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# Social support is positively associated with the immunoglobulin M response to vaccination with pneumococcal polysaccharides

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**Abstract**

Evidence shows that psychosocial factors are associated with immunoglobulin G response to medical vaccinations. As yet, there are no reports of whether the earlier immunoglobulin M response is similarly susceptible. This study examined the association between psychological stress, social support and the immunoglobulin M response to vaccination with pneumococcal capsular polysaccharides. Stressful life events in the previous year and customary social support were measured by standard questionnaires at baseline in 74 healthy students (41 females). The response to five common pneumococcal serotypes was assessed at baseline and five-days following vaccination. Social support, particularly tangible social support, was positively associated with the antibody response to two of five serotypes, after controlling for baseline titre. These associations survived adjustment for demographics and health behaviours. There was no association between life events stress and immunoglobulin M response. It appears that psychosocial factors affect both the immunoglobulin M and immunoglobulin G responses to vaccination.

*Keywords:* Antibody response; Immunoglobulin M; Life events; Pneumococcal vaccination; Social support.

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## 1. Introduction

It is well documented that psychosocial factors are related to the antibody response to medical vaccinations (for reviews, see Burns et al., 2003b; Cohen et al., 2001; Vedhara et al., 1999). Psychological stress, as measured by negative affect, exposure to negative life events or high perceived stress, is negatively associated with the response to a range of vaccines (Burns et al., 2003a; Burns et al., 2002; Marsland et al., 2001; Phillips et al., 2005). In contrast, social support variables such as network size, functional support and marital satisfaction have been found to be positively associated with the response to vaccination (Phillips et al., 2005; Phillips et al., 2006; Pressman et al., 2005).

The humoral response to most pathogenic challenges is characterized by an early rise in antigen-specific immunoglobulin (Ig) M, followed by affinity maturation, isotype switching, and the eventual peak production of mainly IgG antibodies (Boes, 2000). Thus, the earliest and consequently key aspect of adaptive immunity to rapidly progressing infection, whether in individuals primed or unprimed by previous exposure, is the generation of IgM antibodies. Antigen specific IgM, therefore, plays a key role in the clearance of infection (Baumgarth et al., 2000).

However, it is the IgG response and its decay over time that has been studied almost exclusively in the context of psychosocial factors. To date, there are no published studies we know of on the association between psychosocial factors and the IgM response to vaccination challenge in humans. Clues to the sensitivity of the IgM response to psychosocial factors can be found in animal research. Adult rats exposed to an acute stressor either immediately before or following immunization with a benign thymus-dependent protein antigen, key limpet hemocynanin, showed a suppressed IgM response (Fleshner et al., 1996; Kennedy et al., 2005; Moraska and Fleshner, 2001).

Vaccination with pneumococcal polysaccharides has received little attention in the context of psychosocial factors. This is perhaps surprising given that infection with pneumococci is a major cause of serious disease, responsible for 1 million deaths per year globally (Fedson and Scott, 1999). Further, spousal caregivers of dementia patients have been reported to show lower IgG titres to the pneumococcal vaccine six months after vaccination (Glaser et al., 2000). However, as yet the IgM response to the pneumococcal vaccine remains unstudied. Accordingly,

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the present study examined the association between psychological stress and social support and the IgM antibody response to vaccination with pneumococcal polysaccharides. Further, it would seem important to examine individual serotypes rather than the aggregate response, as was the case in this previous study of pneumococcal IgG (Glaser et al., 2000). Examination of individual pneumococcal serotypes allowed testing of whether psychosocial factors preferentially affect serotypes particularly implicated in disease. It was hypothesized that psychological stress would be negatively associated and social support positively associated with the IgM response to pneumococcal vaccination.

## 2. Method

### *2.1. Participants*

Participants were 74 (41 women) University of Birmingham students. Mean age was 23 (*SD* = 3.89) years. In terms of ethnicity, 89% described themselves as "white," 3 % as "Asian," 1 % as "black," and 7% as "other". Ninety-two percent of the sample reported being non-smokers. Participants were excluded if they reported receiving the pneumococcal vaccination previously, were suffering from medical conditions that could affect antibody response (e.g., acute infection, glandular fever), were pregnant, or taking prescribed medication, excluding oral contraceptives. The study was approved by the appropriate Research Ethics Committees.

