Published Ahead of Print on August 31, 2007 as 10.1097/PSY.0b013e318148c682

Depressive Symptoms Predict Mucosal Wound Healing

Jos A. Bosch, PhD, Christopher G. Engeland, PhD, John T. Cacioppo, PhD, and Phillip T. Marucha, DMD, PhD

Objective: There is mounting evidence that psychosocial stress can delay wound healing, but this literature almost exclusively pertains to dermal wound healing. Many surgical procedures involve damage to mucosal tissues and the time course and the role of repair processes, such as inflammation, in the healing of these tissues are markedly different from those in dermal healing. Feelings of depression and social isolation are common among surgical patients, and the present study therefore investigated if these factors predict the rate of mucosal wound healing. **Methods:** Undergraduate students were invited to participate in the study if they reported high or low levels of loneliness or depressive symptoms, corresponding to the upper or lower quintile of their peer group. The UCLA loneliness scale and the Beck Depression Inventory [short form] were used for this screening. A sample of 193 healthy young adults (age range 18–31 years) received a 3.5-mm circular wound on the oral hard palate, under local anesthesia. Healing was monitored by daily videographs of the wound. **Results:** The median healing rate was 7 days. High dysphoric participants were, however, more likely to heal slower than this median healing rate (odds ratio 3.57 (1.58–8.07); $p < .001$). This association remained robust after correction for a broad range of demographic and behavioral variables, including gender, age, ethnicity, and health behaviors. High dysphoric individuals also exhibited significantly larger average wound sizes from day 2 post wounding onward. Loneliness and diurnal cortisol secretion (measured over 5 days) were unrelated to healing. **Conclusion:** Depressive symptoms predict the rate of mucosal wound healing in healthy young adults. We discuss potential pathways that warrant further investigation. **Key words:** wound healing, surgical recovery, mucosa, inflammation, loneliness, depression, stress.

HPA = hypothalamic-pituitary-adrenal; **BDI-sf** = Beck Depression Inventory short form; **UCLA-R** = Revised UCLA Loneliness Scale; **OR** = odds ratio; **AUC** = area under the curve.

INTRODUCTION

Over 70 million surgical procedures are performed each year in the United States (1). Despite the benefits, surgical procedures also involve risks, sometimes severe and wide-ranging, which make surgery a major source of distress (2). For example, the prevalence of depression in surgical patients is approximately 1.5 to 2.5 times higher than in the general population (3). Importantly, emotional distress and depression in this context predict longer hospital stays, slower return to normal daily activities, more frequent pain reporting, an increased use of analgesics, a worse physician- and self-assessed physical state, and a greater likelihood of complications, including death (4–12). Several pathways may account for these associations. Negative affective states can increase physical symptom reporting (13,14), promote dysfunctional coping behaviors such as smoking and drinking alcohol, and lead to medical noncompliance and self-neglect (4). In addition, there is accumulating evidence that emotional distress can directly affect biological recovery processes, such as wound healing, through perturbations of endocrine and immune systems (4).

In 1995, a human study provided initial evidence that emotional distress is associated with delayed wound healing (15). Women caring for a relative with Alzheimer's disease reported greater distress and demonstrated 24% slower healing of a dermal punch biopsy than control participants matched on age, gender, and income (15). This finding has been confirmed and extended in a number of human and animal studies, demonstrating associations between distress and delayed healing with various wound types, including oral wounds (16), skin wounds (17,18), and ulcerating leg wounds (19), as well as altered cytokine and metalloproteinase expression in wound exudate and tissue (20–28). The clinical importance of these findings is not limited to wound closure: slower healing wounds are also more likely to have complications like infection, and poorer esthetic outcomes such as discoloration and scarring (29).

