

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

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Running Head: Loneliness, Isolation & Antibody Response

ABSTRACT

Antibody response to the influenza immunization was investigated in 83 first semester College Freshman. Elevated levels of loneliness throughout the semester and small social networks were independently associated with poorer antibody response to one component of the vaccination. Those with both high levels of loneliness and a small social network had the lowest levels of antibody response. Loneliness was also associated with poor sleep efficiency and quality, and with concurrent elevations in circulating levels of cortisol, but these factors did not mediate associations with the immunization response. There were also moderate to strong associations between loneliness, network size and personality and affective factors, however, only the psychological stress data were consistent with mediation of the association between loneliness and antibody levels.

Keywords: Loneliness, Social Network Size, Vaccine, Sleep, Cortisol, Stress

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

Persons with relatively few social contacts have poorer health than their more socially integrated counterparts. The association between social seclusion and health has been found in numerous prospective community studies and holds after controlling for standard risk factors such as age, race, socioeconomic status, health status at baseline, and health practices such as exercise, alcohol consumption and smoking (House, Landis and Umberson, 1988). In particular, lesser levels of social integration and participation have been related to greater risk for cardiovascular problems (Stansfeld and Fuhrer, 2002), infectious illness (Cohen, Doyle, Skoner et al., 1997) and mortality from all causes (Berkman and Syme, 1979; Welin, Tibblin, Svardsudd et al., 1985).

Loneliness has similarly been associated with poorer health. Although conceptually similar to social isolation, loneliness is the feeling or perception of being alone (Peplau and Perlman, 1982). It has also been defined as the evaluation that one is not achieving a desired level of social interaction (Perlman and 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) while a person who has only a few close social ties may not feel lonely at all (Peplau and Perlman, 1982). Feeling lonely has been associated with poorer self-reported physical health (Berg, Mellstrom, Persson et al., 1981; Fees, Martin and Poon, 1999; Mahon, Yarcheski and Yarcheski, 1993), mortality post-bypass surgery (Herlitz, Wiklund, Caidahl et al., 1998), and abnormal hemodynamic functioning (Cacioppo, Hawkley, Crawford et al., 2002; Sorkin, Rook and Lu, 2002). Loneliness has also been

associated with poorer immune status including poorer natural killer cell function (Kiecolt-Glaser and Et Al., 1984), smaller proliferative response to phytohemagglutinin stimulation (Kiecolt-Glaser, Ricker, George et al., 1984) and higher levels of antibody to Epstein-Barr Virus (suggesting less immune control over this pathogen) (Glaser, Kiecolt-Glaser, Speicher et al., 1985). In contrast, feelings of loneliness predicted less rapid decline in numbers of CD4+ cells in HIV positive men over a three year follow-up suggesting a slower progression of AIDS (Miller, Kemeny, Taylor et al., 1997) and were unrelated to antibody (Ab) formation in response to a low dose Hepatitis B vaccine (Jabaaij, Grosheide, Heijntink et al., 1993).

The study we report compares the effects of social isolation and loneliness on a component of health--immune competence as assessed by the amount of antibody 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, Ernst, Burleson et al., 2000), lonely psychiatric inpatients (Kiecolt-Glaser et al., 1984), and in socially isolated preschool children (Sanchez-Martin, Cardas, Ahedo et al., 2001). Another potential pathway is via differences in health practices (Cohen, 1988; Rook, 1984). Loneliness has been associated with poor sleep quality (Berg et al., 1981; Cacioppo et al., 2000; Cacioppo, Hawkley, Berntson et al., 2002) and alcoholism (Nerviano and Gross, 1976) and isolation with smoking, alcohol consumption, and poorer sleep and exercise habits (Berkman and Syme, 1979). There may also be alternative factors that give rise to the associations between isolation, loneliness, and immune response. For example,

loneliness has been associated with psychological stress, negative affect and depression (Russell, Peplau and Cutrona, 1980) as well as with personality characteristics such as low self-esteem, introversion, hostility and neuroticism (Berg et al., 1981; Cutrona, 1982; Levin and Stokes, 1986; Russell et al., 1980). Many of these variables have also been correlated with immune functioning (Cohen, Doyle, Turner et al., in press; Cohen, Turner, Alper et al., in press; Marsland, Cohen, Rabin et al., 2001; Miller, Cohen, Rabin et al., 1999). It is possible then, that one of these factors mediates associations between loneliness and health-related outcomes.

Others have suggested more specific theories of how isolation and loneliness might influence health. Hawkley and Cacioppo (2003) argued that social isolation influences health via feelings of loneliness since loneliness gauges distress over the current social status quo. The same research group also postulates that this influence on health may occur via changes in restorative behaviors (i.e. the salubrity of sleep; (Cacioppo, Hawkley, Berntson et al., 2002)). Rook (Rook, 1984), on the other hand, suggests that loneliness and isolation may operate on health via discrete health-altering pathways. Specifically, she suggests 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.

