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Bereavement and Marriage are Associated with Antibody Response to Influenza Vaccination in the Elderly.

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Abstract

Stressful life events exposure including bereavement, an event commonly experienced by elderly people, social support, marital status and satisfaction were examined in relation to antibody response to the annual trivalent influenza vaccination in an elderly community sample (N = 184). Antibody response was assessed at baseline, and at one and 12 months following vaccination. Taking into account baseline antibody titer, overall life events exposure and social support were not associated with response to any of the influenza strains. However, bereavement in the year prior to vaccination was negatively associated with the one-month response to the A/Panama and B/Shangdong strains. Being married and having higher marital satisfaction was also associated with higher peak responses to the A/Panama influenza strain at one month. The positive association between marital satisfaction and A/Panama response was particularly evident in the younger half of the married sample. These associations largely withstood adjustment for potential confounders. Thus, in the elderly, peak antibody response was associated with bereavement and marriage, and not the more general factors, life events and social support, related to antibody response in student samples. This suggests the importance of taking a life course approach to examining relationships between psychosocial factors and immunity, and that interventions to modify the impact of these factors should address those most salient for each age group.

Keywords: bereavement, elderly, influenza vaccination, marital status, marital satisfaction, social support, stressful life events

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1. Introduction

The antibody response to vaccination is considered a useful means of studying psychosocial influences on *in vivo* immune function (Burns, Carroll, Ring & Drayson, 2003b; Cohen, Miller & Rabin, 2001; Vedhara, Fox & Wang, 1999b). The most consistent finding is the association between frequent exposure to stressful life events and/or high levels of perceived stress and a poorer antibody response to a variety of vaccinations (Burns et al., 2003b; Cohen et al., 2001; Glaser, Kiecolt-Glaser, Bonneau, Malarkey, Kennedy & Hughes, 1992; Glaser, Kiecolt-Glaser, Malarkey & Sheridan, 1998; Glaser, Sheridan, Malarkey, MacCallum & Kiecolt-Glaser, 2000; Kiecolt-Glaser, Glaser, Gravenstein, Malarkey & Sheridan, 1996; Kohut, Cooper, Nickolaus, Russell & Cunnick, 2002; Miller, Cohen, Pressman, Barkin, Rabin & Treanor, 2004; Phillips, Burns, Carroll, Ring & Drayson, 2005a; Vedhara, Cox, Wilcock, Perks, Hunt, Anderson, Lightman & Shanks, 1999a; Yang and Glaser, 2002). The majority of this research has been carried out in younger samples. Most of the studies in older populations have used the caregiver-control model, in which the vaccination response of elderly people care-giving for a spouse with dementia are compared to those of non care-giving controls. These studies have demonstrated that exposure to this very severe life stressor is associated with poor antibody responses to both influenza (Glaser et al., 1998; Glaser et al., 2000; Kiecolt-Glaser et al., 1996; Vedhara et al., 1999a) and pneumococcal (Glaser et al., 2000) vaccinations. Whether this effect is generalisable to elderly individuals experiencing a range of more mundane stress exposures remains unclear. Although one study has reported that perceived stress was associated with a poorer antibody response to the influenza vaccine in the elderly (Kohut et al., 2002), a recent small scale study found no association between perceived stress and antibody status following this vaccination in elderly nursing home residents (Moynihan, Larson, Treanor, Duberstein, Power, Shore & Ader, 2004). There are no published studies to date on the association between stressful life events exposure and vaccination response in the elderly. In particular, given the likelihood of exposure to bereavement in the elderly, and the negative and long term impact it has (Bodnar and Kiecolt-Glaser, 1994), this specific life event is also worth studying in this context, especially as bereavement has been negatively related to natural killer cell cytotoxicity and lymphocyte proliferation to mitogen (Bartrop, Luckhurst, Lazarus, Kiloh & Penny, 1977; Goodkin, Feaster, Tuttle, Blaney, Kumar, Baum, Shapshak & Fletcher, 1996; Irwin, Daniels, Smith, Bloom & Weiner, 1987; Kemeny, Weiner, Duran, Taylor, Visscher & Fahey, 1995;

Schleifer, Keller, Camerino, Thornton & Stein, 1983; Zisook, Shuchter, Irwin, Darko, Sledge & Resovsky, 1994).

Psychosocial factors other than psychological stress have received less attention in the context of the vaccination model, particularly in the elderly. The relationship between social support and the antibody response has been examined in three studies of student samples. First, greater social support was associated with a stronger combined immune response to the booster third inoculation of the hepatitis B vaccination (Glaser et al., 1992). Second, loneliness and smaller social network size were related to a poorer antibody response to the A/New Caledonian strain of the influenza vaccination (Pressman, Cohen, Miller, Barkin, Rabin & Treanor, 2005). Third, better social support was associated with stronger antibody responses to the A/Panama strain following influenza vaccination (Phillips et al., 2005a). In contrast, in the only study of social support in the elderly, social support was negatively correlated with A/Panama influenza strain antibody status following vaccination (Moynihan et al., 2004). Further examination of the association between social support in the elderly and the antibody response is warranted.

There is also evidence that marriage is beneficial to health; unmarried individuals suffer greater morbidity and mortality from a range of acute and chronic conditions (Gordon and Rosenthal, 1995; House, Landis & Umberson, 1988; Verbrugge, 1979). However, it is not only marital status which has been found to be associated with psychological and physical health, but also the quality of marriage (see e.g., Kiecolt-Glaser and Newton, 2001; Robles and Kiecolt-Glaser, 2003). There is growing evidence that marital quality relates to immune function. Using *in vitro* immune measures, individuals reporting poorer marital quality displayed higher Epstein-Barr virus titers, indicating poorer latent virus control, and a poorer blastogenic response to PHA mitogen (Kiecolt-Glaser, Fisher, Ogrocki, Stout, Speicher & Glaser, 1987; Kiecolt-Glaser, Kennedy, Malkoff, Fisher, Speicher & Glaser, 1988). Marital conflict has also been found to be associated with poorer natural killer cell lysis (Miller, Dopp, Myers, Stevens & Fahey, 1999), poorer blastogenic response to two mitogens, and increased Epstein-Barr virus titers (Kiecolt-Glaser, Glaser, Cacioppo, MacCallum, Snydersmith, Kim & Malarkey, 1997; Kiecolt-Glaser, Malarkey, Chee, Newton, Cacioppo, Mao & Glaser, 1993). As far as we are aware, marital status and satisfaction has not yet been assessed in relation to antibody status following vaccination.

The present study exploited the UK National Health Service initiative to immunize annually persons over the age of 65 years with the trivalent influenza vaccination. The

association between life events exposure in general, and bereavement in particular, social support, marital status and satisfaction, and the antibody response to the vaccination was examined in a sample of those taking part in this programme. It was hypothesized that participants with higher life events exposure, and lower social support would exhibit lower antibody titers following vaccination. It was also hypothesized that individuals who were married and especially those with high marital satisfaction would also show a better antibody response to the vaccine.

