Stressful Life Events Are Associated with Low Secretion Rates of Immunoglobulin A in Saliva in the Middle-Aged and Elderly

Anna C. Phillips¹, Douglas Carroll¹, Phil Evans², Jos A. Bosch¹, Angela Clow², Frank Hucklebridge², and Geoff Der³

¹School of Sport and Exercise Sciences, University of Birmingham, Birmingham, England
²Psychophysiology and Stress Research Group, University of Westminster, London, England
³MRC Social and Public Health Sciences Unit, University of Glasgow, Glasgow, Scotland

Correspondence: Anna C. Phillips, MSc, School of Sport and Exercise Sciences, University of Birmingham, Birmingham, England. Tel 00 44 121 414 7240; Fax 00 44 121 414 4121; email carrolld@bham.ac.uk
Abstract

Whether chronic stress experience is related to down-regulation of secretory immunoglobulin A (S-IgA) was tested in two substantial cohorts, one middle-aged (N = 640) and one elderly (N = 582), comprising similar numbers of men (N = 556) and women (N = 666) and manual (N = 606) and non-manual (N = 602) workers. Participants indicated from a list of major stressful life events up to six they had experienced in the previous two years. They also rated how disruptive and stressful the events were, at the time and now, as well as their perceived seriousness; the products of these impact values and event frequency were adopted as measures of stress load. From unstimulated 2-minute saliva samples, saliva volume and S-IgA concentration were measured, and S-IgA secretion rate determined as their product. There was a negative association between the stress load measures and S-IgA secretion rate, still evident following adjustment for such variables as smoking and saliva volume. The associations also withstood adjustment for sex, cohort, and household occupational status. Although these associations are small in terms of the amount of variance explained, they nonetheless suggest that chronic stress experience either decreases IgA production by the local plasma cells or reduces the efficiency with which S-IgA is transported from the glandular interstitium into saliva. Given the importance of S-IgA in immune defence at mucosal surfaces and the frequency with which infections are initiated at these surfaces, S-IgA down-regulation could be a means by which chronic stress increases susceptibility to upper respiratory tract infection.

Keywords: Life events stress; secretory immunoglobulin A; saliva volume; smoking; age; sex; household occupational status.
1. Introduction

There is now convincing evidence linking measures of chronic psychological stress, most noticeably the experience of stressful life events, to upper respiratory tract infection and disease (see, e.g., Cohen, Tyrell & Smith, 1991; 1993). Up to 95% of all infections are initiated at the mucosal surfaces (Bosch, Ring, de Geus, Veerman & Amerongen, 2002). These surfaces are protected by the secretion of various proteins from the exocrine glands, including the salivary glands. Prominent among such secretory proteins are immunoglobulins, the most predominant of which is secretory immunoglobulin A (S-IgA) (Hood, Weissman & Wood, 1978). Accordingly, S-IgA may be an important mediator in the link between chronic stress and upper respiratory tract infection.

There is now fairly convincing evidence that acute psychological stress whether naturalistic or contrived in the laboratory is associated with increases in S-IgA concentration and/or secretion rate (e.g., (Bosch, de Geus, Kelder, Veerman, Hoogstraten & Amerongen, 2001; Carroll, Ring, Shrimpton, Evans, Willemsen & Hucklebridge, 1996; Kugler, Reintjes, Tewes & Schedlowski, 1996; Ring, Drayson, Walkey, Dale & Carroll, 2002; Willemsen, Ring, Carroll, Evans, Clow & Hucklebridge, 1998; Willemsen, Ring, McKeever & Carroll, 2000; Zeier, Brauchli & Joller-Jemelka, 1996). Further, the inconsistent findings from the numerous studies of examination stress become well reconciled to the model above when the distinction is drawn on temporal grounds between test or examination stress - the acute stress of an imminent or ongoing examination, and academic stress - more chronic exposure to an extended examination period (Bosch, de Geus, Ring, Nieuw Amerongen & Stowell, 2004; Bosch et al., 2002). All six studies of the former report increases in S-IgA concentration or secretion rate (Bosch, Brand, Ligtenberg, Bermond, Hoogstraten & Nieuw Amerongen, 1998; Bristow, Hucklebridge, Clow & Evans, 1997; Evans, Bristow, Hucklebridge, Clow & Pang, 1994; Huwe, Hennig & Netter, 1998; McClelland, Ross & Patel, 1985; Spangler, 1997). In sharp contrast, of the seven studies that have investigated the latter, five (Deinzer and Schuller, 1998; Jemmott, Borysenko, Borysenko, McClelland, Chapman, Meyer & Benson, 1983; Jemmott and Magloire, 1988; Li, Ziu, Qian & Tang, 1997; Mouton, Fillion, Tawadros & Tessier, 1989) have found decreases in S-IgA.
Academic stress aside, the rest of the evidence linking chronic stress and S-IgA down regulation is less than compelling. Most of the studies have examined minor events or daily hassles in small samples of students or female nurses. Of the six studies that have been published to date, only three report negative associations between hassle frequency or change in frequency and S-IgA concentration or secretion rate. The problems with these studies have been enumerated elsewhere (Bosch et al., 2002). Aside from modest sample size, some have used instruments for measuring stress that have little psychometric pedigree and all failed to control for health behaviours, particularly smoking, now known to be related to both S-IgA (Evans, Der, Ford, Hucklebridge, Hunt & Lambert, 2000) and chronic stress (Heslop, Davey Smith, Carroll, Macleod, Hyland & Hart, 2001). Thus, although the balance of evidence tends to favour the hypothesis that chronic stress exposures down-regulate S-IgA, numerous methodological problems counsel caution.