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 freshman 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 and Rabin, 2001). We

chose to study incoming freshman since they are experiencing a period 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 us with the opportunity to determine if lonely and/or isolated individuals are more likely to engage in detrimental health behaviors and if these in turn mediate the relationship between these social factors and immunity.

Levels of loneliness, stress, mood and health behaviors were monitored for two weeks surrounding the influenza immunization with electronic daily diaries and questionnaires. This was followed by 3.5 months of bi-weekly questionnaires assessing continued levels of loneliness, stress, and mood. Biological measures included salivary cortisol (collected over 5 days surrounding vaccination) and specific antibody response which was determined via blood samples drawn at baseline (day of vaccination) as well as one and four months post-vaccination.

Method

Subjects

Participants were college freshman (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. Pregnant or breast-feeding women as well as individuals with immunologically related health problems were excluded. All subjects were paid \$120 for their participation. One subject completed all components of the study except for the 4

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

Procedures

Demographic, psychological, and health practice questionnaires were administered five to six days prior to immunization. Two days prior to immunization participants began 13 days of electronic momentary assessment (EMA) using a palm computer (ThinkPad, IBM Corp.; White Plains, NY). Participants reported their current loneliness and affect four times daily (1, 4, 9, and 11 hours after waking up) when cued by their palm computer. 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 two through six of the protocol, 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, bi-weekly e-mail (or phone) questionnaires were administered to assess stress, mood and loneliness over the following 14 weeks. Antibody levels were assessed at baseline (day of immunization), and at one and four months post-immunization.

Measures of Loneliness and Social Network Size

Loneliness was assessed at study baseline using the short version of the UCLA Loneliness Scale (Russell, 1996). This 8-item scale measures the extent that the participant feels lonely and isolated ($\alpha=0.86$). To capture feelings of loneliness over the ambulatory and follow-up period, participants indicated the extent to which they felt "lonely" and "isolated" at each diary entry (how you feel now) and bi-weekly follow-up (feelings over the last two 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 correlated $.80$. When the 13 EMA and 7 follow-up scores were entered into a principal component factor analysis, all loaded $.50$ 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 administered the Social Networks in Adult Life questionnaire (Convoy Measure) (Antonucci and 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 using a modified version of the subscales (see Feldman, Cohen, Doyle 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 are 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 4-item version of Rosenberg Self-esteem scale (Rosenberg, 1965) at study onset. Participants rated on a scale of one to four how strongly they agreed with each item (e.g. I take a positive attitude towards myself) with one indicating strong disagreement and four indicating strong agreement ($\alpha=.91$). Finally, hostility was determined at study baseline using the 20-item version of the Cook-Medley Hostility Scale (Barefoot, Dodge, Peterson et al., 1989). Participants answered 20-true/false questions indicating their hostile affect, cynicism and aggressive responding ($\alpha=.61$).

Depressive Symptoms, Affect and Psychological Stress

Depressive symptoms were assessed at baseline using the 10-item version of the Center for Epidemiologic Studies Depression scale (CESD-10) (Andresen, Malmgren, Carter et al., 1994). The items were scored on a 4-point scale where 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 ($\alpha=.79$).

Trait Negative and Positive affect (NA & PA) were assessed using adjectives drawn from a factor analytic study of mood adjectives (Usala and Hertzog, 1989) from the Profile of Mood States (Lorr, McNair and Fisher, 1982). This questionnaire uses eight groups of adjectives that gauge how much NA (anxiety, depression, hostility, fear, fatigue) and PA (well-being, vigor and calm) a person generally experiences. Each item was rated on a scale of 0 (not at all accurate) to 4 (extremely accurate) according to how much that trait reflected how participants generally felt. The overall alpha for NA was .85 and .88 for PA.

Mood was also assessed at each diary measure using similar adjectives. The four negative items used are associated with two subcategories of NA: anxiety (jittery, nervous), and depression (unhappy, sad). The overall alpha for the 4-items over the 13 interviews ranged from .84 to .91. The 8 positive items are associated with three subcategories of positive affect: vigor (active, intense, lively, enthusiastic), well-being (happy, cheerful) and calm (calm, relaxed). The overall alphas for the 8-items over the 13 interviews ranged from .86 to .95. Each item was rated on a scale of 0 (not at all accurate) to 4 (extremely accurate) according to how much that word reflected how they felt at that moment. The same items in the diary portion of the study were assessed bi-weekly in the follow-up asking participants how they had felt over the previous two 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 bi-weekly questionnaires (NA alpha=.97, PA alpha=.94).

