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Loneliness, Social Network Size, and Immune Response to Influenza Vaccination in College Freshmen

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Antibody response to the influenza immunization was investigated in 83 1st-semester healthy university freshmen. Elevated levels of loneliness throughout the semester and small social networks were independently associated with poorer antibody response to 1 component of the vaccine. Those with both high levels of loneliness and a small social network had the lowest antibody response. Loneliness was also associated with greater psychological stress and negative affect, less positive affect, poorer sleep efficiency and quality, and elevations in circulating levels of cortisol. However, only the stress data were consistent with mediation of the loneliness–antibody response relation. None of these variables were associated with social network size, and hence none were potential mediators of the relation between network size and immunization response.

Keywords: loneliness, social network size, vaccination, sleep, stress

Social isolation is the objective condition of having few contacts with family and community (Townsend, 1968). Studies of isolation may include the number of individuals with whom a person interacts, the frequency of interactions, the number of types of relationships (e.g., married, friends, social and religious group members), or even the degree of intimacy (Douglas, 1967). There is considerable evidence that social isolation is associated with poorer health. Those with more types of relationships and those who spend more time in social activities are at lower risk for disease and mortality than their more isolated counterparts (see reviews in Berkman, Vaccarino, & Seeman, 1993; Cohen, 1988; House, Landis, & Umberson, 1988). Although evidence for the association between numbers of network members and health is less consistent (see review in Cohen, 1988), low numbers of network members have been associated with increased suicide risk (Trout, 1980), increased risk of functional decline (Bisschop et al., 2003; Mendes de Leon, Gold, Glass, Kaplan, & George, 2001), poor mental health (Mendes de Leon et al., 2001), and increased risk-factor levels for heart disease (i.e., higher cholesterol and blood pressure, or higher levels of smoking; O'Reilly & Thomas, 1989).

Loneliness has similarly been associated with poorer health. Although conceptually similar to social isolation, loneliness is the feeling or perception of being alone (Peplau & Perlman, 1982). It has also been defined as the evaluation that one is not achieving a desired level of social interaction (Perlman & Peplau, 1981). In some cases, social isolation and loneliness are not highly correlated (Cutrona, 1982); for example, a person with a large social network can experience loneliness (e.g., if they lack intimacy in their relationships), whereas a person who has only a few close social ties may not feel lonely at all (Peplau & Perlman, 1982).

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Feeling lonely has been associated with poorer self-reported physical health (Berg, Mellstrom, Persson, & Svanborg, 1981; Fees, Martin, & Poon, 1999; Mahon, Yarcheski, & Yarcheski, 1993), postbypass surgery mortality (Herlitz et al., 1998), and abnormal hemodynamic functioning (Cacioppo, Hawkley, Crawford, et al., 2002; Sorkin, Rook, & Lu, 2002). Loneliness has also been associated with poorer immune status, including poorer natural killer cell function (Kiecolt-Glaser, Garner, et al., 1984), smaller proliferative response to phytohemaglutinin stimulation (Kiecolt-Glaser, Ricker, et al., 1984), and higher levels of antibody (Ab) to the Epstein-Barr virus (suggesting less immune control over this pathogen; Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985). In contrast, feelings of loneliness predicted less rapid decline in numbers of CD4+ cells in HIV-positive men over a 3-year follow-up, suggesting a slower progression of infection (Miller, Kemeny, Taylor, Cole, & Visscher, 1997), and were unrelated to Ab formation in response to a low-dose hepatitis B vaccine (Jabaaij et al., 1993).

The study we report compared the effects of social isolation and loneliness on a component of health: immune competence as assessed by the amount of Ab produced in response to an immunization. It also attempts to identify specific pathways that might link isolation and loneliness to immunity. One potential pathway is the elevation of immune-modulating glucocorticoids. Elevated cortisol levels have been found in chronically lonely college students (Cacioppo et al., 2000), lonely psychiatric inpatients (Kiecolt-Glaser, Ricker, et al., 1984), and socially isolated preschool children (Sanchez-Martin et al., 2001). Another potential pathway is via differences in health practices (e.g., smoking, exercise; Cacioppo, Hawkley, & Bernston, 2003; Cohen, 1988; Rook, 1984). Although some studies have not found differences between lonely and nonlonely individuals (Cacioppo et al., 2000; Cacioppo, Hawkley, Crawford, et al., 2002), loneliness has been found to be associated with alcoholism (Nerviano & Gross, 1976), and isolation has been found to be associated with smoking, alcohol consumption, and poorer exercise habits (Berkman & Syme, 1979). It has also been postulated that differences in restorative processes (e.g., sleep behaviors) that serve to repair and maintain physiological function may be responsible for the health consequences of loneliness and related factors (Hawkley & Cacioppo, 2003). Research to date suggests that the lonely sleep less effectively and less efficiently than do their nonlonely counterparts (Berg et al., 1981; Cacioppo et al., 2000; Cacioppo, Hawkley, Berntson, et al., 2002), and studies have shown that social isolation is related to poor sleep habits and insomnia (Berkman & Syme, 1979; Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997; Hanson & Oestergren, 1987). It seems plausible then that restorative behaviors and/or health practices mediate the associations between loneliness and/or social network size and health-related outcomes.

Others theories of how isolation and loneliness might influence health have also been raised. Hawkley and Cacioppo (2003) argued that social isolation might also influence health via feelings of loneliness because loneliness gauges distress over the current social status quo. Cacioppo et al. (2003) suggested that lonely and isolated individuals have higher levels of stress in their lives and that this contributes to wear and tear on the body, which may in turn influence health. Rook (1984), however, suggested that loneliness and isolation may operate on health via discrete health-altering pathways. Rook specifically suggested that loneliness alters well-being via elevated stress and depression, whereas social isolation is harmful because of an absence of others to prompt positive health practices and deter deviant ones.

