Received: 30 June 2019 | Revised: 17 March 2020 | Accepted: 3 April 2020

DOI: 10.1111/pere.12336

ARTICLE

Personal RELATIONSHIPS WILEY

Relationship satisfaction determines the association between Epstein–Barr virus latency and somatic symptoms after the loss of a spouse

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Funding information
PI: Angie LeRoy, National Heart, Lung, and Blood Institute, Grant/Award Number: 1F32HL146064-0; PI: Christopher Fagundes; National Heart, Lung, and Blood Institute, Grant/Award Number: 1R01HL127260-01

Abstract

The loss of a spouse is associated with a host of negative health outcomes. While bereaved individuals commonly report somatic symptoms, no investigations exist of the association between reactivation of latent Epstein–Barr virus (EBV) and somatic symptoms among this population. Further, how an individual perceives the quality of their lost relationship in retrospect may impact loss outcomes. Among 99 bereaved spouses, elevated EBV antibody titers were associated with somatic symptoms for those who retrospectively reported high or mean levels of relationship satisfaction (RS), but not among those less satisfied. Further, higher RS was associated with greater grief symptoms. This study identifies higher retrospective RS as a possible risk factor for negative physical and mental health outcomes during bereavement.

KEYWORDS

bereavement, Epstein–Barr virus, relationship satisfaction, somatic symptoms

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1 | MARRIAGE, RELATIONSHIP SATISFACTION, AND HEALTH

Social relationships with friends, family, and spouses can all influence an individual's health and wellness. Among these social relationships, marriage plays one of the most central roles in impacting a person's health (for reviews, see Proulx, Helms, & Buehler, 2007; Robles, Slatcher, Trombello, & McGinn, 2014). For instance, married people have lower rates of mortality (Dupre, Beck, & Meadows, 2009) and fewer illnesses (Lorenz, Wickrama, Conger, & Elder Jr, 2006), compared to their unmarried counterparts. This association between marital status and health is so robust that it has been dubbed as the "marriage protection effect" and a "marriage survival advantage" (Rendall, Weden, Favreault, & Waldron, 2011, p. 482).

Relationship satisfaction (RS) is among the most frequently studied relationship quality variables (Berscheid & Reis, 1998) and is an important determinant for health outcomes (Galione, 2016). Broadly, RS refers to an individual's overall evaluation of their romantic relationship (Gerlach, Driebe, & Reinhard, 2018), which can include feelings, thoughts, or behaviors associated with constructs such as love, commitment, self-disclosure, investment, or support (Hendrick, 1988; Rusbult & Buunk, 1993). People in more satisfied romantic relationships report better health and higher levels of well-being than people in less satisfied romantic relationships (Karney & Bradbury, 1995; Williams, 2003). Similarly, hostile couples exhibit greater immune system dysregulation, as indicated by higher antibody titers to latent Epstein–Barr Virus (EBV), compared to less hostile couples (Kiecolt-Glaser et al., 1993). Thus, the positive health outcomes associated with being in a committed romantic relationship depend, in part, on the quality of the relationship (Bookwala, 2012).

RS may moderate the association between marriage and health outcomes more so for women than men (Kiecolt-Glaser & Newton, 2001). RS may play a stronger role in influencing health among married women compared to men because women have greater relationship awareness compared to their male partners (Acitelli, 1992), and thus may serve as more sensitive barometers of relationship quality (Floyd & Markman, 1983). More recently, researchers conducted a meta-analysis investigating whether the association between martial relationship quality and physical health was different for men and women, and failed to detect significant gender differences (Robles et al., 2014). Thus, it is still unclear for whom is relationship quality especially beneficial or detrimental (Robles et al., 2014), and in which relationship contexts.

1.1 | Relationship loss and health

When an individual loses their spouse, they also lose the "marriage survival advantage" (Rendall et al., 2011, p. 482). Although relationship loss can occur within a variety of circumstances (e.g., breakup, divorce, death), in the current report, we focus on the loss of a spouse by death. Individuals facing spousal bereavement (i.e., the death of a spouse), experience a unique form of a relationship loss whereby no opportunity exists to reconnect with their partner in the physical realm. Within the first 6 months after a spouse's death, the surviving spouse is at increased risk for morbidity and mortality (Stroebe, Schut, & Stroebe, 2007), with excess mortality ranging from 40% to 100% (Manor & Eisenbach, 2003). These high rates of morbidity and mortality are likely due, in part, to the emotional and physiological dysregulation that can occur after losing a partner.

The extent to which dysregulation occurs following bereavement may partially depend on prebereavement indicators. For example, Carr et al. (2000) identified that the effect of

widowhood on one's mental health and yearning postbereavement depended on prebereavement indicators of marital quality, the amount of emotional warmth in the marriage, and instrumental dependence in the marriage. Contextual prebereavement factors, such as one's appraisal of caregiving, can also affect postbereavement adjustment (Bass & Bowman, 1990). Among caregivers who ultimately experience the death of their spouse, those who appraised caregiving as being more difficult also appraised bereavement as more difficult (Bass & Bowman, 1990). Several psychosocial factors also influence health after the loss of a spouse, including interpersonal (e.g., financial hardship, loss of social support) and intrapersonal risk factors (e.g., gender, attachment style, mental health problems; see Stroebe, Folkman, Hansson, & Schut, 2006; Stroebe et al., 2007, for a review).