### *2.2. Study design*

The study comprised of two testing sessions: baseline and a 5-day follow-up (range 3-7 days; mean = 5 and *SD* = 0.72 days). At baseline, participants completed questionnaires and provided a single venous blood sample to determine baseline antibody levels. They were then vaccinated with the 23-valent pneumococcal polysaccharide vaccine (Pneumovax II; Sanofi Pasteur MSD). At the follow-up session, blood samples were again taken to assess antibody levels.

### *2.3. Questionnaires*

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*2.3.1. Psychological stress*

The Life Events Scale for Students (Linden, 1984) was used to assess stressful life events exposure. This is a student-specific inventory, and participants were required to select, from a list of 36, those life events that they had experienced in the previous year. It includes both major (e.g., death of your best friend) and minor (e.g., getting an unjustified low mark on a test) events. The inventory includes mainly major life events that are likely to be recalled accurately over such a time frame. Each event has a pre-determined weighting for severity (Linden, 1984) with major events having a higher weighting. Thus, stress exposure can be represented as either a simple frequency count of events or a score which is the aggregate of weighted events.

*2.3.2. Social support*

Participants completed the Medical Outcomes Study Social Support Survey (Sherbourne and Stewart, 1991). This provides an overall measure of structural support (number of close friends), and functional support, the aggregate of scores on 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 5-point Likert-type format with higher scores indicating higher social support. In the present study, the Cronbach's α for each of the subscales ranged from 0.88 to 0.92, indicating acceptable internal reliability.

*2.3.3 Health behaviours*

As in our previous studies (Burns et al., 2002; Phillips et al., 2005), typical health behaviours were assessed using a questionnaire adapted from the Whitehall II study (Marmot et al., 1991). Participants were asked, on average how much they smoked (0, 1–5, 6–10, 11–20, and 21+ cigarettes per day); how much alcohol they drank (0, 1–5, 6-10, 11–20, 21–40, and 40 + units per week); how long they slept (0–3, 4–5, 6–7, 8–9, 10–11, and 12+ h per night). A simple categorical scoring system was used in all cases. Participants also reported how much time they

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spent in activities of light, moderate and vigorous exercise intensity, which were summed to yield a composite exercise score. Finally, they indicated how regularly they ate certain foods from a standard list; this yielded measures of fruit and vegetable consumption and fat intake.

### *2.4. Blood sampling and antibody analysis*

Blood specimens were collected from an ante-cubital vein into 7-ml plain tubes (BD Vacutainer, Meylan Cedex) to assess antibody titers. Samples were allowed to clot at room temperature for 1 h and centrifuged at 3500 rpm for 5 min. The separated serum was frozen at −20°C until assayed. Luminex technology was used to assess specific IgM responses against five common pneumococcal (Pn) serotypes (types 1, 3, 14, 19 and 23) contained in the pneumococcal vaccine. Assessment and selection of these specific Pn serotypes were based on clinical observations linking these common serotypes to invasive disease in Europe (Henriques et al., 2003; Denham and Clarke, 2005; Sleeman et al., 2001). Further details of this assay are described elsewhere (Ferraro et al., 2007; Lal et al., 2005). Serum IgM anti-Pn levels are reported in μg/ml.

### *2.5. Data reduction and analysis*

Given the skew of the data, antibody titres were subjected to $\log_{10}$ transformation. Repeated measures analysis of variance was used to confirm that the vaccine elicited an antibody response for each of the targeted serotypes. Partial eta- squared ($\eta^2$) is reported as a measure of effect size. Hierarchical linear regression analyses were then applied to determine whether psychosocial factors predicted $\log_{10}$ antibody level at follow-up. In all regression models tested, antibody levels for the individual Pn serotypes at baseline were entered at step one. The psychosocial variables were then entered separately at step two. Further, regression analyses were undertaken to adjust for possible confounders. Age, sex and health behaviour variables were entered into these models at step two, and the psychosocial variables at step three.