2. Method

2.1 Participants

One hundred and eighty-four elderly people (80 men and 104 women) were recruited from five medical practices in Birmingham, UK between September and November 2003. All participants were aged 65 years or older and had no history of negative reactions to blood sampling, no acute infection, or known current immune disorder. Baseline demographic information was provided by 154 participants. Participants' mean age at entry to the study was 74.6 (*SD* = 6.26) years and their mean body mass index, based on self-reported height and weight was 25.7 (*SD* = 3.81) kg/m^2. In terms of ethnicity, all but four described themselves as "white": three described themselves as "black", and one as "other". Eighty-nine percent of the sample reported being non-smokers. Participants were asked to indicate when, if ever, they had received an influenza vaccination. Almost all (96%) reported previously receiving an influenza vaccination; the median number of annual influenza vaccinations received was 4 (interquartile range = 5). The study was approved by the appropriate Research Ethics Committees, and all participants provided written informed consent.

2.2 Study Design

The study comprised three sessions. At the initial baseline session, elderly patients attending for their routine annual influenza vaccination were invited to participate. Those who agreed and met the inclusion criteria provided a single venous blood sample before

vaccination to determine baseline antibody status, and took home a questionnaire pack to return by mail. Follow-up sessions took place one month (mean = 28.6; *SD* = 2.7 days) and 12 months (mean = 359.8; *SD* = 10.3 days) later. At the follow-up sessions, participants again provided a venous blood sample to assess antibody status to each vaccine component, and received further questionnaire packs for completion. Both antibody and questionnaire data were available at baseline for 143 participants, and for 136 at one month follow-up. At 12 month follow-up completed questionnaires were returned by 104 participants[1].

2.3 Questionnaires

Standard socio-demographic and clinical information was obtained, including date of birth, current or previous occupation, postcode, height, weight, number of previous influenza vaccinations, and presence of ongoing chronic medical conditions at the initial baseline session. Participants also completed the following questionnaires:

2.3.1 Life Events

Exposure to major life events was measured at baseline for the previous year using the Life Events Survey from the West of Scotland 20-07 study (Carroll, Phillips, Ring, Der & Hunt, 2005; Ford, Ecob, Hunt, Macintyre & West, 1994). It contains 61 items examining several areas of life: health (e.g. period in hospital); marriage/co-habitation (e.g. living apart, divorce or split from long term partner); relationships (e.g. serious disagreement within family); deaths (e.g. spouse / partner died); work (e.g. made redundant or changed work); housing (e.g. problems moving house); finances (e.g. a drop in income); and general (e.g. violence, being attacked). Participants had to indicate whether certain stressful events in these categories have happened or not in the past year at baseline assessment and the past month at the first follow-up. They were then required to rate the seriousness of identified events on a 10-point scale, where 1 = something really small and unimportant and 10 = the worst thing that could happen to you. The present assessment method is based on the well-established Life Events and Difficulties Schedule (Brown and Harris, 1989) and includes the same domains of personal experience. The five items comprising the most serious events subscale, "Deaths", measuring deaths of spouse, close family or friends, was interrogated and a binary variable, bereaved versus non-bereaved, was derived. The remaining subscales

comprising the life events schedule were not analyzed separately due to the low incidence of occurrence of events.

2.3.2 Social Support

Social support was measured at the one month follow-up. The Medical Outcomes Study Social Support Survey (MOSSSS) (Sherbourne and Stewart, 1991) assesses perceived social support, including both structural (i.e. the number of friends and relatives from whom support can be sought) and functional (i.e. the availability of different types of support) measures. The questionnaire addresses four functional support dimensions: emotional/informational (e.g. someone to listen to you when you need to talk); tangible (e.g. someone to help you if you were confined to bed); affectionate (e.g. someone who hugs you); and positive social interaction (e.g. someone to get together with for relaxation). The questionnaire has a five-point Likert-type format ranging from none of the time to all of the time. Internal consistency is high, with all alphas exceeding 0.91, and one-year test-retest reliability values ranging from 0.72 to 0.78 have been reported for the four dimensions (Sherbourne and Stewart, 1991). In the present sample, internal reliability was 0.98.

2.3.3 Marital Status and Satisfaction

At the 12- month follow-up session, participants indicated whether they were: single; divorced/separated; widowed; or married/co-habiting. Marital satisfaction was assessed using a modified form of the Pittsburgh Marital Adjustment Test (Locke and Wallace, 1959) comprising 15 items measuring marital adjustment and satisfaction among married participants and those in long-term committed relationships. Respondents answer a question about their general level of happiness in the present marriage or long-term live-in relationship, their perception of the level of agreement between the spouses on a number of issues, ways of handling disagreement, and regrets that one might have about being in this particular relationship. The maximum score using the current scoring system was 61 with lower scores indicating lower satisfaction. This measure is widely used in marital research due to its reliability and validity in discriminating satisfied and unsatisfied couples (Kiecolt-Glaser et al., 1997); the scale has high internal reliability (alpha = 0.90) (Locke and Wallace, 1959),

and impressive one-month test-retest reliability (r = 0.82 to 0.84) (Freeston and Plechaty, 1997). In the present sample, the internal reliability was 0.81.

2.3.4 Health Behaviours

Associations between psychosocial factors and antibody response could be driven by variations in unhealthy behaviours, such as alcohol consumption, smoking and decreased time spent exercising, which have been associated with exposure to stress (Heslop, Davey Smith, Carroll, Macleod, Hyland & Hart, 2001) and vaccination response (Gluckman, Dvorak & MacGregor, 1977; MacKenzie, MacKenzie & Holt, 1976). In order to be able to test whether or not association between psychosocial factors and the antibody response were attributable to variations in health behaviours in the present study, these behaviours were assessed at the baseline session for the previous year using a questionnaire adapted from the Whitehall II study (Marmot, Davey-Smith, Stansfield, Patel, North, Head, White, Brunner & Feeney, 1991). Participants were asked, on average how much they smoked (0, 1-5, 6-10, 11-20, 21+ cigarettes per day); how much alcohol they drank (0, 1-5, 6-10, 11-20, 21-40, 40+ units per week); how long they slept (0-3, 4-5, 6-7, 8-9, 10-11, 12+ hours per night); and how often they take vitamin/mineral supplements (never, once a month, once a week, a few per week, every day, more than one per day). A simple categorical scoring system was used in all cases, for example if a participant indicated that they slept for 8-9 hours per night, they were allocated a score of 3. Participants also reported how much time they spent in activities of light, moderate and vigorous exercise intensity (0, 1-2, 2-5, 6-8, 9-10, 11+ hours per week). The category scores (0,1,2,3,4, or 5), derived from the above were multiplied by a weighting of 1, 2, and 3 for light, moderate, and vigorous intensity activity respectively, and the products summed to yield a composite exercise score.

Participants were asked whether they were on a special diet of any sort (no, vegetarian, vegan, weight-loss, other), and indicated how often they ate breakfast, how many main/cooked meals they had during the day excluding breakfast, and how many cups/cans of caffeinated drink they usually consumed in a day. Participants also reported how often (never, less than once a week, once or twice a week, most days, once a day, two or three times a day, four or more times a day) they ate each of a list of foods. A categorical scoring system was used to assess frequency. From this dietary information, two main measures were derived: scores for fresh fruit and cooked vegetables were summed to give a measure of fruit

and vegetable consumption; and scores for chips/fried food, crisps/similar, sweets/chocolate, biscuits/cakes/puddings, full fat dairy products, and processed meat were summed to provide an index of fat intake.