Data from the West of Scotland Twenty-07 Study on a large adult community sample, in which both S-IgA (Evans et al., 2000) and major life events were measured, permitted a more convincing test of the hypothesis that chronic stress experience is related to down-regulation of S-IgA. In addition, any putative associations between stress and S-IgA could be adjusted for smoking, as well as for age, sex, and household occupational status.

2. Method

2.1. Participants

Data are derived from the middle and eldest of the three age cohorts of the West of Scotland Twenty-07 Study. Individuals were all from the Glasgow area and have been followed up at regular intervals since the baseline survey in 1987 (Ford, Ecob, Hunt, Macintyre & West, 1994). Members of the middle cohort were all around 44 years old and members of the older cohort were all around 63 years old at the third follow-up when data on life events were collected and a saliva sample taken. The optimum sample size was 1477. However, missing data and improperly collected saliva reduced the sample with full data to 1222, comprising 640 from the middle cohort and 582 from the eldest cohort. The mean age of the middle cohort was 44.6 (SD = 0.84) years and 63.6 (SD = 0.61) years for the eldest.
cohort. Overall, there were 556 (45%) men and 666 (55%) women, and 606 (50%) of the participants came from manual and 602 (50%) from non-manual occupational households. The sex ratios for the two cohorts were virtually identical: 285 (45%) men and 355 (55%) women for the middle cohort and 271 (47%) men and 311 (53%) women for the older cohort. However, the distribution of participants from manual and non-manual occupational households differed significantly between cohorts ($\chi^2 (1) = 21.81, p < 001$); in the middle cohort, 275 (44%) came from manual and 354 (56%) from non-manual occupational households, whereas for the elder cohort the figures were 331 (43%) and 248 (57%), respectively.

2.2 Apparatus and procedure

Participants were tested in a quiet room in their own homes by trained nurses. Demographic information was obtained by interview. Household socioeconomic position was classified as manual and non-manual from the occupational status of the head of household, using the Registrar General’s (1980) classification system of occupations. Head of household was either the participant or his/her partner, depending on which of the two held or had held the highest status occupation.

Major life events over the past two years and their initial and current impact were assessed by presenting participants with eight cards each of which listed a number of major life events in one particular domain. The domains were as follows: health (e.g. serious illness diagnosed), marriage (e.g. living apart or divorce), relationships (e.g. serious disagreement within family), deaths (e.g. spouse died), work (e.g. unemployment), housing (e.g. problem with landlord), finance (e.g. problems paying bills), and general (e.g. burglary or theft). Participants were asked to indicate up to six events which had happened either to them or to someone they cared about. The present analyses focussed on those events that had happened directly to the participant. Following identification of the events, participants were asked to specify, for each event, how much the event disrupted or changed their life and how stressful it was at the time of occurrence, as well as how disruptive and stressful it was now. All of these responses were scored on a 5-point scale, where 1 = a very great deal and 5 = not at all; for the analyses, the values were reversed so that the greater the impact the higher the score.
In addition, participants were asked for each event to indicate how serious the event was 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 included the same domains of personal experience. As concern lay with the overall stress load on participants, four measures were derived from the sums of the product of each life event experienced and its disruptiveness and stressfulness, both at the time of its occurrence and now. In addition, a similar measure was derived from the number of events times their rated seriousness.