The emotional pain that generally results from the loss of a spouse is seen as an inevitable but adaptive response (Kastenbaum, 2016). Fortunately, most bereaved individuals are able to process their grief in a way such that after a period of time, they no longer experience the same degree of emotional distress as they did immediately following the loss (Shear & Mulhare, 2008). In contrast, 10–20% of bereaved individuals are unable to successfully transition into a healthier state of mind and may, instead, develop complications in the grieving (CG) process (Bonanno & Kaltman, 2001; also known as "prolonged grief" or "chronic grief"), which involves persistent grief symptoms (e.g., yearning for the deceased person, intrusive thoughts, excessive ruminations) for at least 6 months after the loss (Shear & Mulhare, 2008). Furthermore, CG may result in chronic medical and mental health problems as well as an increased risk for suicidal ideation and suicidal behaviors (Dell'osso et al., 2011; Prigerson et al., 2009) well beyond the standard 6-month morbidity and mortality risk period. Thus, it is important for us to understand the underpinnings of the bereavement experience, which may impact these severe consequences.

Specifically, it is important to seek a better understanding of where these disparities in grief experiences begin. Why do some develop complicated grief, while others are better able to adjust after the loss of a spouse? One framework that has become a powerful theoretical force in contemporary bereavement research is attachment theory (Stroebe, 2002). A spouse typically serves as a primary attachment figure in adulthood. When long-term relationship partners are together, they serve to reciprocally coregulate multiple physiological and emotional processes (i.e., subjective experience, expressive behavior, and autonomic physiology), which contribute to emotional and physiological stability for partners in a close relationship (Butler & Randall, 2013). The loss of an attachment figure (i.e., a romantic partner) can prompt the dysregulation of multiple biological systems (see LeRoy, Knee, Derrick, & Fagundes, 2019, for a review), which were once reciprocally coregulated by the relationship itself (Sbarra & Hazan, 2008). Separation from the partner may promote a stress response, which includes activation of the sympathetic branch of the autonomic nervous system (ANS), and the hypothalamic pituitary adrenal (ANS) axis. Consequently, immunological changes may occur, including increases in inflammation (Cohen, Granger, & Fuller-Thomson, 2015; Fagundes et al., 2018). Persistent, low-grade inflammation, refers to a steady, low-level of inflammation throughout the body, quantified by a small rise in immune system markers found in the blood or tissue. Increased levels of low-grade inflammation are associated with various diseases and conditions including cardiovascular disease, arthritis, type 2 diabetes, functional decline, and certain cancers (Harris et al., 1999).

While underutilized, herpesvirus reactivation is another marker of immune dysregulation, which may reflect immune system functioning during bereavement. Herpesviruses create latent infections (i.e., hidden until circumstances are suitable for development or manifestation of symptoms), which largely remain dormant in the body (Glaser & Kiecolt-Glaser, 1994). Thus, most adults are infected with the virus, but may never know they are infected if the virus

remains dormant (Steptoe, Hamer, & Chida, 2007; Stowe et al., 2010). However, latent herpesviruses can be reactivated and replicate (Cacioppo et al., 2002). Stress can negatively impact cellular immune function (i.e., a protective immune process) resulting in herpesvirus reactivation and replication, which manifests in increased antibody titers (Glaser et al., 1991, 1993, 1999). Relationship dissolution (e.g., divorce/separation) is linked to higher EBV antibody titers among both men (Kiecolt-Glaser et al., 1988) and women (Kiecolt-Glaser et al., 1987). While others have identified factors that are associated with herpesvirus reactivation among bereaved individuals (Garcini et al., 2018; Guevara, Gilbert, Murdock, Stowe, & Fagundes, 2019), to our knowledge, no research exists on how EBV reactivation may influence somatic symptom complaints in this population.

Researchers (Yao, Crawford, Komaroff, Ablashi, & Jacobson, 2010) identified herpesviruses as one potential culprit behind syndromes without other pathophysiologic explanation (e.g., chronic fatigue syndrome, fibromyalgia), particularly those impacting the central nervous system. Conflicting evidence, however, exists across different populations. For example, no association between herpesvirus infections and functional somatic symptoms were found in a sample of adolescents (Jonker, Schoevers, Klein, & Rosmalen, 2017). Bereaved individuals commonly report somatic symptoms (Herberman, Fullerton, & Ursano, 2013; Utz, Caserta, & Lund, 2012), particularly within the first 6 months after the loss (Stroebe, Stroebe, & Domittner, 1988). Spousal bereavement is most common among older populations, with about 45% of women and 15% of men over 65 becoming widowed (Hansson & Stroebe, 2003). In addition to psychological stress, there are natural age-related increases in EBV antibody titers, which indicates that one's cellular immune system has less control over the latent virus (Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985; Stowe et al., 2007). Thus, older adults may be at greater risk of stress-related reactivation because antibody titers increase naturally with age, and periodic stress-induced viral reactivation likely increases the number of herpesvirus-specific T cells over time (Stowe et al., 2007). These previous findings warrant future investigation of EBV reactivation and somatic symptoms among bereaved spouses. Thus, there is a debate about whether EBV is related to somatic symptoms that are associated with certain illnesses believed to have a strong psychosomatic component (e.g., fibromyalgia or chronic fatigue syndrome; Bansal, Bradley, Bishop, Kiani-Alikhan, & Ford, 2012; Buchwald, Goldenberg, Sullivan, & Komaroff, 1987).

The extent to which a surviving spouse is impacted by the loss may depend on relationship-specific factors. As described in interdependence theory (Kelley, 1983; Kelley & Thibaut, 1978; Thibaut & Kelley, 1959) and in Rusbult's Investment Model (Rusbult, 1980, 1983) commitment in close relationships is influenced by RS, quality of alternatives, and investment, with longer relationships having more investment (Rusbult, 1980). Indeed, these frameworks still apply to bereaved individuals; even after a spouse dies, relationship factors are still present and can potentially influence the surviving partner. For instance, research suggests that dyadic effects (interdependence) continue after one partner passes away (Bourassa, Knowles, Sbarra, & O'Connor, 2016). Thus, relationship-related factors are important to investigate in association with bereavement-related outcomes.