There may also be alternative factors that are similar to loneliness and isolation that give rise to the associations between isolation, loneliness, and physical well-being. Loneliness is strongly correlated with such personality characteristics as low self-esteem, introversion, hostility, and neuroticism (Berg et al., 1981; Cutrona, 1982; Levin & Stokes, 1986; Russell, Peplau, & Cutrona, 1980). Because many of these variables have also been correlated with impaired immune functioning, poor physical health, and greater symptom reporting (e.g., Cohen, Turner, Alper, & Skoner, 2003; Feldman, Cohen, Doyle, Skoner, & Gwaltney, 1999; Miller, Cohen, Rabin, Skoner, & Doyle, 1999), they may be what underlies associations among loneliness, isolation, and health.

We assessed the value of social network size and loneliness in predicting immune function by monitoring Ab response to an influenza immunization in a group of college freshmen who reported that this was their first influenza vaccination. Immunization studies are desirable not only because of their clinical significance but also because of their ability to assess in vivo functional immunity (Cohen, Miller, & Rabin, 2001). We chose to study incoming freshmen because this period of their lives is often coupled with feelings of loneliness (Cutrona, 1982; Weiss, 1973). It is also a time when many radically change their health behaviors (e.g., sleeping patterns, alcohol usage), which may provide the opportunity to determine whether lonely and/or isolated individuals are more likely to engage in detrimental health behaviors and whether these in turn mediate the relationship between social factors and immunity.

Levels of loneliness, social network size, health behaviors, and restorative behaviors were assessed at baseline. We also measured self-esteem, hostility, neuroticism, and extraversion at baseline as possible third (spurious) factors that could result in both loneliness and immunosuppression. We then monitored loneliness, behaviors, moods, and stress with electronic daily diaries for 2 consecutive weeks starting 2 days before vaccination, along with salivary cortisol, which was assessed for 5 days during this period starting 1 day prevaccination. The diary period was followed by 3.5 months of biweekly questionnaires assessing continued levels of loneliness, stress, and mood. Ab levels were determined via blood samples drawn at baseline (the day of vaccination), at 1 month (the point at which maximal titers should be reached), and at 4 months to determine if differences between groups were maintained over time.

Method

Participants

Participants were college freshmen (37 men and 46 women) at Carnegie Mellon University, aged 18 to 25 years (96.4% were 18–19 years), who responded to e-mail advertisements and posters and were recruited in four separate cohorts (September 2000 and 2001 and November 2000 and 2001). All reported no chronic or acute illness, no regular medication regimen (with the exception of birth control), and good health prior to study onset. Individuals who had ever been vaccinated for influenza, who were pregnant or breast-feeding, or who had immunologically related health problems were excluded. All participants were paid $120 for their participation. One participant completed all components of the study ex-

cept for the 4-month blood draw and was included in all analyses except for those looking at 4-month Ab levels.

Design and Procedure

Participants were immunized in conjunction with university-wide flu vaccination clinics in October (Cohorts 1 and 3) and November (Cohorts 2 and 4). Demographic, psychological, and health practice questionnaires were administered 5 to 6 days prior to immunization. Two days prior to immunization, participants began 13 days of ecological momentary assessment (EMA; Stone & Shiffman, 1994) by using a palm computer. Participants reported their current loneliness, stress, and affect four times daily (1, 4, 9, and 11 hr after waking up) when cued by their palm computers. They also reported their health practices once a day (how much they slept, smoked, consumed alcohol, and exercised). Their answers were recorded in the computer's memory and retrieved at the end of the EMA period. On Days 2 through 6 of the protocol (beginning 1 day before immunization), participants gave salivary cortisol samples four times a day at the same time that they completed their momentary questionnaires. Following the last day of EMA, biweekly e-mail (or phone) questionnaires were administered to assess loneliness, stress, and mood over the following 14 weeks. Ab levels were assessed at baseline (day of immunization) and at 1 and 4 months postimmunization.

Materials

Measures of loneliness and social network size. Loneliness was assessed at study baseline by using the short version of the UCLA Loneliness Scale (Russell, 1996). This eight-item scale measures the extent to which the participant feels lonely and isolated ($\alpha = .86$). To capture feelings of loneliness over the ambulatory and follow-up period, we asked participants to indicate the extent to which they felt lonely and isolated at each diary entry (*how you feel now*) and biweekly follow-up (*feelings over the last 2 weeks*). Response options ranged from 0 (*not at all*) to 4 (*extremely*). Responses to the two items were highly correlated across the diary and follow-up entries (mean $r = .92$, $p < .01$) and were combined at each assessment point. The EMA data were averaged across the four daily assessments to create daily loneliness scores. An average of all the daily loneliness scores and an average of all the follow-up scores had a correlation of .80. When the 13 EMA and seven follow-up scores were entered into a principal component factor analysis, all loaded at .50 or better on the same factor. Consequently, we averaged across all of the EMA daily and follow-up assessments to create a single total loneliness score.

We defined social isolation as the objective condition of having few contacts with family and community (Townsend, 1968). Studies of isolation have focused on both poor integration into social networks (e.g., Galle & Gove, 1978) and decreased contact and communication with others (e.g., Trout, 1980). Because we were studying college students, we felt that traditional measures of social integration were not appropriate and instead focused on the issue of contact. We administered the Social Networks in Adult Life Questionnaire (convoy measure; Antonucci & Akiyama, 1987) at baseline to assess social network size. Participants were presented with three concentric circles and told to write the initials of a maximum of 20 people that they knew well and were in contact with at least once a month in the circles. Instructions specified that "People in the innermost circle are those who are close and important to you, and without whom life would be difficult to imagine. The remaining two circles are for people who are successively less close." Total social network size was calculated by summing the number of initials within all three levels.

