LIFE EVENTS, EMOTIONS AND IMMUNE FUNCTION: EVIDENCE FROM WHITEHALL II COHORT STUDY

Short title: Life events, Emotions and Immunity

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Funding: This study was funded by the Danish Research Council (DFF – 4183-00474).

Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract

Stressful life events have been shown to increase vulnerability to infections. However, the effects may be dependent on specific emotional responses associated with these events. In general, negative emotions are thought to exacerbate and positive emotions protect from the adverse effects of stressors on health. In this study, we adopted an evolutionary and functionalist perspective on emotions and hypothesized that both positive and negative emotions in response to stressful events are protective, whereas absence of emotional reactions exacerbates vulnerability to infections. We assessed immune function using 'lymphocytes to white blood cells' ratio as a proxy for current viral infection in =3,008 British civil workers (30% women). No main effect of stressful life events or emotions on lymphocyte ratio was observed in either sex. However, in men, there was an interaction of life events with both positive and negative emotions, as well as a combined measure of general affect. Supporting our hypothesis, stressful life events were associated with impaired immune function in those who reported very low levels of both positive and negative emotions but not in others. We discuss potential benefits of negative and positive emotions in the context of stress and immunity.

Keywords: life events; stress; negative emotions; positive emotions; immunity.

Introduction

Psychological stress is believed to affect immune function and increase vulnerability to infections;[1] yet, the findings regarding the association between stressful life events and immunity are inconsistent.[2] One potential source of this heterogeneity in the findings, which, surprisingly, has been virtually unaccounted for, is the fact that there are substantial individual differences in the ways people react to and cope with stressful events.[3] Indeed, only a few previous studies have systematically investigated how emotional responses moderate the effects of stressful life events on immune function.

Based on functional and evolutionary theories of emotions,[4,5] we argue that negative emotions following stressful life events are appropriate responses to stressors, and thus would mitigate their deleterious consequences on health. We present findings from a large-scale study testing interactive effects of life events and emotional reactions, both positive and negative, on one aspects of immunity, the ratio of lymphocytes to white blood cells.

Existing evidence on the link between stress and immunity

There exists a large body of literature investigating relations between stress and immune function. Segerstrom and Miller[2] review over 300 studies on the topic, showing that there has been a variety of approaches to both defining stress and measuring immune function. Studies suggesting that various types of stress have the potential to modulate aspects of immunity, yet the findings are quite mixed and the specific effects seem to vary depending on the type and the duration of stressors. In considering relations specifically between stressful life events and immunity, researchers have operationalized "stress" as either exposure to objective stressful events, or as a subjective experience of stress, including perceived stress or negative affect.[2] The review concludes that the effects of stressful events on immunity vary according to the kind of

event, while subjective reports of stress do not show a consistent association with immune function.

Biological mechanisms linking stress and immunity

Psychological stress causes a physiological stress response, which activates the sympathetic nervous system and hypothalamus-pituitary-adrenal (HPA) axis. The activated sympathetic nervous system can directly affect immune function by activating adrenoreceptors present on immune cells, or indirectly by modulating the distribution and production of lymphocytes, and the release of proinflammatory substances.[6] The activation of the HPA axis under acute stress can have a protective function against overactivity of the immune system, as it results in increased secretion of cortisol, which has anti-inflammatory properties. However, chronic or repeated activation of the HPA-axis may lead to exhaustion of the stress response, which in turn might result in a failure to down-regulate inflammatory processes and contribute to chronic low-grade inflammation and antigen-specific immunosuppression.[7,8] These biological processes are, however, highly complex and are far from being fully elucidated.[9]

Considering the role of emotions

One of the conceptual model underlying many studies on stress and physical health in general, and immune function in particular, is that stressful circumstances will lead to negative psychological reactions, i.e. perceived stress or negative emotions, which in turn would activate the physiological stress system that has detrimental effects on health.[10]

However, there is substantial inter-individual variability in psychological reactions to objective circumstances. Yet, surprisingly, few studies have asked whether the way individuals deal emotionally with particular stressful circumstances would affect the impact of those stressors on the immune function. In health literature, the general assumption has been that

negative emotions are detrimental,[10,11] while positive emotions can offer protective benefits.[12] Therefore, those who react more negatively to stressful life events are expected to be at an increased risk of adverse health effects. However, while a number of studies show a link between negative emotions and health detriments,[13–15] the findings are far from universal. As mentioned above, with respect to immune function, Segerstrom and Miller's meta-analysis[2] concludes that the evidence for an association between global measures of negative psychological reactions to stress, such as perceived stress or negative affect, and immune changes is insufficient.

