

Loneliness and Telomere Length: Immune and Parasympathetic Function in Associations With Accelerated Aging

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Abstract

Background Lonely people's heightened risks for chronic health conditions and early mortality may emerge in part through cellular aging. Lonelier people have more severe sympathetic responses to acute stress, increasing their risk for herpesvirus reactivation, a possible path to shorter telomeres. Parasympathetic function may modulate this risk.

Purpose The current study aimed to examine the associations among loneliness, herpesvirus reactivation, and telomere length, with parasympathetic activity as a moderator, in healthy middle-aged and older adults.

Methods A sample of 113 healthy men and women of ages 40–85 provided blood samples that were assayed for telomere length, as well as the latent herpesviruses cytomegalovirus (CMV) and Epstein-Barr virus (EBV). They also provided heart rate variability (HRV), a measure of parasympathetic activity, and reported on their feelings of loneliness.

Results Lonelier people with lower HRV (i.e., lower parasympathetic activity) had greater CMV reactivation and shorter telomeres compared with their less lonely counterparts, above and beyond demographics, health

behaviors, resting heart rate, and social network size. However, loneliness was not associated with viral reactivation or telomere length among those with higher HRV. In turn, greater CMV and EBV reactivation was associated with shorter telomeres.

Conclusions Taken together, these data implicate parasympathetic function in novel links between loneliness and accelerated cellular aging.

Keywords Loneliness • Parasympathetic function • Heart rate variability • Latent herpesvirus reactivation • Telomere shortening • Immunosenescence

Introduction

Lonelier people face heightened risk for early mortality. A meta-analysis of 70 studies provided clear evidence: the lonelier are 26% more likely to die upon follow-up than those who feel more socially connected [1]. Loneliness also promotes higher rates of depression, smoking, drinking, illicit drug use, unhealthy diet, and sedentary lifestyles [2–5], but the link between loneliness and early mortality emerges above and beyond these factors, even after accounting for age and health status [1]. Thus, our understanding of the pathways linking loneliness to early mortality remains incomplete.

Telomere shortening, a reflection of cellular aging, predicts mortality and aging-related disease incidence, and thus may help to further explain the risks of loneliness. For example, older adults with shorter telomeres had mortality rates from infectious disease more than eight times higher, and mortality rates from heart disease more than three times higher, compared to those with longer telomeres [6]. Likewise, telomere shortening accompanies many common age-related diseases including cancers, diabetes, and multiple indicators of cardiovascular disease—additional routes to early mortality [7].

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Several findings support a working hypothesis that social dysfunction can advance the aging phenotype. In an ethnically diverse sample, older adults who reported low social support had shorter telomeres than their well-supported counterparts [8]. Loneliness may speed age-related physical deterioration: motor function declined more rapidly in the lonely compared with the socially connected, and lonelier older adults were disproportionately frail relative to less lonely older adults [9, 10]. In accordance with these data, lonelier people may also experience accelerated telomere shortening.

Loneliness may promote aging, in part, by driving viral replication. Latent herpesvirus infections are pervasive: more than half of adults carry cytomegalovirus (CMV) and greater than 90% have been exposed to Epstein-Barr virus (EBV) [11–13]. Once infected, CMV and EBV remain lifelong burdens to the immune system; thus, the ability to suppress viral reactivation reflects the competence of the immune response [11, 14]. Lonelier medical students had greater EBV replication in response to examination stress compared to less lonely students [15]. Similarly, lonelier breast cancer survivors had greater CMV replication than less lonely survivors [16].

These latent infections, particularly CMV, stimulate T-cell proliferation and speed cell division, thus providing a direct path to shorter telomeres [11]. Healthy people who have been infected with CMV and thus have detectable antibodies (i.e., CMV-seropositive) have higher rates of telomere shortening compared to their CMV-seronegative counterparts [13]. Likewise, in the Whitehall study, healthy CMV-seropositive adults ages 53 to 76 showed greater telomere attrition than CMV-seronegative counterparts across 3 years, with a disparity equivalent to 12 chronological years [12]. Patients who received a kidney transplant from a CMV-seropositive donor had a greater rate of telomere shortening over 3 years following transplant relative to kidney recipients from a CMV-negative donor [13]. Taken together, heightened viral replication associated with loneliness may provide a path to telomere shortening.