Personality scales. Neuroticism and extroversion were assessed at baseline by using a modified version of the subscales (see Feldman et al., 1999, for modifications) from Goldberg's Big Five Scale (10 items each; Goldberg, 1992) that required participants to indicate how accurately a list of traits (e.g., anxious, extraverted, sad, talkative) reflected how they generally feel on a scale from 0 (*not at all accurate*) to 4 (*extremely accurate*). The alphas for neuroticism and extraversion were .84 and .92, respectively. Participants also completed the four-item version of the Rosenberg Self-Esteem Scale (Rosenberg, 1965) at study onset. They rated on a scale of 1 to 4 how strongly they agreed with each item (e.g., I take a positive attitude toward myself), with 1 indicating strong disagreement and 4 indicating strong agreement ($\alpha = .91$). Finally, hostility was determined at study baseline by using the 20-item version of the Cook–Medley Hostility Scale (Barefoot, Dodge, Peterson, Dahlstrom, & Williams, 1989). Participants answered 20 true–false questions indicating their hostile affect, cynicism, and aggressive responding. Appropriate (counterbalanced) items were reversed, and the number of true responses was then summed to create a total hostility score ($\alpha = .61$).

Depressive symptoms, affect, and psychological stress. Depressive symptoms were assessed at baseline by using the 10-item version of the Center for Epidemiological Studies—Depression Scale (CESD-10; Andresen, Malmgren, Carter, & Patrick, 1994). The items were scored on a 4-point scale on which 0 indicated that the symptom occurred rarely or none of the time and 3 indicated most of the time. Individual item scores were totaled to yield a summary score, with higher scores indicating more symptoms of depression ($\alpha = .79$).

Mood was assessed at each diary measure by using four negative items associated with two subcategories of negative affect (NA) and eight items associated with positive affect (PA). NA categories were anxiety (jittery, nervous) and depression (unhappy, sad), whereas PA included categories of vigor (active, intense, lively, enthusiastic), well-being (happy, cheerful), and calm (calm, relaxed). Each item was rated on a scale from 0 (*not at all accurate*) to 4 (*extremely accurate*) according to how much that word reflected how participants felt at that moment. For each interview, appropriate items were summed to create separate NA and PA scales. The overall alphas for the four NA items over the 13 interviews ranged from .84 to .91. The overall alphas for the eight PA items over the 13 interviews ranged from .86 to .95. The same items in the diary portion of the study were assessed biweekly in the follow-up by asking participants how they had felt over the previous 2 weeks. Average NA and PA scores over the study were created by taking the respective means of NA and PA across each of the 13 diary days and the seven biweekly questionnaires (NA $\alpha = .97$, PA $\alpha = .94$).

Psychological stress data were also gathered at each diary entry as well as biweekly over the follow-up. At each assessment, participants reported the extent to which they felt overwhelmed and stressed. Likert scale response options were identical to those for the ambulatory–biweekly loneliness ratings. The two items were highly correlated (mean $r = .84$, $p < .01$). We took the mean of the two questions at each assessment, averaged the means within a day, and then created an average daily score by taking the mean of all days assessed.

Health practices and restorative behaviors. Health practices were assessed by questionnaire at baseline with an inventory that has been used in published research by Cohen et al. (1997). Participants were classified as smokers if they smoked cigarettes, cigars, or pipes on a daily basis. Alcohol use was determined by counting the number of alcoholic drinks consumed during a typical week. A drink was considered a bottle or can of beer, a glass of wine, or a shot of hard liquor. Sleep duration, efficiency (proportion of time in bed that a participant spends sleeping), sleep quality, and napping behavior over the last month were assessed with the Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Physical activity was assessed by asking participants how often they engaged in strenuous activity (number of days) every week by using an item from the Paffenbarger Activity Questionnaire (Paffenbarger, Blair, Lee, & Hyde, 1993).

All of the health behaviors were also assessed once each day by EMA and were averaged across the 13 EMA days. Alcohol consumption and smoking were determined by number of drinks or units smoked; physical activity was determined by the number of times and number of minutes

spent exercising; and sleep was determined by the following three measures based on questions from the Pittsburgh Sleep Quality Index: sleep duration (hours), sleep loss (minutes), and sleep quality, which was rated on a scale from 0 (*very poor*) to 4 (*very good*). Average scores were tabulated across the 13 EMA days for each of these variables. Missing days were not included when calculating averages. Of the participants, 6% to 16% were missing data at any given time point.

Cortisol. From 1 day prior to immunization to 3 days postimmunization, participants provided salivary cortisol samples four times daily by lightly chewing on a cotton dental roll for 1 min and then placing it in a collection container (Salivette, Sartstedt Corp., Numbrecht, Germany). Participants were required to record a security code (provided by their palm computer) on their salivette at the time of sampling to ensure compliance. Cortisol data were excluded if there was no code on the salivette, if they missed a morning sample for that day, or if they had fewer than three samples on a given day (<10% of daily values were excluded). Salivary cortisol was assayed with a time-resolved immunoassay with a cortisol-biotin conjugate as a tracer. Total cortisol produced over a day was measured by calculating the area-under-the-curve (AUC). This represents the total volume of cortisol secretion over the day. We also examined cortisol levels at each time point averaged across the 5 days. Cortisol data were log transformed prior to analyses.