2.4 Blood samples, vaccinations and immunological assays

At the baseline and the two follow-up sessions, venous blood was collected from an ante-cubital vein into two 7 ml plain tubes (BD Vacutainer, Meylan Cedex). Following blood sampling at the initial session, participants received an influenza vaccine from the nurse at their general practice via intramuscular injection into the upper arm. The 2003-04 influenza vaccine contained three viral strains: A/New Caledonia/20/99 (H1N1)-like strain - A/New Caledonia/20/99 (IVR-116); A/Moscow/10/99 (H3N2)-like strain - A/Panama/2007/99 (RESVIR-17); and B/Hong Kong/330/2001-like strain - B/Shangdong/7/97. The blood samples, which were allowed to clot for at least one hour, were centrifuged at 3500 rpm for 5 min and the separated serum was frozen at –20 °C until assayed for antibody titers. Anti-influenza antibody titers were measured by the serology laboratory of Glaxo Smith Kline Beecham at Dresden, Germany, using a haemagglutination inhibition test as described in the World Health Organisation Manual on Animal Influenza Diagnosis and Surveillance . Wild type flu strains were used for the antigenic analysis; these were A/New Caledonia/20/99, A/Panama/2007/99, and B/Shangdong/7/97.

2.5 Data Reduction and Analysis

Inter-relationships among the psychosocial measures and demographic and health behaviour variables were analysed using correlations for continuous variables and t-tests and chi-square for the binary variables. Due to the skewed distribution, antibody levels at baseline, one-month, and 12-month follow-up were subject to $\log_{10}$ transformation. These were then compared across the three measurement points (baseline, one month, and 12 months) using MANOVA with appropriate post-hoc testing to determine whether logged antibody titer varied significantly from baseline to each of the follow-ups, and between the two follow-ups for each viral strain. Effect sizes are reported in terms of η^2. The basic immunological data are also reported in terms of the number of participants showing a four-fold increase in antibody titer from baseline, taken as the conventional clinical criterion of

adequate protection, at the two follow-up sessions. Hierarchical regression was then conducted using log antibody titer at follow-up to each viral strain as the dependent variables. Log baseline titer was entered at step one to control for baseline antibody status. Each psychosocial independent variable was then entered at step two. For these purposes, marital status was characterised as married/co-habiting (= 1) versus single/divorced/separated/widowed (= 0). Similar regression analyses were undertaken for demographic and health behaviour variables. Any such variables related to follow-up antibody titer were then treated as potential confounders of any association between the psychosocial variables and antibody status. Thus, they were entered along with baseline titer at step one, with the psychosocial independent variable again being entered at step two. Change in R^2 was taken as the measure of effect size. A regression strategy of this sort using the logged titer data controlling for baseline has been used in a number of recent influenza vaccination studies (Miller et al., 2004; Phillips et al., 2005a; Phillips, Carroll, Burns & Drayson, 2005b; Pressman et al., 2005). Any variations in degrees of freedom reflect occasional missing data.

3. Results

3.1 Questionnaire Data

The median (interquartile range) number of life events was 2 (4). The mean (*SD*) life events score, weighted for self-rated severity, was 16.7 (21.30). Forty-five (32%) participants had suffered bereavement in the year prior to vaccination; of these 45, only seven had experienced spousal bereavement. The mean (*SD*) number of close friends was 7.3 (6.50), and total functional social support score was 74.2 (17.04). Sixty-six (63%) of the participants sampled were married/cohabiting, and their mean (*SD*) marital satisfaction score was 50.2 (7.86).

Correlations among the continuous psychosocial and demographic measures are presented in Table 1. Life events score correlated negatively with social support score, and marital satisfaction score was negatively correlated with the number of close friends but positively correlated with functional social support score. T-tests indicated that married individuals (mean = 80.5, SD = 11.68) had higher functional social support scores than unmarried participants (mean = 60.8, SD = 18.14), $t(95) = 6.45$, $p < .001$. There were no

significant differences between married and unmarried participants on the other psychosocial measures, nor, as indicated by chi-square, were married individuals more or less likely to report bereavement. However, married/cohabiting participants were more likely to be from manual occupational households than unmarried participants, $\chi^2(1) = 4.62$, $p = .03$. Bereaved and non-bereaved participants did not differ in terms of the number of close friends, functional social support score or marital satisfaction, nor were the bereaved less likely to be married. None of the demographic variables were related to life events score, structural and functional social support measures, or marital satisfaction with two exceptions; men (mean = 78.8, SD = 14.66) had higher social support scores than women (mean = 70.6, SD = 18.00), $t(132) = 2.84$, $p = .005$, and were more likely to be married, $\chi^2(1) = 13.48$, $p < .001$. Whether or not participants reported suffering from a chronic illness at baseline, was unrelated to any of the psychosocial measures, nor were health behaviours, with one exception; there was a negative correlation between the frequency and intensity of exercise and marital satisfaction, see Table 1.

[Insert Table 1 about here]

3.2 Vaccination Response

The geometric mean *(95%CI)* antibody titer for each of the influenza strains at each time point is displayed in Table 1. The number of participants with and without a four-fold increase to each of the three viral strains at one and 12 month follow-up is presented in Table 2. The majority of participants responded with an initial increase in antibody titer from baseline to one month, although only a minority met the four-fold response criterion. One month represents the approximate time of peak response to influenza antigens. Antibody titers had declined back to baseline by 12 months, which indicates the wisdom of vaccinating the elderly annually with the influenza vaccine (World Health Organization). Given the absence of antibody responses above baseline at 12 months, and the restricted variation in the 12-month titers, subsequent analysis focused on the one-month follow-up antibody data.

[Insert Tables 2 and 3 about here]

3.3 Associations between Stressful Life Events, Bereavement, and Antibody Response

Taking into account baseline antibody status, no statistically significant associations emerged between the life events scores and antibody titer for any of the three influenza viral strains at one month. However, examination of the Deaths subscale indicated that bereavement in the year prior to vaccination was negatively associated with the antibody response at one month to both A/Panama, B = -0.16, 95%CI = -0.30 to -0.02, β = -.15, t = 2.31, p = .02, ΔR^2 = .022, and B/Shangdong, B = -0.21, 95%CI = -0.34 to -0.09, β = -.21, t = 3.42, p = .001, ΔR^2 = .040. These associations are presented in Figure 1 which displays the mean logged antibody titers at one month adjusted for baseline.

[Insert Figure 1 about here]

3.4 Associations between Social Support and Antibody Response

There were no statistically significant associations between antibody titer and either structural social support (network size), or the functional social support score.