Smoking behaviour was determined by responses to the question, ‘Do you ever smoke tobacco now? I am thinking of a pipe, cigars and your own roll ups as well as cigarettes you might buy.’ If the answer was ‘No’, participants were asked, ‘Did you ever used to smoke any kind of tobacco?’ On this basis, participants were characterised as ‘never smokers’, ex smokers’, or ‘current smokers’.

Saliva samples were taken at the end of the interview, using standard salivettes (Sarstedt Ltd, Leicester, UK). Participants were instructed to swallow hard to dry out the mouth and then immediately to place the swab under the tongue. They were asked to hold the swab as still as possible for 2 minutes, timed precisely by the nurse interviewers using portable digital timers. After exactly 2 minutes, participants removed the swab, returning it to the salivette case. It should be conceded that the use of absorbent cotton materials to collect saliva has been observed to produce lower S-IgA concentrations (Shirtcliff, Granger, Schwartz & Curran, 2001); however, it is reasonable to consider that any such reduction would be a constant error. All samples were frozen within 2 hours of collection and remained frozen at -20 degrees C until assay. Samples were dispatched from Glasgow to London by air for assay in four batches and recovered after thawing by centrifugation at 1000g for 10 minutes. Double antibody sandwich ELISA, described in detail elsewhere (Carroll et al., 1996), was used to determine S-IgA concentration. Intra-assay % coefficient of variation was 3.8 and inter-assay % coefficient of variation was 7.6. Prior to assay, saliva volume was determined gravimetrically. Saliva sample collection and volume determination for S-IgA analysis conformed to a procedure described previously (Zeier et al., 1996). The focus of analysis was S-IgA secretion rates (μg/2min), which were calculated as the product of saliva volume (ml) and S-IgA concentration (μg/ml). Given the distribution of S-IgA secretion rate
values in this sample (Evans et al., 2000), a natural log transformation was applied prior to statistical analyses.

2.3 Data analyses

Analysis was undertaken using SPSS version 12. ANOVA was used to compare life events scores between cohorts, sexes, household occupational groups, and smoking status groups. Eta-squared ($\eta^2$) was derived as the ratio of the independent variable sums of squares and the total sums of squares, and used as an indicator of effect size. Similar analyses were applied to the log $n$ transformed S-IgA secretion rate values. To test the main hypothesis, linear regression was conducted, with log $n$ transformed S-IgA secretion rate values as the dependent variable. Initially, simple linear regression was used to establish whether there were indications of an association between stressful life events exposure and secretion rate. In subsequent hierarchical regression analyses, assay batch, saliva volume, and smoking behaviour were entered at step 1. Since the batch variable reflected inter-assay variation, it could be a potential confounder. Adjustment for saliva volume would help establish whether any associations between S-IgA secretion rates and stressful life events exposure were driven by variations in saliva volume or reflected a link with actual variations in S-IgA production and/or transport (Willemsen et al., 1998). The importance of controlling for smoking behaviour when examining possible relationships between psychosocial variables and S-IgA has already been demonstrated (Evans et al., 2000). In these analyses, the life events measures were entered at step 2. In subsequent analyses, batch, smoking, and saliva volume were again entered at step 1, with possible moderating variables, sex, age cohort, and household occupational status, entered at step 2, and the life events variables being relegated to step 3. The main results of these regressions are presented in Tables.

3. Results

3.1 Life Events

The median number of major stressful life events happening to the participants over the last two years was 1 (interquartile range = 2). Although very few events were
experienced, they were clearly regarded as serious; the average seriousness score was 7.12 (SD = 9.21) on a scale of 1-10. With regard to the stress load, the mean total disruption scores at the time of the event and now were 3.65 (SD = 4.85) and 2.52 (SD = 3.61) respectively, and the mean total stressfulness scores then and now were 4.10 (SD = 5.22) and 2.53 (SD = 3.62).