## 3. Results

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### *3.1. Questionnaire data*

The mean (*SD*) number of life events was 7.2 (3.36). The mean (*SD*) number of close friends was 10.7 (7.07), and mean (*SD*) total functional social support score was 78.6 (14.45). Means *(SD)* on the functional support dimensions were: positive social interaction 16.9 (3.42), tangible, 15.5 (3.96), emotional 16.8 (3.23), and affectionate, 12.4 (3.03).

### *3.2. Vaccination response*

The geometric mean (*95% CI*) antibody titre for each Pn serotype at each time point is displayed in Table 1. Participants responded with an increase in antibody titre from baseline to 5-day follow-up for all five serotypes.

[Insert Table 1 about here]

### *3.3. Associations between psychological stress, social support, and antibody response*

Taking into account baseline antibody status, no associations emerged between life event stress and antibody response to any of the measured Pn serotypes. This was the case irrespective of whether the number of life events or weighted score was used. However, aggregate functional support was positively associated with antibody response to Pn serotype 3, $\beta = .18$, $t = 2.21$, $p = .03$, $\Delta R^2 = .03$; the greater the support the better the antibody response. For serotype 23, the positive association between aggregate functional support and response to the Pn serotype 23 did not quite meet the conventional criteria for statistical significance, $\beta = .10$, $t = 1.63$, $p = .10$, $\Delta R^2 = .01$. No associations emerged for the other serotypes. Subscale analysis for serotype 3 revealed that tangible, $\beta = .17$, $t = 2.01$, $p = .05$, $\Delta R^2 = .03$, emotional $\beta = .18$, $t = 2.21$, $p = .04$, $\Delta R^2 = .03$, and affectionate, $\beta = .19$, $t = 2.35$, $p = .02$, $\Delta R^2 = .04$, support were all positively related to antibody response (see Figure 1); participants with greater access to these different types of support mounted a better antibody response. For serotype 23, only tangible support was associated with antibody response, $\beta = .13$, $t = 2.07$, $p = .04$, $\Delta R^2 = .02$ (see Figure 1). Age was not associated with response to any of the serotypes. However, women showed a better response to Pn serotype 1 than men, $F(1, 73) = 5.72$, $p < .02$, $\eta^2 = 0.491$. In addition, health behaviours

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(e.g., smoking, exercise, caffeine, and alcohol consumption) were unrelated to antibody response. The associations reported above withstood adjustment for these demographic and health behaviour variables in regression analyses.

[Insert Figure 1 about here]

## 4. Discussion

To our knowledge, this is the first demonstration in humans of an association between social support and the IgM response to vaccination. Participants who had greater access to tangible support mounted a better antibody response to Pn serotypes 3 and 23 of the pneumococcal polysaccharide vaccine. In addition, those with greater access to emotional and affectionate support had a better antibody response to the Pn 3 serotype. This finding is broadly in line with existing studies which have found positive relationships between social support and IgG response to influenza vaccination (Phillips et al., 2005; Pressman et al., 2005). Also consistent with the results of other studies using polyvalent vaccinations (e.g. influenza), the present association between psychosocial variables and antibody response emerged only for some serotypes. One explanation for this specificity could be that antigens which are less immunogenic are more susceptible to exogenous influence (Cohen et al., 2001). It is worth noting in this regard that by far the smallest antibody titres at 5-day follow-up were observed for the Pn 3 and 23 serotypes.

