening to reduce loneliness may limit the progression of this negative cascade. Other researchers have proposed additional pathways linking loneliness and health, suggesting multiple complementary mechanisms leading from loneliness to poor health (Hawkley & Cacioppo, 2010).

The present data provided limited evidence for a negative feedback loop; the symptom cluster marginally predicted changes in loneliness over time in Study 2 only.⁵ Theoretically, loneliness may lead to a downward spiral whereby loneliness enhances the symptom cluster which then exacerbates loneliness. Research is needed to further test whether the change process is unidirectional or cyclical, one limitation of the current study. Understanding how pain, depression, and fatigue might exacerbate loneliness is an intriguing question. On one hand, socially supportive relationships may help people cope with these symptoms. On the other hand, persistent distress may cause people to feel alienated and lonely. Another interesting research avenue is testing whether pain, depression, and fatigue develop sequentially, as some research suggests (Nicassio et al., 2002; Stepanski et al., 2009). Specifically, these symptoms may cluster together because one symptom causes the development of a second, and so on.

The current results demonstrated consistent significant relationships between loneliness and the symptom cluster. However, the

⁵ The symptom cluster also marginally predicted changes in loneliness over time in Study 1 using our secondary fatigue measure (MFSI-SF), but not the primary measure (RAND-36).

proportion of variance explained in longitudinal symptom cluster levels by loneliness was relatively small, one limitation of the current studies. These results should be interpreted in light of the samples under investigation; on average, participants' loneliness scores were on the lower end of the spectrum. Thus, the current results likely underestimate the true effects. Furthermore, loneliness may be the start of a negative cascade, as described above. Accordingly, even small changes in symptom cluster levels may have larger impacts via downstream consequences on inflammation, exacerbated loneliness, and long-term health problems. Additional research using more diverse samples would provide insight into the magnitude of both the immediate and long-term consequences of loneliness.

Loneliness was reliably linked to the development of pain, depression, and fatigue over time in both of the current samples. However, these symptoms are likely multifaceted and multidetermined. For example, pain progresses with the development of certain diseases (e.g., rheumatoid arthritis) and fatigue is a frequent side effect of cancer treatments like chemotherapy. Thus, loneliness and other behavioral and physiological risk factors may work in tandem to promote pain, depression, and fatigue.

Conclusion

In sum, lonelier people experienced more concurrent pain, depression, and fatigue and greater increases in the pain, depression, and fatigue symptom cluster from one year to the next. These data suggest novel interventions for simultaneously treating pain, depression, and fatigue and provide a glimpse into the pathways through which loneliness can impact health.

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