3.5 Associations between Marital Status and Antibody Response

Whether or not participants were married/cohabiting was significantly associated with antibody titer to A/Panama at one month, such that married/cohabiting individuals showed a larger antibody response to this viral strain than single/separated/divorced/widowed individuals, B = 0.18, 95%CI = 0.03 to 0.33, β = .17, t = 2.30, p = .02, ΔR^2 = .027. This association is illustrated in Figure 2 which again shows the mean logged antibody titers at one month adjusted for baseline. The analysis was repeated omitting the three participants who were divorced and the one participant who was widowed during the 12 months of the study from the unmarried group. The outcome was unchanged, B = 0.18, 95%CI = 0.02 to 0.24, β = .16, t = 2.17, p = .03, ΔR^2 = .026. As male participants were significantly more likely to be married (86%) than female participants (48%), adjustment for sex was undertaken by entering this variable along with baseline antibody titer in step one of the regression model. The association between marital status and antibody titer remained significant, B = 0.21, 95%CI = 0.01 to 0.42, β = .19, t = 2.05, p = .05, ΔR^2 = .036. Within the unmarried category, the vast majority were widowed individuals (N = 25, 24%), with nine (9%) single participants, and

four (4%) who were divorced/separated. Comparisons were made between these subgroups; they did not differ in terms of sex, BMI, number of previous vaccinations, occupational status, presence of chronic illness, health behaviours, or antibody response. However, there were significant age differences between the subgroups, $F(2,35) = 3.65$, $p = .04$, $\eta^2 = .173$, post-hoc LSD analysis showed that widowed participants were significantly older than single and married participants with mean differences of 5.4 and 3.7 years, respectively, $p = .02$ in each case. The variation in antibody response with marital status would appear to be largely driven by differences between married and widowed participants; the widowed showed a poorer response to A/Panama, adjusting for age, than those who were married, B = 0.20, 95%CI = 0.01 to 0.39, $\beta = .17$, $t = 2.08$, $p = .04$, $\Delta R^2 = .018$.

[Insert Figure 2 about here]

3.6 Associations between Marital Satisfaction and Follow-up Antibody Response

For those participants who were married/cohabiting, their total marital satisfaction score was positively associated with antibody titer to A/Panama at one month, B = 0.01, 95%CI = 0.00 to 0.33, $\beta = .20$, $t = 2.17$, $p = .03$, $\Delta R^2 = .040$. This association is illustrated in Figure 3, which presents the mean logged antibody titers at one month adjusted for baseline for those above and below the median of marital satisfaction scores. We also examined whether antibody response varied between participants who were unmarried, relatively happily married and less happily married. The two married groups were based on a median split of the marital satisfaction scores. Comparisons between these subgroups using ANCOVA, with baseline titer as a covariate, revealed a significant difference for the one-month A/Panama antibody response, $F(2,95) = 4.94$, $p = .009$, $\eta^2 = .094$. Post-hoc analyses indicated that participants who scored greater than the median in terms of marital satisfaction had higher one-month antibody titers than both unmarried (mean difference = .29, $p = .002$), and less happily married (mean difference = .21, $p = .03$) participants, whereas the latter two groups did not differ from one another (mean difference = .009, $p = .32$). The outcome of this analysis is depicted in Figure 4.

[Insert Figures 3 and 4 about here]

3.7 Associations between Demographic and Health Behavior Variables, and Antibody Response

As relationships between psychosocial factors and antibody response appeared for the A/Panama and B/Shangdong strains, associations with potential confounding variables were only examined for these two strains. Sex, BMI and manual versus non-manual occupational status were not significantly associated with antibody titer. However, age was significantly associated with antibody titer following control for baseline titer; older participants had significantly smaller antibody responses to A/Panama, B = –0.01, 95%CI = –0.02 to 0, β = –.11, t = –2.04, p = .04, ΔR^2 = .013, at one month. In addition, the number of previous influenza vaccinations received was negatively associated with the one month antibody response to A/Panama, B = –0.02, 95%CI = –0.03 to –0.001, β = –.11, t = –2.14, p = .03, ΔR^2 = .012; those who had received more vaccinations showed a poorer response to the present vaccine. Age and number of vaccinations were significantly positively correlated, see Table 1. Thus, in subsequent regression models controlling for potential confounders age was entered rather than the number of previous vaccinations. The presence or absence of chronic illness at baseline was significantly related to the one-month antibody response to the A/Panama viral strain, B = –0.17, 95%CI = –0.29 to –0.04, β = –.15, t = 2.52, p =.01, ΔR^2 = .021. Consequently, the associations between psychosocial factors and response to A/Panama at one month were revisited, adjusting for chronic illness as well as baseline antibody titer at step 1. None of the health behaviours measured was associated with antibody response to A/Panama or B/Shangdong.

3.8 Association Psychosocial Factors and Antibody Titer following Adjustment for Potential Confounders

The associations between antibody response and psychosocial variables reported above were revisited entering age or chronic illness at step one of the model, for the A/Panama strain along with baseline antibody titer. The association between bereavement and A/Panama antibody titer remain significant following separate adjustment for age, B = -0.15, 95%CI = -0.29 to -0.02, β = -.14, t = 2.21, p =.03, ΔR^2 = .020, and chronic illness, B = -0.18, 95%CI = -0.32 to -0.04, β = -.16, t = 2.52, p =.01, ΔR^2 = .025. The association between A/Panama antibody titer at one month and marital status remained significant following

adjustment for age, B = 0.16, 95%CI = 0.01 to 0.31, β = .15, t = 2.05, p =.04, ΔR^2 = .021, and chronic illness, B = 0.17, 95%CI = 0.02 to 0.33, β = .16, t = 2.19, p =.03, ΔR^2 = .025. The differences in one month A/Panama antibody response between unmarried, unhappily married and happily married participants was still significant following adjustment for both age, $F(1,94) = 4.81$, p = .01, η^2 = .093, and chronic illness, $F(1,90) = 4.46$, p = .01, η^2 = .090. The association between marital satisfaction and A/Panama response remained significant following adjustment for age, B = 0.01, 95%CI = 0 to 0.03, β = .21, t = 2.18, p =.03, ΔR^2 = .045, but was slightly attenuated following adjustment for chronic illness, B = 0.01, 95%CI = 0 to 0.03, β = .19, t = 1.83, p =.07, ΔR^2 = .034. In regression models adjusting for both age and chronic illness simultaneously, the association between bereavement and A/Panama antibody titer remained significant, B = -0.17, 95%CI = -0.31 to -0.03, β = -.15, t = 2.38, p =.02, ΔR^2 = .022, as did the associations with both marital status, B = 0.16, 95%CI = 0 to 0.31, β = .14, t = 2.00, p =.05, ΔR^2 = .020, and marital satisfaction, B = 0.01, 95%CI = 0 to 0.03, β = .20, t = 1.98, p =.05, ΔR^2 = .039.

