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Spousal bereavement after dementia caregiving: A turning point for immune health

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ABSTRACT

Losing a spouse can increase the risk for premature mortality, and declines in immune health are thought to play a role. Most of the supporting data have come from cross-sectional studies comparing already-bereaved individuals to matched controls, which provides valuable information about health disparities between groups but does not reveal health changes over time. Moreover, the health consequences of bereavement may be unique for dementia family caregivers, a large and growing segment of the population. The current study sought to evaluate the course of health around 52 dementia spousal caregivers' bereavement by capturing lymphocyte proliferation to Con A and PHA and self-rated health before and after spousal loss. To investigate the moderating role of the social environment, we examined associations between social ties and health trajectories before and after spousal loss. Using piecewise linear mixed models to allow for turning points in caregivers' trajectories, we found that, for the average caregiver, lymphocyte proliferation to both mitogens weakened as bereavement neared and continued to decline after the loss, but at a slower pace. In tandem, perceived health degraded as bereavement approached but rebounded thereafter. Further, we found that socially isolated caregivers showed marked declines in immune responses to Con A and PHA over time both before and after bereavement, whereas their socially connected counterparts had shallower declines to PHA and maintained a level immune response to Con A. In addition, socially isolated caregivers reported poorer health before and after bereavement compared to their counterparts, whose self-rated health declined as the loss neared but later recovered to exceed prior levels. These findings shed new light on the dynamics of immune function in response to spousal bereavement after dementia caregiving: longitudinal data reveal a pattern of health recovery following caregivers' loss, particularly among those with more robust social networks prior to bereavement.

1. Introduction

1.1. Bereavement, health, and immune function

Losing a spouse can increase risk for an earlier death. Multiple meta-analyses have shown that, compared to married counterparts, recently bereaved individuals are likely to die earlier from a range of causes—all-cause, cardiovascular, and infectious (Brenn and Ytterstad, 2016; King et al., 2017). Immune data mirror these risks in cross-sectional studies, as bereaved individuals tend to have poorer lymphocyte proliferation in response to mitogens, lower natural killer cell activity, and higher inflammation compared to controls (e.g., Buckley et al., 2012; Fagundes et al., 2018; Gerra et al., 2003). However, many prior studies have been unable to characterize the *response* to bereavement because they lacked immune function data prior to spousal loss.

In the few longitudinal studies that assessed spouses' pre-loss immune function, findings have been mixed. Some reported no changes following bereavement (Irwin et al., 1987; Pettingale et al., 1994), and others found that lymphocyte proliferative responses to mitogens dropped in the months following the loss (Kemeny et al., 1995;

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Schleifer et al., 1983). In one of the two studies documenting significant changes, effects were apparent only among men with HIV but not healthy men, and both studies' sample sizes were small (n = 8 and 21). Thus, whether immune function reliably changes in response to spousal death warrants further examination.

1.2. Bereavement after caregiving

The literature investigating immune and mortality risks of bereavement also may be enriched by a caregiving perspective. In terms of societal impact, the unique health implications of dementia family caregivers' bereavement are especially important to consider. Over 16 million Americans currently serve as unpaid dementia caregivers (Alzheimer's Association, 2019). With an aging population and rising prevalence of dementias, the number of spousal caregivers who experience bereavement in this role will continue to increase. Providing care to a spouse with such a progressive, incurable condition can be very challenging, as dementia caregivers must face the gradual deterioration of their loved one long before the physical loss. If dementia caregivers are vulnerable to the health risks of spousal bereavement, then their health may pay an especially high toll as spousal loss compounds the already elevated risks that some caregivers face (for exceptions, see Allen et al., 2017; Roth et al., 2019), due in part to stress and strain in the role (e.g., Kiecolt-Glaser et al., 2003; Potier et al., 2018).

Alternatively, bereavement itself may not pose the same health risks for caregivers that it does for non-caregivers. One study found that bereaved men whose partners had dementia were *less* likely to die earlier compared to those whose late partners had no documented dementia, suggesting that the mortality risks typically associated with spousal loss may not extend to bereaved dementia caregivers (Shah et al., 2016). In a longitudinal study of dementia spousal caregivers, cardiovascular risk declined in the months following bereavement (Mausbach et al., 2007). Likewise, dementia spousal caregivers showed declines in physical symptoms (Grant et al., 2002) and depression (Mausbach et al., 2007; Schulz et al., 2003) as well as improvements in immune responses to influenza vaccine (Glaser et al., 2000) after bereavement, unlike the marked increases in depression and mortality risks among people whose spouses died unexpectedly (Burton et al., 2006; Shah et al., 2013). If immune changes parallel mortality, cardiovascular, and mental health patterns (Schulz et al., 1997), dementia spousal caregivers' immune function may remain stable or recover rather than plummet in response to the loss.

1.3. Bereavement and social ties

There are less data on changes in dementia spousal caregivers' social networks around bereavement. According to social support deterioration theory, network members rally around those confronted with a major stressor, but support wanes quickly (Kaniasty and Norris, 1993). Consistent with the theory, a five-year longitudinal study showed that dementia caregivers' support networks steadily decreased (Clay et al., 2008). Among spousal caregivers of terminally ill patients and controls, non-caregivers' social contact increased following bereavement, whereas strained caregivers' social contact remained infrequent post-bereavement (Burton et al., 2006). Robinson-Whelen et al. (2001) found that former dementia caregivers were still lonelier than controls years after bereavement.

A robust social network may buffer against potential bereavement-related immune declines. People with larger social networks tend to have better immune function and, in turn, lower mortality than their more socially isolated counterparts (e.g., Heffner et al., 2011). In a 63-study meta-analysis (Holt-Lunstad et al., 2010), larger social networks predicted lower mortality more strongly than the effects of not smoking or influenza vaccination. Social ties also promote psychological well-being during bereavement. In one study, socially connected widows were less likely to become distressed than their isolated counterparts (Vachon et al., 1982). Social isolation after years of serving as a dementia caregiver may reinforce a trajectory toward poorer immune function. Conversely, bereavement may present an opportunity for isolated caregivers to rebuild their social networks and guard against health declines.