Psychological stress data were also gathered at each diary entry as well as bi-weekly over the follow-up. At each assessment subjects reported the extent that they felt “overwhelmed” and “stressed”. Likert scale response options were identical to those for the ambulatory/bi-weekly 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

Health practices were assessed by questionnaire at baseline with an inventory that has been used in other published research from this laboratory (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 (PSQI) (Buysse, Reynolds, Monk et al., 1989). Physical activity was assessed by asking participants how often they engaged in strenuous activity (number of days/weeks) every week using an item from the Paffenberger Activity Questionnaire (Paffenbarger, Blair, Lee et al., 1993).

All of the health behaviors were assessed once each day by EMA and were averaged across the 13 EMA days. Alcohol consumption and smoking were determined by number of drinks/units smoked; physical activity by the number of times exercised and number of minutes exercised; and sleep by three measures based on questions from the PSQI (Buysse et al., 1989)--sleep duration (hours), sleep loss (minutes), and sleep quality (rated on a 0 (very poor) to 4 (very good) scale). Average scores were tabulated for each of these variables. Missing days were not included when calculating averages. Missing data ranged from approximately 6%-16% at any given time point.

Cortisol

From one day prior to immunization to three days post, participants provided salivary cortisol samples four times daily by lightly chewing on a cotton dental roll for one minute 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 was 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 five days. Cortisol data were log transformed prior to analyses.

Vaccine and Measure of Antibody Titers

A 20-ml blood sample was obtained via antecubital venipuncture just before vaccination, and subsequently at one month, and four months post-vaccination. The Fluzone vaccine was administered on day 3 of the study and consisted of three antigens: A/New Caledonia, A/Sidney, and B/Yamanashi or B/Victoria (substituted for B/Yamanashi in the 2001 vaccine). For the statistical analyses, the two B viruses were collapsed together. (Separate analyses of the B viruses result in identical conclusions). Antigen-specific Ab titers were determined using a standard hemagglutination inhibition protocol (Miller, Cohen, Pressman et al., 2003).

Results

Statistical Analyses

Antibody and cortisol levels were log (base-10) transformed and total loneliness, baseline CES-D and average 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.

We used multiple linear regressions to predict the post-immunization Ab levels, health behaviors, and cortisol levels. We first entered the standard controls including sex, cohort, 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 R squared change and F values when there was a main effect of the regression step. Subjects who had maximal titers at baseline were excluded from immune analyses due to our inability to gauge their response to the antigen (New Caledonia N=5; Panama N=6; N=0 for B viruses).

Immunization studies are generally done in vulnerable populations like the elderly where one expects substantial variability in immune response (Cohen et al., 2001; Glaser, Kiecolt-Glaser, Malarkey et al., 1998; Vedhara, Cox, Wilcock et al., 1999). Preliminary analyses revealed that despite our young healthy population, there was some variability in response to the three components of the vaccination but substantially greater variance in change from baseline to follow-ups was found in response (in log titers) to the New Caledonia virus ($t=8.8$, $p<.001$ at 1 month and $t= 9.3$ $p<.001$ at 4 months in comparison to Panama; $t=4.7$, $P<.001$ and $t=6.2$, $p<.001$ in comparison to B viruses). Consistent with these relative restrictions of variance, we found no associations between psychosocial variables and the Panama and B viruses. Consequently, the analyses discussed below are restricted to only the A/New Caledonia component of the vaccination.

Are social network size and loneliness associated with antibody response?

Separate analyses assessed whether social network size and loneliness were associated with Ab response at one and four months for the A/New Caledonia antigen. Smaller social networks were associated with lower Ab production at both one ($\Delta R^2=.07$, $F_{(2,71)} 4.57$, $p<.05$) and four months ($\Delta R^2=.07$, $F_{(2,70)} 5.10$, $p<.01$). As apparent from Figure 1, this association was attributable to lower Ab production in the most isolated tertile.

INSERT FIGURE 1 ABOUT HERE

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 one month and four months using both the UCLA and total loneliness in separate analyses. Higher levels of total loneliness were associated in a linear fashion with lower Ab levels at both one month ($\Delta R^2=.04$, $F_{(1,72)} 4.72$, $p<.05$) and four months ($\Delta R^2=.04$, $F_{(1,71)} 5.07$, $p<.05$) for the A/New Caledonia vaccination. 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 will focus on the total loneliness measure.

INSERT FIGURE 2 ABOUT HERE

What mechanism underlies the relationship between social variables and antibody response?

For a variable to be considered a mediator, it must correlate with the independent predictor, 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 and Kenny, 1986). We were interested in whether or not health

behaviors, cortisol, personality and/or affective factors operated as pathways linking social variables with immunization response. We began by testing whether each of the proposed pathways was individually associated with loneliness and/or network size.