The middle cohort identified more stressful life events than the elder cohort, F (1,1220) = 8.81, \( p = .003, \eta^2 = .007 \), and their total stress load at the time of exposure was higher, in terms of disruption, F (1,1220) = 7.79, \( p = .005, \eta^2 = .006 \), stress, F (1,1220) = 8.75, \( p = .003, \eta^2 = .007 \), and seriousness, F (1,1220) = 4.89, \( p = .03, \eta^2 = .004 \). Men and women did not differ in the number of events exposed to or in terms of the total contemporary and present stress load arising from such exposures, nor did manual and non-manual occupational household groups. The summary data are presented in Table 1.

There were 420 (34%) current smokers in the sample, 330 (27%) ex smokers, and 472 (39%) never smokers. The life events data for smokers, ex smokers, and never smokers are presented in Table 2. Smokers had been exposed to more life events than current non-smokers, F (2,1219) = 5.21, \( p = .006, \eta^2 = .008 \), rated them as more serious, F (2,1219) = 7.73, \( p < .001, \eta^2 = .013 \), experienced more disruption then, F (2,1219) = 5.99, \( p = .003, \eta^2 = .010 \), and now, F (2,1219) = 5.24, \( p = .005, \eta^2 = .009 \), and experienced more stress at the time, F (2,1219) = 5.78, \( p = .003, \eta^2 = .009 \), and now, F (2,1219) = 3.40, \( p = .03, \eta^2 = .006 \).

3.2 Secretory Immunoglobulin A

Log, S-IgA secretion rates were significantly higher in the middle than the older cohort, F (1,1220) = 12.04, \( p = .001, \eta^2 = .010 \); this would appear to be driven largely by cohort differences in saliva volume, F (1,1220) = 23.82, \( p < .001, \eta^2 = .019 \). Men had higher log, S-IgA secretion rates than women, F (1,1220) = 18.45, \( p < .001, \eta^2 = .015 \), again with significantly higher saliva volumes, F (1,1220) = 6.27, \( p = .01, \eta^2 = .005 \). Non-manual occupational household groups had higher secretion rates than manual occupational household groups, F (1,1206) = 5.38, \( p = .02, \eta^2 = .004 \), which again appeared to be driven by differences in saliva volume, F (1,1206) = 6.21, \( p = .01, \eta^2 = .005 \). The summary data are presented in Table 3. Finally, log, S-IgA secretion rates were attenuated, F (2,1219) = 8.73, \( p \).
3.3 Life events and Secretory Immunoglobulin A Secretion Rate

Simple linear regression revealed statistically significant negative associations between the five stressful life events variables and log S-IgA secretion rate: for disruption then, $\beta = -.06$, $t = 1.99$, $p = .05$, $R^2 = .003$; stress then, $\beta = -.06$, $t = 2.24$, $p = .03$, $R^2 = .004$; disruption now, $\beta = -.06$, $t = 2.17$, $p = .03$, $R^2 = .004$; stress now, $\beta = -.06$, $t = 2.14$, $p = .03$, $R^2 = .004$; and seriousness, $\beta = -.07$, $t = 2.30$, $p = .02$, $R^2 = .004$.

In multiple hierarchical regressions models in which assay batch, saliva volume, and smoking was entered at step 1 and the life events variables at step 2, the negative associations between stressful life events experience and S-IgA secretion rate were attenuated, but all bar one remained statistically significant. As might be expected from the analyses above, the step 1 variables were all significantly associated with log S-IgA secretion rate: for batch, $\beta = -.14$, $t = 6.78$, $p < .001$; for saliva volume, $\beta = .67$, $t = 32.87$, $p < .001$; for smoking $\beta = -.09$, $t = 4.13$, $p < .001$. The step 1 model, incorporating all three variables accounted for almost half the variance in log S-IgA secretion rate, $\Delta R^2 = .487$. The associations between log S-IgA secretion rate and the life events variables emerging at step 2 in these models are summarised in Table 4. Although for the most part, remaining statistically significant, it is important to note that the residual associations like the original bivariate associations are small in terms of the amount of variance they explain. In the next set of multiple hierarchical regression models, batch, saliva volume and smoking were entered at step 1. In these models, though,
the major demographic variables, age cohort, sex, and household occupational status, were entered at step 2, with the life events variables entered at step 3. Only sex emerged from step 2 entry as a significant predictor of log S-IgA secretion rate, $\beta = -.10$, $t = 3.70$, $p < .001$. The full step 2 model accounted for around 1%, $\Delta R^2 = .012$, of additional variance in log S-IgA secretion rate. The associations between log S-IgA secretion rate and the life events variables emerging at step 3 in these models are also summarised in Table 4; the associations are virtually unchanged from those that emerged from the previous two-step hierarchical models.