The absence of any significant association between psychological stress and IgM response seemingly contrasts with the results from animal research (Fleshner et al., 1996; Kennedy et al., 2005; Moraska and Fleshner, 2001). However, the acute stress manipulations in these animal studies cannot be compared to the present conceptualization of stress based on human exposure to negative life events. In a human vaccine study, elderly caregivers were observed to show a less sustained IgG response to pneumococcal vaccination (Glaser et al., 2000). This was interpreted as reflecting the chronic stress of caregiving. However, in this study, caregivers did not differ significantly from controls on perceived stress, but did report poorer social support. Accordingly, it may have been social support that was driving the observed differences between caregivers and controls in IgG response, and so the discrepancy in results

may be more apparent than real. It is worth noting that in the present study the 4-week IgG response to pneumococcal vaccination was also associated social support, but not with psychological stress (Gallagher et al, in press).

The present study has a number of limitations. First, the sample size was small. However, it was of the same order of magnitude as samples in many previous vaccination studies (Burns et al., 2002; Marsland et al., 2001; Pressman et al., 2005). Second, this was an observational study and it remains possible that the observed relationships were a result of confounding. Nevertheless, statistical adjustment for age, sex, and health behaviours failed to attenuate the associations. Third, life events checklists of the sort used in the current study are not without their limitations, nevertheless in the present context such checklists are a common means of stress assessment and the alternatives, such as perceived stress scales, are not without difficulties (Brief et al., 1988). Further, life events temporally distant from vaccination have been shown to affect the IgG response to numerous vaccinations (Burns et al., 2003a; Phillips et al., 2005). Nevertheless, it remains possible that a more proximal measure of psychological stress might have influenced vaccination response. Finally, the selection and assessment of specific Pn serotypes, as previously discussed, could also be viewed as a limitation. However, the serotypes chosen represent some of the most common strains linked to invasive disease in Europe (Denham and Clarke, 2005; Sleeman et al., 2001). Further, the serotypes chosen were heterogeneous in immunogenicity.

Regarding clinical implications, it should be noted that IgM concentration *per se* does not confer protection against pneumonia. However, IgM plays a key role in the clearance of infection by enhancing IgG production and promoting an efficient neutralizing IgG response (Baumgarth et al., 2000). Thus, IgM acts as an immunoregulator, a process referred to as 'antibody feedback regulation' (Heyman, 2000).

In summary, previous research on psychosocial factors and antibody responses has exclusively reported findings regarding the later IgG responses to medical vaccination. We extend this work by finding that such factors may also influence the early IgM response to bacterial thymus-independent antigens. Those reporting less social support mounted weaker early IgM responses against two pneumcoccal serotypes which are commonly implicated in pneumococcal disease in Europe.

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Table 1. Geometric mean (95% confidence intervals) antibody titres (ug/ml) for each pneumococcal serotype at baseline and 5-day follow-up.

| **Pneumoccocal strain** | **Baseline** | **5-days** | **ANOVA** |
|---|---|---|---|
| Type 1 | 7.7 | 52.4[a] | $F(1, 73) = 171.97$, $p < .001$ |
| | (1.4 - 43.7) | (5.1 - 537.0) | $\eta^2 = .702$ |
| Type 3 | 2.9 | 6.6 [a] | $F(21,73) = 66.74$, $p < .001$ |
| | (2.8 - 144.5) | (1.5 - 64.6) | $\eta^2 = .478$ |
| Type 14 | 33.1 | 76.1 [a] | $F(1,73) = 70.52$, $p < .001$ |
| | (3.5 - 316.2) | (1.9 - 117.5) | $\eta^2 = .491$ |
| Type 19 | 20.0 | 34.9 [a] | $F(1, 73) = 56.15$, $p < .001$ |
| | (3.0 - 131.8) | (5.2 - 229.1) | $\eta^2 = .435$ |
| Type 23 | 9.2 | 18.0 [a] | $F(1,73) = 54.28$, $p < .001$ |
| | (1.6 - 436.5) | (1.2 - 269.2) | $\eta^2 = .426$ |

[a] Significant difference between baseline and 5-day

NB. It is worth noting that a minority of participants showed a decrease in IgM titre following vaccination. This is likely to be due to prior naturalistic exposure (Brueggemann et al., 2003).

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**Figure 1**. High and low social support mean and standard error IgM antibody levels at 5-day follow-up, adjusted for baseline IgM levels, for Pn serotypes 3 and 23; median splits were used to generate the binary functional social support subscale variables.