In a relatively small spousally bereaved sample, former marital harmony was found to be associated with more loneliness, crying, and postbereavement hallucinations or illusions (Grimby, 1993). Similarly, Carr et al. (2000) found that higher quality marriages were linked to higher levels of anxiety and yearning. On the other hand, Stroebe, Abakoumkin, and Stroebe (2010) identified that the more positively a widow rated their marital quality, the less intensely they yearned for their partner 6 months after the death. Although literature suggests that retrospectively reporting on marital quality variables might be susceptible to

"sanctification" (Lopata, 1996), a process whereby the late spouse and marriage is viewed in an overly positive light, most work with bereaved individuals involve participants retrospectively reporting on relationship quality variables. Thus, from both a theoretical and empirical standpoint, it follows that retrospective RS may influence how an individual is impacted when they lose their partner. However, there lacks a clear consensus on how it may influence grief outcomes following the death of a spouse.

1.2 | Present study

The present study investigates an important relationship factor, retrospective RS, that may determine mental and physical health outcomes after the death of a spouse, a major life stressor. We hypothesized that (1) higher EBV antibody titers would be associated with greater reports of somatic symptoms, and (2) the relationship between EBV antibody titers and somatic symptoms would be strengthened by the quality of the lost relationship. Specifically, we expected that those who were more satisfied in their relationship would report more somatic symptoms in relation to their EBV antibody titers than those less satisfied. Lastly, we hypothesized that retrospective RS would be positively related to grief symptoms; those who reported being satisfied in their relationship with their lost spouse would report more grief symptoms than those who were less satisfied (Hypothesis 3).

2 | METHOD

2.1 | Participants

One hundred and one bereaved individuals who had recently lost their spouse, no more than 14 weeks before the visit ($M = 11.86$ weeks, $SD = 2.33$), participated in the study. Out of the 101 participants, two were EBV seronegative and were removed from the analyses, yielding a final sample of 99 recently bereaved spouses, who were on average 68 years of age ($SD = 9.68$), and mostly female (67.3%). Participants were contacted and recruited through information from obituaries, support groups, flyer distribution, online postings, and community events. Exclusion criteria included significant visual or auditory impairment, being pregnant or nursing, autoimmune and inflammatory diseases, having experienced bereavement due to the loss of another loved one in the last year, divorced within the past year, and previously widowed. All participants were English-speakers to ensure understanding of the questionnaires.

2.2 | Procedure

Trained research assistants administered assessments at the participants' home or in the Bioscience Research Collaborative Community Research Center in the Texas Medical Center. During these visits, participants completed a questionnaire packet, including demographic and clinical questionnaires. anthropometric measurements, including weight, height, and waist circumference and nonfasting blood samples, were collected during the early hours of the morning. All samples were collected between 7:30 and 11:00 a.m. to control for diurnal variation; we also collected data early in the day to limit variability in activity, diet, and stress experienced in the hours before the visit.

Participants were asked to avoid any strenuous physical activity 48 hr before all visits. Participants were rescheduled for a different time if they were ill or did not follow the exercise restriction; one participant was rescheduled due to a sore throat, and one participant was rescheduled due to "coming down with a cold." All participants provided informed consent and procedures were approved by the Institutional Review Board.

2.3 | Determination of EBV viral-capsid (VC) IgG antibody titers

We targeted viral capsid antigen (VCA), a structural antigen (part of virus capsid), because VCA is more likely to reflect true reactivation (i.e., production of infectious virus) compared to early antigen (EA; i.e., a nonstructural antigen). EBV VCA antibody titers were assessed following standard protocol (Stowe et al., 2014). Ninety-six well microtiter plates, coated with virally infected cells, were obtained from EuroImmun (Morris Plains, NJ). Antigen source for VCA plates were inactivated cell lysates of lymphocytes infected with the P3HR1 strain of EBV. Plasma samples with high IFA-scored antibody titers (i.e., 2,560), obtained from past studies, were used as the top standard for EBV-VCA. Eight two-fold serial dilutions of the top standards were made with PBS in separate tubes. After diluting, the VCA standards were 2,560, 1,280, 640, 320, 160, 80, 40, and 20. One hundred microliters of positive and negative controls, standards, and diluted patient samples (all dilutions were at 1:101) were pipetted in duplicate into individual microplate wells followed by a 30 min incubation (all steps were carried out at room temperature). The plates were then washed three times with 350 ul wash buffer (provided) using an Embla microplate washer (Molecular Devices, Menlo Park, CA). Next, 100 ul of enzyme conjugate (peroxidase labeled anti-human IgG) was pipetted into the wells followed by another 30 min incubation period. The plates were then washed three times, and 100 ul of chromogen substrate (TMB/H_2O_2) was pipetted into the wells. The plates were then covered to protect from direct light and incubated for 15 min. One hundred microliters of 0.5 M sulphuric acid) was added to each well to stop the reaction. Absorbance was then read at 450 nm (reference wavelength 590 nm) using a SpectraMax Plus 384 (Molecular Devices). The values of the unknown samples were assigned in relation to the standard curve. Only participants who were seropositive for EBV were used in the analyses (see participants section).

2.4 | Self-report assessments

2.4.1 | Basic demographic information and health behaviors

Participants reported variables such as age, gender, race, and ethnicity. Participants answered an open-ended item about their alcohol use, "How many alcoholic drinks (12 ounces of beer, 5 ounces of wine, or 1.5 ounces of hard liquor) do you normally have in a week? Please enter 0 if you do not drink," and a yes/no item that asked, "Do you currently smoke or use nicotine?" Body Mass Index (BMI) was computed as weight in kilograms divided by height in meters squared. Using the record of the spouse's date of death collected during eligibility screening, we calculated a "days since death" variable, which referred to the time (in days) between the spouse's death and the study visit. Age, gender, income, BMI, sleep, alcohol use, smoking status, comorbidities, and days since the spouse's passing were used as covariates in the analyses.