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has been proposed as a potential mediator of these effects (4,18). For example, animal studies have shown that glucocorticoid antagonists can partially restore the effects of restraint stress on wound healing, wound cytokine production, and wound infection (22,28,30,31). Human blister-wound studies demonstrated an inverse association between cortisol levels at the time of wounding and local inflammatory cytokine and metalloproteinase production (20,27). Also, dermal wounds healed slower in participants who exhibited larger cortisol responses to awakening (17). Not all human studies find associations with cortisol, however (32), and the role of other aspects of HPA functioning, like diurnal profile, has yet to be explored.

The current study investigated the associations between loneliness (the negative emotional experience of being socially isolated), dysphoria (experiencing depressive symptoms), and wound healing. Loneliness and dysphoria predict a wide range of health outcomes (33–35), likely through compromising health-promoting and restorative behaviors as well as direct effects on biological processes (34,36–38). For example, lonely individuals respond less well to vaccination (39), are at greater risk of developing high blood pressure (35), and have poorer sleep (40). Likewise, higher levels of depressive symptoms are associated with higher inflammatory activity, poorer surgical outcomes, and worse cardiovascular

From the College of Dentistry (J.A.B., C.G.E., P.T.M.), University of Illinois at Chicago, Chicago, Illinois; School of Sport and Exercise Sciences (J.A.B.), University of Birmingham, Birmingham, UK; Department of Psychology (J.T.C.), University of Chicago, Chicago, Illinois; and Institute for Behavioral Medicine Research (J.A.B., C.G.E., P.T.M.), Ohio State University, Columbus, Ohio.

Address correspondence and reprint requests to Phillip T. Marucha, University of Illinois at Chicago, College of Dentistry, Department of Periodontics (MC 859), 801 S. Paulina St., Chicago, IL 60612. E-mail: marucha@uic.edu

Received for publication December 15, 2006; revision received April 11, 2007.

This study was funded by Grant NIDCR, P50 DE-13749 from the National Institute of Dental and Craniofacial Research.

DOI: 10.1097/PSY.0b013e318148c682

0033-3174/07/6907-0597

health (4,34,37,38,41). The co-occurrence of loneliness and dysphoria is well established (42,43) and prospective research has recently identified loneliness as an independent predictor of symptoms of depression (44). Notwithstanding, loneliness and dysphoria can be regarded as separate constructs. Although consistently correlated, the coefficients are moderate in size and there is substantial independent variation (44); they are also likely to have nonoverlapping genetic determinants (45,46). Thus, it is possible that loneliness and dysphoria will have independent effects on wound healing (38).

Whereas nearly all stress studies have focused on dermal wound healing, the present study examined mucosal wound healing. The mucosa form a vital interface with the outside world, essential to life-supporting processes such as exchanging gases, nutrients, and waste products (47). Mucosal wounds heal much faster and with less inflammation than skin wounds and, for reasons not completely understood, do so with minimal scarring (48). These and other distinctive features of mucosal healing suggest that current data on stress and dermal wound healing do not necessarily generalize to other tissue types (49,50). Previously we demonstrated that oral mucosal wounds, placed during a week of academic examinations, healed 40% slower than wounds placed during summer vacation (16). In the current study, we monitored mucosal healing in healthy young adults who were selected on the basis of reporting high or low levels of loneliness or depressive symptoms. We hypothesized that participants who report high levels of loneliness or dysphoria would show delayed mucosal wound healing. A range of potentially confounding demographic factors and health behaviors were measured in parallel. A possible mediating role of diurnal cortisol secretion on wound healing was also assessed.