Health Behavior. Loneliness (controlling for sex, cohort, and race) was not associated with physical activity, smoking, alcohol consumption, nor with sleep duration assessed by EMA and baseline questionnaires. It was however, associated with poorer sleep efficiency ($\Delta R^2=.07$, $F_{(1,72)} 6.3$, $p<.05$) (assessed at baseline), marginally higher sleep loss ($\Delta R^2=.04$, $F_{(1,78)} 3.2$, $p=.08$). and poorer sleep quality ($\Delta R^2=.04$, $F_{(1,78)} 3.4$, $p=.07$) over the diary period. Social network size was not related to any of the assessed health practices.

Cortisol. Network size and total loneliness were not associated with average cortisol AUC nor with mean levels at the 4 time points. Since cortisol levels were only sampled 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 hour post wake-up) and evening samples (11 hours post wake-up) (1 hour $\Delta R^2=.10$, $F_{(1,50)} 7.0$, $p<.05$; 11 hours $\Delta R^2=.08$, $F_{(1,50)} 4.4$, $p<.05$).

Personality, Affect and Psychological stress. Loneliness was associated with elevated levels of neuroticism and hostility, and marginally lower levels of extraversion, while network size was positively correlated with extraversion (see Table 1). Loneliness was also highly correlated with NA, psychological stress, depressive symptoms, and negatively correlated with PA while large social network size was associated with more PA (see Table 1).

INSERT TABLE ONE ABOUT HERE

Mediation Test. Cortisol measures and health behaviors associated with loneliness were considered as potential mediators of the loneliness-antibody response relationship. However, none of the variables associated with loneliness were significantly related to Ab levels, therefore none were potential mediators.

Extraversion, neuroticism, self-esteem and hostility were unrelated to Ab levels, and were therefore not potential mediators. To test Rook's hypothesis that distress mediates the influence of loneliness on health outcomes, we entered NA and PA measures (diary & baseline assessments), as well as average stress into a stepwise regression to determine whether these variables would lessen the association between loneliness and Ab response. Only psychological stress entered the equation revealing an association with both the one and four month response to A/New Caledonia (1 month: $\Delta R^2=.04$, $F_{(1,72)} 5.2$, $p<.05$; 4 months: $\Delta R^2=.04$, $F_{(1,71)} 5.6$, $p<.05$) as we previously reported, stress averaged over the EMA period (2 weeks) was associated with Ab response (Miller et al., 2003). Stress explained approximately 50% of the association of loneliness with Ab levels and reduced this relationship to $p>.05$ (1 month: $\Delta R^2=.02$, $F_{(1,71)} 2.7$, $p=.10$; 4 months: $\Delta R^2=.02$, $F_{(1,70)} 3.0$, $p=.09$). The association between social network size and immune response was not significantly altered by the inclusion of these variables

Is the association of network size with immunization attributable to loneliness?

Hawkey and Cacioppo (Hawkey and Cacioppo, 2003) predict that social network size will influence health 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 Caldonia at both time points. When loneliness was entered in the first block, the network effects were reduced to 6% at one and four months but remained statistically significant ($p=.02$). Hence loneliness accounted for only 14% of the variability ($[(\text{initial } \Delta R^2 - \text{new } \Delta R^2) / \text{initial } \Delta R^2] = [.07 - .06 / .07] = .14$) initially accounted for by social network size.

Does the influence of loneliness depend on 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: $\Delta R^2=.03$, $F_{(1,70)} 3.6$, $p=.06$; 4 months: $\Delta R^2=.04$, $F_{(1,69)} 3.5$, $p=.07$), and social networks size (1 month: $\Delta R^2=.06$, $F_{(2,70)} 4.0$, $p<.05$; 4 months: $\Delta R^2=.06$, $F_{(2,69)} 4.3$, $p<.05$). The interaction between social network size and loneliness was significant at both one month ($\Delta R^2=.09$, $F_{(2,68)} 6.6$, $p<.01$) and four months ($\Delta R^2=.07$, $F_{(2,67)} 5.4$, $p<.01$) (see Figures 3 and 4). Individuals most at risk were those who were socially isolated at baseline as well as lonely throughout the four months of the study. Interestingly, loneliness was not associated with lower Ab response when social network size was large, while network size was not associated with Ab response when loneliness was low.

INSERT FIGURE 3 and 4 ABOUT HERE

Discussion

The mere existence of social ties, independent of subjective loneliness, was associated with immune response to the influenza vaccination. Being in the lowest tertile

of social network size (4-12 members in the total network) was associated with less antibody production than the other two tertiles (ranging from 13-20 contacts). College students have many opportunities for social contacts via roommates, dormitories, classes, university organizations, and jobs. Consequently, availability of contacts is an unlikely explanation for isolation. Also, individuals with few contacts 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. Alternatively, they may lack social support to buffer the stress occurring during the first semester of school. However, these explanations seem unlikely due the lack of association between network size, stress, depression and self-esteem.