4. Discussion

The present analyses testify to a negative association between the experience of stressful life events and S-IgA secretion rate. As such, they support the contention (Bosch et al., 2002) that in contrast to the S-IgA enhancing effects of acute psychological stress (Bosch et al., 2001; Carroll et al., 1996; Kugler et al., 1996; Ring et al., 2002; Willemsen et al., 1998; Willemsen et al., 2000; Zeier et al., 1996), chronic stress might effect a down-regulation of S-IgA. Aside from the evidence from the specific chronic exposure of academic stress (Bosch et al., 2002), support for down-regulation has largely relied on studies reporting a negative relationship between S-IgA and university students’ experience of daily hassles and fairly minor irritants (Evans, Bristow, Hucklebridge, Clow & Walters, 1993; Farne, Boni, Corallo, Gnugnoli & Sacco, 1992; Martin and Dobbin, 1988). To our knowledge, the present study is the first to show that the experience of serious and major life events over a protracted period in substantial cohorts of middle aged and elderly men and women is negatively related to S-IgA secretion rates. In addition, it is clear from these analyses that these associations embrace impact both currently and at the time of exposure.

The importance of controlling for smoking behaviour in this context has been emphasised elsewhere (Bosch et al., 2002; Evans et al., 2000). In the present sample, current smokers had lower S-IgA secretion rates than ex smokers and never smokers. Smoking would also in turn seem to vary with variations in psychological stress (Heslop et al., 2001).
In the present study, smokers had higher life events scores than non-smokers. Thus any relationship between chronic stress and S-IgA may be confounded by variations in smoking behaviour. However, the negative associations between our life events measures and S-IgA largely withstood adjustment for smoking, as well as for assay batch and saliva volume. That assay batch has a substantial effect on S-IgA secretion rate has been reported in prior aggregate analyses of all three cohorts from this study (Evans et al., 2000). The current analyses confirm the importance of controlling for inter-assay variability in large scale epidemiological studies of immune parameters.

By statistical adjustment we were able to establish that the observed relationships between life events and S-IgA secretion rate were not, for the most part, driven by variations in saliva volume. This is important because it permits us to eliminate one fairly parsimonious but less interesting explanation that for those participants with a high stress load the glands simply release less saliva into mouth. The earlier analyses of all three cohorts from this study indicated that the positive association between S-IgA secretion rates and household occupational status were essentially the result of lower salivary flow in the lower household occupational status groups (Evans et al., 2000). That this was not the case in the present analyses indicates that life events stress either decreases IgA production by the local plasma cells or reduces the efficiency with which S-IgA is transported from the glandular interstitium into saliva.

The value of measuring total S-IgA levels, as opposed to antigen-specific S-IgA, has been the subject of considerable debate (Jemmott and McClelland, 1989; Stone, Cox, Valdimarsdottir, Jandorf & Neale, 1987). This debate stems from the common misconception that S-IgA is a measure of adaptive immune responses, i.e., responses that are driven by exposure to a previously encountered antigen. If this were indeed the case then only the levels of S-IgA molecules that are specifically directed against particular antigens would matter for host protection rendering the measurement of total S-IgA levels less meaningful. However, total S-IgA consists, for the most part, of so-called ‘natural antibodies’ (Bos, Cebra & Kroese, 2000). These natural antibodies have a broader specificity to recognize many different types of antigen, and their levels are independent of re-exposure to specific antigens (Stoel, Jiang, van Diemen, Bun, Dammers, Thurnheer, Kroese, Cebra & Bos, 2005). Hence, total immunoglobulin levels are the key to monitoring this aspect of immunity. This
perspective is consistent with evidence showing that total S-IgA levels are predictive of susceptibility to respiratory, oral, and aural infections (Evans, Hucklebridge, Clow & Doyle, 1995; Jemmott and McClelland, 1989; Kuby, 1997). Thus, measuring total S-IgA levels is an immunologically meaningful measure of mucosal host resistance.