We argue for a more nuanced perspective, emphasizing that negative emotions in response to stress may in fact be beneficial (references blinded for review). Indeed, psychological literature suggests that experience of negative emotions following traumatic events is an integral part of healthy coping.[19] Accordingly, in the health psychology literature, emerging studies also suggest that moderate levels of negative emotions in the context of difficult life circumstances might exert protective effects on health.[16,17]

The hypothesis that negative emotions may moderate the effects of stressful life events on health has up to date not been extensively explored, however. We are aware of only four studies that investigated potential interactions between stressful events and negative emotions on immune function, which have yielded mixed findings. González-Quijano et al.[20] found that trait anxiety interacted with stressful life events in predicting immunity, operationalized as lymphoproliferative response to mitogens, in a sample of 85 male college students. Non-anxious individuals who recently experienced stressful life events had poorer immune function compared to non-anxious individual who did not experience any stressful events. In anxious individuals, immune function was lowered independent of life events.

Solomon et al.[21] investigated immune function using a range of immune measures including lymphocyte subtypes, lymphoid cell mitogenesis (PHA and PWM), and NK cell cytotoxicity, in 68 persons who experienced an earthquake. Participants were asked about the level of life disruption caused by the earthquake as well as about the distress caused by the earthquake (including negative emotions such as anxiety or fear). The authors found that the level of disruption and distress interacted in predicting immune function. In participants with low disruption, higher levels of distress were associated with lower immunity. In contrast, high distress was associated with *better* immune function in participants with moderate and high levels of disruption, suggesting that psychological distress proportional to the objective level of life disruption resulted in optimal immune function. The authors underscore that rather than distress itself, it is its appropriateness in a particular situation that may affect immunity. They speculate that such proportional emotional responses may reflect realistic appraisal of the circumstances, leading to most adaptive behaviors and better adjustment.

Cohen et al.[13] investigated the role of life events, perceived stress, and negative emotions as predictors of susceptibility to common cold, in 394 healthy volunteers. While their analyses included the test of interaction between life events and the subjective measures of stress and negative emotions, regrettably, the authors reported no other details of the analyses than that the interactions were statistically non-significant.

Linn et al.[22] studied immune function, assessed using a range of measures, among 98 men aged 40 to 60 years, half of whom experienced a recent serious illness in family or death. The groups were dichotomously divided into depressed and non-depressed, and the main and interactive effects of death or illness and depression were investigated. While the authors found a main effect of depression on immune function, but no statistically significant interactions.

However, just like the other three studies, this study was limited to small sample sizes reducing the ability to detect interactions.

In the present study we investigated whether emotional reactions modified the relation between stressful life events and objectively measured immune function. We hypothesized that in the presence of life events that are negative emotionally laden (e.g. death of a relative or divorce), not only positive, but also negative emotional reactions reduce the effects of the event on immune function.

Method

Participants and study design

Data from Whitehall II cohort study were used to investigate the interactive effects of negative life events and emotions on immune activity. The original sample at Phase 1, recruited in 1985-1988, included 10,308 British civil service workers.[23] Even though Whitehall II is an ongoing longitudinal study, we only used historical data from Phase 1 because some of the variables of interest were only collected then. Only a fraction of participants (N = 3144) were administered blood tests to assess white blood cell count. Further 136 participants were excluded due to missing information on one or more exposure variables or the covariates. The final sample included 3008 participants (30% women), aged from 34 to 56 (*M* = 45 years, *SD* = 6). Thirty three percent of the sample had highest occupational grade (administration), 48% were professionals/executives and 19% had the lowest grade (clerical/support). The overwhelming majority of the sample (94%) where white. Compared to those who took part in Phase 1, but were excluded from the present study, the included participants were not significantly different

in age or likelihood of reporting any longstanding illness at baseline, but were more likely to be male and white and have higher socio-economic status.

The Whitehall II study is approved by the London-Harrow Research Ethics Committee and the Scotland Research Ethics Committee. All participants who had clinical examination were asked to give written informed consent.

Measures

Life events. Participants were asked about a list of recent life events ranging in severity. Due to the focus of the present study on adverse situations, we selected negative life events where negative emotional reactions are most likely to occur:[24] break up of a close relationship (as a proxy for divorce or separation) and death of a relative. These two events were combined into one binary variable due to a small fraction of people who experienced both events in the same year.