The current study aimed to characterize dementia spousal caregivers' immune health in the years leading up to and following bereavement. Lymphocyte proliferation to two mitogens, concanavalin (Con) A and phytohemagglutinin (PHA), indexed the robustness of the immune response, with higher values being more favorable. Self-rated health, a secondary outcome, provided a clinically relevant counterpart (Grant et al., 2002). Prior work offered two competing hypotheses. If the acute health risks of bereavement exist regardless of context, caregivers would show a sudden drop in immune function and self-rated health post-bereavement. Alternatively, if the health risks of spousal bereavement depend on the context of the death, as studies of bereaved caregivers suggest (e.g., Mausbach et al., 2007), dementia spousal caregivers may show little change or recovery in immune function and self-rated health post-bereavement. We also examined the course of caregivers' social ties, without directional predictions given the mixed literature. Finally, we hypothesized that caregivers with larger social networks pre-bereavement would have more favorable changes in lymphocyte proliferation and self-rated health compared to their more isolated counterparts. In contrast, caregivers who were more socially isolated pre-bereavement were predicted to show more severe drops and poorer recovery in immune function and self-rated health post-bereavement.

2. Method

2.1. Participants and procedure

Bereaved spousal dementia caregivers were part of a larger longitudinal study of caregiving, stress, and health in older adults (Glaser et al., 2000; Kiecolt-Glaser et al., 1991, 2003). Caregivers were recruited from local dementia evaluation centers in area hospitals, neurologists' referrals, local Alzheimer's Disease Association support groups, monthly newsletters, and respite care programs. Caregivers had to provide five or more hours of care per week to participate. We excluded caregivers with immunologically related health problems such as cancer or recent surgeries and those taking any medications with broad immunological consequences. The Ohio State University Biomedical Research Review Committee approved the project; all participants gave written informed consent before participation.

Caregivers were included in the current sample if they experienced bereavement during the study and had data before and after the care recipient's death. Caregivers were required to provide data for at least three visits, with at least one visit before and one after the care recipient's death. Of 131 caregivers, 53 experienced bereavement during the study, and all but one met our analytic criteria. Among these 52 caregivers, most (85%) provided four or more years of data in years 1992 − 1998. Their data spanned 2.5 years pre-bereavement to 4.5 years post-bereavement (Supplemental Fig. S1). The majority were women (77%) and White (87%); they ranged in age from 52 to 88 years old (M = 71.3, SD = 8.1) in the year of bereavement. Over half of individuals with dementia had been placed in a care facility (63%). By the time of bereavement, spouses had provided care for 7.4 years on average (SD = 3.1) for a mean of 8.7 h per day (SD = 6.0). Refer to Table 1 for additional participant characteristics. Caregivers completed questionnaires and interviews and provided blood samples once yearly. During annual visits, current caregivers were asked whether and when the care recipient had died in the prior year; appointments were not timed to the bereavement date. A subset of caregivers who participated in an ancillary flu vaccine study also gave three additional blood samples one, three, and six months after each interview.

Table 1
Description of bereaved spousal caregivers.

Variable	MEAN (SD) or N (%)	Range
Caregiver age at bereavement	71 (8)	52–88
Female	40 (77%)	
White	45 (87%)	
Care recipient in care facility	33 (63%)	
Education		
Some high school	3 (5.8%)	
High school diploma	17 (32.7%)	
Some college	17 (32.7%)	
College degree	8 (15.4%)	
Graduate/Professional degree	6 (11.5%)	
Length of caregiving (years)	7.4 (3.1)	1.6–12.4
Daily care (hours)	8.7 (6.0)	0.1–21.1
Body mass index	25.8 (4.2)	18.0–37.9
Comorbidities	3.2 (1.8)	0.5–8.6
Pre-bereavement social network size	20.2 (8.1)	6.0–41.5
Post-bereavement social network size	21.8 (7.0)	8.5–35.8
Pre-bereavement self-rated health	1.7 (0.6)	0 − 3
Post-bereavement self-rated health	2.0 (0.5)	1 − 3
Pre-bereavement lymphocyte proliferation to Con A	0.18 (0.09)	0.03–0.41
Post-bereavement lymphocyte proliferation to Con A	0.12 (0.07)	− 0.03–0.34
Pre-bereavement lymphocyte proliferation to PHA	0.29 (0.11)	0.04–0.55
Post-bereavement lymphocyte proliferation to PHA	0.22 (0.09)	− 0.003–0.49

Note: Body mass index and comorbidities reflect the person-level averages. Pre-bereavement and post-bereavement means are reported for social network size, self-rated health, and lymphocyte proliferation to Con A and PHA given the focus on change in these variables.

2.2. Self-report measures

2.2.1. Social ties

A well-established measure, the Social Network Index (SNI) (Cohen et al., 1997) captured the size of a caregiver's social network. For each of 12 possible social roles (e.g., being a parent, child, spouse, student, church member), caregivers listed the number of people with whom they had regular contact (at least once every two weeks). The sum of network members across all roles indicated a caregiver's network size.

2.2.2. Self-rated health

Each year caregivers were asked to rate their overall health as poor, fair, good, or excellent. This single item strongly predicts physician-diagnosed illness and mortality (Bamia et al., 2017; Cohen et al., 2015), and thus serves as a valuable clinical indicator of physical health. Self-rated health was treated as a continuous variable to maximize statistical power and to capture its conceptualization as an illness-wellness continuum (Christian et al., 2011; Wilson et al., 2014).

2.2.3. Comorbidities

Caregivers completed the Older Adults Resources Survey, a reliable and valid inventory of 26 possible chronic conditions (Fillenbaum and Smyer, 1981). Summed physical health conditions were treated as a continuous covariate to account for the contributions of preexisting medical illness to immune function and self-rated health.