2.4.2 | Sleep disturbance

The Pittsburgh Sleep Quality Index (PSQI) was used as a measure of sleep disturbance. The PSQI is a widely used instrument for the evaluation of sleep quality across seven areas (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction) that are aggregated in a global score ranging from 0 to 21 (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Higher scores on the global score are indicative of greater sleep-related disturbances. Participants' PSGI global score was used as a covariate in the current analyses.

2.4.3 | Relationship factors

To assess RS, participants completed one item of the Couples Satisfaction Index (CSI), "In general, how satisfied were you with your relationship spouse/partner?" on a 0 (*not at all*) to 5 (*completely*) scale (Funk & Rogge, 2007). To be more appropriate for the context of spousal bereavement, we adapted the original version of this item to read in the past tense rather than present tense. Thus, rather than, "...how satisfied *are* you..." we asked, "how satisfied *were* you..." To assess the duration of the relationship, participants answered the open-ended question, "How long was your marriage to your spouse?" in years.

2.4.4 | Somatic symptoms

To assess current somatic symptoms, we used the Symptom Checklist 90 (SCL-90-R; Derogatis, 1994). The SCL-90-R is a clinical self-report measure, which assesses a broad range of psychological distress symptoms. Here, we utilized the Somatization subscale, which includes 12 items to assess distress stemming from perceptions of bodily dysfunction (e.g., "headache" or "numbness or tingling in parts of your body"). Participants rate each item on a 5-point severity scale of symptom experience, ranging from "*Not at all*" to "*Extremely*." Raw scores were first derived by summing the values for the item responses within the Somatization subscale. Next, the raw score was divided by the number of items each participant endorsed. Then, we converted the raw scores into standard (normalized) *T*-scores to reflect adult sex-specific non-patient norms for Somatization according to the SCL-90-R manual (Derogatis, 1994). The somatization subscale yielded adequate reliability in the current sample ($\alpha = .80$).

2.4.5 | Grief symptoms

The Inventory of Complicated Grief was used to measure the degree to which participants experience grief symptoms by answering 19 items on a frequency scale of 0 (*never*) to 4 (*always*; Prigerson et al., 1999). Example items include, "I feel dazed or stunned over what happened," and, "I hear the voice of the person who died speak to me." This measure was designed and validated as a tool to help practitioners distinguish diagnoses of complicated grief from other bereavement-related emotional disorders such as depression, among those who had lost a spouse (Prigerson et al., 1995). Items were summed to compute a total score ($\alpha = .92$), with higher scores indicating higher grief symptoms.

2.4.6 | Medical comorbidities

The Charlson Index (Charlson, Szatrowski, Peterson, & Gold, 1994), the most widely used comorbidity index for predicting mortality, was used to assess medical comorbidities. The measure assigns weights to 19 comorbid medical conditions based on their potential influence on 1-year mortality. This was used as a covariate in the analyses.

3 | RESULTS

3.1 | Analytic strategy

3.1.1 | Imputation procedure

Multiple imputation using fully conditional specification (FCS) was employed to impute missing income data for five participants. Multiple imputation produces unbiased parameter estimates that appropriately reflect the true variability of the missing data and has been shown through simulation studies to be a more valid and less biased analytical approach than listwise deletion (Horton & Lipsitz, 2001). The FCS approach to multiple imputation is flexible in that it does not rely on normality assumptions (Raghunathan, Lepkowski, Van Hoewyk, & Solenberger, 2001) and preserves power (Liu & De, 2015). Following standard practice, the imputation procedure was repeated five times in order to approximate the true measurement variance represented in real data. All analyses were completed with each of the full imputed data sets, and the coefficients generated by each separate data set were averaged to produce final estimates (Graham, 2009).

3.1.2 | Testing regression assumptions

Preliminary statistical analyses included descriptive statistics and assessment of normality of distributions. We checked the EBV antibody titer counts to ensure they were biologically possible. It was determined there were no meaningful outliers, which were quantitatively defined as more than three interquartile ranges from the hinges of a standard boxplot (Howell, 2012). We also examined for skewness and kurtosis. The EBV antibody titer data were skewed, as would be expected. Accordingly, the EBV antibody titer variables were base 10 log-transformed to approximate to a normal distribution. Before conducting multiple linear regression analyses to test each of the hypotheses, we examined assumptions of normality, linearity, and homoscedasticity. We examined residuals to confirm they were normally distributed.

3.1.3 | Identification of potential covariates

We were careful not to adjust for extraneous factors to reduce the risk of overfitting the models. We determined covariates for each regression model based on existing empirical literature reporting a relationship between potential covariates and the key outcomes of interest for each of our Hypotheses (Hypotheses 1 and 2: Somatic symptoms; Hypothesis 3: Grief symptoms). Somatic symptoms have been found to be associated with gender (Canino, Rubio-Stipec,

Canino, & Escobar, 1992), as well as health behaviors (e.g., smoking, Williams, Hudson, & Redd, 1982 and alcohol use, Holst, Tolstrup, Sørensen, & Becker, 2017). The presence of medical illness can influence the interpretation of somatic symptoms (Robbins & Kirmayer, 1991), and sleep disturbances may influence grief symptoms (Hardison, Neimeyer, & Lichstein, 2005; Owen, Iddon, Hodges, Summers, & Robbins, 1997). These covariates were kept consistent across the analyses.

3.1.4 | Regression analyses

To test Hypotheses 1 and 3, we conducted a two-step hierarchical multiple regression to determine whether EBV antibody titers were positively associated with somatic symptoms over and above the covariates (gender, sleep, alcohol use, smoking status, and medical comorbidities). EBV antibody titers, the independent variable of interest, was entered at Step 1 (*Unadjusted Model*; Table 3). The demographic and health-related covariates were entered at Step 2 (*Adjusted Model*; Table 3).