The way lonelier people process and respond to stressors may help to account for their health risks. Though the lonelier experience similar numbers of major life events compared with their less lonely counterparts, they feel more stressed [17] and have more adverse inflammatory responses as well as greater cardiac sympathetic activation to acute social stressors [18–20]. Thus, high parasympathetic function, indexed by baseline levels of heart rate variability (HRV), may protect people from the immune risks possibly associated with loneliness. As a measure of vagus nerve activity, HRV may reflect the capacity to adapt and respond to environmental demands [21, 22]. Indeed, compared to people with lower HRV, people with higher HRV report fewer difficulties with emotion regulation [23], demonstrate superior

performance on stressful tasks that challenge emotion regulation [24], and show heightened activation of the amygdala and medial prefrontal cortex, brain regions relevant to emotional appraisal and threat assessment, during emotion regulation tasks [21]. Indeed, if the negative health consequences of loneliness are due to dysregulated threat processing and exaggerated sympathetic reactivity, loneliness' harmful associations may emerge only in the context of lower parasympathetic function, that is, lower HRV, and people with higher HRV may be protected from loneliness-related immune risks.

The current study tested the proposed associations among loneliness, HRV, herpesvirus reactivation, and telomere length in a sample of healthy middle-aged and older adults. We first hypothesized that HRV would moderate loneliness' links to EBV and CMV replication, and telomere length, such that lonelier people with lower parasympathetic activity would have greater EBV and CMV replication, as well as shorter telomeres, compared with less lonely people. Likewise, we predicted that higher HRV would protect lonelier people from greater herpesvirus reactivation and shorter telomeres. Finally, we expected that people with greater EBV, and particularly CMV, replication would have shorter telomeres.

Method

Participants

Participants were from the baseline sample of a clinical trial assessing the potential anti-inflammatory effects of omega-3 supplementation [25]. Adult men and women ages 40–88 were eligible if they engaged in less than 2 hr of vigorous physical activity per week, and had a body mass index (BMI) between 22.5 and 40 [25]. Individuals were ineligible to participate if they had a convulsive, autoimmune, or inflammatory disease, or if they had diabetes, chronic obstructive pulmonary disease, symptomatic ischemic heart disease, liver/kidney failure, gastroesophageal reflux disease, or a prior cancer history (except basal or squamous cell). People were also excluded if they abused drugs or alcohol, or smoked cigarettes. Those taking medications for depression, anxiety, cholesterol, or cardiovascular problems were also excluded.

Of the 138 people who participated in the parent study, the 113 who had telomere data comprise our analytic sample, as these data were not collected for early participants. Their ages ranged 40–85 ($M = 51$). Those missing telomere data did not significantly differ from those with telomere data on age, education, or key variables of interest: loneliness, HRV, CMV antibody titers, or EBV antibody titers ($ps > .05$). Additional sample characteristics are listed in [Table 1](#).

Table 1 Sample descriptive statistics

	<i>N</i> (%) or Mean(SD)	Range
Age	51.0(7.8)	40–85
Gender (% women)	93(67.4%)	
Race	Caucasian	109(79.0%)
	African American	22(15.9%)
	Asian	4(2.9%)
	Native American	2(1.5%)
	Mixed race	1(0.7%)
Education (years)	16.7(2.8)	12–25
BMI	30.6(4.5)	22.0–40.7
Depression history (%yes)	52(42.3%)	
Number of social contacts	24.9(9.6)	6–50
Resting heart rate	70.7(9.2)	52.0–92.6
HRV (RMSSD)	28.2(16.7)	5.5–99.5
Loneliness (NYUL)	7.8(3.1)	4–20
Ln(EBV)	3.01(0.38)	2.31–3.81
Ln(CMV)	2.93(0.40)	2.00–3.81
Telomere length (T/S)	1.07(0.17)	0.65–1.45

Data Collection Procedure

The Ohio State University Institutional Review Board approved the project; all subjects provided written informed consent prior to participation. Participants arrived at the Clinical Research Center, a hospital research unit, at 7:45 a.m., and a catheter was inserted in their arm. After eating a standardized breakfast, participants were asked to sit quietly for 20 minutes to provide baseline HRV. Following the rest period, blood was drawn to assess telomere length and viral antibody titers for latent herpesviruses EBV and CMV.