Like earlier work (Jabaajj et al., 1993), we failed to find a relationship between baseline loneliness (assessed by the UCLA scale) and Ab response. However, our total loneliness score was associated with poorer Ab response to vaccination. Because our score gauged feelings repeatedly over four months post-vaccination, it was both contemporaneous with the immunization response and a more reliable measure of chronic loneliness (thought to pose the greatest threat to well-being (Weiss, 1973)). In contrast, the UCLA loneliness scale may have picked up the transient loneliness associated with moving to a new school which may not have the same health implications as long lasting feelings.

Hawkley and Cacioppo (Hawkley and Cacioppo, 2003) postulated that isolation should influence health via perceptions of loneliness. However, social network size and loneliness were not correlated here. Moreover, when loneliness was included as a covariate in a regression of social network size predicting Ab levels, there was only a

small reduction in the variability accounted for by social network size and the relation remained significant. Intriguingly, when individuals reported large social networks, the degree of loneliness had no detrimental impact on Ab levels, while network size remained unassociated with poor immune response when loneliness was low. In short, neither loneliness without objective isolation nor objective isolation without loneliness have detrimental biological consequences.

Despite considerable conceptual overlap with affect and personality characteristics, associations between social network size, loneliness, and Ab response were not mediated by these factors. Although loneliness was correlated with more NA, less PA, more depression and negative personality variables, and large network size was associated with higher extraversion and PA, none of these variables were associated with Ab response. Psychological stress, however, was associated with Ab levels (As reported previously: Miller et al., 2003) and with loneliness. When it was included as a mediator, it decreased the association between loneliness and Ab response by 50%. This provides partial support for Rook's theory (Rook, 1984) that loneliness impacts health via feelings of distress. However, since approximately 50% of the variability explained by loneliness remained after controlling for stress, there are other pathways at work as well beyond personality and affective factors. Network size was not associated with stress nor was its association with Ab levels altered by the inclusion of stress in the equation.

Cortisol was not the mechanism responsible for 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, since none of the cortisol measures (AUC and at all time points) were related to Ab response, they are not plausible mediators.

Social network size and loneliness were not associated with health practices with the exception of sleep patterns. High total loneliness was associated with poorer sleep efficiency at baseline and marginally associated with more sleep loss and poorer sleep quality over the diary assessment. This finding is in line with Cacioppo et al. (2002) who showed that lonely participants had poorer sleep efficiency both in a natural setting as well as in a laboratory assessment. In the current study, however, sleep quality and efficiency were not associated with Ab response. Rook (1984) theorized that social networks prevent deviant behavior during periods of rapid personal change. However, health practices were not associated with network size in our Freshman. Because the first year of university is a period of transition, it is plausible that other un-assessed behaviors (e.g. substance abuse, nutrition, caffeine intake) could mediate the association between isolation and immune function. In line with this theory, coping via substance abuse has been associated with poor Ab response to a hepatitis B vaccination (Burns, Carroll, Ring et al., 2002). Alternatively, health behaviors of Freshman 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 find influences of social network size and/or loneliness.

The prospective nature of our social network-immune finding precludes the possibility of reverse causality. Although we have excluded several key factors (stress, affect, personality), 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 and 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, Desouza, Ratto-Kim et al., 2002), only 6-7% of our subjects would have been below this level during follow-up. Interestingly, all of these subjects 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 only related to one of the three viruses in the influenza vaccine? We think this is attributable to greater variability in response to the A/New Caledonia virus. The A/New Caledonia virus had the greatest range of change from baseline to one and four months. On the other hand, it is always possible that there is something about this specific viral immunization that makes it more susceptible to psychological manipulation.

In sum, both social network size and loneliness were associated with the production of less Ab in response to immunization. Loneliness and social network size were not correlated with one another and were relatively independent associations with Ab, however they do appear to have a synergistic relationship with Ab response. Specifically, loneliness was not associated with detriments in immunity when social

network size was large, and network size was not associated with poor immune response when loneliness was low. Loneliness was associated with poor sleep efficiency, sleep quality and with concurrent elevations in circulating levels of cortisol. To our knowledge, this is the first in vivo evidence that loneliness and social network size are associated with immunization response.

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ACKNOWLEDGEMENTS

This research was supported by a grant from the National Institute of Mental Health (MH50430) and supplemental funding from the John D. and Catherine T. MacArthur Foundation Research Network on Socioeconomic Status and Health. It was facilitated by grants from the National, Heart, Lung, and Blood Institute to the Pittsburgh Mind-Body Center (HL65111 & HL65112). Ms. Pressman's efforts were supported by a Post-Graduate Scholarship from the Natural Science & Engineering Research Council of Canada. Dr. Cohen's participation was facilitated by a Senior Scientist Award from the National Institute of Mental Health (MH00721). Dr. Miller's efforts were supported by a Gran-in-Aid from the American Heart Association (0160367Z) and a Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression.