2.2.4. Care recipients' dementia severity

Caregivers completed the well-established Blessed Dementia Scale (Erkinjuntti et al., 1988). Dementia severity was treated as an ancillary covariate in models with immune function or self-rated health as the outcome, to explore whether the associations between pre-loss social ties and health could be explained by care recipients' disease severity.

2.2.5. Depressive symptoms

In ancillary analyses, caregivers' pre-loss depressive symptoms were included as a covariate to evaluate whether associations between pre-loss social ties and health could be explained by concurrent depression, a well-established predictor of immune function common among caregivers (Kiecolt-Glaser et al., 1991; Kiecolt-Glaser and Glaser, 2002). The Beck Depression Inventory provided a reliable measure of depressive symptoms ($\alpha s = 0.84 - 0.87$) (Beck et al., 1988).

2.3. Functional immune assays

All blood samples were drawn between 8:00 and 11:00 a.m. to control for diurnal variation. To provide a measure of immunocompetence, lymphocyte proliferation was assessed in response to two mitogens, concanavalin A (Con A) and phytohemagglutinin (PHA). Peripheral blood mononuclear cells (PBMCs) were treated with mitogen concentrations of 2.5, 5.0, and 10.0 μg/mL and incubated in 5% CO_2 at 37 °C for approximately 68 h, as previously described (Kiecolt-Glaser et al., 2001). Samples were run in triplicate using Cell Titer 96 aqueous nonradioactive cell proliferation assays (Promega; Madison, WI). Lymphocyte proliferation to each mitogen was calculated by subtracting media-only values from those for each of the concentrations, with lower values indexing poorer proliferative responses. For those who gave additional blood samples one, three, and six months after the interview, yearly averages were created to coincide with the annual interview data and reduce measurement error.

2.4. Statistical approach

Hypotheses were assessed using piecewise linear mixed models in SAS 9.4 (Cary, NC; see Huang, 2015). Corresponding equations are presented in Supplemental Material (p. S1). Random subject-specific intercepts were included to account for the within-subject correlation among repeated measures. The Kenward-Roger degrees of freedom adjustment was used to control type I error (Kenward and Roger, 1997). Continuous between-person variables were grand-mean-centered, and within-person variables were person-mean-centered. Residual plots revealed that all models met assumptions of normality and homoscedasticity.

In a first step, trajectories of social ties, immune function (lymphocyte proliferation to Con A and PHA), and self-rated health were examined in univariate models. Years since care recipient's death—i.e., the bereavement date subtracted from the study visit date—was treated as a continuous variable. Intercept and slope spline terms allowed discontinuity in levels and trajectories at the point of bereavement. For these terms (time since death, intercept spline, and time slope spline), Cohen's f^2 was calculated to express the size of statistically significant effects (small: $f^2 \geq 0.02$, medium: $f^2 \geq 0.15$, large: $f^2 \geq 0.35$) (Cohen, 1988). Post-bereavement slopes and intercepts were constructed by adding the spline term to the slope or intercept effect, respectively, with the ESTIMATE command; thus, they are presented in the Results but do not appear in the tables (see also equations in Supplemental Material, p. S1).

Second, the role of social ties in the course of immune function and self-rated health was assessed. Because the first step revealed significant changes in social ties before and after bereavement, we began by examining the mean of pre-bereavement social ties as a moderator of the time slope, intercept spline, and slope spline terms. Significant interaction effects were probed at one standard deviation above and below the mean. Covariates included age, sex, body mass index (BMI), and medical comorbidities. Consistent with past work (Kiecolt-Glaser et al., 2001), the models of responses to Con A and PHA additionally accounted for the within-subject effects of mitogen concentration, as well as the moderating effects of concentration on the time slope, intercept spline, and slope spline terms. We also explored whether the effects of social ties differed by concentration, and whether social ties effects held