The present study suffers from a number of limitations. First, although the present life events scale has a sound pedigree and a paper using it has been published elsewhere (Carroll, Phillips, Ring, Der & Hunt, 2005), the manner of its administration could have imposed an arbitrary cap on the total stress load scores derived. Participants were permitted to select up to six life events only, rather than being free to nominate as many events as had occurred. However, participants on average selected only a small number of events and only nine (1%) reported having experienced six events, whereas 1061 (87%) reported between zero and two events, which strongly suggests that the methodology was not unduly constraining. Second, only one measure of S-IgA was taken, a concern given circadian variation (Hucklebridge, Clow & Evans, 1998). However, in a large cohort study, more comprehensive monitoring was not practicable. Further, S-IgA would appear to reasonably stable from around three hours after wakening (Hucklebridge et al., 1998), and early morning testing was rare. In addition, individual differences in S-IgA has been found to show good test-retest reliability across two to four days (Ring et al., 2002), one to two weeks (Bosch et al., 2001), and four weeks (Willemsen et al., 1998). Third, it should be conceded that the associations that emerged from the present analyses are small in terms of the amount of variance explained. However, they are consistent and remain significant in four out of five cases following adjustment for assay batch, saliva volume, and smoking that account for around half the variance in S-IgA secretion rate. Further, they are of the same order of magnitude as the effect sizes reported in a recent meta-analysis of life events and immunoglobulins (Segerstrom and Miller, 2004); it would appear that samples of the current size are needed for such associations to achieve statistical significance. Nevertheless, their size does raise the question as to whether associations of this magnitude are of idiopathic clinical significance.

In conclusion, the experience of major life events both at the time and now was negatively associated with S-IgA secretion rate. This association would not appear to be driven by variations in saliva volume. As such, a high life stress load would seem to compromise either production or transport. Given the prominent role of S-IgA in immune
defence at mucosal surfaces and the frequency with which infections are initiated at these surfaces, it is plausible that S-IgA affords a pathway by which chronic stress increases susceptibility to upper respiratory tract infection.
References


Stressful life events are associated with low secretion rates of immunoglobulin A in saliva in the middle-aged and elderly, *Brain, Behavior and Immunity*, 20, 191-197.*

http://dx.doi.org/10.1016/j.bbi.2005.06.006  IF 4.91

http://dx.doi.org/10.1016/j.bbi.2005.06.006 IF 4.91

Table 1
Life Events Descriptive Statistics by Age Cohort, Sex and Household Occupational Status

<table>
<thead>
<tr>
<th></th>
<th>Middle</th>
<th>Eldest</th>
<th>Men</th>
<th>Women</th>
<th>Manual</th>
<th>Non-manual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events</td>
<td>1.16 (1.37)</td>
<td>0.95 (1.15)*</td>
<td>1.07 (1.27)</td>
<td>1.05 (1.28)</td>
<td>1.04 (1.23)</td>
<td>1.08 (1.31)</td>
</tr>
<tr>
<td>Disruption then</td>
<td>4.02 (5.22)</td>
<td>3.25 (4.37)*</td>
<td>3.59 (4.75)</td>
<td>3.71 (4.93)</td>
<td>3.55 (4.61)</td>
<td>3.72 (5.03)</td>
</tr>
<tr>
<td>Stressful then</td>
<td>4.52 (5.61)</td>
<td>3.64 (4.71)*</td>
<td>3.94 (4.96)</td>
<td>4.24 (5.42)</td>
<td>4.02 (5.10)</td>
<td>4.16 (5.29)</td>
</tr>
<tr>
<td>Disruption now</td>
<td>2.67 (3.71)</td>
<td>2.35 (3.50)</td>
<td>2.52 (3.68)</td>
<td>2.51 (3.56)</td>
<td>2.52 (3.63)</td>
<td>2.49 (3.58)</td>
</tr>
<tr>
<td>Stressful now</td>
<td>2.70 (3.66)</td>
<td>2.34 (3.56)</td>
<td>2.47 (3.59)</td>
<td>2.59 (3.64)</td>
<td>2.55 (3.70)</td>
<td>2.49 (3.49)</td>
</tr>
<tr>
<td>Seriousness</td>
<td>7.68 (9.82)</td>
<td>6.51 (8.45)*</td>
<td>6.91 (8.92)</td>
<td>7.29 (9.45)</td>
<td>7.06 (8.89)</td>
<td>7.11 (9.40)</td>
</tr>
</tbody>
</table>