Emotions. Positive and negative emotions were assessed using the Bradburn affect balance scale.[25] The scale consists of five items used to assess positive emotions in the past few weeks (e.g. "*Did you feel particularly excited or interested in something?*") and five items used to assess negative emotions (e.g., "*Did you feel depressed or very unhappy*?"). Items are rated on a 4-point Likert scale from 0 (not at all) to 3 (a great deal). Scores for items on each subscale are summed and range from 0 to 15, where higher scores indicate higher affect strength. These two subscales were used separately in the analyses. The original scale also included an affect balance score where the score for negative affect is subtracted from the score for positive affect. Such an approach presupposes that negative and positive emotions cancel each other out. As mentioned in the introduction, we hypothesize that this is not the case and rather that the two types of

emotions can coexist, indicating the degree of emotional complexity.[26] Therefore, we also created an *affect strength* score by summing the scores for positive and negative affect.

Immune function. To measure immune activity, we used the ratio of lymphocytes to white blood cells (continuous variable). Lymphocytes belong to one of the subtypes of white blood cells in the immune system. Increased concentrations of peripheral lymphocytes are typically, but not exclusively, due to a reactive lymphocytosis associated with viral infections. In order to correct the number of lymphocytes for the total number of white blood cells, we used the ratio of lymphocytes over the total number of white blood cells as a proxy for recent viral infections in the present study.

Statistical Analyses

We used linear regression to test whether life events and the three types of affect variables (positive, negative and affect strength) had main and interactive effects on immune activity. Positive and negative affect were added to the same model, so that they were mutually controlled for (Tables 2-5). The analyses also controlled for age and socioeconomic position at baseline [Administrative; Professional/Executive; Clerical/Support]. In addition, pre-existing health conditions may affect both the immune function and emotions; therefore we also controlled for any long-standing illness present at baseline (one yes/no item). Because of the gender differences in self-reporting of health and emotions[27,28] we stratified the analyses by gender.

Results

Women were on average approximately one year older than men (*p* for gender differences <.001) and had significantly lower SES (i.e. 7% of men had lowest occupational grade compared to 45% of women, while 42% of men had highest occupational grade compared to 12% of

women, *p* for gender differences <.001). Thirty one percent reported longstanding illness at baseline (no gender differences, $p = .80$). Twenty nine percent of men and 39% of women reported at least one of the two considered life events (*p* for gender differences <.001). Mean negative affect was 2.73 ($SD = 2.28$) in men and 2.87 ($SD = 2.47$) in women (no significant gender difference, $p = .11$); mean positive affect was 6.28 ($SD = 2.89$) in men and 5.85 ($SD = 3.10$) in women (*p* for gender differences <.001); observed range for both measures was 0-15. Mean lymphocytes white blood cells ratio was 0.31 ($SD = 0.16$) in men and 0.29 ($SD = 0.17$) in women (*p* for gender differences = .04); observed range was 0.00 – 0.80. Neither exposure to life events nor any of the affect measures had statistically significant correlation with immune activity.

In the main effect models (Tables 1 and 2), we did not observe a statistically significant association between life events and immune function in either men or women. Nor was there a statistically significant main effect of negative or positive affect (mutually controlled for) or affect strength on immune activity in men or women. However, as shown in Tables 3 and 4, in men, affect modified the association between life events and immune activity. Specifically, exposure to death of a relative or divorce was associated with higher leukocyte to the total number of white blood cells ratio, but only at low values of affect measures (Tables 3 and 4). As shown in Table 3, the modifying effects of both negative and positive emotions were only marginally significant; however, interestingly, the trend for both positive and negative affect went in *the same direction*, i.e. both negative and positive emotions were associated with reduced effect of life events on immune function, at approximately the same rate. The protective effect of emotions was more evident when the two measures of affect were combined into one affect strength measure (Table 4). This is illustrated in Figure 1. We conducted a simple slope

analysis to investigate the boundary conditions at which affect strength is protective against the effects of traumatic life events on the immune function in men. Recent experience of death or divorce was only predictive of higher lymphocytes to white blood cell ratios in combination with very low levels of affect strength (b = 0.029, SE = 0.014, p = .044 at the level of affect strength 1.5 SD below the mean.). In women, the interactions between life events and affect were not statistically significant in predicting immune activity.