3.1.5 | Moderation analyses

To test our moderation hypothesis, we used the approach recommended by Aiken, West, and Reno (1991). EBV antibody titers and RS (grand mean centered) were entered as predictors. A product term was entered into a multiple regression model to test the interaction hypotheses, along with covariates (consistent with those included in the models testing Hypotheses 1 and 3). For significant interactions, we ran simple slopes analyses to examine conditional effects. We defined "high" and "low" levels of RS in simple slopes analyses as one standard deviation above and below mean levels.

3.2 | Regression results

Descriptive statistics for all study variables are presented in Table 1. Bivariate correlations between variables of interest are presented in Table 2.

Hypothesis 1 We hypothesized that higher EBV antibody titers would be associated with greater reports of somatic symptoms. The two-step hierarchical multiple regression revealed that at Step 1, EBV antibody titers accounted for 21% of the variability in somatic symptoms, $F(1, 97) = 7.86$, $p = .006$. At Step 2, introducing the demographic and health-related factors (i.e., gender, sleep, alcohol use, smoking status, and medical comorbidities) into the model explained an additional 28.5% of variability in somatic symptoms, $F(6, 92) = 7.05$, $p < .001$. Indeed, these data support Hypothesis 1; EBV antibody titers were positively associated with somatic symptoms in both the adjusted and unadjusted models (Table 3).

Hypothesis 2 (Moderation). We hypothesized that the relationship between EBV antibody titers and somatic symptoms would be strengthened by relationship quality. When only the main effects and interaction term were entered into the (unadjusted) model, the EBV antibody titers × relationship satisfaction interaction was only trending toward significance ($b = 3.49$, $p = .09$, CI [−.54, 7.51]). The main effect terms (EBV antibody titers, RS) and the EBV antibody titers × relationship satisfaction interaction terms explained a

significant portion (11.7%; $p = .008$) of the variance in somatic symptoms. Using the same covariates as was used to test Hypothesis 1, there was a significant EBV antibody titers × relationship satisfaction interaction in the adjusted model ($b = 4.29$, $p = .02$, CI [.59, 7.99]). The covariates explained an additional 25.9% of variance in somatic symptoms, a statistically significant portion ($p < .001$). A simple slopes analysis revealed that EBV antibody titers were only significantly associated with somatic symptoms among those with high RS (i.e., 1 *SD* above the mean; $b = 8.09$, $p = .002$) and those with mean levels of RS ($b = 4.29$, $p = .01$); there was no significant association among those who were less

TABLE 1 Study sample characteristics

Variable	Number (%) or Mean (*SD*)
EBV antibody titers	2.63 (0.44)
Somatic symptoms	51.24 (9.10)
Relationship satisfaction	4.15 (1.02)
Grief symptoms	23.02 (11.15)
Age	68.27 (9.14)
Sex (Females)	68 (67.30)
Race	
White	83 (88.30)
Black or African American	5 (5.30)
Asian	3 (3.20)
Other	3 (3.20)
Ethnicity	
Hispanic or Latino	10 (10.60)
Not Hispanic or Latino	76 (80.90)
Not applicable	8 (8.50)
Income	
Less than $34,999	8 (8.00)
$35,000–$49,999	10 (9.9)
$50,000–74,999	20 (19.8)
$75,000–$99,999	13 (12.9)
$100,000 and greater	45 (44.6)
Body mass index	27.16 (4.98)
Sleep disturbance	7.26 (3.57)
Alcohol use	3.59 (4.70)
Smoking status	3 (3)
Comorbidities	0.37 (1.00)
Days since passing	83.11 (16.41)

Notes: EBV variable was base 10 logarithm transformed; Somatic symptoms values reflect mean t scores; Alcohol use refers to number of alcoholic drinks per week; Smoking status reflects those who smoke or use nicotine.

Abbreviation: EBV, Epstein–Barr virus.

TABLE 2 Zero-order correlations between variables included in the models

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13
1. EBV	—												
2. Somatic symptoms	.27**	—											
3. Relationship satisfaction	−.04	−.13	—										
4. Grief symptoms	.00	.22*	.25*	—									
5. Age	.10	−.17	.11	−.18	—								
6. Sex	.25*	.19	−.07	−.16	−.19	—							
7. Income	−.16	−.14	.05	−.05	−.07	−.06	—						
8. Body mass index	.23*	.03	.07	.06	−.08	−.07	.04	—					
9. Sleep disturbance	.00	.47**	.01	.31**	−.17	−.02	.06	−.03	—				
10. Alcohol use	−.15	.00	−.10	.06	−.00	−.04	.03	−.12	.21*	—			
11. Smoking status	.06	.25*	−.09	.02	−.10	−.00	−.04	.01	.25*	.01	—		
12. Comorbidities	.16	.09	.10	.10	.13	−.23*	−.02	−.02	.14	−.12	−.06	—	
13. Days since passing	.13	−.10	−.17	−.10	.12	−.04	.01	.01	−.09	−.14	.12	−.03	—

Notes: Gender coded as 0 = male, 1 = female; Smoking status coded as 1 = smoker/nicotine-user, 0 = nonsmoker/nicotine user.
*$p < .05$, **$p < .01$.

satisfied (i.e., 1 *SD* below the mean; $b = 1.43$, $p = .58$; see Figure 1). When added to an unadjusted (without covariates) main effects model (which included only EBV antibody titers and retrospective RS), the addition of the EBV × relationship satisfaction interaction term yields ΔR^2 of .027; thus, the interaction accounted for 2.7% of the variance in somatic symptoms. To further examine the interaction, we used the Johnson-Neyman technique to identify the region of significance (Bauer & Curran, 2005) for the significant EBV antibody titer × retrospective RS interaction (Hypothesis 2, adjusted model). The region of significance includes participants who reported ≥4.02 on the retrospective RS item. 47.48% of participants' scores fall within this region of significance (≥4.02); 52.52% of participants fall outside this region (≤4.02).