Questionnaires and Interviews

Loneliness was measured with the 4-item short form of the New York University Loneliness (NYUL) scale [26], which assessed the extent to which participants felt chronically alone and socially isolated [27]. The scale includes the following items: “When I am completely alone, I feel lonely: 1-almost never, to 5-most of the time”; “How often do you feel lonely?” (1-never, to 7-all of the time); “When you feel lonely, how lonely do you feel?” (1-I never feel lonely, to 6-extremely lonely); and “Compared to other people your own age, how lonely do you think you are?” (1-much less lonely, to 5-much lonelier). Items are summed so that higher scores indicate greater loneliness. The NYUL scale is associated with other loneliness measures [26, 28] and the items showed sufficient internal consistency in our sample ($\alpha = 0.84$).

Depression history was included as a key covariate given its consistent association with shortened telomeres

[29]. Indeed, according to a meta-analysis of 34,347 people in 38 studies, depression was associated with shorter telomeres when measured by clinical interview, but not by self-reported depressive symptoms [29]. Furthermore, in a large national Dutch study, people with remitted major depressive disorder (MDD) had shorter telomeres than did healthy controls, and did not differ from those with current MDD [30]. Taken together, this prior work suggests that a history of depression, beyond self-reported symptoms, may confer continued risk for shorter telomeres. The mood disorder modules of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental disorders-IV (DSM-IV), nonpatient version provided data on lifetime occurrence [31]. Trained interviewers administered the modules, and diagnoses were determined through consensus. Of those with telomere data, 46 participants (41%) met criteria for a lifetime diagnosis of a mood disorder: MDD, dysthymia, or depression not otherwise specified.

Social isolation was determined using a well-established measure of social network size, the Social Network Index [32]. For each of 12 possible social roles (e.g., parent, child, spouse, student, church member), participants listed the number of people with whom they had regular contact. The sum across all roles indicated a person’s network size, and a smaller network reflected greater isolation. Social isolation was treated as a covariate due to its association with mortality, and to distinguish associations with subjective feelings of loneliness from those with objective network size [1].

The Pittsburgh Sleep Quality Index (PSQI) measured sleep quality over the prior month [33]. Nine items that

reflect seven components of sleep—subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction—sum to form a global sleep score. Values range 0–21, where higher scores indicate worse sleep quality and those 5 or greater indicate clinically significant sleep problems. The PSQI can distinguish between people with and without objective sleep disturbances [33]. In a study of 80 insomnia patients, the PSQI demonstrated strong test–retest reliability across 2 days ($r = 0.90$) and up to 8 weeks ($r = 0.86$) [34]. Sleep problems were tested as an ancillary covariate due to their relation to telomere length [35, 36].

HRV

For HRV measurement, interbeat intervals (IBIs) were continuously collected noninvasively with the Polar s810 wristwatch and Wearlink 31 belt band using a standard 1000 Hz sampling rate, in accordance with established recommendations [37, 38]. Before HRV analysis, visual artifact correction was performed on the raw IBI series. To capture resting HRV, we extracted the IBI series at a 10-min interval, 5 min into the 20-min rest period, and calculated a standard time-domain measure of HRV, the root mean square of successive differences (RMSSD) using Kubios (Kuopio, Finland). In short intervals (e.g., 10 min), RMSSD corresponds closely to spectral measures of high-frequency HRV, but is more robust to changes in respiration than are spectral measures [38]. Average resting heart rate was also calculated during the rest period and used as a covariate in analyses due to the dependency of HRV on heart rate [39].

Assays

Telomere length

Average telomere length was measured in peripheral blood lymphocytes with quantitative polymerase chain reaction (qPCR) and expressed as the ratio of the abundance of telomeres versus the abundance of a single copy gene (human beta-globin) (T/S). Details of the assay have been described elsewhere [35]. The inter-assay coefficient of variation was 4.3% for this study. The formula that converts the T/S ratio to base pair units follows: base pairs = $(3,274 + 2,413 * (t/s))$ [40].