(Tables 1-4, Figure 1)

Discussion

The present study investigated whether emotional reactions modified the effect of recent traumatic life events on aspects of immunity. Even though stress and emotions have been previously extensively investigated in relation to the immune function, only four previous studies have specifically addressed the interaction between the occurrence of stressful life events and subjective emotional experience (e.g. perceived stress or negative affect), with mixed results.[13,20–22] We hypothesized that in the context of emotionally laden life events such as death in family or divorce, negative emotions may mitigate the effects of stressful life events on immunity. Importantly, the benefits of emotions would not be confined to positive emotions, but will also extend to negative emotions.

Consistent with our hypothesis, we found that recent experience of divorce or death in family was associated with increased lymphocyte to white blood cell ratio, an indicator of ongoing viral infection, but only in those men who exhibited very low levels of both positive and negative affect. While it has previously been recognized that emotions play an important role in health, including immune function,[2] previous models of emotions and health often assume that negative emotions are universally detrimental and exacerbate the effects of objective stressors,

while positive emotions might mitigate those effects. The findings of the current study fail to support those notions. We show that in the presence of stressful life events, the association between emotions and immune activity tends to go in the same direction for positive and negative emotions. This finding is consistent with the literature in psychology arguing that experience of mixed emotions (not only positive ones) during difficult times may be one of the healthiest responses to adversity and may facilitate recovery.[19,26,29,30]

There may be several explanations for why emotions might buffer the effects of stressful life events on immunity, and our results do not allow us to disambiguate between the different possibilities. Our measure of emotions reflected a. presence of emotions, b. awareness of emotions (otherwise the participants would not be able to indicate that they had the emotions) and c. to some extent, disclosure of emotions (admitting to having the emotions when filling out questionnaire. Furthermore even though in this study emotions were measured after the traumatic life events happened, it is not clear from the measures to what extent the emotions were due to those events. Thus it is impossible to say whether it is emotions in general (e.g. tendency to experience negative and positive emotions as a personality trait) or specific emotions in reactions to adversity that might buffer the effects of adversity on the immune function.

Awareness and acceptance of emotions is the cornerstone of many anxiety stress reductions therapies.[31] In addition, individuals who report that they are upset may also be more likely to explicitly express their emotions in everyday life and less likely to suppress negative emotions. Studies have shown that expressing emotions through writing is associated with measurable physical health benefits, including improved immune function.[32,33] Expressing negative emotions has also been linked to reduced risk myocardial infarction and stroke.[34] while sustained suppression of emotions is associated with an increased risk of cardiovascular

problems.[35,36] Finally, those who report negative emotional experiences may also be more likely to engage in support seeking behaviors.

The results of this study were limited to men. One possible reason for the gender differences could be that men have been shown to have a weaker immune system and are more prone to infections than women.[37] Indeed, in our study, men had on average higher lymphocyte to white blood cell ratio than women, a small, but statistically significant difference. More importantly, there exist gender differences in regulation of negative emotion, [38] specific regulatory strategies, [39] how emotions are socialized, as well as confidence in expression of emotions.[40] There is evidence to suggest that women have larger repertoires of emotion regulation strategies[41] and that men are less likely to engage in positive regulatory strategies such as reappraisal, active coping and acceptance.[41] In sum, lack of reported emotion in men may be more likely to reflect lower levels of emotion processing, or more suppression as compared to women.

Furthermore, it is also important to keep in mind when interpreting the results that the men surveyed in this study were a rather selected sample: they were all civil servants; moreover, 42% of them held high level administrative positions. The way individuals deal with emotions is likely dependent on their education and socio-economic position. Thus, the results of this study may not necessarily generalize to the entire population of men.

Two additional methodological considerations need to be mentioned. First, we were limited to the historical data and the measures of immune function that were collected when the Whitehall II cohort was established. There is a greater variety of measures of immune markers available today and future research needs to replicate our findings using other methods of immune function assessment.

Furthermore, the list of events administered at Phase 1 of Whitehall II study was rather short and did not include many adverse situations where negative emotions are likely to arise. Therefore the effects of stressful life events, both with or without presence of negative emotions, might have been underestimated.

Conclusions

Despite these potential limitations, the findings suggest that treating negative emotions as a universal health risk factor is unwarranted and underscore the need for a more nuanced approach within emotions and health research. Further research is needed to address the psychological, social and physiological mechanisms explaining health protective effects of negative emotions.

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Figure 1. Interaction between life events in the past 12 months, affect strength and lymphocyte to white blood cell ratio.