Given the effects of age on the antibody response to A/Panama, interactions between psychosocial factors and age were examined for this strain again using hierarchical regression. In these models, as recommended to avoid multicolinearity (Aiken and West, 1991; West, Aiken & Krull, 1996), age and the psychosocial variables were mean centred and their products derived to test for interaction effects. Again, baseline titer was entered at step 1, with age and the psychosocial main effects (using mean centred variables) entered at step 2, and the interaction at step 3. There was a significant marital satisfaction x age interaction effect, B = 0.00, 95%CI = -0.01 to 0.00, β = -.20, t = 1.96, p =.05, ΔR^2 = .032. This interaction effect is illustrated in Figure 5 using the change in logged antibody titer data. It would seem that marital satisfaction is more important for antibody response in the younger half of the sample. As recommended (Aiken and West, 1991; West et al., 1996), subsequent analyses of the individual slopes showed that marital satisfaction was significantly associated with A/Panama antibody response for the younger half of the sample, B = 0.02, 95%CI = 0 to 0.04, β = .34, t = 2.57, p = .01, ΔR^2 = .115, but not the older half, B = -0.01, 95%CI = -0.02 to 0.01, β = -.06, t = 0.70, p = .49, ΔR^2 = .004. Similar analyses were conducted for chronic illness, but no significant interaction effects emerged.

[Insert Figure 5 about here]

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4. Discussion

Participants' overall stressful life events exposure was not significantly associated with the antibody response to influenza vaccination. However, one particular life event, bereavement, was negatively associated with one-month antibody titer against the A/Panama and B/Shangdong strains. In addition, although social network size and functional social support were not related to antibody response, married/cohabiting participants showed a better antibody response to the A/Panama strain at one month than those who were not married, particularly widowed, participants. It is important to note that the unmarried participants were not the same individuals as those who reported bereavement in the year prior to vaccination; only 16 percent of the bereaved participants had experienced a spousal bereavement, and there was no association between bereavement and marital status. Also, for those who were married or cohabiting, higher marital satisfaction was related to higher titers to A/Panama at one month. To our knowledge, this is the first study to demonstrate that bereavement, marital status, and marital satisfaction are associated with the antibody response to vaccination. Further, these associations remained statistically significant following adjustment for age and the presence of chronic illness at baseline, with the exception of the relationship between marital satisfaction and A/Panama which was slightly attenuated after controlling for chronic illness.

The negative association between bereavement and antibody status following vaccination is in line with previous studies of bereavement and immune function. Bereavement has been associated with *in vitro* functional immune measures such as decreased natural killer cell cytotoxicity and poorer lymphocyte proliferation to mitogen (Bartrop et al., 1977; Goodkin et al., 1996; Irwin et al., 1987; Kemeny et al., 1995; Schleifer et al., 1983; Zisook et al., 1994). The present findings regarding marital status and satisfaction also extend the results of previous studies showing that poorer marital quality, in terms of adjustment and negative marital interactions, are associated with inferior functional immunity evidenced through reduced proliferation to some mitogens, poorer latent virus control (Kiecolt-Glaser et al., 1987; Kiecolt-Glaser et al., 1997; Kiecolt-Glaser et al., 1988; Kiecolt-Glaser et al., 1993), and weaker natural killer cell cytotoxicity (Miller et al., 1999). Further, it is possible that the variations between elderly care-givers and controls in terms of vaccination response (Glaser et

al., 1998; Glaser et al., 2000; Kiecolt-Glaser et al., 1996; Vedhara et al., 1999a) may be driven, at least in part, by the effects of care-giving on marital quality and satisfaction, although more specific measurement of stressful life events and marital parameters would be necessary to support this speculation. Whatever the case, our findings resonate with the broad consensus that both marriage (Gordon and Rosenthal, 1995; House et al., 1988; Johnson, Backlund, Sorlie & Loveless, 2000; Verbrugge, 1979), and marital satisfaction (Coyne and DeLongis, 1986; Kiecolt-Glaser and Newton, 2001; Robles and Kiecolt-Glaser, 2003) are beneficial for health and bereavement is detrimental to health (Bowling, 1994; Manor and Eisenbach, 2003; Parkes, Benjamin & Fitzgerald, 1969).

There were no interaction effects on antibody response of sex and either marital status or marital satisfaction. The absence of an interaction effect for sex and marital status resonates with the finding that the negative impact of being unmarried on health would appear to be equal for the sexes (Johnson et al., 2000), although other studies have shown that the detrimental effects of being unmarried are greater for men than for women (see e.g., (Ross, Mirowsky & Goldsteen, 1990). The lack of an interaction between marital satisfaction and sex is somewhat at odds with previous findings that marital conflict had a greater immunological impact on women than men (Kiecolt-Glaser et al., 1993). However, in a study of older adults, both men and women's blastogenic response to T-cell mitogen stimulation was equally affected by negative marital behaviour (Kiecolt-Glaser et al., 1997). Although there was no interaction between age and marital status, there was a significant interaction effect of age and marital satisfaction score on the response to A/Panama; higher marital satisfaction impacted positively on antibody response only in the younger half of the sample. The effect of age within elderly samples on the immunological impact of marital satisfaction has yet to receive dedicated study. The present findings suggest that it would be a fruitful line of enquiry. Given the cross-sectional nature of the present data, future studies would benefit from having a longitudinal design.

The absence of an association between overall life events and antibody response to influenza vaccination in the present study contrasts with the results of our previous research on young participants (Burns, Carroll, Drayson, Whitham & Ring, 2003a; Phillips et al., 2005a). In our most recent student study, the modal number of life events experienced in the past year was six, with no participants reporting one or less events (Phillips et al., 2005a), whereas in the present elderly sample, the modal number of major life events in the year prior to vaccination was zero, with 31% of the sample reporting no events, and a further 17%

reporting only one. However, in the student studies, less serious events were included in the scale, for example, getting an unjustified low mark on a test or minor financial problems, along with more major events. In the present study, only exposure to major life events was measured. Accordingly, the absence of an association between antibody response and overall life events may reflect the use of a scale including only serious life events. However, the results for bereavement would argue against this explanation. In addition, it is also possible that the elderly simply experience fewer general life events than younger samples. There is certainly evidence to this effect: elderly individuals encountered fewer major life events than middle-aged participants in a large cohort study in the west of Scotland using the same life events measure as the present study, but retrospectively over two years. Middle-aged participants identified a mean of 2.0 events whereas the mean number of events for the elderly was 1.7 (Carroll et al., 2005). These data also suggest that our participants were not unusual in experiencing few life events, given that the mean number of events reported over one year was 2.9. Accordingly, it may be that individual differences in general life events exposure are less important for immunity as people age, whereas bereavement, a specific life event that the elderly are more likely to encounter than the young (45 percent of the present sample experienced bereavement in the previous year compared to 7 percent in our student sample) assumes greater prominence.

Contrary to expectations, social support was also not related to antibody response. Previous vaccination studies reporting that either low social support or social isolation was associated with poorer vaccination response, were conducted with student samples (Glaser et al., 1992; Phillips et al., 2005; Pressman et al., 2005). The only study in an elderly sample to examine social support in this context reported a negative association: the better the support the lower the absolute antibody titer (Moynihan et al., 2004). It is possible that in an elderly population, general social support is less critical, whereas the specific social support resource of a happy marriage becomes more important for health, including susceptibility to infection.