Vaccine and measure of Ab titers. A 20-mL blood sample was obtained via antecubital venipuncture just before vaccination and subsequently at 1 month and 4 months postvaccination. The Fluzone vaccine was administered on Day 3 of the study and consisted of three antigens: A/New Caledonia, A/Panama, and B/Yamanashi or B/Victoria (substituted for B/Yamanashi in the 2001 vaccine). Because a different B virus was included in the vaccine in 2001 than in 2000, the sample size for each B virus was considered too small to provide sufficient power. Consequently, we collapsed across the two B viruses in our analyses; however, independent analyses of the separated B viruses revealed identical conclusions.

A standard hemagglutination inhibition protocol was used to quantify Ab titers to each of the vaccine components. To quantify the volume of Ab that a participant had, his or her serum was diluted with various saline concentrations and then added to a red blood cell culture that contained influenza. The titer is the reciprocal of the highest dilution at which a person's serum continues to prevent red cells from clumping. Thus, higher titer values indicate greater volumes of Ab to the vaccine component. All samples were run in duplicate as well as a nonantigen control in both the 2000–2001 and the 2001–2002 samples, and all time points for each participant were run in the same assay contemporaneously. The antigens used were as follows: A/New Caledonia/20/99 with a hemagglutination (HA) titer of 1024 used at 4 hemagglutinating units (HAU)/25 μL, A/Panama/2007/99 with an HA of 32 used at 4HAU/25 μL, B/Yamamashi/166/98 with an HA of 1024 used at 4HAU/25 μL, and B/Victoria/504/00 was used at 4HAU/25 μL. The A/New Caledonia and B viruses were obtained from the World Health Organization collaborating center, whereas an egg pool of A/Panama virus was grown from a Charles River Laboratories (Wilmington, MA) seed lot (4XAPA010914).

Results

Statistical Analyses and Data Cleaning

Ab and cortisol levels were log (base-10) transformed, and total loneliness, baseline CESD-10, and NA were square-root transformed to better approximate normal distributions. Social network size from our convoy measure could not be normalized with any transformation; therefore, it was trichotomized and dummy coded (small network, $n = 29$; medium network, $n = 25$; large network, $n = 29$). We used multiple linear regressions to predict the postimmunization Ab levels, health behaviors, and cortisol levels. We first entered the standard controls, including sex, year of immunization (to control for possible differences in the vaccines and assays), race (Caucasian, other), and baseline Ab levels (for immunization response analyses), followed by the appropriate psychological variables in a second step. A third step was included when interactions were tested. Separate regressions were done for each of the three components of the trivalent vaccine according to the suggestion of Cohen et al. (2001). We report the change in multiple correlation-squared values and F values when there was a main effect of the regression step. Participants who had maximal titers at baseline were excluded from immune analyses because of our inability to gauge their response to the antigen (A/New Caledonia, $n = 5$; A/Panama, $n = 6$; both B viruses, $n = 0$). Loneliness was associated with baseline titers of A/New Caledonia ($r = -.35$, $p < .01$) but with no other antigens, whereas social network size was not associated with baseline levels of Ab in any influenza strain.

Because our sampling schedule was designed to capture diurnal fluctuations in mood and cortisol, it was important to carefully monitor participants' compliance with the ambulatory monitoring procedures. On an a priori basis, we chose to include only those diary entries within 60 min of target in either direction. When this definition was applied, 3,756 of the 4,316 diary entries (87%) met our criteria for compliance. Only these values were used in the analyses below (e.g., computing average loneliness scores, average NA, average PA, cortisol levels).

Social Network Size, Loneliness, and Ab Response

Separate analyses assessed whether social network size and loneliness were associated with Ab response at both follow-up points for the various antigen components. Smaller social networks were associated with lower Ab production at both 1 month ($\Delta R^2 = .07$), $F(2, 71) = 4.91$, $p < .05$, and 4 months ($\Delta R^2 = .08$), $F(2, 70) = 5.35$, $p < .01$, in response to the A/New Caledonia virus but not to the A/Panama or the B viruses. In both cases, the association with A/New Caledonia was attributable to lower Ab production in the most isolated tertile (see Figure 1).

The two measures of loneliness—total loneliness score (4-month mean) and the UCLA Loneliness Scale—were correlated ($r = .49$, $p < .01$). We examined response to the immunization at 1 month and 4 months by using both the UCLA scale and the total loneliness score in separate analyses. Higher levels of total loneliness were associated with lower Ab levels at both 1 month ($\Delta R^2 = .04$), $F(1, 72) = 4.79$, $p < .05$, and 4 months ($\Delta R^2 = .04$), $F(1, 71) = 5.04$, $p < .05$, for the A/New Caledonia vaccination but again not for the other vaccine components. As apparent from Figure 2, the association was linear with each increase in loneliness associated with lower Ab production. The UCLA scale was not related to Ab response; therefore, our subsequent loneliness analyses focus on the total loneliness measure. Furthermore, because the A/New Caledonia virus was the only component associated with loneliness and isolation, further analyses focus on this element of the Ab response.