EBV and CMV antibody titers

Plasma was stored at -80°C until assayed with Euroimmun EBV enzyme-linked immunosorbent assay (ELISA) plates that measure EBV virus capsid antigen (VCA) IgG 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, as previously described [41]. Latent viruses reactivate with varying magnitude; thus all analyses treated antibody titers as continuous variables [41].

Analytic Plan

Regression models were used to evaluate hypotheses. To minimize the number of tests, we began by modeling the two-way interaction between loneliness and HRV, both treated as continuous variables, on three focal outcomes: telomere length, EBV antibody titers (for EBV+ individuals), and CMV antibody titers (for CMV+ individuals). Covariates included age, sex, race (white versus nonwhite), years of education, body mass index (BMI), social network size, resting heart rate, and depression history. EBV and CMV antibody titers were natural-log transformed to correct residuals; telomere data did not require transformation. Nonsignificant interaction terms were removed in final models; statistically significant interaction effects were probed across the range of HRV. Then, we examined the hypothesis that higher EBV and CMV antibody titers would be linked to shorter telomeres using separate regression models with age, sex, race, education, BMI, and depression history as covariates. Testing moderated mediation models was deemed inappropriate given the considerable loss of data with all paths included ($N = 43$ for CMV; $N = 83$ for EBV). Ancillary analyses tested the robustness of our findings by adjusting for additional health-relevant behaviors: sleep and past-week alcohol use.

Results

Descriptive Statistics

Most of our participants were white (79%), women (67%), who were educated at a college level or higher (71.7%). Of the 113 participants with telomere data, 55 (48.7%) had CMV-positive sera; 106 (93.8%) were EBV-seropositive. All but 2 CMV-seropositive individuals also were EBV-seropositive. See Table 1 for additional sample characteristics.

Loneliness, HRV, and Telomere Length

As hypothesized, loneliness significantly predicted telomere length, moderated by HRV ($b = 0.001$, $SE = 0.0004$, $p = .012$, 95% CI: 0.0003 to 0.002, Table 2). Displayed in Fig. 1, greater loneliness was significantly associated with shorter telomeres among individuals with lower HRV (e.g., 1 SD below the mean, which was at the

~14th percentile; $b = -0.026$, $SE = 0.010$, $p = .009$, 95% CI: -0.047 to -0.007), but not among those at the mean of HRV (~58th percentile, $p = 0.178$, 95% CI: -0.023 to 0.004) or higher (e.g., 1 SD above the mean, at the ~87th percentile; $p = .398$, 95% CI: -0.011 to 0.026). To interpret, as depicted by the gray dotted line in Fig. 1, among those with lower HRV (i.e., 1 SD below the mean), there was a difference of 482.6 base pairs between lonelier people (i.e., those 1 SD above the mean, who had 5,687 base pairs, on average) and less lonely people (i.e., those 1 SD below the mean, who had 6,169.6 base pairs, on average).

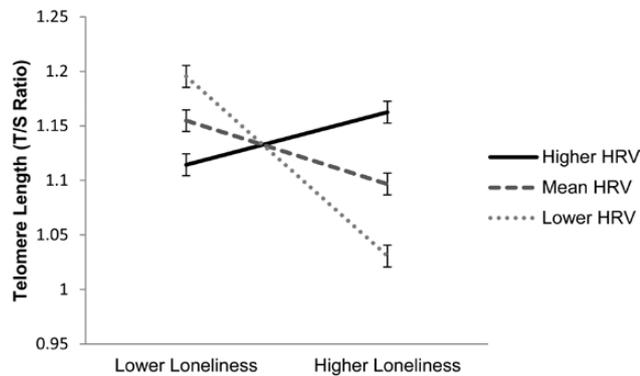


Fig. 1 Loneliness and HRV interacted to predict telomere length ($b = 0.001$, $SE = 0.0004$, $p = .012$, 95% CI: 0.0003 to 0.002). Among those with lower HRV, greater loneliness was associated with shorter telomere length (dotted line, plotted 1 SD below the mean, at approximately the 14th percentile, $p = .009$, 95% CI: -0.047 to -0.007); the link between loneliness and telomere length was nonsignificant among those at the mean of HRV (dashed line, approximately 58th percentile, $p = .178$, 95% CI: -0.023 to 0.004) or higher (solid line, plotted 1 SD above the mean, at approximately the 87th percentile, $p = .398$, 95% CI: -0.011 to 0.026).