There was evidence of strain specificity in the current study. Other studies of the antibody response to influenza vaccination have also shown effects that appear only for certain strains (Burns et al., 2003a; Miller et al., 2004; Phillips et al., 2005a; Phillips et al., 2005b; Vedhara et al., 1999a). It is difficult at this stage to determine why particular vaccine strains are sensitive to certain types of psychosocial influence, although differences in strain novelty and participants' prior exposure to each viral strain have been proposed as possible explanations (Vedhara et al., 1999a). It is worth noting that reasonably stable circumstances

and characteristics, such as marital status and satisfaction in the present study, and social support (Phillips et al., 2005a) and neuroticism (Phillips et al., 2005b) in our previous study, were associated with the A/Panama response. In addition, exposure variables such as bereavement in the present study, and overall life events exposure in the previous student study, were associated with the response to the B/Shangdong strain. Thus, whereas different psychosocial factors would appear to influence antibody response in the elderly and the young, there would appear to be some consistency in which type of variables affect which strains of the vaccine. However, it should be noted that bereavement was also related to the A/Panama antibody response in the present sample.

The present study is not without its limitations. First, the psychosocial assessments were performed at different time points during the 12 months of the study. However, the questionnaires which were included at later sessions, social support and marriage, were those generally considered to reflect characteristics unlikely to vary much with time, reflected in the high test-retest reliabilities that have been previously reported for the social support and marital satisfaction measures. Further, subsequent questioning of our participants revealed that during the 12 months of the study, only one spousal death and three divorces had occurred and the association between marriage and antibody response remained significant following removal of these individuals from the unmarried group. We concede that the timing of these measures means that it is not possible to draw inferences of causality. However, inferences of causality are always problematic in observational studies, even where they are prospective (Christenfeld, Sloan, Carroll & Greenland, 2004).

Second, marital status was only determined for 104 of the original 143 respondents, and marital quality was assessed in the 66 individuals identified as married/cohabiting. However, these participants did not differ from the remainder of the sample in terms of sex, BMI and life events exposure, although those for whom marital status was assessed were significantly younger, mean = 73.2, SD = 5.94, than those for whom this information was unavailable, mean = 75.6, SD = 5.60, $t(142) = 2.51$, $p = .01$. Importantly, there were no differences in the antibody response to vaccination.

Third, it should be conceded that the associations which emerged did so in the context of analyses of the antibody response to three viral strains. Accordingly, a fair number of statistical comparisons were undertaken, increasing the likelihood of Type I errors. The analyses reported examined six psychosocial factors making a total of 18 primary regression analyses. From these, four (22%) significant effects emerged, a number far exceeding that

expected by chance. Further, the associations revealed by the analyses were all in the expected direction, and were consistent in that positive relationships emerged for both marital status and satisfaction.

In summary, experiencing bereavement in the year prior to vaccination was negatively associated with the peak antibody response to A/Panama and B/Shangdong. In addition, being married and having high marital satisfaction were associated with a better antibody response to the A/Panama influenza strain. Overall life events exposure and social support were not related to the antibody response to any of the influenza viral strains. It would appear that the psychosocial factors that affect antibody response in the elderly differ somewhat from those that influence the response in younger populations. It is possible that as people age, specific factors, such as marriage and bereavement, assume greater significance for immunity, whereas for the young, general factors, such as overall life events exposure and social support, are more salient. This highlights the importance of adopting a life course approach to examining associations between psychosocial factors and immune response. In addition, interventions to modify the impact of psychosocial factors on immunity might sensibly focus on the specific variables implicated as salient for particular age groups. It is reasonable to assume that variations in response to vaccination reflect variations in host resistance to the relevant infectious pathogens (Patriarca, 1994). However, future vaccination studies would benefit from the inclusion of objective clinical outcome measures to determine whether the effects of psychosocial variables on vaccine response have implications for infection.

[1] Those who remained in the study were slightly older (mean = 73.2, SD = 5.95) than those who did not complete all three sessions (mean = 75.4, SD = 5.79), $F(1,141) = 4.58$, $p = .03$, $\eta^2 = .031$, but did not differ on any other variables; importantly, they did not differ in terms of baseline antibody titers.

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Table 1: Correlations Between the Continuous Demographic and Psychosocial Variables.

	Life Events Score	No. Close Friends	Social Support Score	Marital Satisfaction Score	Age	No. of Vaccinations	BMI
No. Close Friends	-.03						
Social Support Score	-.19*	.11					
Marital Satisfaction Score	-.22	-.30*	.46***				
Age	.06	.03	-.11	.01			
No. of Vaccinations	.16	.13	-.03	-.05	.28***		
BMI	.13	-.03	.18	.04	-.19*	-.02	
Exercise Score	-.12	.17	-.03	-.41**	-.20*	-.17*	-.15

* $p < .05$

** $p < .01$

*** $p < .001$

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Table 2. *Geometric Mean (95% Confidence Intervals) Antibody Titers for each Influenza Viral Strain Initial Baseline and at the One Month and Twelve Month Follow-ups*

Viral Strain	Pre-vaccination	One-month Follow-up	Twelve-month Follow-up	MANOVA (p<.001)
A/New Caledonia/20/99	34.4	66.4	36.6	F(2,115) = 54.23
	(4-302)	*(7-603)*	*(4-302)*	p <.001, η^2 = .485 [a,b]
A/Panama/2007/99	64.6	115.6	67.2	F(2,115) = 38.52
	(5-813)	*(10-1318)*	*(6-813)*	p <.001, η^2 = .401 [a,b]
B/Shangdong/7/97	64.6	121.6	69.2	F(2,115) = 74.88
	(6-692)	*(13-1148)*	*(7-661)*	p <.001, η^2 = .255 [a,b]

[a] significant difference between pre-vaccination and one month follow-up titers

[b] significant difference between one month and 12 month follow- up titers

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Table 3. *Number (%) of Participants With (Responders) and Without (Non-Responders) a Four-Fold Response to Each Influenza Viral Strain at One Month and Twelve Month Follow-ups*

Follow-up	Strain	Responders	Non-Responders
One Month	A/New Caledonia/20/99	21 (15%)	119
	A/Panama/2007/99	18 (13%)	122
	B/Shangdong/7/97	21 (15%)	119
Twelve Months	A/New Caledonia/20/99	3 (3%)	114
	A/Panama/2007/99	9 (8%)	108
	B/Shangdong/7/97	5 (4%)	112

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Figure Captions

Figure 1: Bereaved participants had lower mean antibody titers at one month relative to baseline to the A/Panama and B/Shangdong strains than participants who had not been bereaved in the year prior to vaccination.

