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Loneliness Predicts Pain, Depression, and Fatigue: Understanding the Role of Immune Dysregulation

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Abstract

Objective—The pain, depression, and fatigue symptom cluster is an important health concern. Loneliness is a common risk factor for these symptoms. Little is known about the physiological mechanisms linking loneliness to the symptom cluster; immune dysregulation is a promising candidate. Latent herpesvirus reactivation, which is reflected by elevated herpesvirus antibody

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Conflicts of Interest
All authors declare that there are no financial conflicts of interest.

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Lisa M. Jaremka: substantial contributions to the analysis and interpretation of data, primary person responsible for writing and revising the article, final approval of the version to be published
Christopher P. Fagundes: substantial contributions to the analysis and interpretation of data, helped revise the article for important intellectual content, final approval of the version to be published
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titers, provides a window into immune dysregulation. Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) are two common herpesviruses.

Methods—Participants were 200 breast cancer survivors who were 2 months to 3 years post-treatment at the time of the study. They completed questionnaires and provided a blood sample that was assayed for CMV and EBV antibody titers.

Results—Lonelier participants experienced more pain, depression, and fatigue than those who felt more socially connected. Lonelier participants also had higher CMV antibody titers which, in turn, were associated with higher levels of the pain, depression, and fatigue symptom cluster. Contrary to expectations, EBV antibody titers were not associated with either loneliness or the symptom cluster.

Conclusions—The pain, depression, and fatigue symptom cluster is a notable clinical problem, especially among cancer survivors. Accordingly, understanding the risk factors for these symptoms is important. The current study suggests that loneliness enhances risk for immune dysregulation and the pain, depression, and fatigue symptom cluster. The present data also provide a glimpse into the pathways through which loneliness may impact health.

Keywords

Loneliness; pain; depression; fatigue; symptom cluster; herpesvirus; immune dysregulation; Epstein-Barr virus; Cytomegalovirus

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Pain, depression, and fatigue function as a symptom cluster within an array of populations, such as multiple sclerosis patients, cancer survivors, and community dwelling adults (Walker et al., 1993; Bower et al., 2000; Nicassio et al., 2002; Bair et al., 2003; Ohayon and Schatzberg, 2003; Reyes-Gibby et al., 2003; Fleishman, 2004; Motl and McAuley, 2009, 2010; Thornton et al., 2010; Laird et al., 2011). For example, cancer survivors were 2 – 4 times more likely to simultaneously experience pain, depression, and fatigue than the probability of simultaneously experiencing these symptoms by chance alone (Laird et al., 2011). Loneliness, a socially painful state of perceived social isolation, may be a common risk factor for pain, depression, and fatigue. For example, people who felt socially disconnected were able to tolerate less physical pain than those who felt more socially connected, suggesting that feeling unconnected to those around you may increase pain sensitivity (Oishi et al., 2012). In addition, lonelier people became more depressed and fatigued over time than people who felt more socially connected (Cacioppo et al., 2010; Hawkley et al., 2010a).

Little is known about the physiological mechanisms linking loneliness to the pain, depression, and fatigue symptom cluster. Immune dysregulation is one promising candidate; growing evidence suggests loneliness and immune dysregulation are closely related. For example, lonelier medical students and lonelier psychiatric inpatients had lower natural killer cell activity, an important anti-tumor and anti-viral defense, than those with more social connections (Kiecolt-Glaser et al., 1984a, 1984b). People who were lonelier had smaller antibody responses to an influenza virus vaccine than those who were less lonely, reflecting a poorer vaccine-related immune response (Pressman et al., 2005). Compared with people who felt more socially connected, lonelier people had higher monocyte chemotactic protein-1 (MCP-1; Hackett et al., 2012), a cytokine implicated in inflammatory diseases such as rheumatoid arthritis and atherosclerosis (Deshmane et al., 2009). Interleukin-6 (IL-6), a proinflammatory cytokine that is linked to increased risk for age-related diseases (Ershler and Keller, 2000), was higher after acute stress among those experiencing greater loneliness compared with those who were less lonely (Jaremka et al., in press; Hackett et al., 2012). In addition, proinflammatory genes were over-expressed and anti-inflammatory

genes were under-expressed in lonelier individuals compared with less lonely individuals (Cole et al., 2007). Lonelier medical students had higher Epstein-Barr virus (EBV) antibody titers than medical students who felt more socially connected (Glaser et al., 1985a). Similarly, lonelier HIV-infected men had higher human herpesvirus 6 (HHV-6) antibody titers than those who were less lonely (Dixon et al., 2006). Because elevated herpesvirus antibody titers reflect poor cellular immune system control over the latent virus, the EBV and HHV-6 data suggest that lonely people may have dysregulated cellular immunity.