Table 1. Main effects of life events (death of a family member or divorce), positive and negative affect on lymphocytes to white blood cells ratio, controlling for age, socioeconomic position (SEP), and baseline longstanding illness.

MEN (N = 2101)				
	b	*β*	*SE*	*p*
SEP [Clerical/Support]	.028	.044	.014	.053
SEP [Professional/Executive]	.007	.023	.007	.33
Age	-.002	-.066	.001	.003
Longstanding illness [Yes]	.002	.005	.008	.83
Death or divorce [Yes]	.002	.005	.008	.83
Negative Affect	-.002	-.027	.002	.24
Positive Affect	-.001	-.021	.001	.34
WOMEN (N = 907)				
	b	*β*	*SE*	*p*
SEP [Clerical/Support]	.038	.111	.019	.041
SEP [Professional/Executive]	.038	.110	.018	.037
Age	.001	.033	.001	.35
Longstanding illness [Yes]	.007	.018	.012	.60
Death or divorce [Yes]	.019	.052	.012	.12
Negative Affect	-.004	-.056	.002	.11
Positive Affect	.001	.010	.002	.77

Table 2. Main effects of life events (death of a family member or divorce) and affect strength on lymphocytes to white blood cells ratio, controlling for age, socioeconomic position (SEP), and baseline longstanding illness.

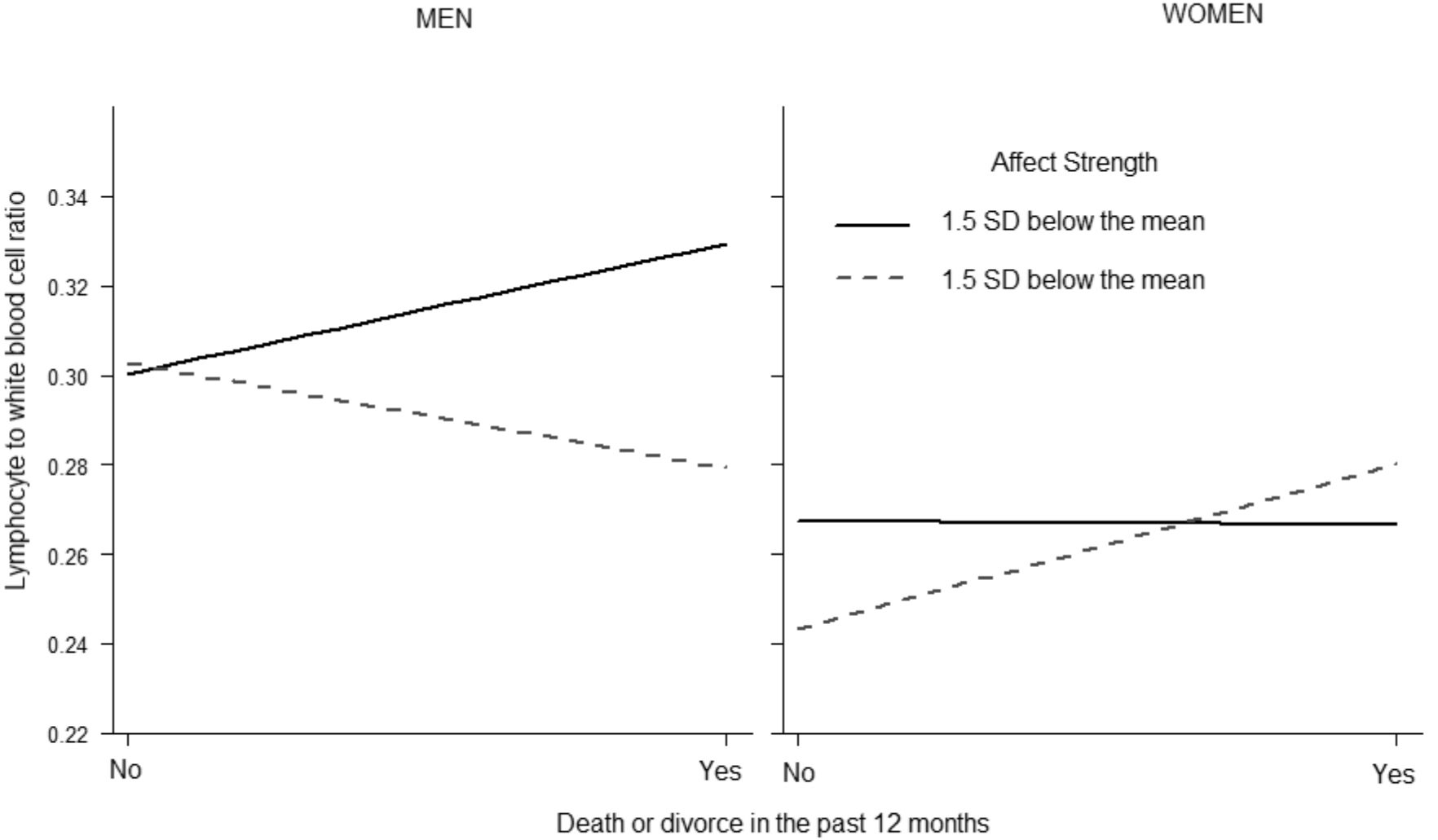
MEN (N = 2101)				
	b	*β*	*SE*	*p*
SEP [Clerical/Support]	.027	.044	.014	.056
SEP [Professional/Executive]	.007	.022	.008	.34
Age	-.002	-.066	.001	.003
Longstanding illness [Yes]	.001	.004	.008	.86
Death or divorce [Yes]	.002	.004	.008	.84
Affect Strength	-.001	-.030	.001	.18
WOMEN (N = 907)				
	b	*β*	*SE*	*p*
SEP [Clerical/Support]	.036	.104	.019	.055
SEP [Professional/Executive]	.037	.107	.018	.044
Age	.001	.038	.001	.28
Longstanding illness [Yes]	.004	.012	.012	.72
Death or divorce [Yes]	.017	.048	.012	.15
Affect Strength	-.001	-.020	.002	.55