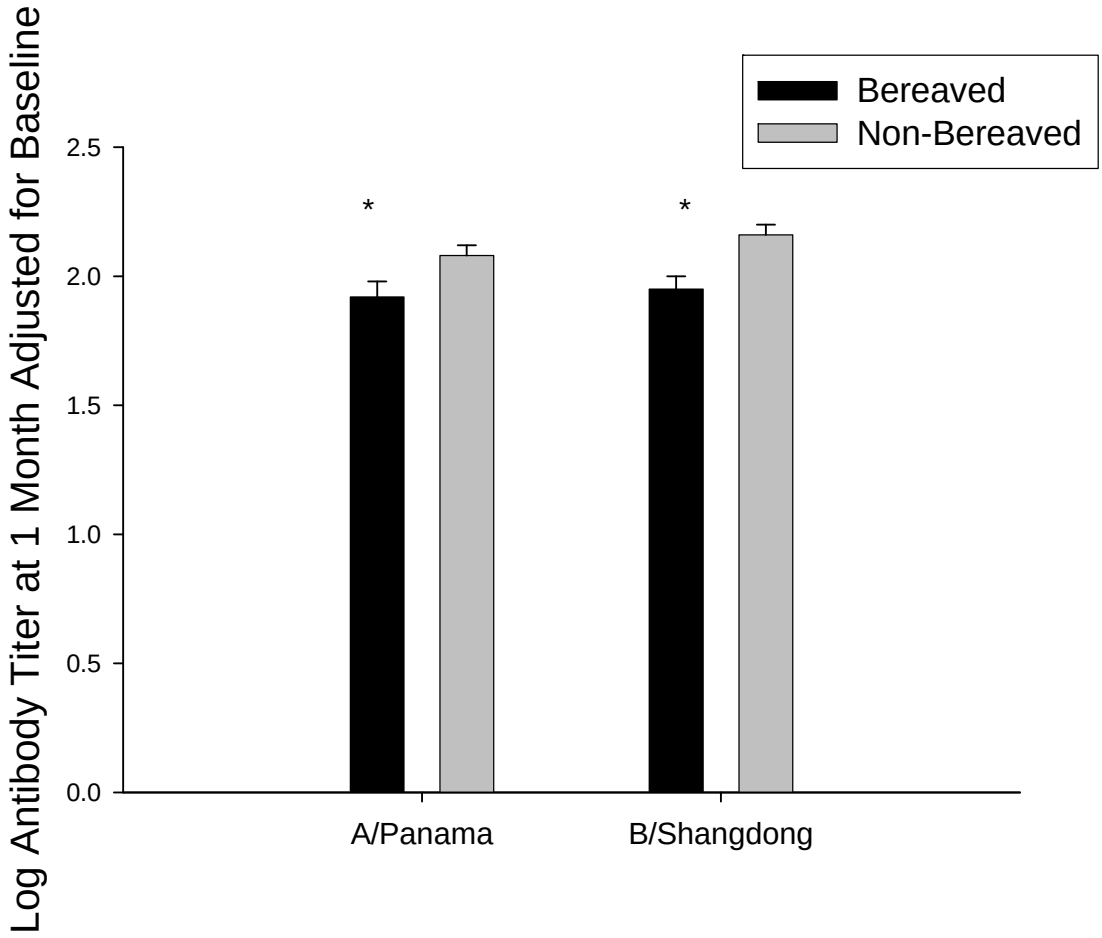
Figure 2: Married/cohabiting participants had higher mean antibody titres at one month relative to baseline to the A/Panama strain than non-married and non-cohabiting participants.

Figure 3: Participants with higher marital satisfaction scores had higher mean antibody titers at one month relative to baseline to the A/Panama strain than participants with lower marital satisfaction scores.

Figure 4: Participants with higher marital satisfaction scores had higher mean antibody titers at one month relative to baseline to the A/Panama strain than participants with lower marital satisfaction scores and those who were unmarried.

Figure 5: The positive association between marital satisfaction antibody titer to A/Panama at one month relative to baseline appeared for participants younger than the mean age but not for those older than the mean age.

Phillips, A.C., Carroll, D., Burns, V.E., Ring, C., & Drayson, M. (2006). Bereavement and marriage are associated with antibody response to influenza vaccination in the elderly. Brain, Behavior and Immunity, 20, 279-289.



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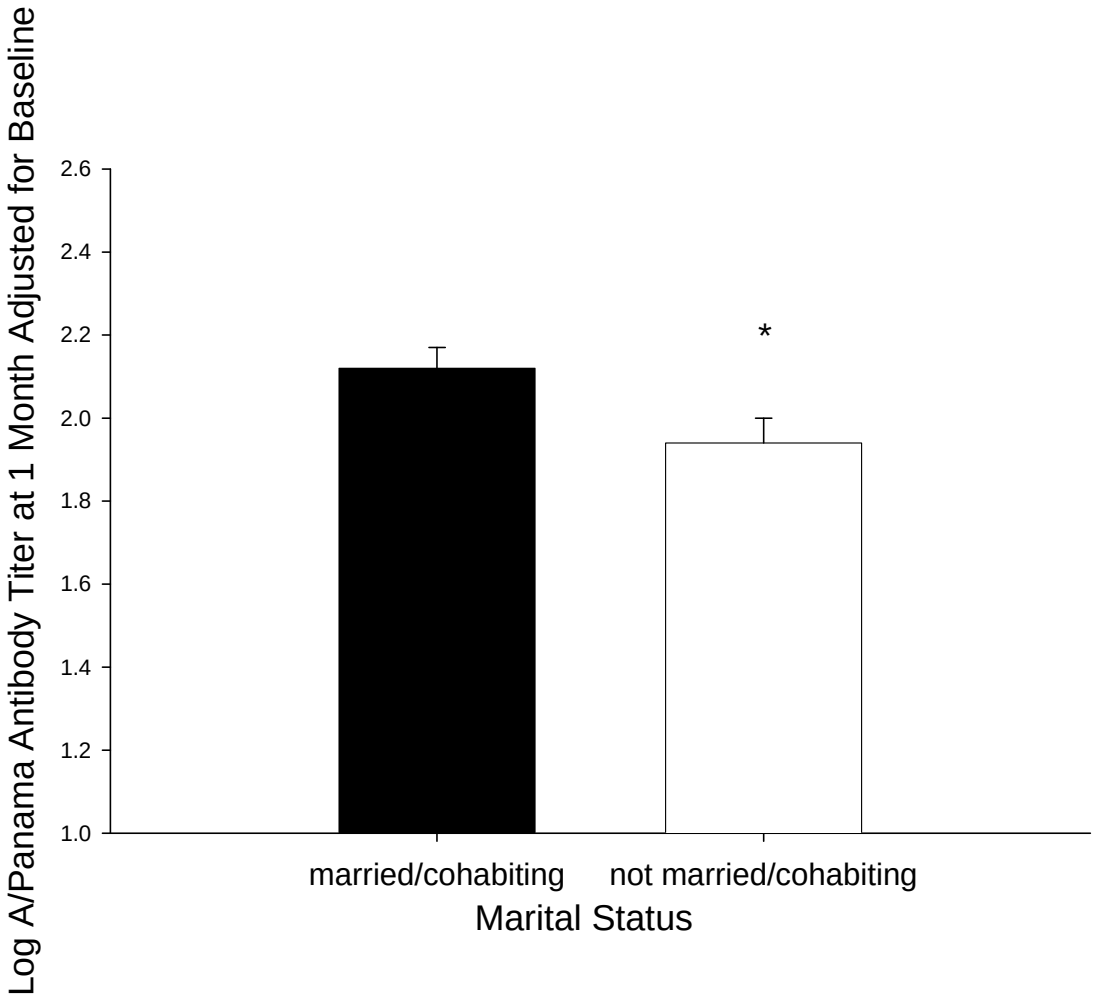