Test of Spurious (Third Factor) Explanations

It is possible that personality characteristics that are thought to influence the development of social networks and our perceptions of them might account for the relations we found by affecting

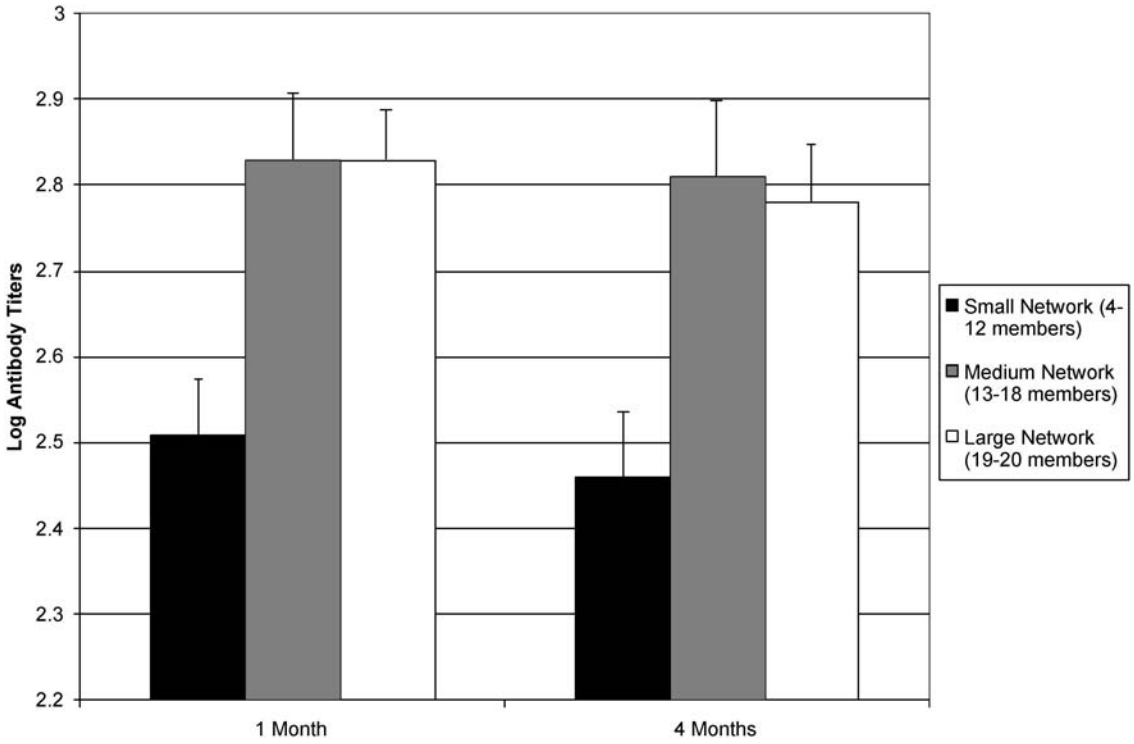

Figure 1. Antibody levels at 1 and 4 months, adjusted for control variables (unstandardized predicted means). Error bars represent standard errors of the mean.

isolation and loneliness as well as immune response to the vaccine. Bivariate correlations revealed that loneliness was associated with elevated levels of neuroticism ($r = .34$, $p < .01$), higher hostility scores ($r = .30$, $p < .01$), and marginally lower levels of extraversion ($r = -.19$, $p = .09$) but was not associated with self-esteem. Analyses of variance examining the independent relationships between social network tertiles and these potential third factors revealed no associations, with the exception of extraversion ($r = .22$, $p < .05$). None of these variables were associated with A/New Caledonia Ab levels, and covarying them did not greatly reduce the association between social network and immune response or between loneliness and immune response.

Test of Mediators

We were interested in whether stress and mood, health and restorative behaviors, or cortisol operated as pathways linking social variables with immunization response. For a variable to be considered a mediator, it must correlate with the independent predictor and account for variations in the dependent variable, and when controlled for, the relationship between the independent and the dependent variable must be significantly reduced (Baron & Kenny, 1986). We began by examining the potential roles of stress and affect. Loneliness was positively correlated with NA ($r = .74$, $p < .01$), psychological stress ($r = .31$, $p < .01$), and depressive symptoms ($r = .52$, $p < .01$) and negatively correlated with PA ($r = -.31$, $p < .01$). Individual analyses of variance assessing the relation between each of these variables and social network-size tertiles revealed no associations. To test the hypothesis that distress mediates the influence of loneliness on health outcomes, we tested each of NA, PA, stress, and depression in independent regressions to determine if they were associated with Ab response. Only psychological stress was significantly associated with response to A/New Caledonia: 1 month ($\Delta R^2 = .04$), $F(1, 72) = 4.83$, $p < .05$; 4 months ($\Delta R^2 = .04$), $F(1, 71) = 4.91$, $p < .05$. This is similar to our previous finding that stress over the EMA period was related to Ab levels (Miller et al., 2004). We also entered these variables into a stepwise regression to determine whether they would lessen the association between loneliness and Ab response. Only stress entered the first step of the equation, and when loneliness was added to in a second step, stress reduced the association of loneliness with Ab levels reported earlier by 50%: 1 month ($\Delta R^2 = .02$), $F(1, 71) = 2.80$, $p = .10$; 4 months ($\Delta R^2 = .02$), $F(1, 70) = 3.07$, $p = .08$. In contrast, a similar analysis substituting social network size for loneliness did not indicate any reduction of the association when stress was added to the equation.

We then considered the roles of health and restorative behaviors. Social network size was not related to any of the health or restorative behaviors. Loneliness (controlling for sex, cohort, and race) was associated with poorer sleep efficiency assessed at baseline ($\Delta R^2 = .07$), $F(1, 72) = 6.34$, $p < .05$, and marginally associated with higher sleep loss ($\Delta R^2 = .04$), $F(1, 78) = 3.16$, $p = .08$, and poorer sleep quality ($\Delta R^2 = .04$), $F(1, 78) = 3.42$, $p = .07$, over the diary period, but not with any of the other behaviors. However, none of these variables associated with loneliness were significantly related to Ab levels; therefore, none were potential mediators.