Immune dysregulation has also been associated with each of the symptoms in the cluster: pain, depression, and fatigue (Marchand et al., 2005; Collado-Hidalgo et al., 2006; Dowlati et al., 2010). The experience of pain is partially mediated by elevated inflammation (Marchand et al., 2005). Compared to people with fewer depressive symptoms, those with more depressive symptoms had higher cytomegalovirus (CMV) antibody titers and more persistent inflammation following an influenza virus vaccine (Glaser et al., 2003; Phillips et al., 2008). Elevated CMV antibody titers were also associated with greater fatigue (Fagundes et al., 2012). Because pain, depression, and fatigue behave as a symptom cluster, it is useful to investigate their immunological correlates simultaneously.

Latent herpesvirus reactivation provides a window into immune dysregulation and may be one common immunological correlate of loneliness and the symptom cluster. Herpesviruses are ubiquitous; around 95% of adults are infected with EBV (Fagundes et al., 2012; WHO, 2012) and 60% of adults are infected with CMV (Staras et al., 2006). After the initial infection, herpesviruses create life-long, latent infections. When the cellular immune system is compromised, the virus may reactivate and replicate in latently infected cells, which is reflected by elevated herpesvirus antibody titers. Accordingly, higher antibody titers are thought to reflect poorer cellular immune system control over viral latency (Glaser and Jones, 1994).

Overview of Current Research

The goal of the current research was to examine the links among loneliness, latent herpesvirus reactivation (which reflects immune dysregulation), and the full pain, depression, and fatigue symptom cluster. We assessed antibody titers to two common herpesviruses, EBV and CMV (Staras et al., 2006; Fagundes et al., 2012; WHO, 2012). We hypothesized that, compared to those who felt more socially connected, lonelier people would have higher EBV and CMV antibody titers and greater pain, depression, and fatigue.

Cancer survivors are more at risk for developing pain, depression, and fatigue than people without a history of cancer (Bower et al., 2000; Reyes-Gibby et al., 2006). Accordingly, our sample of breast cancer survivors provided an opportune way to understand the factors that promote the symptom cluster among a particularly vulnerable group.

Methods

Participants

Participants were female stage 0-IIIA breast cancer survivors ($N = 200$) from the baseline pre-randomization sample of an ongoing clinical trial addressing the use of yoga for cancer-related fatigue. Survivors were recruited through cancer clinics and media announcements if they had completed cancer treatment (except for selective estrogen receptor modulators/aromatase inhibitors) between 2 months and 3 years prior to enrollment in the study. Individuals were ineligible if they engaged in over 5 hours of vigorous physical activity per week, or if they had a BMI over 44, symptomatic ischemic heart disease, uncontrolled hypertension, liver or kidney failure, or a prior history of cancer (except basal or squamous

cell). The average age of women in our sample was 51.58 (*SD* = 9.24, range 27–76) and the majority of women were White (89%). Herpesvirus data were available for 161 women; of these participants, 156 (97%) were EBV seropositive and 84 (52%) were CMV seropositive, which is consistent with prior data (Staras et al., 2006; Fagundes et al., 2012; WHO, 2012). Additional sample characteristics are listed in Table 1. The project was approved by The Ohio State University Institutional Review Board; all participants provided written informed consent before participating.

Procedure

Participants filled out questionnaires upon arrival at the Clinical Research Center (CRC), a hospital research unit. A research nurse collected a blood sample to assess EBV and CMV antibody titers.

Questionnaires

Loneliness was measured with the UCLA Loneliness Scale, which assesses perceptions of social isolation and loneliness (Russell, 1996). The scale is highly reliable, demonstrates construct and convergent validity, and is one of the most commonly used loneliness measures. Higher numbers reflect more loneliness.