Hypothesis 3 We hypothesized that retrospective RS would be positively associated with grief symptoms. Consistent with our analytic methods used to test Hypothesis 1, a two-step hierarchical multiple regression revealed that at Step 1 (unadjusted model), EBV antibody titers accounted for 6.1% of the variability in somatic symptoms, $F(1, 98) = 7.53$, $p = .008$. At Step 2, introducing the demographic and health-related factors (i.e., gender, sleep, alcohol use, smoking status, and medical comorbidities) into the model explained an additional 12.3% of variability in somatic symptoms, $F(6, 93) = 2.84$, $p = .02$. Indeed, these data support Hypothesis 3; retrospective RS was positively associated with grief symptoms in both the adjusted and unadjusted models (Table 4).

3.3 | Ancillary analyses

In ancillary analyses, we investigated whether Hypotheses 1–3 were supported by further adjusted models, which included additional covariates: age, income, BMI, and days since spouse's passing.[1] Hypotheses 1–3 were further supported, even when controlling for this full battery of covariates (i.e., age, gender, income, BMI, sleep, alcohol use, smoking status, medical comorbidities, and days since spouse's passing).[2] In addition, based on previous research, we

TABLE 3 Hypothesis 1: Multiple linear regression results depicting self-reported somatic symptoms as a function of EBV antibody titers and covariates of interest

Variable	*b*	*SE*	*t*	Sig	CI	sr	R^2	ΔR^2
Unadjusted model (Step 1)							.21	.21**
EBV antibody titers	5.71	2.04	2.80	.006**	[1.67, 9.75]	.27		
Adjusted model (Step 2)							.50	.29*
Sleep	1.16	.23	4.95	<.001***	[.69, 1.62]	.42		
Smoking status	6.38	4.71	.12	.18	[−2.98, 15.75]	.12		
Alcohol use	−.13	.18	−.74	.46	[−.48, .22]	−.06		
Gender	2.59	1.78	1.45	.15	[−.96, 6.13]	.12		
Comorbidities	.14	.86	.17	.87	[−1.57, 1.85]	.01		
EBV antibody titers	4.61	1.90	2.42	.02*	[.83, 8.39]	.21		

Note: CI 95%; Alcohol use refers to drinks per week.
*$p < .05$, **$p < .01$, ***$p < .001$.

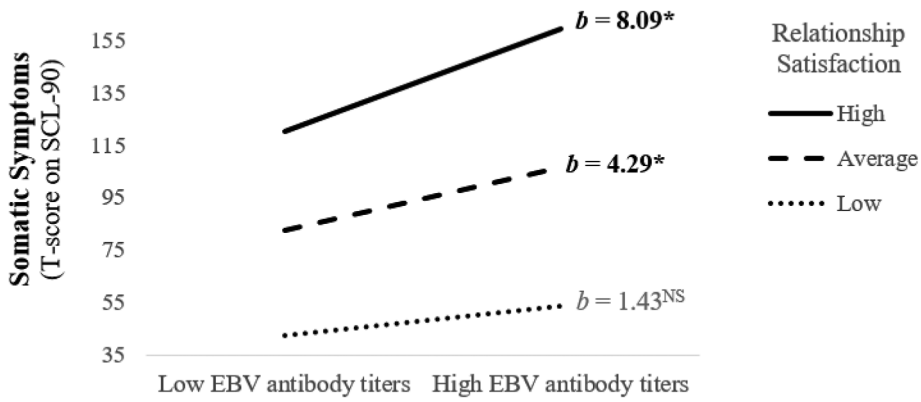

FIGURE 1 Relationship satisfaction (RS) strengthens the relationship between Epstein–Barr virus (EBV) antibody titers and somatic symptoms; no relationship exists for those at below average levels of RS

TABLE 4 Hypothesis 3: Multiple linear regression results depicting self-reported grief symptoms as a function of retrospective relationship satisfaction and covariates of interest

Variable	*b*	*SE*	*t*	Sig	CI	sr	R^2	ΔR^2
Unadjusted model (Step 1)	z						.06	.07**
Relationship satisfaction	3.07	1.13	2.73	.008**	[.84, 5.31]	.27		
Adjusted model (Step 2)							.19	.20*
Sleep	1.06	.33	3.24	.002**	[.41, 1.71]	.30		
Smoking status	−2.80	6.58	−.42	.67	[−15.87, 10.28]	−.04		
Alcohol use	.03	.24	.14	.89	[−.45, .52]	.01		
Gender	−3.89	2.38	−1.63	.11	[−8.62, .84]	−.15		
Comorbidities	−.68	1.18	−.58	.56	[−3.01, 1.65]	−.05		
Relationship satisfaction	2.97	1.09	2.82	.008*	[.80, 5.14]	.25		

Note: CI 95%.
†p =.05, *p < .05, **p <.01, ***p < .001.

explored a possible gender effect for the relationship between EBV antibody titers and somatic symptoms.[3] Indeed, the EBV antibody titer × gender interaction was significant ($p < .001$). When we ran the adjusted regression model for Hypothesis 1 separately on the bereaved men's data and the bereaved women's data, the association between EBV antibody titers and somatic symptoms was only significant among men ($p = .005$), but not among women ($p = .56$). We also tested the three-way EBV antibody titers × retrospective relationship satisfaction × gender interaction, but the interaction term was not significant ($p = .164$).