METHODS

Participants

The Beck Depression Inventory short form (BDI-sf) and the Revised UCLA Loneliness Scale (UCLA-R) were administered to 1630 undergraduate Ohio State University students. Participants were recruited from those scoring in the upper or lower quintile on one or both of these questionnaires. The cut-offs were determined a priori on the basis of previous research in a similar population (51). For the UCLA-R, the inclusion criterion was a score of $\leq$28 or $\geq$46; for the BDI-sf, the inclusion criterion was a score of $\leq$1 or $\geq$8. A BDI-sf score $\geq$8 also corresponds to the cut-off for suspected clinical depression (52,53). Eligible participants were invited by phone to participate in a study on "psychosocial factors, wound healing, and inflammation" without disclosing the predetermined psychological selection criteria. The following initial exclusion criteria were applied: a) suffering from an infectious, inflammatory, coagulation, or endocrine disorder, including diabetes; b) suffering from conditions that make the individual a poor surgical risk (e.g., cardiovascular problems, allergies to materials used during the surgical procedure); c) pregnancy; d) oral health conditions that require prompt treatment, which was subsequently checked by clinical examination. To eliminate potential confounds, no first-term freshmen were enrolled in the study because of potentially elevated loneliness, and no participants were wounded during major examination periods because of potential effects of stress (16). Refusal to participate and the application of these exclusion criteria resulted in a final sample size of 193 undergraduates (mean age = 20.1 years, range 18–31; n = 98 females). As intended, the selection criteria resulted in a study sample enriched with participants high on loneliness and/or depressive scores (BDI-sf survey sample: 2.1 $\pm$ 4.2 (mean $\pm$ standard deviation (SD)); BDI-sf study sample: 4.0 $\pm$ 3.8; UCLA-R survey sample: 32.0 $\pm$ 9.2; UCLA-R study sample: 36.3 $\pm$ 11.6). The survey and study samples were comparable with regard to gender (survey sample: 44.6% male; study sample: 46.4% male) and age (survey sample: 20.5 $\pm$ 2.2 years; study sample: 20.2 $\pm$ 2.1 years). Differences in ethnic composition were observed, in that the final study sample had a higher proportion of African Americans (survey sample: 6.4%; study sample: 15.3%), which reflects the additional recruiting efforts to include this student group. The proportion of Asian participants was smaller (survey sample: 6.1%; study sample: 3.2%). Participants were compensated $360 for their time in the study. Informed consent was obtained from each participant and The Ohio State Institutional Review Board approved the study. The study was conducted between May 2001 and August 2003.

Procedures

The wounding procedure was performed at the School of Dentistry Research Clinic of The Ohio State University. The interval between the initial survey and clinic appointment varied between 3 and 10 weeks; both the BDI-sf and UCLA-R were re-administered on arrival in the clinic. These more proximal scores were used as predictors in subsequent analyses. Participants attended between 10 AM and 11:30 AM. After a 30-minute rest period, a 3.5-mm circular oral wound was placed on the hard palate under local anesthesia (2% lidocaine), approximately 3 mm from the marginal gingival of the first and second molars, using a 3.5-mm tissue punch. A scalpel was then used to remove the surface epithelium and superficial connective tissue, creating a uniform 1.5-mm deep wound. The side of the mouth to be wounded was determined by random coin toss. All wounds were placed by the same periodontologist (P.T.M.). The periodontologist and clinic personnel remained uninformed about the participant's psychosocial status as determined by the questionnaire.

Psychological Measures

The BDI-sf, a widely used and well-validated self-report measure of depressive symptoms, boasts good reliability statistics, correlates well with other measures of depression, and predicts clinical ratings of depression (52,53). Also, in the present study, internal reliability was high (Cronbach's α = 0.84). The BDI-sf comprises 13 items that assess the severity of depressive symptoms experienced during the past 2 weeks, on a 4-point Likert scale (0 "not" to 4 "very much"). Various BDI-sf scores (range 5–8) have been suggested as cut-offs to classify depressed individuals. These cut-points are empirically derived on the basis of predicting the incidence of clinical depression in different populations, and are also related to alterations in immune system functioning (54,55). A score of $\geq$8 was employed in the present study.

Loneliness was measured using the UCLA-R Loneliness Scale (56). For this 20-item scale, participants again responded using a 4-point Likert-scale format. Scores correlate with measures of shyness and self-esteem, and high scores on this measure have been associated with alterations in immune system functioning (34,36). This scale is acknowledged to have good psychometric properties (56). In this study, reliability was again high (Cronbach's α = 0.94).

Additional questionnaires were administered for post hoc analyses, of which the Spielberger Trait Anxiety Questionnaire (57) and Impact of Events Scale (58) were used in this manuscript.