The authors extend their gratitude to Ellen Conser, Elena Balestreire, Ruomei Liang, Leona Middleton, and Kristen Weinzierl for their help with data collection and management; to Dr. Clemens Kirschbaum for conducting the salivary cortisol assays; to Rosalyn Battaglia for performing the hemagglutination inhibition protocol; and to Diane Dawson, Janet Franzen and Sharon McCartney for administering the vaccinations and taking blood samples. Correspondence concerning this article should be addressed to Sarah Pressman at the Department of Psychology, Carnegie Mellon University, 5000 Forbes Avenue, Pittsburgh, PA, USA 15213. Electronic mail may be sent to press@cmu.edu.

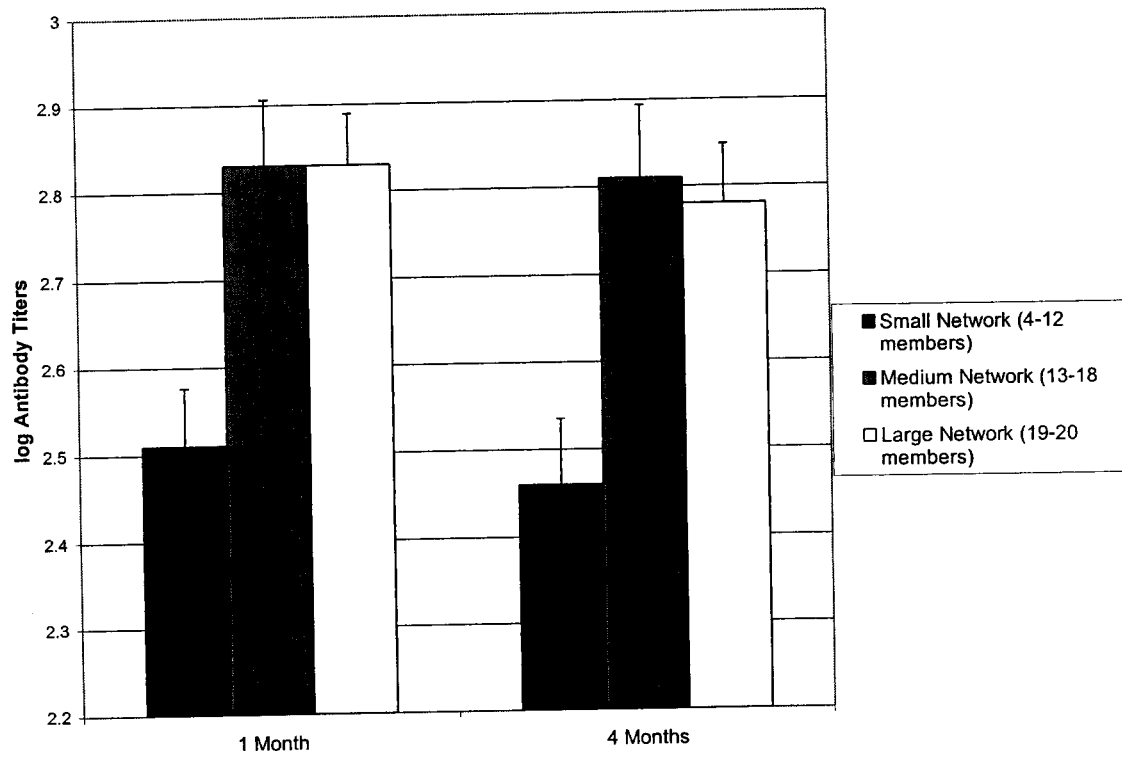


Figure 1. Antibody levels at one and four months adjusted for control variables (unstandardized predicted means). The association between social network size and antibody response was significant ($p < .01$).