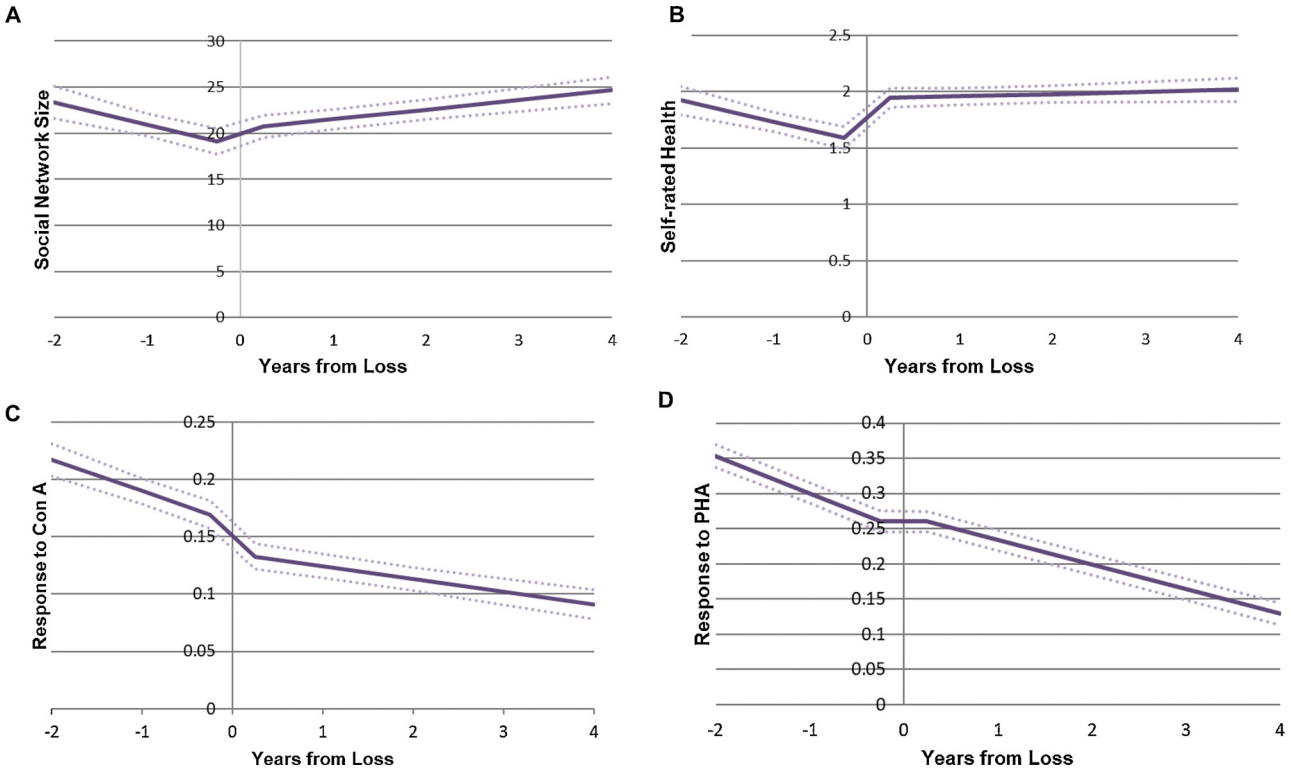

Fig. 1. Model-based estimates for changes in social network size, self-rated health, and blastogenic responses to Con A and PHA before and after dementia spousal caregivers' bereavement. Dotted lines represent standard error bands. Con A = Concanavalin A; PHA = phytohemagglutinin.

after including care recipients' dementia severity and placement in a care facility, as well as caregivers' pre-loss depressive symptoms, education, length of caregiving, and average hours per day spent caregiving (See Supplemental Table S1).

Next, we examined post-bereavement social ties as a predictor of post-bereavement changes in immune function and self-rated health. If post-bereavement social ties emerged as a significant predictor, we examined whether the effect held controlling for pre-bereavement social ties.

Follow-up analyses explored patterns of depressive symptoms over the course of bereavement as well as whether patterns of social ties, immune function, and self-rated health differed between caregivers whose spouses were placed in a care facility and those who remained at home.

3. Results

3.1. Does bereavement mark a turning point in dementia spousal caregivers' social networks, immune function, and self-rated health?

As depicted in Fig. 1A, for the average caregiver, social networks shrank as the loss approached (Table 2 , p = 0.031, Cohen's f^2 = 0.01), and steadily regrew thereafter ($p_{slope\ spline}$ = .003, Cohen's f^2 = 0.05; $Estimate_{post\text{-}loss\ slope}$ = 1.05, SE = 0.41, p = 0.012). Shown in Fig. 1C-D, lymphocyte proliferation to both mitogens declined as bereavement neared (Table 2, $p_{Con\ A}$ = 0.001, Cohen's f^2 = 0.04; $p_{PHA} \leq 0.0001$, Cohen's f^2 = 0.50). Consistent with the hypothesis that bereavement is stressful, caregivers' lymphocyte proliferation to Con A dropped suddenly after bereavement (Table 2, $p_{intercept\ spline}$ = 0.014). By contrast, there was sudden improvement in lymphocyte proliferation to PHA, but this uptick was small enough to be camouflaged by subsequent declines (Table 2, $p_{intercept\ spline}$ = 0.009). Lymphocyte proliferation to both mitogens continued to decline after the loss, but at a slower pace—by 66% in lymphocyte proliferation to Con A and 40% to PHA ($Estimate_{Con\ A\ post\text{-}loss\ slope}$ = −0.01, SE = 0.003, p = 0.0003; $Estimate_{PHA\ post\text{-}loss\ slope}$ = −0.03, SE = 0.002, p < 0.0001). Depicted in Fig. 1B, self-rated health also declined as the loss approached (Table 2, Estimate = −0.19, SE = 0.08, p = 0.022, Cohen's f^2 = 0.01) but rebounded afterward, increasing by 33% ($Estimate_{intercept\ spline}$ = 0.39, SE = 0.11, p = 0.001, Cohen's f^2 = 0.07; $Estimate_{post\text{-}loss\ slope}$ = 0.02, p > 0.250).

Table 2
Piecewise models of social network size, self-rated health, and immune function before and after spousal dementia caregivers' bereavement.

Effect	Social Network Size				Self-rated Health				Response to Con A				Response to PHA			
	b	SE	DF	p	B	SE	DF	p	b	SE	DF	p	b	SE	DF	p
Intercept	18.49*	1.57	185	< .0001	1.55*	0.11	190	< .0001	0.16*	0.02	141	< .0001	0.25*	0.02	70.6	< .0001
Intercept spline	1.98	1.51	170	0.191	0.39*	0.11	167	0.001	−0.03*	0.01	557	0.014	0.02*	0.01	551	0.009
Time since loss (Pre-loss slope)	−2.42*	1.11	178	0.031	−0.19*	0.08	176	0.022	−0.03*	0.01	572	0.001	−0.05*	0.01	556	< .0001
Slope spline	3.48*	1.16	174	0.003	0.21*	0.08	172	0.016	0.02*	0.01	566	0.050	0.02*	0.01	554	0.004

Note: Spline terms reflect changes in the intercept and time slope at the point of spousal loss. Con A = Concanavalin A; PHA = phytohemagglutinin. *, p < 0.05. $N_{caregivers}$ = 52.