The RAND SF-36 1.0 pain and vitality subscales have good psychometric properties and have been used extensively within cancer populations (Hays et al., 1993; VanderZee et al., 1996; Bower et al., 2000). The pain subscale is not tied to any specific disease, and the vitality subscale is a commonly used index of fatigue. Both composites were coded so that higher number reflected worse symptoms.

The Multidimensional Fatigue Symptom Inventory (MFSI) – Short Form (Stein et al., 2004) is a widely used fatigue measure. The total score is comprised of the general, physical, emotional, and mental fatigue subscales minus the vigor subscale. The MFSI-SF has good psychometric properties with higher numbers representing more fatigue.

The Center for Epidemiological Studies Depression (CES-D) Scale is one on the most commonly used measures of depressive symptoms (Radloff, 1977). The CES-D can discriminate between depressed and non-depressed individuals and has good test-retest reliability and construct validity. Depressive symptomology was treated as a continuous variable in the current study with higher numbers reflecting more depressive symptoms.

The Pittsburgh Sleep Quality Index measured sleep quality over the past month (PSQI; Buysse et al., 1989). The PSQI can distinguish between people with and without sleep disturbances, indicating acceptable discriminant validity. Greater sleep disturbances are related to more loneliness, pain, depression, and fatigue (Hawkley et al., 2010a; Palesh et al., 2010; Kurina et al., 2011). Therefore, the PSQI provided a way to disentangle sleep from the links between loneliness and the pain, depression, and fatigue symptom cluster.

The Charlson index is a widely utilized comorbidity measure originally developed for breast cancer patients and later extended to other cancer and non-cancer populations (Charlson et al., 1994). The measure uses participants' self-reported health information to assign weights to 19 medical conditions (e.g., diabetes, cancer) based on their ability to influence 1-year mortality. The Charlson was included to account for relationships between comorbidities and loneliness, pain, depression, and fatigue (Given et al., 2001; Joynt et al., 2003; Hawkley and Cacioppo, 2010).

Exercise was measured with a combination of one-item about hours of vigorous exercise per week and a shortened version of the Community Healthy Activities Model Program for

Seniors questionnaire, a well-validated measure of physical activity among middle-aged and older adults (CHAMPS: Stewart et al., 2001). Intense and regular exercise are associated with low levels of fatigue, depression, and certain types of chronic pain (Berlin et al., 2006; Landmark et al., 2011). Loneliness is also related to lower levels of physical activity, both cross-sectionally and over-time (Hawkley et al., 2009). Accordingly, the exercise index provided a way to assess the relationships between loneliness and the symptom cluster independent of exercise levels.

Immune Assays

Plasma was stored at −80 °C until assayed with Euroimmun EBV ELISA plates that measure EBV virus capsid antigen (VCA) antibody titers (Morris Plains, NJ). CMV IgG antibody titers were also determined using Euroimmun CMV ELISA plates (Morris Plains, NJ). CMV and EBV VCA IgG antibody titers were assessed following company instructions with some modifications (Fagundes et al., 2012). Specifically, for each ELISA plate three controls that were included in each kit (one positive sample, one negative sample, and three calibrators) were run in duplicate. Plasma samples were initially diluted 1:101 with a dilution buffer according to the recommended protocol provided by the company. Then, six serial two-fold dilutions of each sample were assayed. The last dilution factor with a positive IgG value determined the IgG antibody titer. Calculated viral titers for each sample were plotted and samples were rerun if the end point did not fall within the linear range (±15%). CMV IgG antibody titers were determined following the same protocol as EBV VCA IgG antibody titers, except the samples were initially screened for seropositivity status. Only CMV seropositive samples were serially diluted to assess the CMV antibody titer. Antibody titers were treated as continuous variables in all of our analyses based on the extant literature showing that latent virus reactivation occurs to varying degrees, and therefore should be represented as continuous (Glaser and Jones, 1994).

Data Analytic Strategy

The distributions of the immune data were checked for normality and the presence of outliers. No outliers were detected using a cutoff of plus or minus 4 standard deviations from the sample mean. The EBV and CMV data were highly skewed. Accordingly, each measure was $\log_{10}$ transformed prior to analyses.