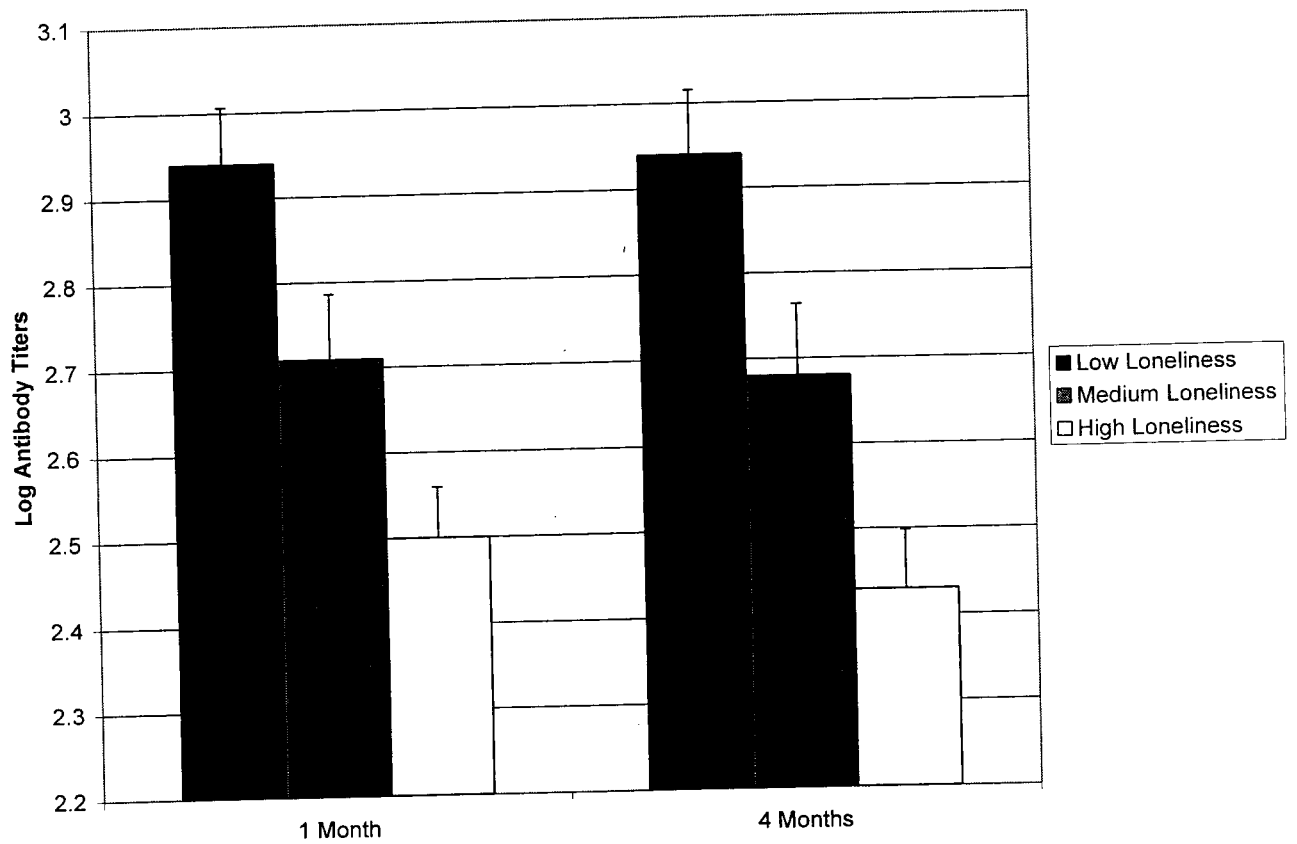


Figure 2. Antibody levels at one and four months adjusted for control variables (unstandardized predicted means). The association between loneliness and antibody response was significant ($p < .05$). Loneliness was analyzed as a continuous variable and is displayed in tertiles for graphing purposes only.