Loneliness, HRV, and Latent Herpesvirus Reactivation

CMV antibody titers

As hypothesized, greater loneliness significantly predicted higher CMV antibody titers (i.e., greater CMV reactivation) dependent on HRV ($b = -0.003$, $SE = 0.001$, $p = .041$, 95% CI: -0.005 to -0.0001 , Table 2). As depicted in Fig. 2, greater loneliness was significantly associated with higher CMV titers (greater CMV reactivation) among individuals with lower HRV (e.g., 1 SD below the mean, which was at the ~14th percentile, $b = 0.063$, $SE = 0.027$, $p = 0.028$, 95% CI: 0.007 to 0.119), but not among those at the mean of HRV (~87th percentile, $p = 0.400$, 95% CI: -0.024 to 0.059) or higher (e.g., 1 SD above the mean, at the ~95th percentile, $p = 0.384$, 95% CI: -0.092 to 0.036).

EBV antibody titers

As shown in Table 2, there was no difference between people with higher and lower HRV in the link between loneliness and EBV antibody titers ($p = 0.245$, 95% CI: -0.003 to 0.001). With the interaction term removed, there was also no association between loneliness and EBV antibody titers ($p = 0.850$, 95% CI: -0.033 to 0.027).

Latent Herpesvirus Reactivation and Telomere Length

Accounting for age, sex, race, education, BMI, and depression history, among CMV-seropositive people, individuals with higher CMV antibody titers (greater CMV reactivation) had significantly shorter telomeres compared to those with lower CMV titers ($b = -0.118$,

Table 2 Loneliness and HRV predicting latent herpesvirus reactivation and telomere length

	Telomere length			Ln(EBV titers)			Ln(CMV titers)		
	<i>b</i>	<i>SE</i>	95% <i>CI</i>	<i>b</i>	<i>SE</i>	95% <i>CI</i>	<i>b</i>	<i>SE</i>	95% <i>CI</i>
Intercept	1.412	0.058	[1.120, 1.705]	2.870	0.320	[2.232, 3.508]	2.006	0.457	[1.079, 2.933]
Age	-0.003	0.003	[-0.009, 0.002]	-0.002	0.007	[-0.016, 0.011]	0.010	0.008	[-0.006, 0.026]
Sex	-0.078	0.046	[-0.169, 0.013]	0.049	0.106	[-0.163, 0.261]	-0.073	0.163	[-0.404, 0.257]
Race	-0.006	0.050	[-0.106, 0.094]	-0.102	0.106	[-0.314, 0.110]	0.023	0.123	[-0.227, 0.273]
Education (years)	0.011	0.006	[-0.002, 0.023]	-0.019	0.014	[-0.046, 0.010]	-0.014	0.018	[-0.051, 0.023]
BMI	-0.003	0.005	[-0.013, 0.006]	-0.002	0.010	[-0.022, 0.018]	0.017	0.014	[-0.012, 0.045]
Depression history	0.004	0.040	[-0.074, 0.083]	0.115	0.089	[-0.063, 0.292]	-0.107	0.111	[-0.332, 0.117]
Social network size	-0.002	0.002	[-0.006, 0.002]	0.007	0.005	[-0.002, 0.016]	0.020	0.007	[0.006, 0.034]
Resting heart rate	0.006	0.003	[-0.067, 0.012]	-0.004	0.007	[-0.018, 0.011]	0.010	0.009	[-0.008, 0.029]
HRV	-0.008	0.004	[-0.015, -0.0004]	0.005	0.008	[-0.010, 0.020]	0.029	0.013	[0.003, 0.055]
Loneliness	-0.039	0.014	[-0.067, -0.012]	0.028	0.031	[-0.033, 0.089]	0.098	0.040	[0.016, 0.180]
HRV * Loneliness	0.001	0.0004	[0.0003, 0.002]	-0.001	0.001	[-0.003, 0.001]	-0.003	0.001	[-0.005, -0.0001]

Due to the small numbers of participants of races other than white, race was dichotomized between white or not. HRV was measured using the time-domain metric RMSSD.