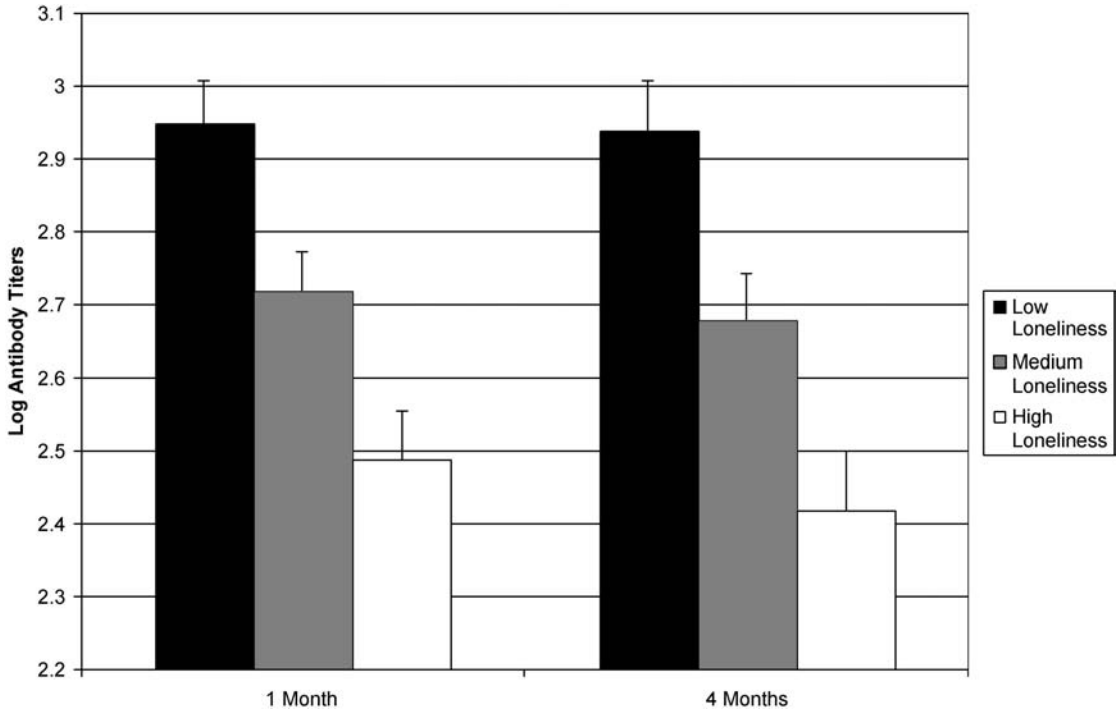

Figure 2. Antibody levels at 1 and 4 months, adjusted for control variables (unstandardized predicted means). Loneliness was analyzed as a continuous variable and is displayed in tertiles for graphing purposes only. Error bars represent standard errors of the mean.

Finally, we examined whether cortisol could have acted as a mediating pathway. Neither network size nor total loneliness was associated with average cortisol AUC or with mean levels at the four time points (controlling for sex, cohort, and race). Because cortisol levels were sampled only during the first week of the study, we examined whether cortisol was related to loneliness over the surrounding EMA period. Although it was not related to average AUC, further analysis revealed that diary loneliness was associated with higher average cortisol levels at the early morning (1-hr postwake-up) and evening samples (11-hr postwake-up): 1 hr ($\Delta R^2 = .10$), $F(1, 50) = 7.01$, $p < .05$; 11 hr ($\Delta R^2 = .08$), $F(1, 50) = 4.40$, $p < .05$. However, none of the variables associated with loneliness were significantly related to Ab levels; therefore, none were potential mediators.

Loneliness as a Mediator of the Association of Social Network Size and Immunity

Hawkley and Cacioppo (2003) predicted that one way that social network size could influence health is via perceptions of loneliness. Social network size and loneliness were not correlated ($r = -.09$, $p = .40$). Alone, social network size accounted for approximately 7% of the Ab response to A/New Caledonia at both time points. When loneliness was entered in the first block, the network effects were reduced to 6% at 1 and 4 months but remained statistically significant ($p = .02$ for both). Hence, loneliness accounted for only 14% of the variability [(initial ΔR^2 − new ΔR^2)/initial $\Delta R^2 = (.07 - .06/.07) = .14$] initially accounted for by social network size.

Interaction of Loneliness and Social Network Size

To examine possible synergistic effects of loneliness and social network size on Ab response, we entered loneliness and social network size together followed by the product of the two in the next step. When loneliness and social network size were included in the same regression to test for independent associations with Ab change, neither association was reduced substantially—loneliness: 1 month ($\Delta R^2 = .03$), $F(1, 70) = 3.62$, $p = .06$; 4 months ($\Delta R^2 = .04$), $F(1, 69) = 3.49$, $p = .07$; and social network size: 1 month ($\Delta R^2 = .06$), $F(2, 70) = 4.00$, $p < .05$; 4 months ($\Delta R^2 = .06$), $F(2, 69) = 4.26$, $p < .05$. The interaction between social network size and loneliness was significant at both 1 month ($\Delta R^2 = .08$), $F(2, 68) = 6.24$, $p < .01$, and 4 months ($\Delta R^2 = .06$), $F(2, 67) = 5.03$, $p < .01$. Figure 3 shows the interaction at 1 month. The 4th month is not depicted graphically, but it is identical to the findings at 1 month. Individuals most at risk were those who were socially isolated at baseline as well as lonely throughout the 4 months of the study. Furthermore, we found that loneliness was not associated with lower Ab response when social network size was large, whereas network size was not associated with Ab response when loneliness was low.