* *p* < .05

http://dx.doi.org/10.1016/j.bbi.2005.06.006 IF 4.91

Table 2
Life Events Scores according to Smoking Status

<table>
<thead>
<tr>
<th></th>
<th>Current Smoker</th>
<th>Ex Smoker</th>
<th>Never Smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Number of events</td>
<td>1.22 (1.34)</td>
<td>0.98 (1.21)</td>
<td>0.97 (1.24)</td>
</tr>
<tr>
<td>Disruption then</td>
<td>4.31 (5.11)</td>
<td>3.30 (4.66)</td>
<td>3.31 (4.68)</td>
</tr>
<tr>
<td>Stressful then</td>
<td>4.80 (5.52)</td>
<td>3.74 (5.05)</td>
<td>3.74 (4.99)</td>
</tr>
<tr>
<td>Disruption now</td>
<td>2.97 (3.88)</td>
<td>2.22 (3.17)</td>
<td>2.31 (3.63)</td>
</tr>
<tr>
<td>Stressful now</td>
<td>2.90 (3.78)</td>
<td>2.28 (3.28)</td>
<td>2.38 (3.67)</td>
</tr>
<tr>
<td>Seriousness</td>
<td>8.54 (10.04)</td>
<td>6.43 (8.63)</td>
<td>6.34 (8.68)</td>
</tr>
</tbody>
</table>
Stressful life events are associated with low secretion rates of immunoglobulin A in saliva in the middle-aged and elderly, *Brain, Behavior and Immunity*, 20, 191-197.*

http://dx.doi.org/10.1016/j.bbi.2005.06.006 IF 4.91

Table 3
Salivary Descriptive Statistics by Age Cohort, Sex and Household Occupational Status

<table>
<thead>
<tr>
<th></th>
<th>Middle</th>
<th>Eldest</th>
<th>Men</th>
<th>Women</th>
<th>Manual</th>
<th>Non-manual</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Saliva volume (ml)</td>
<td>0.74 (0.59)</td>
<td>0.58 (0.52)*</td>
<td>0.71 (0.57)</td>
<td>0.63 (0.55)*</td>
<td>0.62 (0.55)</td>
<td>0.70 (0.57)*</td>
</tr>
<tr>
<td>S-IgA secretion rate (μg/2min)</td>
<td>102 (384)</td>
<td>84 (162)</td>
<td>100 (163)</td>
<td>88 (377)</td>
<td>83 (148)</td>
<td>105 (399)</td>
</tr>
<tr>
<td>log n S-IgA secretion rate</td>
<td>3.63 (1.49)</td>
<td>3.32 (1.66)*</td>
<td>3.70 (1.53)</td>
<td>3.31 (1.60)*</td>
<td>3.38 (1.63)</td>
<td>3.59 (1.53)*</td>
</tr>
</tbody>
</table>

* p < .05
Table 4
Associations between Secretory Immunoglobulin A Secretion Rate and Life Experience following Adjustment for Potential Confounding Variables.

<table>
<thead>
<tr>
<th>Step</th>
<th>$\beta$</th>
<th>t</th>
<th>$\Delta R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1: Assay Batch, Saliva Volume, and Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disruption then</td>
<td>-0.04</td>
<td>2.10*</td>
<td>0.002</td>
</tr>
<tr>
<td>Stressful then</td>
<td>-0.04</td>
<td>1.99*</td>
<td>0.002</td>
</tr>
<tr>
<td>Disruption now</td>
<td>-0.04</td>
<td>2.04*</td>
<td>0.002</td>
</tr>
<tr>
<td>Stressful now</td>
<td>-0.04</td>
<td>1.76$^#$</td>
<td>0.001</td>
</tr>
<tr>
<td>Seriousness</td>
<td>-0.04</td>
<td>2.02*</td>
<td>0.002</td>
</tr>
<tr>
<td>Step 2: Age Cohort, Sex, and Household Occupational Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disruption then</td>
<td>-0.05</td>
<td>2.21*</td>
<td>0.002</td>
</tr>
<tr>
<td>Stressful then</td>
<td>-0.04</td>
<td>2.03*</td>
<td>0.002</td>
</tr>
<tr>
<td>Disruption now</td>
<td>-0.05</td>
<td>2.17*</td>
<td>0.002</td>
</tr>
<tr>
<td>Stressful now</td>
<td>-0.04</td>
<td>1.84$^#$</td>
<td>0.001</td>
</tr>
<tr>
<td>Seriousness</td>
<td>-0.04</td>
<td>2.08*</td>
<td>0.002</td>
</tr>
</tbody>
</table>

* $p \leq 0.05$
$^\# p \leq 0.08$