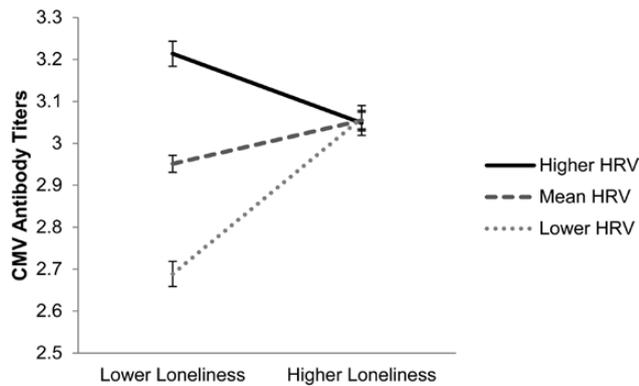


Fig. 2 Loneliness and HRV interacted to predict natural-log-transformed CMV reactivation ($b = -0.003$, $SE = 0.001$, $p = .041$, 95% CI: -0.005 to -0.0001). Among those with lower HRV, greater loneliness was associated with higher CMV antibody titers, that is, greater viral reactivation, (dotted line, 1 SD below the mean, at approximately the 14th percentile, $p = .028$, 95% CI: 0.007 to 0.112); the link between loneliness and CMV antibody titers was not significant at the mean of HRV (dashed line, approximately 87th percentile, $p = .400$, 95% CI: -0.024 to 0.059) or higher (solid line, 1 SD above the mean, approximately 95th percentile, $p = .384$, 95% CI: -0.092 to 0.036).

$SE = 0.053$, $p = .032$, 95% CI: -0.224 to -0.011). Similarly, among EBV-positive people, those with higher EBV titers (greater EBV reactivation) had shorter telomeres compared with people with lower EBV antibody titers ($b = -0.109$, $SE = 0.044$, $p = .014$, 95% CI: -0.196 to -0.023).

Secondary Analyses

In secondary analyses, we tested the robustness of our moderation results adjusting for additional health-relevant behaviors—sleep quality and recent alcohol consumption. Taking these factors into account, HRV continued to moderate the effects of loneliness on CMV antibody titers ($ps < .043$) and telomere length ($ps < .016$). Because sleep problems were associated with lower HRV in our sample ($r = -0.20$, $p = .036$) and sleep quality has moderated the health effects of risk factors in prior work [36], we explored whether it played a moderating role between loneliness and CMV titers and telomere length. Indeed, we found that sleep problems significantly moderated the link between loneliness and telomere length ($b = -0.005$, $SE = 0.002$, $p = .044$, 95% CI: -0.01 to -0.0001). Among those with considerable sleep dysfunction (scores of 10 or greater), loneliness was associated with shorter telomeres ($b = -0.024$, $SE = 0.012$, $p = .045$, 95% CI: -0.046 to -0.001), but associations were nonsignificant among those with PSQI scores lower than 10. When the interaction between loneliness and HRV was introduced back into the model, the moderating association of sleep was no longer significant ($p = .117$) and the interaction with HRV maintained statistical significance ($p = .039$). Sleep

did not moderate the link between loneliness and latent CMV reactivation ($p = .141$).

Discussion

Among healthy middle-aged and older adults ranging from ages 40 to 85, lonelier people with lower HRV had shorter telomeres and greater CMV reactivation compared with less lonely people with lower HRV. Loneliness was unrelated to telomere shortening and herpesvirus reactivation among those with higher HRV. Greater CMV and EBV reactivation was also associated with shorter telomeres. Taken together, this study provides cross-sectional evidence for factors linking loneliness to accelerated immune aging.