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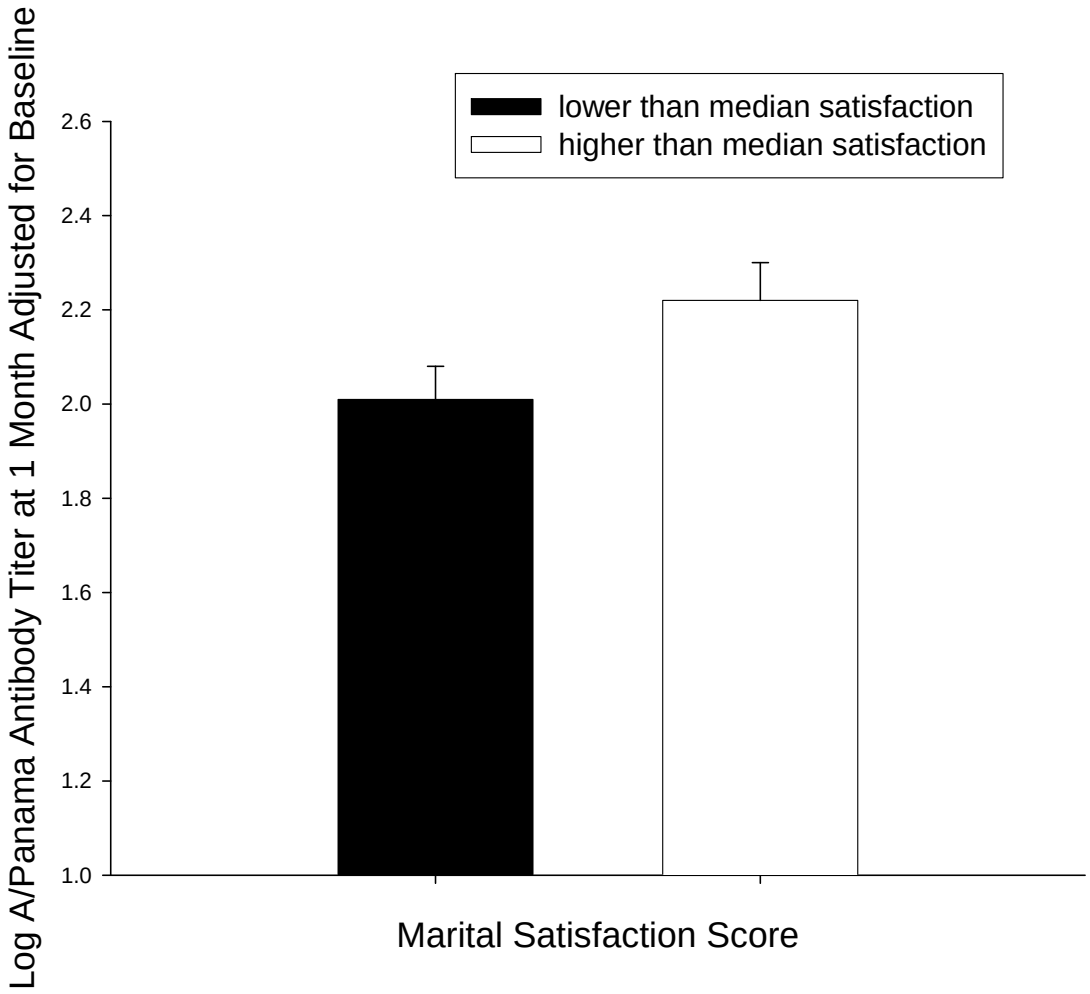

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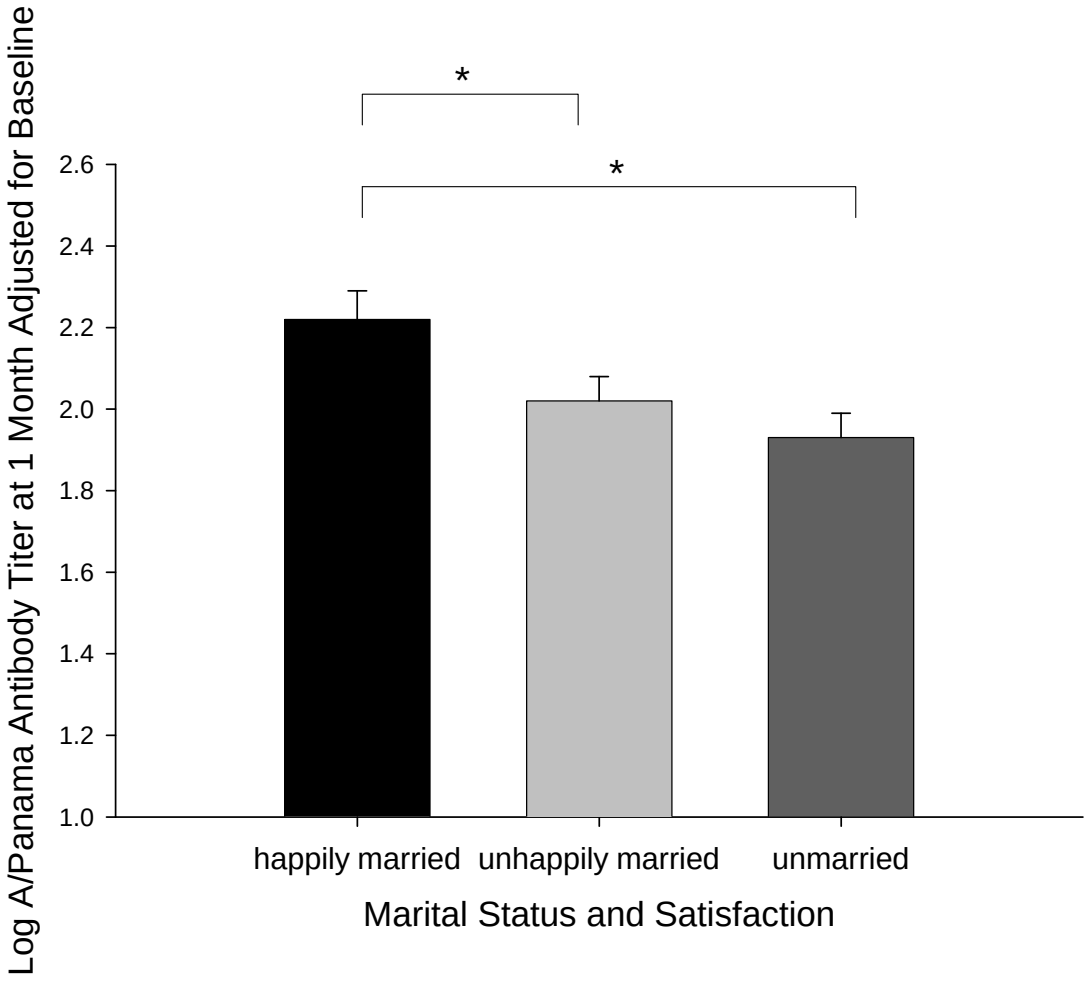

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