Discussion

Low numbers of social ties were associated with a poorer immune response to one component of the influenza vaccination. Being in the lowest tertile of social network size (4–12 members in the total network) was associated with less Ab production than

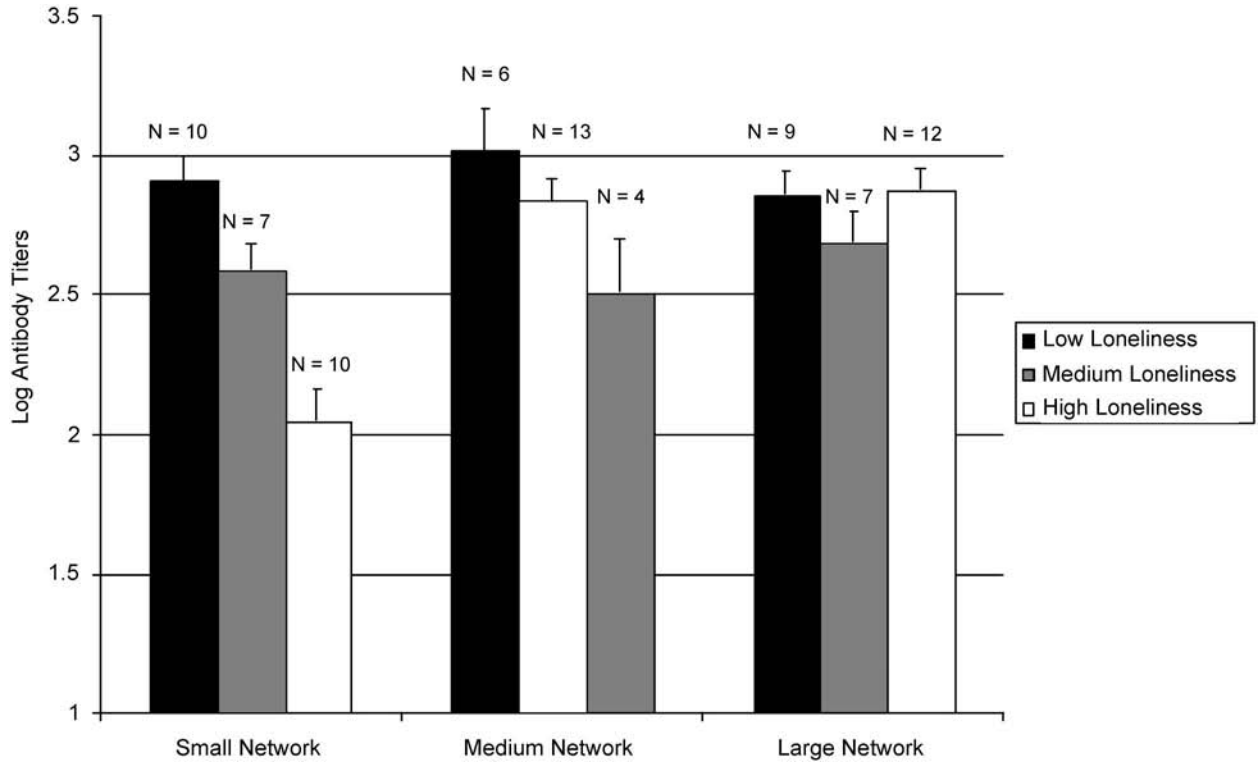

Figure 3. Mean antibody levels at 1 month, adjusted for control variables (unstandardized predicted means). Loneliness was analyzed as a continuous variable and is displayed in tertiles for graphing purposes only. Error bars represent standard errors of the mean.

were the other two tertiles (ranging from 13 to 20 contacts). This association was independent of feelings of loneliness. College students have many opportunities for social contacts via roommates, dormitories, classes, and university organizations; consequently, availability of social ties is an unlikely explanation for isolation. Implications for health may arise because these individuals lack social support to buffer the stress that occurs during the first semester of school. Alternatively, individuals with few ties may perceive themselves to be stigmatized because of the relative embeddedness of their counterparts with larger social networks and the cultural values associated with being popular. However, these explanations seem unlikely because network size was not associated with stress, depression, or self-esteem. Finally, an explanation based on the hypothesis that greater network size is associated with greater probability of exposure to more viruses and hence development of immunity to the viruses in the vaccine does not appear to be the root of this finding as there were no social network group differences in baseline Ab levels.

Loneliness (as assessed by the diary and interview data) was associated with poorer Ab response to the A/New Caledonia virus component of the vaccination at both 1 and 4 months postimmunization. Baseline levels of loneliness, as assessed by the UCLA scale, however, were not related to vaccination response. This was consistent with the failure of an earlier study (Jabaaij et al., 1993) to find an association of baseline loneliness as assessed by the UCLA scale and Ab response. We may have been able to tease out this association because the score was based on multiple measurements over 4 months and was both contemporaneous with the immunization response and a more reliable measure of chronic loneliness. In contrast, the baseline assessment may have merely picked up the transient loneliness associated with moving to a new school. This is consistent with the argument that chronic feelings of loneliness are more important predictors of health and well-being (Weiss, 1973). It may be that acute levels of loneliness do not have the same immune implications of chronic loneliness. This is in line with Cacioppo et al.'s (2003) argument that the two measures might have distinct mechanisms by which they operate on health.

We pursued the possibility of several mediating pathways that might have linked social isolation or loneliness to poorer immune response. Recall that Rook (1984) predicted that the association of social isolation and health would be mediated by health practices, whereas the association of loneliness and health would be mediated by stress and negative affect. Rook (1984) argued that social networks prevent deviant behavior during periods of rapid personal change. This suggests that socially isolated persons may have poorer health practices and restorative behaviors. However, neither health practices nor restorative behaviors were associated with network size in our freshmen. Because the first year of university is a period of transition, it is plausible that other unassessed behaviors (e.g., substance abuse, nutrition, caffeine intake) could mediate the association between social network size and immune function. For example, coping via substance abuse has been associated with poor Ab response to a hepatitis B vaccination

(Burns, Carroll, Ring, Harrison, & Drayson, 2002). Alternatively, health behaviors of freshmen may be too variable and influenced by external factors (e.g., exams and assignments altering sleep patterns, variable access to cigarettes and alcohol due to age restrictions) to be sensitive to the influences of social networks.