4 | DISCUSSION

In the current sample, the negative effects of herpesvirus reactivation on individuals' health during spousal bereavement depended on the *quality* of their former relationship. We identified a positive relationship between EBV antibody titers and somatic symptoms among those who

reported average or above average retrospective RS; in contrast, there was no relationship between EBV antibody titers and somatic symptoms among those who were less satisfied in their relationships. In line with our hypotheses, those who reported being more satisfied in the relationship they lost also reported more grief symptoms about 3 months after losing their spouse. Although EBV antibody titers were not directly associated with RS or grief, the association between EBV antibody titers and somatic symptoms was significant only among those who reported average or above levels of RS. Such findings demonstrate the importance of RS among a large portion of bereaved individuals in the study.

Further, when exploring the data, we found that the association between EBV antibody titers (i.e., EBV reactivation, an index of stress-related immune dysregulation) and perceived somatic symptoms *may* differ by gender. In a related study, bereaved females demonstrated greater EBV antibody titers than bereaved males (Guevara et al., 2019). If our exploratory findings reflect a gender difference in the true population, this may suggest that although bereaved women have higher EBV antibody titers than men, men may be suffering from the consequences of those elevated titers in the form of somatic symptoms more so than women. However, these exploratory findings must be considered with great caution. The current study did not measure women's menstruation cycle and/or menopause-related hormone changes, which can influence perception of somatic symptoms. Further, our limited sample size inhibits our ability to draw confident conclusions from these exploratory findings. Thus, this study cannot adequately address the question of whether the impact of EBV reactivation may influence somatic symptoms differently based on gender. Given that distinct inflammatory response patterns are evident among men and women with higher depressive symptoms (Majd et al., 2018), a larger bereaved study sample with appropriate covariates considered, would be ideal for a more systematic investigation of these gender effects in the future.

Regarding the influence of relationship quality on grief symptoms, our findings are consistent with work from Stroebe et al. (2010) demonstrating that higher self-reported RS is associated with more intense yearning in widowhood. Interestingly, however, a separate longitudinal study utilizing a younger sample of unmarried couples, found that having higher relationship quality before a breakup was associated with smaller declines in life satisfaction following the break-up, but was not associated with the magnitude of changes in psychological distress (Rhoades, Kamp Dush, Atkins, Stanley, & Markman, 2011). Rhoades et al. (2011), did however, report larger declines in life satisfaction after a breakup when individuals reported having planned to marry their partner before the relationship ended. Future research may examine the potentially differential influence of marital status among young and older bereaved adults, as well as the importance of relationship quality for these groups.

Research suggests that the more one is satisfied with their romantic relationship, the more the person includes their partner in their sense of identity (Aron, Aron, & Smollan, 1992). As relationships develop, people become more interdependent as they incorporate their relationship and relationship partner more fully into their self-concept and sense of identity (Aron & Aron, 1996; Aron, Lewandowski Jr., Mashek, & Aron, 2013). Married individuals benefit from a stronger sense of identity due to their increased interdependence (Dush & Amato, 2005). Similar to other life transitions, the experience of losing a spouse can cause a person to reform their identity from spouse/husband/wife to widower. Given these findings by other relationship researchers, it makes sense that under conditions of relationship loss, individuals with the highest retrospective RS would theoretically be the most affected because their sense of identity would be the most impacted. Future work should further elucidate how the findings presented here are, or perhaps are rather not, in line with theories of interpersonal relationships.

The current study had several strengths. One major strength of this study is the lack of common method variance associated with a biomarker—in this case, EBV antibody titers, as a measure of latent EBV reactivation. Common method variance refers to variance that is attributable to the measurement method rather than to the constructs the measures represent and is a main source of measurement error in research involving self-report measures alone (Podsakoff, Mackenzie, Lee, & Podsakoff, 2003). Thus, we can be more confident in our finding that EBV antibody titers are associated with somatic symptoms in the current sample because common method variance is greatly reduced by using a biomarker as the independent variable. Further, our study identified who is most at risk for negative health outcomes associated with changes in cellular immune functioning following a major life stressor. Herpesviruses cause persistent latent infections, which remain dormant in latently infected cells until reactivated (e.g., by stress; Steptoe et al., 2007). The presence of a latent herpesvirus is ubiquitous in adulthood, with more than 90% of adults EBV seropositive (Glaser & Kiecolt-Glaser, 1994). Because elevated EBV antibody titers represent poorer cellular immune control over virus latency, EBV antibody titers offer a broad measure of one's cellular immune system function. Thus, a major strength of the present study is the identification of perceived somatic symptoms as one potential consequence of poor cellular immune function.

Because bereavement is often a highly stressful life event, these results can help us to better understand the relationship between one's cellular immune system and experience of symptoms following such a stressor, while also controlling for age-related declines in cellular immune function. Our results indicate that decreased cellular immune function (i.e., higher EBV antibody titers) does not always translate into somatic symptoms following a major-life stressor; that is, EBV antibody titers were most strongly related to somatic symptoms among those who rated their marriage as being higher quality. Because cellular immunity decreases with age (Glaser et al., 1985; Stowe et al., 2007) and our sample was comprised of older adults (M_{age} = 68.27 years), these results indicate that EBV-related somatic symptoms among older adults are not purely driven by age-related decreases in cell-mediated immunity. Future research might ask whether these findings vary based on one's age by comparing the relationship between EBV antibody titers and somatic symptoms among older and younger adults.

Despite these strengths, this study also has several limitations. First, these data were cross-sectional, which limits the causal interpretation of our findings. In the future, researchers should employ longitudinal methods to allow for the use of mediation models to test the associations reported in the current study. Secondly, to reduce participant burden in this vulnerable population, which comes with answering a large number of self-report questions about their lost loved one, we only included one item of the CSI (Funk & Rogge, 2007). Thus, future research should investigate these variables with the full CSI or a different, more nuanced, relationship quality measure than the single item used in the current study. To that end, because we recruited participants after their spouse had died, we measured RS retrospectively. This creates a methodological weakness, especially since bereaved individuals may retrospectively report an overly idealized image of their spouse and previous relationships (Lopata, 1996). As such, our findings are limited in their generalizability since we are unable to tease apart whether relationship loss affected participants' retrospective reporting of RS. Nevertheless, while participants may be more likely to see their relationship through rose-colored glasses after the death of their spouse, the variability (albeit small) in retrospective reporting of satisfaction in the current sample, did impact the association between individuals' immune dysregulation and their perception of somatic symptoms. Thus, the present research provides more clarity about the circumstances surrounding romantic relationships under which reactivation of EBV might contribute to perceived somatic symptoms.