Because we had two measures of fatigue, we created two symptom cluster composites, operationalized as the z-scored averages of pain, depression, and fatigue. The primary composite used the MFSI fatigue scale whereas our alternative composite used the SF-36 vitality subscale. In both cases, higher cluster scores reflect worse symptoms. The intercorrelations between all possible pairs of variables were moderate to large (all p values < .001) and both composites had good internal consistency (α = .88 in both cases).

A series of linear regressions were performed using SPSS 19.0 (IBM, New York). First, we tested the relationship between loneliness and the symptom cluster. Next, we tested whether loneliness was related to latent herpesvirus reactivation and whether latent herpesvirus reactivation was related to the symptom cluster composites. Because we only had EBV and CMV antibody titer data for women who were seropositive for each virus, the herpesvirus analyses were limited to women seropositive for the respective herpesvirus.

We then tested two possible meditational models. First, we investigated whether latent herpesvirus reactivation mediated the relationship between loneliness and the symptom cluster. We also examined whether the relationship between loneliness and latent herpesvirus reactivation was mediated by the symptom cluster, which would be consistent with the argument that the links between immune dysregulation and the symptom cluster are

cyclical. To test mediation, we used bias-corrected bootstrapping techniques with 5000 bootstrap samples to estimate the confidence interval (CI) of the indirect effects (Preacher and Hayes, 2008). Bootstrapping mediation tests are preferred over other methods because they do not assume a normal sampling distribution of the indirect effects (Preacher and Hayes, 2008).

Supplementary analyses investigated each individual symptom (pain, depression, and fatigue) and their relationships to loneliness and herpesvirus reactivation. Similar to the symptom cluster analyses, we first tested the relationship between loneliness and each symptom. We then examined whether the relationship between loneliness and the symptom was mediated by latent herpesvirus reactivation and whether the relationship between loneliness and latent herpesvirus reactivation was mediated by the symptom.

We selected potential confounds a priori based on their theoretical and empirical relationships to loneliness, EBV and CMV antibody titers, pain, depression, and fatigue. Every model had the following control variables: body mass index (BMI: kg/m^2), age, sleep quality, exercise levels, comorbidities, cancer stage, and time since cancer treatment ended (Given et al., 2001; Joynt et al., 2003; Berlin et al., 2006; Hawkley et al., 2009, 2010a; Hawkley and Cacioppo, 2010; Palesh et al., 2010; Kurina et al., 2011; Landmark et al., 2011). We also conducted ancillary analyses adding menopausal status, type of cancer treatment, and duration of cancer treatment as covariates. The results remained the same when controlling for these variables; to retain statistical power and model parsimony we did not include them in our final analyses

Results

CMV seropositive people did not differ from those who were seronegative on loneliness, pain, depression, fatigue, or either symptom cluster composite (all p values > .196). We did not test for EBV seropositivity differences because 97% of our sample was seropositive. In addition, EBV antibody titers were unrelated to loneliness and the symptom cluster composites and thus EBV is not discussed further (all p values > .406).

All below analyses use the MFSI-SF fatigue measure; the patterns are identical using the the SF-36 fatigue measure. Reported beta coefficients are standardized. A correlation matrix of the primary study variables is presented in Table 2.

Loneliness and the Symptom Cluster

As expected, participants who were lonelier had higher symptom cluster composite scores than those who were less lonely, $\beta = 0.35$, $t(187) = 6.54$, $p < .001$. We also analyzed the relationship between loneliness and the symptom cluster composite among participants who were seropositive for CMV or EBV respectively in order to ensure the relationship held among the subset of participants who were included in the EBV and CMV analyses. Consistent with the results using the full sample, among participants who were seropositive for EBV or CMV respectively, participants who were lonelier had higher symptom cluster composite scores than those who were less lonely (all p values < .05). Lonelier participants also had higher CMV antibody titers than less lonely participants [$\beta = 0.31$, $t(74) = 2.65$, $p = .010$], and elevated CMV antibody titers were related to higher symptom cluster scores [$\beta = 0.24$, $t(74) = 2.63$, $p = .010$].

We found partial evidence that the relationship between loneliness and the symptom cluster was mediated by CMV antibody titers (Figure 1); people who were lonelier had higher symptom cluster scores than those who were less lonely, and this was partially explained by elevated CMV antibody titers [N = 84; 91% CI: 0.0001, 0.01].