In contrast to network size, high loneliness was associated with poorer sleep efficiency at baseline and marginally associated with more sleep loss and poorer sleep quality over the diary assessment. These results are consistent with evidence from both the laboratory and field that lonely college students have poorer sleep efficiency (Cacioppo et al., 2000; Cacioppo, Hawkley, Berntson, et al., 2002). However, neither these particular restorative behaviors nor any of the health behavior measures were associated with response to the immunization. In some cases, the behaviors had low base rates restricting the possibility of associations (e.g., 78% did not smoke, and 50% did not drink alcohol). In contrast, the sleep habits of many of the students were highly irregular in November through December, when midterms, projects, and exams were prevalent (e.g., sleep loss ranged from 0 to 120 min per night). These irregularities may have similarly clouded any possible relation.

Stress was predicted to play a role in the link between loneliness and response to the immunization (Cacioppo et al., 2003; Rook, 1984). In our sample, increased loneliness was associated with greater NA, depression, and psychological stress and with lower levels of PA. All of these variables have been related to markers of immunocompetence in earlier studies (e.g., Cohen, Doyle, Turner, Alper, & Skoner, 2003; Cohen, Turner, et al., 2003; Marsland, Cohen, Rabin, & Manuck, 2001; Miller et al., 1999), and psychological stress has been associated with Ab response to immunization (e.g., Burns, Carroll, Drayson, Whitham, & Ring, 2003; Glaser et al., 1992; Glaser, Kiecolt-Glaser, Malarkey, & Sheridan, 1998; Miller et al., 2004; Vedhara et al., 1999). When these variables were stepped in as covariates, only stress entered the regression, which decreased the association between loneliness and Ab response by 50%. This provides partial support for previous theories that suggest loneliness may impact health via feelings of distress (Cacioppo et al., 2003; Rook, 1984). However, as approximately 50% of the variability explained by loneliness remained after controlling for stress, there are other pathways at work as well. Larger networks were not associated with any of these variables; therefore, they are not potential mediators.

Finally, we tested whether cortisol levels could explain the associations between either network size or loneliness and immunity. Although loneliness was associated with cortisol levels, it was only for loneliness levels reported around the time of the cortisol sampling period. Furthermore, because none of the cortisol measures (AUC and at all time points) were related to Ab response, they are not plausible mediators. One possible explanation for this null finding may be the highly irregular sleep habits of students, as discussed earlier. Cortisol data from that period may be too irregular to capture associations with Ab months later.

In short, we have not found any possible pathways linking social isolation to immune response, although stress does seem to play a major role in linking loneliness to Ab response to the immunization. Hawkley and Cacioppo (2003) postulated that one way isolation might influence health is via perceptions of loneliness. However, in this study, social network size and loneliness were not correlated, nor did covarying loneliness significantly reduce the association of isolation with immune response. There was, however, a synergistic effect of number of ties and loneliness that suggests that there may be some common mechanism(s) we have not identified. Individuals who had low levels of loneliness were protected from the lower immune response associated with isolation, and those with high numbers of social contacts were protected from the lower response associated with loneliness. Relevant here is a study by Reynolds and Kaplan (1990) showing increased risk of cancer and cancer-related mortality in women who reported both fewer contacts and feelings of isolation, but some degree of protection for those who reported only one or the other. The ability of these two variables to substitute for one another suggests that there may be some common pathway that is influenced by extreme levels of both variables.

The prospective nature of our social network-immune finding precludes the possibility of reverse causality. Although we have excluded several key factors (personality measures), it is still possible that some unmeasured third variable may be responsible for both the low levels of network members and suppressed Ab response. The loneliness finding, however, is cross-sectional, precluding causal inferences about the relationship between loneliness and Ab response. Given that the central nervous system and the immune axis have bidirectional communication (Maier & Watkins, 1998), it is conceivable that immune processes cause feelings of loneliness or that there is another unconsidered variable responsible. We must also consider the clinical implications of suppressed immune response to an influenza immunization. Statistical significance is not clinical significance and may not mean that these individuals are less protected from the flu virus. If we chose 40 titers as a protective level (Cox et al., 2002), only 6%–7% of our participants would have been below this level during follow-up. It is interesting to note that all of these participants had both small social networks and high levels of loneliness. Nonetheless, it remains intriguing that there was sufficient variability in Ab response in a young healthy population to find the associations we report.

Why were social network size and loneliness related to only one of the four viruses in the influenza vaccine? There was no a priori prediction that these variables would be associated with only one component of the vaccination component; however, A-type viruses are known to show more antigenic drift (i.e., mutate more easily and cause more infection; Nicholson, Webster, & Hay, 1998), which may play a role in individual variability in response. In line with this, previous studies have found psychological associations with only the A components of the same vaccination (e.g., Burns et al., 2003); however, because many psychoneuroimmunology studies average over viruses (see review in Cohen et al., 2001), it is impossible to know the extent to which A viruses drive previously found associations between psychological factors and immune response. It remains unclear why these factors were associated with only one of the two A viruses.

In sum, social network size and loneliness were independently associated with the production of less Ab in response to one component of the influenza immunization in a young, healthy population. Our evidence is consistent with stress partially mediating the association between loneliness and immune response, but we have no support for a pathway linking social isolation and response.

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