Assessment of Wound Size

Wounds were videographed daily between approximately 10 AM and 11 AM using an intra-oral camera. A standard-sized 6-mm diameter template was placed around the wound as a reference measure to prevent variation due to camera magnification and angulation. Videotaped images were blind coded and wound size was measured (Canvas 7 software, ACD Systems of America Inc., Victoria, British Columbia) by two raters (interrater r = .87). Wound size was expressed as the ratio of the wound surface area relative to the standard label size. Wounds were classified as healed when closure exceeded >95%. Thus, in conformity with previous research (15,16,18), for each post wounding day 2 healing outcomes could be determined—the average wound size (relative to standard) and the proportion of healed participants.

Demographic, Anthropometric, and Health Behavior Measures

Questionnaires were used to assess variables that might confound or mediate the relationship between psychosocial factors and wound healing. These variables included demographic factors such as age, gender, ethnicity, parental socioeconomic status (income, education), as well as health practices and lifestyle variables. Participants indicated their average weekly use of alcoholic drinks (a can/bottle [12 oz.] of beer, a glass [8 oz.] of wine, and a shot [2 oz.] of liquor were scored as one drink), caffeinated drinks, cigarettes and other means of nicotine, recreational drugs, vitamins, and dietary supplements. Alcohol and nicotine consumption, and weekly sleep were assessed by self-report 1 week before wounding, on the day of wounding, and 1 week post wounding. Other measured variables included use of recreational drugs, sleep, oral hygiene behaviors, exercise, and body mass index (kg/(height in meters) (2). To assess exercise, participants were asked if they engaged in activities, at least once a week, sufficiently vigorous to break sweat, and if so, how many times and for how many hours per week. Sleep quality was measured using the Pittsburgh Sleep Quality Index, a 19-item self-report questionnaire that assesses sleep quality over a 1 month timeframe. The questionnaire includes measures of subjective sleep quality, time needed to fall asleep, sleep duration, and use of sleeping medication (59).

Cortisol

Participants were signaled seven times a day (7 AM, 9:30 AM, 10:30 AM, 2:30 PM, 3:30 PM, 7:30 PM, 8:30 PM) by a preprogrammed wristwatch (Seiko, RC-4500 WristMac, Tokyo, Japan) and instructed to immediately take a saliva sample by placing a cotton roll (Salivette, Sarstedt, Leicester, UK) in the mouth until soaked, and complete a short questionnaire on current mood and activities. Determinations were made using Cortisol Coat-A-Count RIA kits (Diagnostic Products Corporation, Los Angeles, California). The intra-assay variation was 4.3%, the inter-assay variation was 5.2%, and the sensitivity was 0.25 ng/ml.

Data Analysis

The primary analyses focused on the association between depressive symptoms, loneliness, and wound healing. The data did not meet the proportional hazards assumption for survival analysis. Therefore, logistic regression analysis was used to predict healing as a binary outcome: "fast healing" (faster than median healing rate) versus "slow healing" (slower than median healing rate). Categorization on the basis of healing rate was chosen in the absence of established clinical criteria to differentiate slow and fast healing. Odds ratios (ORs) are presented as measures of effect size. In these analyses, the OR reflects the relative likelihood of being a slow healer among individuals scoring above predetermined values on the BDI-sf or UCLA-R. To gauge the statistical significance of the associations, 95% confidence intervals are also reported. The χ^2 tests and t tests were used to compare demographic and behavioral variables between groups of participants who had high versus low values on the predictor variables. Data that deviated >3 SD from the mean were considered outliers and excluded from the analyses. Occasional missing wound data were recovered by interpolation (<1% of data points). Data were analyzed using SPSS 14 (Chicago, Illinois).

RESULTS

Missing Data

Participants with ≥4 days of missing wound-healing data were excluded from analyses ($n = 7$). The data from three participants were excluded because wound sizes were 3 SD above the mean for the larger part of the healing curve.[1] Hence, the number of valid cases was 183.