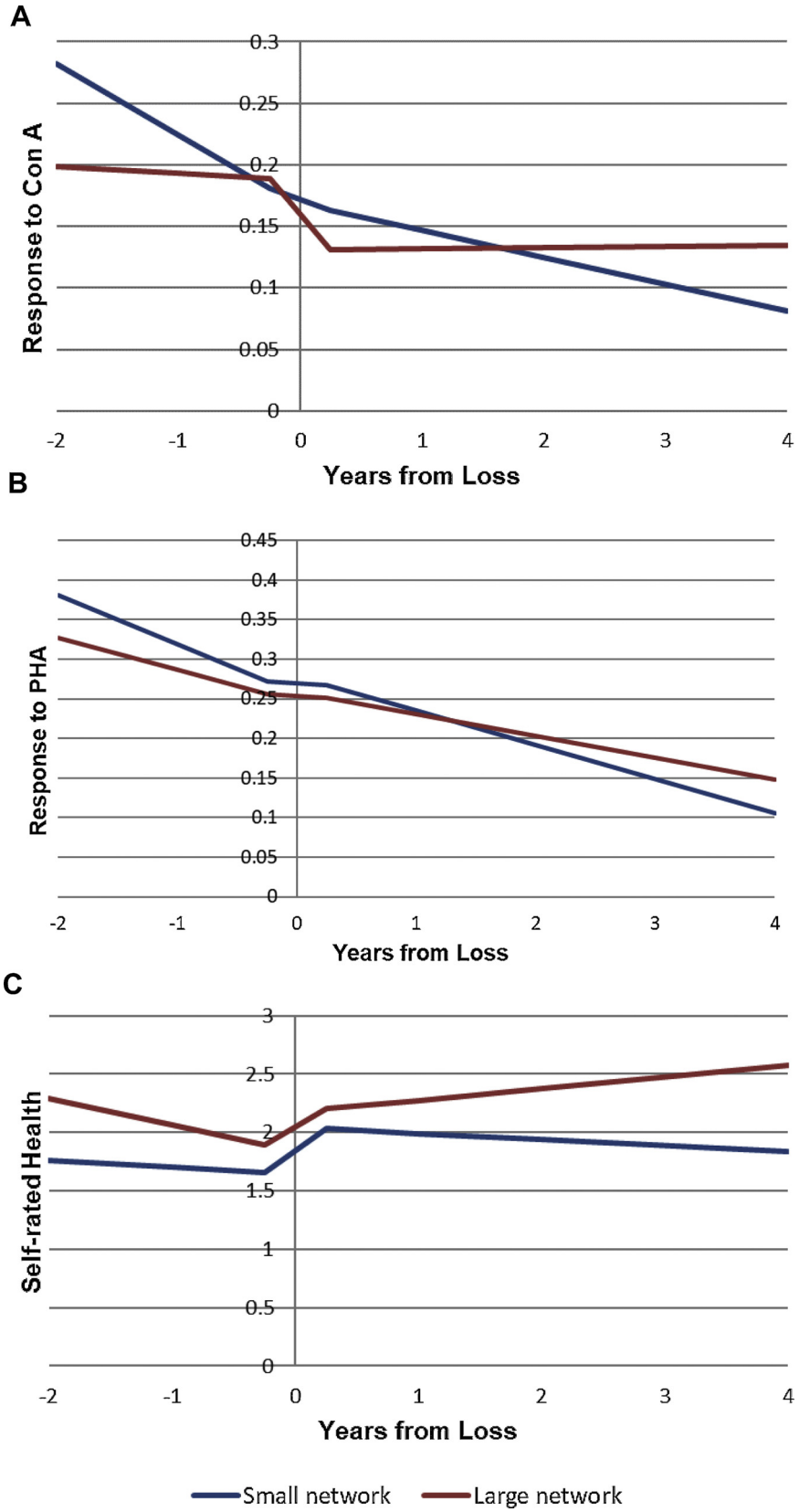

Fig. 2. Model-based estimates of immune function and self-rated health trajectories by social network size. Small network size is depicted in blue (12 social ties, i.e., 1 SD below the mean), and large network size is shown in red (28 social ties, i.e., 1 SD above the mean). Con A = Concanavalin A; PHA = phytohemagglutinin. See Supplemental Figure S2 for plots with standard error bands (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Table 3
Pre-loss social network size predicting trajectories of immune function before and after bereavement.

Effect	Response to Con A				Response to PHA			
	b	SE	DF	p	b	SE	DF	p
Intercept	0.11*	0.038	106	0.005	0.27*	0.048	106	< .0001
Age	−0.0002	0.0013	46	0.893	−0.0034	0.0019	46	0.077
BMI	0.0004	0.0033	538	0.904	0.0053	0.0027	538	0.053
Comorbidities	0.0010	0.0021	534	0.629	−0.0024	0.0017	534	0.168
Female	−0.017	0.025	46.5	0.505	0.0044	0.036	46.5	0.902
Intercept spline	0.062*	0.028	536	0.029	0.022	0.014	536	0.365
Time since loss (pre-loss slope)	−0.096*	0.020	540	< .0001	−0.073*	0.016	540	< .0001
Slope spline	0.051*	0.021	537	0.015	0.016	0.018	537	0.368
Concentration 2.5 vs. 10.0	0.065*	0.019	530	0.001	−0.017	0.016	530	0.284
Concentration 5.0 vs. 10.0	0.060*	0.019	530	0.001	−0.013	0.016	530	0.420
Intercept spline * Conc. 2.5 v. 10.0	−0.029	0.023	530	0.202	0.011	0.019	530	0.578
Intercept spline * Conc. 5.0 v. 10.0	−0.017	0.023	530	0.457	0.012	0.019	530	0.542
Slope * Conc. 2.5 v. 10.0	−0.0035	0.015	530	0.821	−0.011	0.013	530	0.411
Slope * Conc. 5.0 v. 10.0	0.0009	0.015	530	0.952	−0.0061	0.013	530	0.636
Slope spline * Conc. 2.5 v. 10.0	0.014	0.017	530	0.397	0.016	0.014	530	0.256
Slope spline * Conc. 5.0 v. 10.0	0.0072	0.017	530	0.664	0.0076	0.014	530	0.584
Social network size	0.0013	0.0015	98.1	0.372	−0.0007	0.0019	98.1	0.728
Intercept spline * Social network size	−0.0037*	0.0011	536	0.001	−0.0006	0.0009	536	0.532
Slope * Social network size	0.0033*	0.0007	541	< .0001	0.0014*	0.0006	541	0.025
Slope spline * Social network size	−0.0018*	0.0008	537	0.019	−0.0004	0.0007	537	0.558

Note: Spline terms reflect changes in the intercept and time slope at the point of spousal loss. BMI = body mass index; Con A = Concanavalin A; PHA = phytohemagglutinin; Conc = mitogen concentration. *, $p < 0.05$. $N_{caregivers} = 52$.