Table 3. Interactive effects of life events (death of a family member or divorce) and positive and negative affect on lymphocytes to white blood cells ratio, controlling for age, socioeconomic position (SEP), and baseline longstanding illness.

MEN (N = 2101)				
	b	*β*	*SE*	*p*
SEP [Clerical/Support]	.028	.045	.014	.051
SEP [Professional/Executive]	.008	.024	.007	.29
Age	-.002	-.068	.001	.002
Longstanding illness [Yes]	.002	.007	.008	.75
Death or divorce [Yes]	.049	.137	.022	.029
Negative Affect	-.000	-.001	.002	.98
Positive Affect	.000	.007	.001	.80
Death or divorce [Yes]* Negative Affect	-.005	-.064	.003	.10
Death or divorce [Yes]* Positive Affect	-.005	-.101	.003	.063
WOMEN (N = 907)				
	b	*β*	*SE*	*p*
SEP [Clerical/Support]	.038	.111	.019	.042
SEP [Professional/Executive]	.038	.110	.018	.037
Age	.001	.031	.001	.38
Longstanding illness [Yes]	.007	.020	.012	.55
Death or divorce [Yes]	-.016	-.046	.032	.61
Negative Affect	-.005	-.075	.003	.091
Positive Affect	-.001	-.019	.002	.65
Death or divorce [Yes]* Negative Affect	.003	.041	.005	.50
Death or divorce [Yes]* Positive Affect	.004	.084	.004	.26

Table 4. Interactive effects of life events (death of a family member or divorce) and affect strength on lymphocytes to white blood cells ratio, controlling for age, socioeconomic position (SEP), and baseline longstanding illness.

MEN (N = 2101)				
	b	*β*	*SE*	*p*
SEP [Clerical/Support]	.027	.044	.014	.053
SEP [Professional/Executive]	.008	.024	.008	.30
Age	-.002	-.068	.001	.002
Longstanding illness [Yes]	.002	.006	.008	.78
Death or divorce [Yes]	.049	.138	.022	.027
Affect Strength	.000	.005	.001	.85
Death or divorce [Yes]* Affect Strength	-.005	-.148	.002	.022
WOMEN (N = 907)				
	b	*β*	*SE*	*p*
SEP [Clerical/Support]	.036	.104	.019	.056
SEP [Professional/Executive]	.037	.107	.018	.043
Age	.001	.036	.001	.30
Longstanding illness [Yes]	.005	.014	.012	.67
Death or divorce [Yes]	-.016	-.046	.032	.61
Affect Strength	-.002	-.050	.002	.25
Death or divorce [Yes]* Affect Strength	.004	.105	.003	.26


MEN
WOMEN
Affect Strength
1.5 SD below the mean
1.5 SD below the mean
Lymphocyte to white blood cell ratio
0.34
0.32
0.30
0.28
0.26
0.24
0.22
No
Yes
No
Yes
Death or divorce in the past 12 months