Supplemental Analyses

Loneliness and pain—Lonelier participants experienced significantly more pain than less lonely participants, β = 0.16, $t(187) = 2.29$, $p = .023$. Contrary to expectations, CMV antibody titers were unrelated to pain [β = 0.10, $t(74) = 0.87$, $p = .387$]. The association between loneliness and pain was not mediated by CMV antibody titers [N = 84; 90% CI: −0.20, 0.12] .

Loneliness and depression—Lonelier participants experienced significantly more depression than less lonely participants, β = 0.33, $t(187) = 5.67$, $p < .001$. Furthermore, people with higher CMV antibody titers experienced more depression than those with lower CMV antibody titers, β = 0.25, $t(74) = 2.59$, $p = .012$. We found partial evidence that the relationship between loneliness and depression was mediated by CMV antibody titers; people who were lonelier experienced more depression than those who were less lonely, and this was partially explained by elevated CMV antibody titers [N = 84; 92% CI: 0.003, 0.15].

Loneliness and fatigue—Lonelier participants experienced significantly more fatigue than less lonely participants, β = 0.31, $t(187) = 5.60$, $p < .001$. Follow-up tests revealed that this result held for the general, emotional, mental, and vigor MFSI-SF subscales. The physical fatigue subscale was not significantly related to loneliness ($p = .172$).

People with higher CMV antibody titers experienced more fatigue than those with lower CMV antibody titers, β = 0.23, $t(74) = 2.51$, $p = .014$. We found partial evidence that the relationship between loneliness and fatigue was mediated by CMV antibody titers; people who were lonelier experienced more fatigue than those who were less lonely, and this was partially explained by elevated CMV antibody titers [N = 84; 92% CI: 0.001, 0.31].

Alternative mediational pathway—The primary analyses tested whether the relationship between loneliness and the symptom cluster was mediated by latent herpesvirus reactivation. We also examined the reverse possibility that the relationship between loneliness and latent herpesvirus reactivation was mediated by the symptom cluster. We found partial support for this alternative; lonelier people had higher CMV antibody titers than those who felt more socially connected, and this was partially explained by higher symptom cluster scores [N = 84; 91% CI: 0.0001, 0.01]. These results were replicated with depression [N = 84; 95% CI: 0.0001, 0.01] and fatigue [N = 84; 92% CI: 0.0001, 0.01] as individual mediators but were not replicated with pain [N = 84; 90% CI: −0.002, 0.004].

Discussion

The pain, depression, and fatigue symptom cluster is a notable clinical problem, especially among cancer survivors. Accordingly, understanding the risk factors for these symptoms is important. In the current study, lonelier breast cancer survivors experienced more pain, depression, and fatigue than their less lonely counterparts. Lonelier individuals also had higher CMV antibody titers, which in turn, were related to higher levels of the symptom cluster. Supplemental analyses revealed that the relationships among CMV antibody titers and the individual symptoms were strongest for depression and fatigue.

One prior study demonstrated that loneliness was related to elevated EBV antibody titers among a younger sample of medical students (Glaser et al., 1985a). However, EBV antibody titers were not associated with loneliness or the symptom cluster in the current sample. Aging is associated with decrements in cellular immunity and thus poorer control over viral latency (Glaser et al., 1985b). Accordingly, the elevated antibody titers in this older adult

sample may have created a ceiling effect, making it difficult to detect loneliness-related differences in EBV antibody titers.

EBV and CMV reactivation are influenced by different mechanisms, which may explain why CMV, but not EBV reactivation, was associated with loneliness and the symptom cluster. For example, astronauts had different patterns of latent EBV and CMV reactivation during space flight (Mehta and Pierson, 2007). Similarly, latent EBV and CMV showed different reactivation patterns during academic stress (Matalka et al., 2000). Consistent with the results from the current study, other work from our lab demonstrated that elevated CMV antibody titers, but not EBV antibody titers, were associated with greater fatigue among women newly diagnosed with breast cancer or awaiting a positive diagnostic result (Fagundes et al., 2012).