Table 4
Pre-loss social network size predicting trajectories of self-rated health before and after bereavement.

Effect	b	SE	DF	p
Intercept	1.50*	0.31	154	< .0001
Age	0.002	0.01	44.6	0.830
BMI	0.04	0.04	163	0.294
Comorbidities	−0.003	0.02	157	0.907
Female	−0.22	0.17	45.1	0.203
Intercept spline	0.45	0.29	159	0.126
Time since loss (pre-loss slope)	0.07	0.20	166	0.748
Slope spline	−0.23	0.22	163	0.285
Social network size	0.01	0.01	168	0.367
Intercept spline * Social network size	−0.004	0.01	160	0.778
Slope * Social network size	−0.01	0.01	165	0.222
Slope spline * Social network size	0.02*	0.01	162	0.033

Note: Spline terms reflect changes in the intercept and time slope at the point of spousal loss. BMI = body mass index. *, $p < 0.05$. $N_{caregivers} = 52$.

3.2. Do pre-loss social ties predict trajectories of immune function and self-rated health before and after dementia spousal caregivers' bereavement?

3.2.1. Lymphocyte proliferation to Con A

In terms of lymphocyte proliferation to Con A, the course of immune function varied by the size of caregivers' social networks prior to the loss (Fig. 2A and Table 3, $p_{intercept\ spline} = 0.001$, Cohen's $f^2 = 0.02$; $p_{slope\ spline} = 0.019$, Cohen's $f^2 = 0.01$). Caregivers with larger networks pre-bereavement had steady levels of lymphocyte proliferation to Con A leading up to the loss ($p_{slope} = 0.513$), which then dropped at the point of bereavement ($Estimate_{pre\text{-}loss\ intercept} = 0.19$, SE = 0.03, $p < 0.0001$; $Estimate_{post\text{-}loss\ intercept} = 0.13$, SE = 0.03, $p < 0.0001$) and leveled off thereafter ($p_{slope} = 0.800$). In contrast, among caregivers with smaller networks pre-bereavement, lymphocyte proliferation steadily declined both before (Estimate = −0.10, SE = 0.02, $p < 0.0001$) and after the loss (Estimate = −0.04, SE = 0.01, $p < 0.0001$) with little change at the point of bereavement itself ($Estimate_{pre\text{-}loss\ intercept} = 0.17$, SE = 0.02, $p < 0.0001$; $Estimate_{post\text{-}loss\ intercept} = 0.17$, SE = 0.02, $p < 0.0001$). Effects of pre-loss social ties on lymphocyte proliferation to Con A did not differ across the three mitogen concentrations (ps > 0.05) and were robust to the inclusion of care recipients' dementia severity, caregivers' pre-loss depressive symptoms, caregiver education, length of caregiving, average hours per day spent caregiving, and placement in a care facility (Supplemental Table S1).

3.2.2. Lymphocyte proliferation to PHA

As shown in Fig. 2B, caregivers' pre-loss social ties was linked to changes in lymphocyte proliferation to PHA (Table 3, Estimate = 0.001, SE = 0.001, p = 0.025, Cohen's $f^2 = 0.01$), but did not influence their post-loss turning points (ps > 0.05). Namely, those with larger networks had shallower declines in immune responses to PHA both before (Estimate = −0.04, SE = 0.01, $p < 0.0001$) and after the loss (Estimate = −0.03, SE = 0.004, $p < 0.0001$), compared to the steeper declines of those with smaller networks ($Estimate_{pre\text{-}loss\ slope} = -0.06$, SE = 0.01, $p < 0.0001$; $Estimate_{post\text{-}loss\ slope} = -0.04$, SE = 0.003, $p < 0.0001$). Regardless of network size, post-bereavement immune declines were shallower than pre-bereavement declines. Effects of pre-loss social ties on lymphocyte proliferation to PHA did not differ across the three mitogen concentrations (ps > 0.05) and were robust to the inclusion of ancillary covariates (Supplemental Table S1).

3.2.3. Self-rated health

Depicted in Fig. 2C, turning points in caregivers' self-rated health differed as a function of their pre-bereavement social ties (Table 4, p = 0.033, Cohen's $f^2 = 0.02$). Among caregivers with larger networks, there were more marked shifts in self-rated health, from significant declines as bereavement neared (Estimate = −0.23, SE = 0.10, p = 0.022), to linear improvements thereafter (Estimate = 0.10, SE = 0.05, p = 0.048). In contrast, among caregivers with smaller networks, trajectories of self-rated health were not significantly different from zero before or after bereavement (ps > 0.05). Regardless of network size, self-rated health improved after the loss (Fig. 2). Effects of pre-loss social ties on self-rated health were robust to the inclusion of ancillary covariates (Supplemental Table S1).

3.3. Do post-loss social ties predict trajectories of immune function and self-rated health following bereavement?

Having found that social network trajectories changed from pre- to post-bereavement, we examined whether post-bereavement social ties

uniquely predicted post-bereavement changes in immune function and self-rated health. Former caregivers with larger social networks after bereavement had smaller post-loss declines in lymphocyte proliferation to Con A compared to caregivers with smaller post-loss networks (Estimate = 0.002, SE = 0.0004, $p < 0.0001$). However, this effect was no longer significant ($p = 0.158$) when pre-loss social ties were taken into account. Similarly, former caregivers with larger social networks after bereavement had smaller post-bereavement declines in immune responses to PHA (Estimate = 0.002, SE = 0.0004, $p < 0.0001$), but this effect was no longer significant ($p = 0.627$) when pre-loss social ties were included in the model. The effect of post-bereavement social ties on post-bereavement changes in self-rated health was not significant ($p = 0.510$).