Just as the mortality risks of loneliness remain after accounting for a host of potential mechanisms [1], the conditional links of loneliness to herpesvirus reactivation and telomeres were not explained by demographic, behavioral, or psychological risk factors: chronic conditions, physical activity, smoking, age, sex, race, education, BMI, sleep problems, alcohol use, or depression history. Furthermore, associations held after accounting for smaller social network size, an indicator of objective social isolation and a consistent predictor of heightened mortality and disease risks [1]. The 482.6 bp difference between lonelier and less lonely people with lower HRV was notable, similar in size or greater than the telomere differences between men and women [42], between people who have had a myocardial infarction before age 50 and those who have not [43], and between current smokers and people who have never smoked [44], according to a synthetic review [45].

With few exceptions (e.g., 10), the health correlates of loneliness have not been teased apart from those of social isolation; our differentiation of the two represents a strength of the present study. Consistent with weak correlations in past work [1], loneliness and social isolation were unrelated in our sample. Indeed, loneliness, or perceived social isolation, reflects the feeling that one's social ties are insufficient, so that one may feel socially deprived regardless of the objective network size.

Parasympathetic Function as a Key Moderator of Loneliness, Latent Herpesvirus Reactivation, and Telomere Length

According to an evolutionary perspective, human survival has relied on the formation and function of social groups; thus, social connections fulfill a basic desire to belong and provide a sense of safety [46]. The notion that social isolation posed a danger to our ancestors' survival may explain why people who feel disconnected are hypervigilant to potential threat [46, 47], perceive life events as more disruptive [17], and exhibit more adverse inflammatory responses and greater sympathetic reactivity to stressors [18, 19]. Our

finding that HRV modulated the links between loneliness, latent herpesvirus reactivation, and cellular aging aligns with the working conclusion that higher parasympathetic function may play a key protective role.

Indeed, loneliness seems to trigger larger sympathetic responses to social stress, leaving parasympathetic function unperturbed; thus, better parasympathetic function may counterbalance sympathetic cascades. One study compared lonely and nonlonely people's sympathetic and parasympathetic cardiac parameters, both at baseline and in reaction to a stressful speech and arithmetic task [19]. The two groups had equivalent baseline levels of HRV and similar HRV reactivity to the task, but the lonely group had greater heart rate elevation and prejection period shortening during the stressor compared with the nonlonely, consistent with a sympathetically driven response. Thus, higher parasympathetic activity is likely to provide a stronger counterbalance to lonelier people's heightened sympathetic reactivity, whereas lower parasympathetic activity may leave lonelier individuals vulnerable to the effects of repeated sympathetic activation, which includes heightened inflammation. Certainly, autonomic imbalance seems to escalate long-term health risks [48]. Parasympathetic function also modulates the immune system directly via the cholinergic pathway [49], providing another route by which the vagus nerve may counteract loneliness-related sympathetic hyper-activation and its potential immune consequences.

Moreover, loneliness and parasympathetic function share overlapping neural substrates, offering another path by which higher parasympathetic activity may directly alter lonelier people's threat processing biases, effectively preempting the peripheral stress response that allows herpesviruses to reactivate [11]. In particular, parasympathetic function is associated with activity in the dorsal and ventral medial regions of the prefrontal cortex—together responsible for executive function, threat detection, and coordinating responses to threat [21]. Similarly, a high-performance electrical neuroimaging study showed that lonely people had stronger implicit attentional biases to social versus nonsocial threatening images, and this activity emerged in the dorsal region of the prefrontal cortex, like that associated with parasympathetic function [47]. People with higher HRV may also more effectively anticipate and avoid the negative impact of social stressors, providing another way to neutralize risks associated with loneliness [21].

Furthermore, higher parasympathetic activity does not appear to prevent feelings of loneliness altogether, nor does loneliness seem to reduce parasympathetic function: in our study ($r = -0.06$, $p > .250$) and other work with healthy adults, the two were not consistently related [19, 20]. Also, poorer sleep has been associated with lower HRV and identified as a key moderator of health outcomes [36]. Although sleep problems were significantly

correlated with lower HRV in our sample, and moderated the link between greater loneliness and shorter telomeres, it did not explain or supersede the moderating role of HRV between loneliness and telomere length.