[1]Including these outliers did not alter the overall pattern of results.

Depressive Symptoms, Loneliness, and Healing Rate

At 7 days post wounding, approximately 50% of all participants were healed. This median time point was used as the criterion to differentiate fast healers from slow healers in the logistic regression analyses (see Statistical Methods for rationale). Logistic regression showed a significant association between depressive symptoms and the time needed to heal (OR per SD on the BDI-sf 1.50 (1.10–2.06); $p = .007$). This indicates that in this population, the likelihood to be a slow healer increased by 50% with each SD increase in depressive symptoms. Scores on the UCLA-R Loneliness Scale were not significantly associated with wound healing status (OR per SD on the UCLA 1.26 (0.93–1.70); $p = .13$).

The BDI-sf is intended as a screening instrument in which scores above a cut-off, typically 8, are considered to signify clinical depression (52,53). This cut-off was applied (BDI-sf ≥8) to distinguish dysphoric from nondysphoric individuals, which was also the initial upper selection cut-off. Analyses indicated that dysphoric individuals ($n = 40$) were over 3.5 times more likely than nondysphoric individuals ($n = 143$) to exhibit a slower than median healing rate (Table 1). The proportion of healed participants and mean wound sizes across test days are presented in Figure 1. Figure 1A shows that, from day 5 onwards, a significantly smaller proportion of individuals in the high dysphoric versus low dysphoric group were considered healed (likelihood ratios, range = 3.9–10.6; $0.001 < p < .05$).

Figure 1B extends this analysis to wound size, demonstrating that from day 2 until day 7 post wounding, high dysphoric individuals also exhibited larger average wound sizes (i.e., slower healing) than low dysphoric participants. Multivariate analysis of variance yielded a significant effect of BDI-sf on wound size, both when utilizing BDI-sf as a continuous variable ($F(8,166) = 2.56$; $p = .01$) or as a dichotomized variable ($F(8,166) = 2.51$; $p = .01$). These multivariate findings were confirmed in subsequent univariate analyses, which again yielded identical results when BDI-sf was utilized as a dichotomized or continuous variable (as an indication of range); the largest significant effect was found for day 3 ($F(1,178) = 16.06$; $p < .001$) and the smallest significant effect was found for day 7 ($F(1,179) = 6.13$; $p = .01$); no significant association was observed for day 1 and day 8 post wounding ($F(1,179) < 1.5$; $p > .22$). These findings remained essentially unaltered after correction for the influence of gender, smoking status, alcohol consumption, average hours of sleep, ethnicity, and oral hygiene habits (i.e., similar covariates used as shown in the analyses presented in Table 1). Replicating earlier findings (60), these post hoc analyses also demonstrated a significant multivariate effect of gender, with larger average wound sizes for women ($F(8,166) = 2.56$; $p = .01$) in the earlier phases of wound repair (univariate analyses yielded significant gender differences from days 1 to 5).

Dysphoria and Wound Healing: Testing Potential Confounds and Pathways

Subsequent analyses focused on wound healing rate, being the parameter of primary clinical interest. Four hierarchical

TABLE 1. Results of Logistic Regression Analyses, Assessing Depression as a Predictor of Faster Than Median (Within 7 Days) Versus Slower Than Median (≥8 Days) Mucosal Wound Healing

	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
Dysphoria (BDI-sf ≥8)	3.57* (1.58–8.07)	3.79* (1.64–8.74)	4.15* (1.75–8.82)	3.68* (1.37–9.89)
Age		0.91 (0.78–1.05)	0.90 (0.77–1.05)	0.90 (0.77–1.05)
Gender (female)		1.44 (0.77–2.70)	1.40 (0.72–2.70)	1.45 (0.73–2.86)
African-American		0.60 (0.25–1.43)	0.48 (0.19–1.19)	0.48 (0.19–1.21)
Other ethnic[a]		1.48 (0.53–4.16)	1.65 (0.58–4.71)	1.61 (0.56–4.63)
Smoking status			1.47 (0.63–3.40)	1.42 (0.57–3.18)
Alcohol (>10 drinks/week)			2.37** (0.89–6.27)	2.45** (0.92–6.54)
Sleep (hours /night)			0.96 (0.74–1.25)	0.97 (0.75–1.25)
Tooth brushing (#/day)			0.96 (0.69–1.35)	0.96 (0.68–1.35)
Dental flossing ("no")			1.49 (0.74–3.01)	1.52 (0.75–3.09)
UCLA Loneliness Scale[b]				0.98 (0.69–1.46)