Another factor omitted from the current investigation is the idea of "continuing bonds" during bereavement. Continuing bonds (CBs) can be defined as an ongoing connection between the bereaved and the deceased that is maintained over time (Klass, Silverman, & Nickman, 2014), and has recently regained interest in the bereavement literature (Root & Exline, 2014). After a spouse dies, relationship factors are still present and can potentially influence the surviving partner. For instance, research suggests that dyadic effects (interdependence) continue after one partner passes away (Bourassa et al., 2016). Empirical literature suggests that the role of CBs in bereavement is complex; whether maintaining a connection with a deceased loved one is adaptive appears to depend on whether a bereaved individual can gain feelings of comfort and support from their CB with the deceased (Field & Filanosky, 2009). Future research should investigate how expression of CBs may coexist with relationship factors (e.g., interdependence, RS) and may interact to predict mental (e.g., grief symptoms) and physical (e.g., somatic symptoms) health outcomes during bereavement.

Findings from our study suggest the need for additional research aimed to understand how the quality of a relationship impacts grief and symptom presentation during bereavement. This information is essential to inform the development of diagnostic and assessment tools needed to facilitate case conceptualization and treatment for bereaved individuals using context-sensitive frameworks. Current trends emphasize a move away from population medicine to personalized medicine by focusing on individualized treatments that could better meet patients' needs based on individual characteristics, including biological, sociocultural, and clinical patterns and/or comorbidities. Similarly, research has shown a "widowhood effect," whereby a portion of health declines prior to the death of a spouse, suggesting that interventions might be most beneficial if they precede bereavement (Vable, Subramanian, Rist, & Glymour, 2015). Taken together, qualitative information about a person's marital/partner relationship in the face of loss could provide valuable information for providers to tailor interventions that would facilitate the healing process by addressing the sociocultural aspects most important to each individual. Likewise, facilitating an understanding of the links between EBV reactivation, relationship factors, emotional and somatic symptoms after the loss of a spouse could also aid in recovery and the restoration of well-being. Nonetheless, important to note is that providing proper assessment and treatment requires that providers receive interdisciplinary training that would better equip them to address the complex mental and physical health needs of bereaved individuals.

5 | CONCLUSIONS

In conclusion, in addition to its impact on health within an intact romantic relationship, RS influences subsequent health outcomes even after the loss of a spouse, retrospectively. We found that the negative effects of herpesvirus reactivation on somatic symptoms during spousal bereavement depends on the quality of their former relationship. Those who were less satisfied with their relationship did not experience the same increase in somatic symptoms associated with reactivation of EBV, a latent herpesvirus reactivated by stress, as those who were highly satisfied. Further, being satisfied in one's relationship was associated with more grief symptoms at about 3 months after the death of a spouse, compared to being less satisfied. Thus, in the context of health during spousal bereavement, the enduring sentiment, "the more you love, the more you lose," may ring true. These findings add to our growing understanding of how relationship factors influence both mental and physical health outcomes after the death of a spouse.

ACKNOWLEDGMENTS

This work would have not been possible without the men and women who, after losing a spouse, graciously gave their time to participating in this research. This work was supported by the National Heart, Lung, and Blood Institute (1R01HL127260-01, PI: Christopher Fagundes and NRSA 1F32HL146064-01, PI: Angie LeRoy). The efforts made by Patricia Morales and Kristi Parker for project coordination are gratefully acknowledged, and Levi Saucedo for data management. We also would like to acknowledge Ryan and Nola Majoros for their support of this project. As part of IARR's encouragement of open research practices, the author(s) have provided the following information: This research was not preregistered. The data used in the research are not currently available as these data are part of a larger R01 study currently being conducted; the National Institutes of Health prohibits the disclosure of data while the project is still in the data collection phase.

ENDNOTES

[1] Herpesvirus reactivation has been associated with age (Stowe, Peek, Cutchin, & Goodwin, 2012), race (Dowd, Palermo, Chyu, Adam, & McDade, 2014), and Socioeconomic Status (SES) variables (Fagundes et al., 2012). Further, BMI can influence immune parameters (Bennett et al., 2012; Fagundes, Glaser, Malarkey, & Kiecolt-Glaser, 2013), and has been included in other studies of immune dysregulation and pain among older adults (Seiler et al., 2017).

[2] EBV antibody titers were positively associated with somatic symptoms even when controlling for age, gender, income, BMI, sleep, alcohol use, smoking status, medical comorbidities, and days since spouse's passing ($b = 5.08$, $p = .01$; Hypothesis 1); The EBV antibody titer × relationship satisfaction interaction (Hypothesis 2) also remained significant ($b = 3.54$, $p = .05$; with simple slopes in a consistent direction) when included in a model with these covariates, as did the association between retrospective relationship satisfaction and grief symptoms ($b = 3.20$, $p = .004$).

[3] Researchers suggest relationship satisfaction may play a stronger role in influencing health among married women compared to men (Acitelli, 1992). In addition, bereaved females demonstrated greater EBV antibody titers than bereaved males, in a related study (Guevara et al., 2019).

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How to cite this article: LeRoy AS, Petit WE, Brown RL, et al. Relationship satisfaction determines the association between Epstein–Barr virus latency and somatic symptoms after the loss of a spouse. *Pers Relationship*. 2020;1–22. https://doi.org/10.1111/pere.12336