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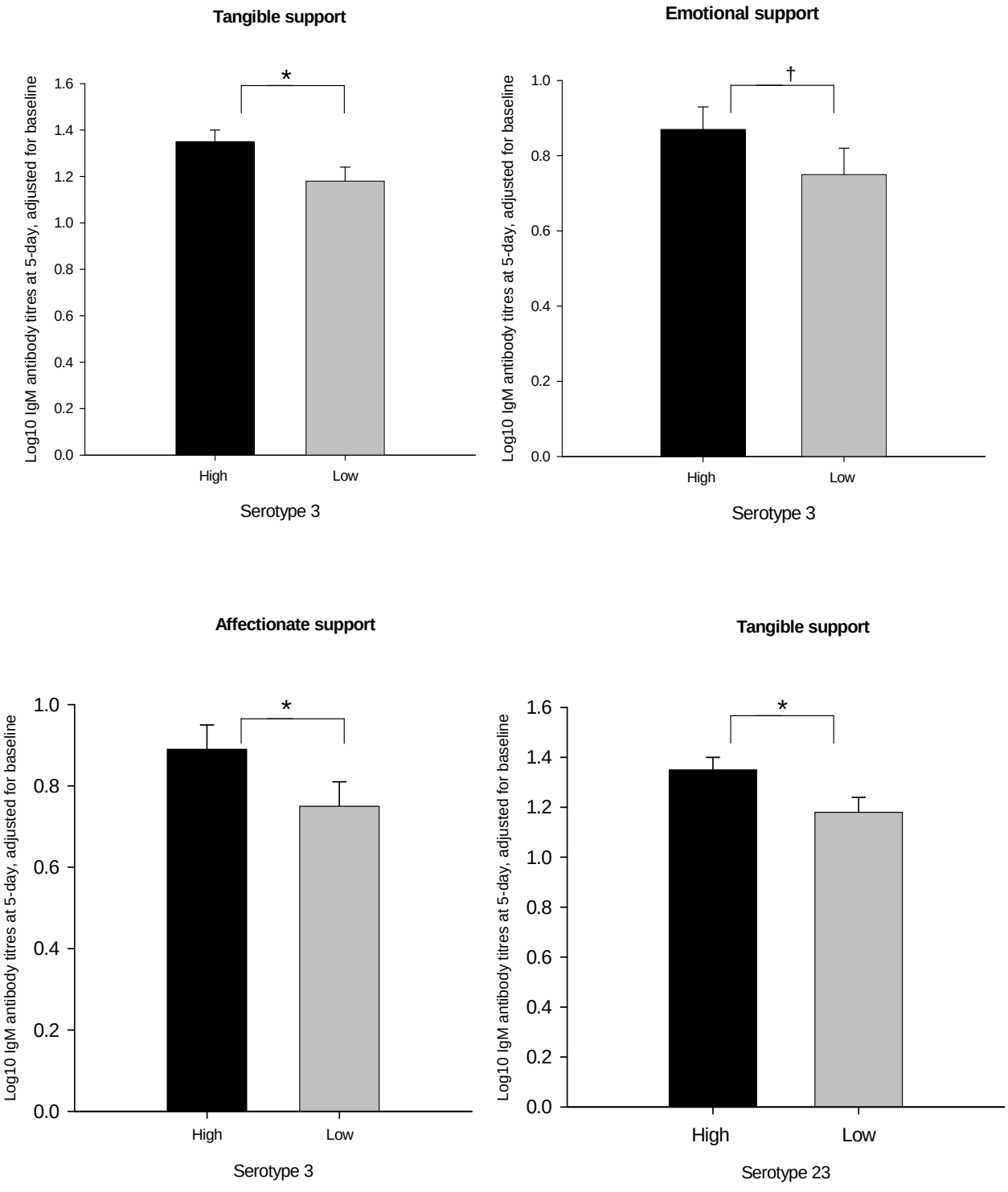


* = $P < .05$ ; † = $P < .10$