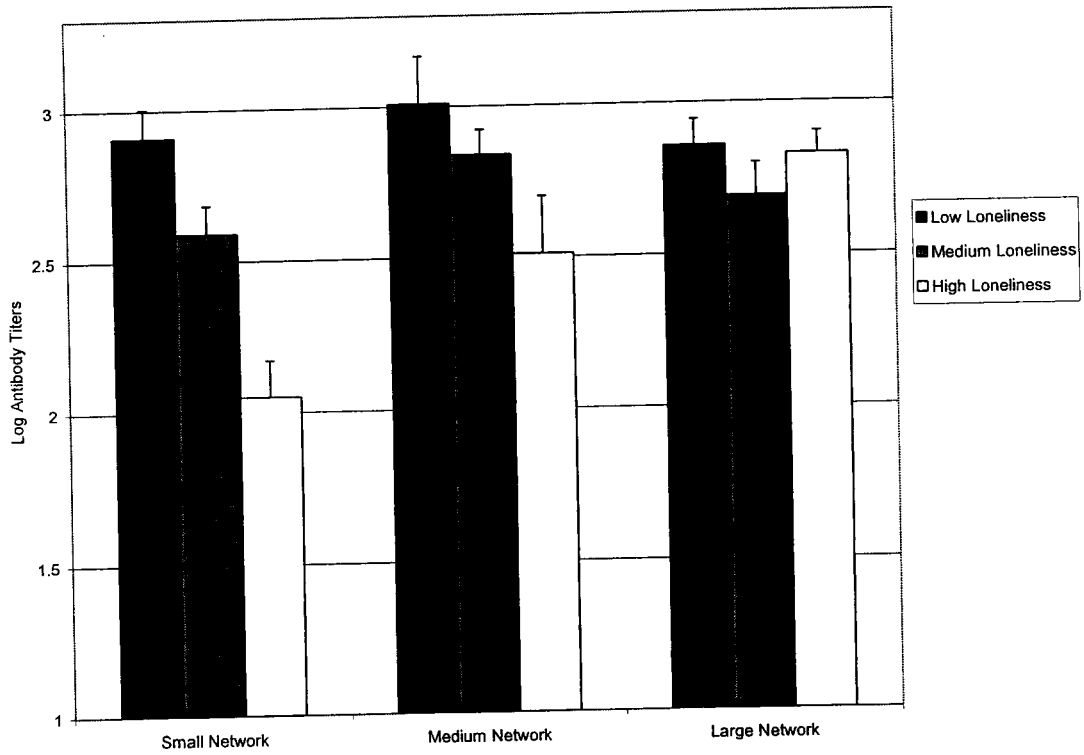


Figure 3. Mean antibody levels at one month adjusted for control variables (unstandardized predicted means). High levels of loneliness were associated with poor AB response for those with small social networks but not for those with larger networks.

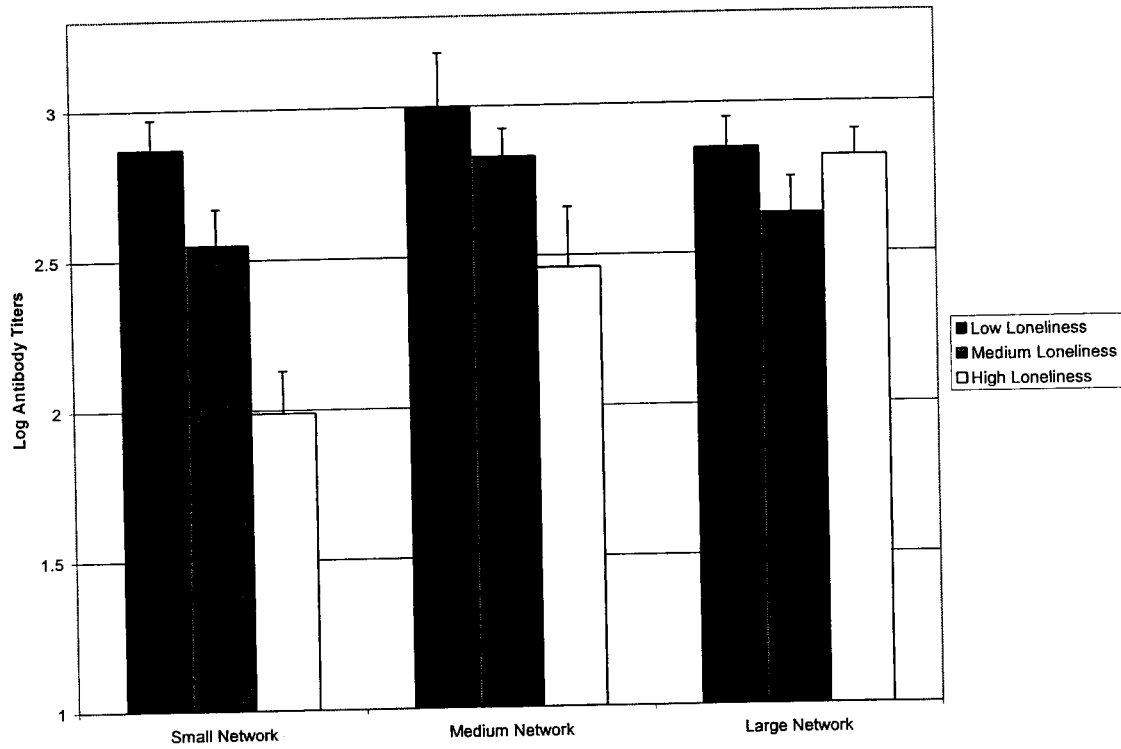


Figure 4. Mean antibody levels at four months adjusted for control variables (unstandardized predicted means). High levels of loneliness were associated with poor AB response for those with small social networks but not for those with larger networks.

Table 1
*Correlations between Total Loneliness, Social
 Network Size and Psychological Variables*

List	Loneliness ^a	Network Size ^a
Neuroticism	.34**	-.13
Self Esteem	-0.008	.10
Extraversion	-.020 †	.22*
Hostility	0.30 **	-.033
Baseline Negative Affect	.29**	.014
Average Negative Affect	.74**	-.061
Baseline Positive Affect	-.33**	.23*
Average Positive Affect	-.31**	-.011
Baseline Depression	.52**	-.083
Average Stress	.31**	-.048

* $p < .05$

** $p < .01$

† $p < .08$

^a Pearson correlation coefficients.