3.4. Ancillary analyses

Follow-up analyses explored changes in depressive symptoms across the course of bereavement and revealed a non-significant drop in depressive symptoms after bereavement ($Estimate_{Intercept\ spline} = -0.55$, SE = 0.32, $p = 0.085$), consistent with past work. Depressive symptoms did not decline significantly as bereavement approached ($p = 0.438$) and remained stable in the years following bereavement ($p = 0.619$). Bereavement-related changes in social networks did not differ between caregivers who had placed their spouses in a care facility and those who had not (ps > 0.268). Facility placement also did not predict bereavement-related changes in self-rated health (ps > 0.194) or lymphocyte proliferation to Con A (ps > 0.183) or PHA (ps > 0.104).

4. Discussion

According to longitudinal data from dementia spousal caregivers before and after spousal loss, bereavement marked a significant turning point in caregivers' social networks, immune function, and self-rated health. In parallel, social networks shrank and health declined as the loss approached; thereafter, networks regrew, self-rated health rebounded, and immune function declined but at a slower pace. Caregivers with larger networks prior to bereavement enjoyed a more favorable course of health compared to those who were more socially isolated before the loss. These data suggest that bereavement serves as a critical juncture after which caregivers may experience some degree of relief and recovery. Indeed, dementia family caregivers, who make up a large and growing segment of the population, may not face the acute health risks of physical bereavement that are thought to afflict non-caregiving spouses.

4.1. Bereavement's health implications: the critical role of context

Losing a spouse has long been considered one of the most potent stressors in the human experience. Spousal bereavement famously topped the Holmes-Rahe Life Stress Inventory as the strongest predictor of major illness (Holmes and Rahe, 1967), outranking other stressful life events such as mortgage foreclosure, job loss, and imprisonment. Likewise, many landmark studies linking psychosocial stress to immune function chose to focus on bereavement as a universal exemplar of stress and suffering (e.g., Irwin et al., 1987; Kemeny et al., 1995).

To our knowledge, the current study is among the first to examine longitudinal changes in dementia spousal caregivers' immune function before and after spousal loss. If bereavement's health risks exist irrespective of the caregiving role, the data would have shown significant drops or downturns in immune function and self-rated health following the loss, compared to pre-loss levels. Indeed, our models allowed for changes in the trajectories (i.e., slopes) and for sudden drops or upticks in levels (i.e., intercepts) at the time of bereavement, to capture acute health changes following the loss (Brenn and Ytterstad, 2016).

With this approach, we did not see overwhelming evidence for increases in dementia caregivers' health risks following bereavement, in alignment with other physical and mental health data from bereaved dementia caregivers (Glaser et al., 2000; Mausbach et al., 2007; Schulz et al., 1997). On the one hand, consistent with the hypothesis that bereavement is universally stressful, caregivers' lymphocyte proliferation to Con A dropped suddenly after bereavement. On the other hand, there were sudden *improvements* in lymphocyte proliferation to PHA and in self-rated health. Neither of the opposing immune changes to Con A and PHA were large; the uptick in lymphocyte proliferation to PHA was small enough to be obscured by subsequent declines. However, self-rated health improved by 33%, restoring caregivers' health to what they described as "good," on average (a score of 2 on a scale ranging from 0, "poor," to 3, "excellent"). Mirroring this favorable trend, immune declines slowed after bereavement—by 66% in lymphocyte proliferation to Con A and 40% to PHA. Immunosenescence may explain the monotonic downward trend in both markers of immune function (Bennett et al., 2013; Heyman and Gianturco, 1973; Kiecolt-Glaser et al., 2003).

Next, we found that pre-loss social ties further distinguished caregivers' health trajectories, with more socially isolated caregivers showing less favorable patterns. It is well established that stress accelerates immune aging and that social resources may slow such decline (e.g., Heffner et al., 2011; Kiecolt-Glaser et al., 2003). Indeed, without the wealth of resources conferred by a large social network, isolated caregivers' immune function showed steeper declines both before and after the loss compared to those of their counterparts. Based on prior studies of health after spousal bereavement, socially isolated caregivers would be expected to show larger drops in immune function and self-rated health after the loss, which would demonstrate greater risk for bereavement-related health problems. However, the majority of socially isolated caregivers' immune decline occurred *outside* of the acute bereavement period; these declines may have been driven by the stress of caregiving and anticipatory grief (Schulz et al., 2003), as well as difficulty with assembling a new life after years of caregiving (Robinson-Whelen et al., 2001). Instead, it was the socially connected whose lymphocyte proliferation to Con A dropped suddenly following the loss, but who then staved off long-term immune decline. In view of the entire sampling period, socially connected caregivers' lymphocyte proliferation to Con A formed a pattern that appears to reflect a normative response to a major event rather than one that foreshadows longer-term health risks. This underscores the value of longitudinal data years before and after loss.

The fact that socially connected caregivers' drops in immune responses to Con A were not matched by drops in responses to PHA or self-rated health further affirms that this immune dip did not foreshadow clinically relevant health risks. In fact, after the loss, socially connected and isolated caregivers alike had shallower subsequent declines in PHA lymphocyte responses and reported an uptick in self-rated health. Thereafter, socially connected caregivers' perceived health continued to progress toward "excellent," steadily diverging from isolated caregivers whose perceptions of their health remained level.