Related Immune Pathways: Latent Herpesvirus Reactivation and Telomere Length

Approximately half of those with telomere data had prior exposure to CMV and thus had measurable antibodies, consistent with its prevalence in epidemiological studies [11]. This reduced subsample and the cross-sectional design prevented a meaningful evaluation of moderated mediation. EBV is ubiquitous among adults [11]; likewise, 94% of our participants with telomere data tested positive for EBV, and all but two of our CMV-seropositive participants were also EBV-seropositive. This underscores the widespread relevance of our findings, and the possible importance of CMV-EBV co-occurrence for health risks. Indeed, multiple pathogen load may explain why loneliness was associated with CMV but not EBV titers in our sample—a pattern consistent with two independent studies of breast cancer survivors [16, 41]. People with greater EBV and CMV reactivation had shorter telomeres; this dose–response relationship extends prior work showing group differences in telomere length as a function of CMV seropositivity [12]. Particularly for CMV, the biological path is clear and well-established: herpesvirus reactivation speeds T-cell replication, thereby shortening telomeres [11, 13].

Inflammation may play a key role in a cascade leading from loneliness to herpesvirus reactivation, to telomere shortening. Lonelier people show larger inflammatory responses to psychosocial stress [18]. Latent CMV and EBV infections promote inflammation [50]. Thereafter, herpesvirus replication and elevated inflammation may operate in tandem to escalate the health risks of loneliness. Indeed, heightened inflammation is strongly associated with telomere shortening [51] as well as greater risks for age-related diseases [52]. Furthermore, among a large sample of older women, CMV-seropositive women with elevated IL-6 were 20 times more likely to be frail compared with CMV-seropositive women with lower IL-6 or CMV-seronegative women [53]. Thus, inflammation may reinforce the risks of loneliness and herpesvirus replication to accelerate cellular aging, and the anti-inflammatory effects of vagal activity may play a protective role in this path as well [49]. Future studies must test these mechanisms prospectively.

Limitations, Behavioral Medicine Implications, and Conclusions

One limitation of the current study is the relatively smaller number of people who were CMV-seropositive

and of nonwhite races. Although we would not predict that telomere shortening induces loneliness and lowers HRV, the cross-sectional design prevents causal, directional conclusions. Multi-timescale longitudinal work will be best suited to assess exactly how the dynamics of loneliness, parasympathetic function, latent herpesvirus reactivation, and telomere shortening unfold over time. Future work should also examine these associations in more heterogeneous samples with a representative range of chronic health conditions.

Numerous intervention trials have been conducted investigating the efficacy of various treatment strategies for reducing feelings of loneliness. A meta-analysis attempting to identify empirically supported treatments for loneliness using evidence from randomized controlled trials concluded that increasing social support is not enough to combat loneliness on its own [54]. Instead, interventions such as cognitive-behavioral therapy, which seek to identify and reframe maladaptive social cognitions and beliefs (e.g., “No one loves me”) appear to be the most efficacious treatments for loneliness, based on empirical evidence [54]. For example, Navy recruits who participated in a 9-week cognitive-behavioral intervention during basic training reported lower levels of loneliness at the end of training compared with those in an active control group [55]. Additionally, a more recent study demonstrated that a mindfulness-based stress reduction intervention successfully reduced loneliness as well as proinflammatory gene expression [56], demonstrating the potential health benefits of interventions targeting loneliness.

Encouraging evidence from clinical populations suggests that HRV is also amenable to improvement via biofeedback or exercise training [57, 58]; in turn, increases in parasympathetic activity confer benefits for executive function [57]. Future research should examine whether increased parasympathetic function prospectively reverses immune aging associated with loneliness and low HRV.

Loneliness has well-established risks for early mortality. The current study provides the first evidence of key associations that link loneliness and herpesvirus reactivation to cellular aging via shorter telomeres, an important predictor of aging-related disease risk and death. The central role of parasympathetic function in these associations underscores the potential importance of the vagus nerve in a cascade that may lead from loneliness to accelerated cellular aging.

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Compliance with Ethical Standards

Authors’ Statement of Conflict of Interest and Adherence to Ethical Standards The authors have no conflicts of interest to disclose.

Ethical Approval The material in the manuscript has been acquired according to modern ethical standards and has been approved by the appropriate Institutional Review Board.

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