The current research underscores the relevance of the symptom cluster in explaining the links between loneliness and poor physical health; pain, depression, and fatigue often accompany serious illness and place people at risk for poor health and premature mortality (Becker et al., 1997; Schulz et al., 2000; Hardy and Studenski, 2008). The current study also highlights immune dysregulation as a potential mechanism linking loneliness and health. Increased herpesvirus replication may promote inflammation (Glaser et al., 2006; Roberts et al., 2010), which elevates risk for age-related diseases such as cancer, cardiovascular disease, and frailty (Ershler and Keller, 2000; Aggarwal et al., 2006). Indeed, people who were lonelier had higher baseline and stress-induced inflammation compared to those who felt more socially connected (Jaremka et al., in press; Hackett et al., 2012).

Other researchers have proposed additional complimentary pathways linking loneliness and poor health (Cacioppo et al., 2002; Hawkley and Cacioppo, 2003). For instance, people who were lonelier at study entry had larger systolic blood pressure increases over 4-years than people who were less lonely (Hawkley et al., 2010b); elevated systolic blood pressure is a well known cardiovascular disease risk factor (Chobanian et al., 2003). In addition, the experience of loneliness is stressful (Hawkley et al., 2003). Chronic stress, potentially via its effects on the endocrine and immune systems, enhances risk for a variety of health problems (Glaser and Kiecolt-Glaser, 2005). Lonelier people experience more sleep disturbances and engage in less physical activity than less lonely people (Hawkley et al., 2009; Kurina et al., 2011). Both sleep problems and physical inactivity place people at risk for pain, depression, fatigue and poor health (Berlin et al., 2006; McNeely et al., 2006; Cappuccio et al., 2010; Palesh et al., 2010; Landmark et al., 2011). Interestingly, inactivity may also elevate herpesvirus antibody titers and sleep disturbances dysregulate cellular immunity (Esterling et al., 1992; Irwin, 2002), suggesting that some mechanisms may work in tandem to influence both the symptom cluster and health.

Breast cancer survivors were more fatigued in our sample compared to others (e.g., Bower et al., 2000). This likely occurred because the women were from the baseline sample of a clinical trial designed to reduce fatigue, and we excluded woman who exercised on a regular basis. Accordingly, the range of pain, depression, and fatigue in our sample was sizeable and is a notable strength of the study.

The present data provide evidence that the relationship between loneliness and the symptom cluster was linked to elevated CMV antibody titers. Specifically, the current study found partial support that the relationship between loneliness and the symptom cluster was mediated by CMV antibody titers and the link between loneliness and CMV antibody titers was mediated by the symptom cluster. Prior research suggests that dysregulated immune function may enhance risk for pain, depression and fatigue (Cleeland et al., 2003), and pain, depression, and fatigue may further alter immune function (Buemi et al., 1997; Stewart et

al., 2009). The cross-sectional nature of the current study does not disentangle the uni-directional or cyclical nature of these relationships, one key limitation of the current research. Thus, additional research is needed to test the directionality of the relationships among loneliness, immune dysregulation, and the symptom cluster. For example longitudinal or panel data would useful to test whether loneliness is related to changes in CMV antibody titers and the symptom cluster over time.

Loneliness is a socially stressful experience and breast cancer diagnosis and its associated treatments are stressful events. Because stress and cortisol modulate immune function (Glaser and Kiecolt-Glaser, 2005), our sample of breast cancer survivors may have been at particular risk for immune dysregulation. Future work should investigate the role of stress and cortisol in the relationships found in the current study and whether the association between loneliness and herpesvirus reactivation exists in a more normative population. Additional work is also needed to examine other related social phenomena, such as social integration and social support, and how these factors shape herpesvirus reactivation and pain, depression, and fatigue.

In sum, the pain, depression, and fatigue symptom cluster is an important health concern. The current data suggest that loneliness is an important predictor of elevated CMV antibody titers and higher levels of the symptom cluster. Consequently, the present study suggests that loneliness enhances risk for immune dysregulation and the pain, depression, and fatigue symptom cluster. These data also provide a glimpse into the pathways through which loneliness may impact physical and mental well-being.