Comparing our findings of bereaved caregivers to the broader patterns in the bereavement literature, the current study's results suggest that the health consequences of bereavement may be unique among dementia caregivers, underscoring the importance of bereavement's context. Indeed, in our sample, caregivers' health and social networks declined most rapidly *prior* to the physical loss. This may be due to anticipatory grief (Cheung et al., 2018), persistent caregiver burden, or end-of-life care, a particularly difficult phase (Schulz et al., 2003). Dementia family caregivers face a complex interplay of practical and emotional demands as they grieve the loss of their loved one's personhood prior to the physical death itself. This shifts the significance of spouses' physical death, which the majority of dementia caregivers report as a relief (Schulz et al., 2003). Indeed, for dementia spousal caregivers, the physical loss may mark a sensitive period for health with a prime opportunity for reorganization and thriving.

Likewise, our data suggest that dementia spousal caregivers may not

be among those at greatest risk for health problems in the acute phase of bereavement. Instead, this increased risk for cardiovascular events and early mortality may be driven by the dysregulating effects of sudden, unexpected loss among non-caregiving spouses. In a longitudinal study that assessed individuals prior to spousal loss, Burton et al. (2006) directly compared depressive symptoms of those whose spouse died unexpectedly, non-caregiving spouses, and caregivers with low-stress and high-stress demands. Only those who were widowed unexpectedly had significantly elevated depressive symptoms 6 and 18 months after the loss, relative to pre-bereavement levels. Bonanno et al. (2005) found that bereaved people who experienced chronic grief or depression were more likely to have had a healthy spouse and little social support. Future population-level studies should investigate whether caregiving status and expectations for death moderate the effects of bereavement on immune function and health outcomes.

4.2. Distinguishing patterns over time from between-person health disparities

Although our data showed that bereavement was, overall, a positive turning point for dementia spousal caregivers' health, a subset of bereaved caregivers may remain at heightened risk for health problems compared to other people. The health risks of caregiver burden are well-documented: among more than 3000 caregivers, those who reported high strain were 1.5 times as likely to die within 5 years as their less-strained counterparts (Perkins et al., 2013). Recent meta-analyses and reviews have demonstrated that immune differences between caregivers and non-caregivers vary across studies (Allen et al., 2017; Roth et al., 2019), and that strained caregivers in particular show the most consistent risks for poorer immune function (Potier et al., 2018). One study found that immune differences persisted after care recipients had passed: current and former dementia caregivers had similarly elevated inflammation compared to non-caregiving controls (Kiecolt-Glaser et al., 2003). Our data suggest that any enduring disparity may be due to incomplete recovery from caregiving strain, not to the compounding risks of caregiving with the physical loss itself. Cross-sectional bereavement studies that include caregivers may conflate the lingering health risks of caregiving stress and anticipatory grief with that of the physical bereavement. Future work should explore whether caregivers' anticipatory grief carries its own health risks and compare its relative magnitude to bereavement's health consequences among non-caregivers.

4.3. Importance of pre-loss social ties: intervention implications

Our data suggest that larger social networks prior to bereavement may guide caregivers toward a path of reversing any negative consequences of caregiving on perceived health, even if aging stifles full immune recovery. Only greater pre-loss social integration explained post-loss improvements in self-rated health; post-loss social integration did not predict these health changes. Smaller post-loss network size did track with steeper post-loss declines in immune function, but immune patterns were more strongly predicted by pre-loss network size. These results underscore the importance of caregivers' preexisting social resources for setting the course of health through bereavement and the subsequent years. Caregivers with larger networks in place prior to bereavement may be better equipped to cope with bereavement and effectively reorganize their lives after the caregiving role has ended. According to Bergman and Haley (2009), caregivers with larger networks prior to the physical loss used fewer bereavement and hospice services and reported less need for additional emotional and instrumental support compared to their isolated counterparts.

Meta-analytic studies show promising evidence that interventions targeting caregivers' social environments can improve their psychological well-being (Abrahams et al., 2018). The current findings suggest that support interventions *prior to bereavement* may be especially beneficial for subsequent physical health. Previous work has found that a well-timed support program may boost post-loss well-being: among 406 caregivers randomly assigned to a counseling and social support intervention or usual care prior to bereavement, participants in the intervention group had steeper declines in depression up to six years post-bereavement (Haley et al., 2008). Given that social support naturally deteriorates after the onset of a stressor (Kaniasty and Norris, 1993), healthcare systems and service providers should proactively help caregivers to bolster their social networks long before the anticipated end-of-life phase.

4.4. Limitations

Among our study's limitations was the small, largely female sample: although the ratio reflects the disproportionate number of female caregivers in the population, it prevented us from testing gender moderation. Most participants were of White race, precluding our ability to directly compare the observed associations by race. The experience of spousal dementia caregivers' bereavement may not generalize to that of non-spouses providing care for individuals with other health conditions. Our primary goal was to characterize dementia spousal caregivers' immune health trajectories around bereavement; we did not have parallel data from a bereaved control group. Future studies should directly compare the pre- and post-bereavement health trajectories of caregivers and non-caregiving spouses. Likewise, the sample was not large enough to model care recipient placement into a care facility as a separate transition; larger population-based longitudinal studies should model institutionalization as a second change point. Further, in the current study it is impossible to attribute pre-loss declines in immune function and self-rated health only to continuing caregiver burden or specifically to end-of-life stress and anticipatory grief. Indeed, regardless of the disease stage, strained caregivers have shown steady declines in health (Kiecolt-Glaser et al., 2003; Potier et al., 2018), and near the end of the spouse's life, anticipatory grief and caregiving burden may be intertwined (Cheung et al., 2018).

4.5. Conclusions

The current study is among the first to characterize dementia caregivers' immune function, self-rated health, and social network changes years before and after spousal bereavement. Findings reveal that the physical death of an ill spouse may mark a positive turning point in health, especially for caregivers with greater preexisting social resources. Indeed, the context of the physical loss plays a critical role in shaping the course of health and the timing of health risks. Only longitudinal data that track individuals long before bereavement may begin to disentangle the potential long-reaching consequences of caregiving from those of spousal loss.

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Appendix A. Supplementary data

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