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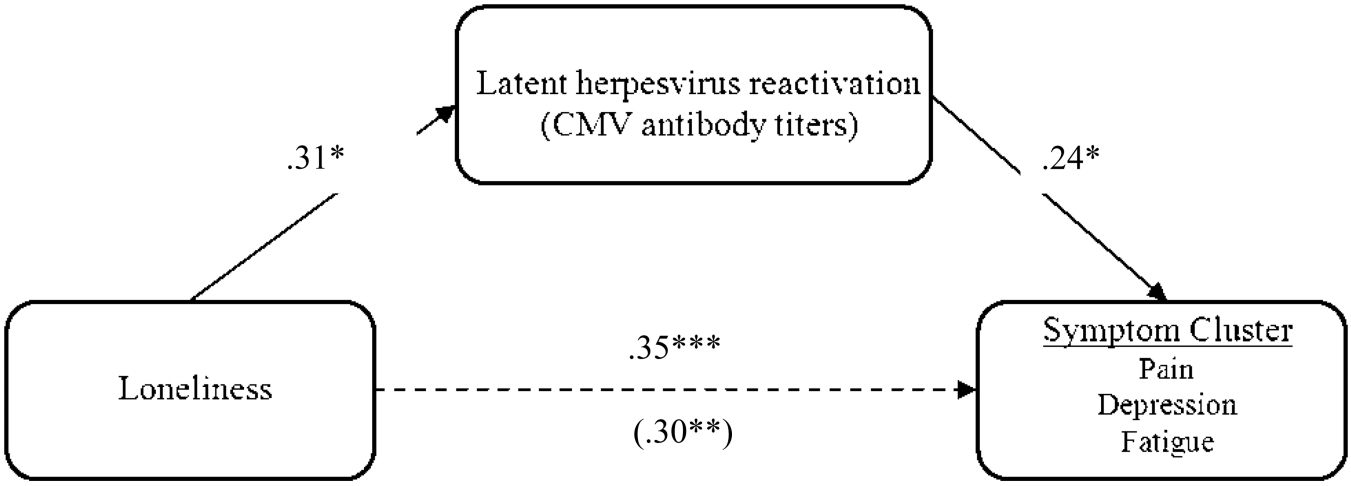

Figure 1.

Note: N = 84. Beta coefficients are standardized. *p<.05, **p<.01***p<.001. The relationship between loneliness and the symptom cluster controlling for CMV antibody is written in parenthesis. The test of the indirect effect was significant at the 91% confidence interval. .31* .24* .35*** (.30**)

Table 1

Study sample characteristics.

Characteristic	Category	Number (%) (N = 200)	Mean (SD)
Race	White	177(88.50)	---
	Black	18(9.00)	---
	Other	5(2.50)	---
Education	High school or below	12(6.00)	---
	Some college or college graduate	111(55.50)	---
	Graduate or professional training	77(38.50)	---
Marital Status	Single	27(13.50)	---
	Married	140(70.00)	---
	Separated/divorced/widowed	33(16.5)	---
Stage	0	18(9.00)	---
	I	89(44.50)	---
	II	75(37.50)	---
	III	18(9.00)	---
Age	N/A	---	51.58(9.24)
Months since Tx	N/A	---	10.66(7.84)
BMI	N/A	---	27.75(5.65)
Loneliness	N/A	---	38.73(8.27)

Table 2

Correlation table between primary study variables and covariates.

	1	2	3	4	5	6	7	8	9	10	11
BMI	-										
Age	.12	-									
Comorbidities	.03	.21**	-								
Cancer stage	−.03	−.06	.04	-							
Time since tx ended	.13	.08	−.03	−.06	-						
Sleep quality+	.11	−.03	.08	.10	−.02	-					
Exercise levels	−.13	.03	−.08	.00	−.11	−.09	-				
Loneliness	.08	.10	−.03	−.01	.15*	.29***	.05	-			
EBV antibody titers	−.00	.01	−.18*	−.11	−.14	−.01	−.09	−.06	-		
CMV antibody titers	.19	.10	−.16	.06	−.22*	−.07	−.05	.24*	.28**	-	
Symptom cluster (MFSI)	.17*	−.15*	.04	.10	.05	.63***	−.14*	.47***	.03	.18	-
Symptom cluster (SF-36)	.18*	−.13*	.06	.06	.04	.58***	−.18**	.45***	.04	.18	.97***

Note. N ~= 200 for all correlations except any involving EBV and CMV, which only include the subset of participants seropositive for each herpesvirus.

+ Higher numbers reflect worse sleep quality

* $p \leq .05$,

** $p \leq .01$,

*** $p \leq .001$.