OR = odds ratio; CI = confidence interval; BDI-sf = Beck Depression Inventory short form.
* $p < .05$; ** $p \leq .09$.
[a] Asian ($n = 6$); Hispanic ($n = 7$); Native American ($n = 1$); and "other" ($n = 5$).
[b] Each unit represents 1 standard deviation.

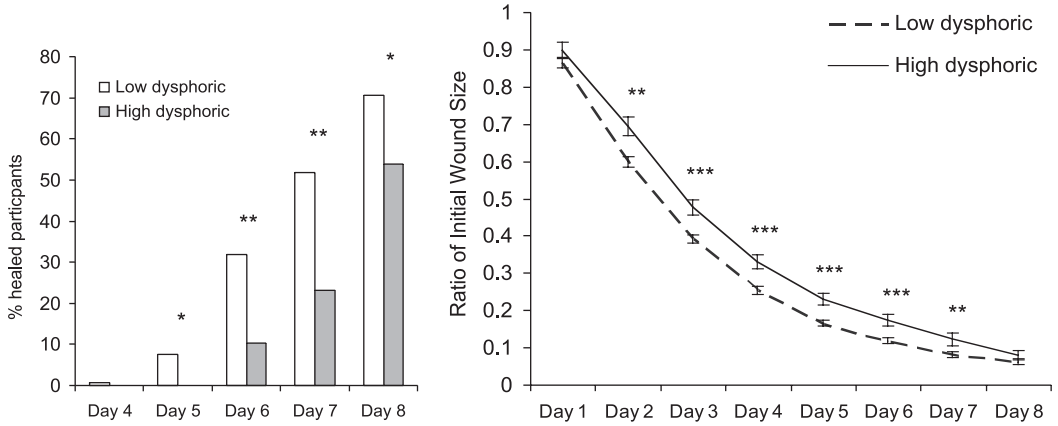

Figure 1. Proportion of healed participants (left panel) and mean wound sizes (right panel) for each day post wounding. A smaller proportion of high dysphoric individuals (BDI-sf ≥8) were healed on each study day and this group also had larger average wound sizes. Results of χ^2 tests and analysis of variance, respectively: *$p \leq .05$; **$p \leq .01$; ***$p \leq .001$.

logistic regression models (Table 1) tested the influence of potentially confounding variables: Model 1 presents the unadjusted effect of depressive symptoms; Model 2 assesses the contribution of depressive symptoms adjusted for age, gender, and ethnicity; Model 3 expands this analysis by including health-related behaviors in the model, such as smoking, alcohol consumption, average hours of sleep, and oral hygiene habits; Model 4 additionally corrects for loneliness. These analyses indicate that the association between dysphoria and wound healing was robust and not confounded or mediated by these variables. The inclusion of these control variables tended to strengthen the relationship between dysphoria and wound healing, indicative of a suppressor effect. Further post hoc analyses included anxiety and the impact of recent life events in the analyses as potentially relevant factors. Although dysphoric individuals reported higher levels of trait anxiety as well as more intrusions and avoidance behavior resulting from recent events, these variables did not account for the association between healing rate and dysphoria.

To test if the selection of our healing cut-off (day 7) played a role in the observed effects, we again applied all four logistic regression models and used days 6 and 8 to differentiate slow from fast healers. These analyses yielded essentially similar results with ORs ranging between 2.4 and 4.1 (all <0.01), affirming the robustness of the findings.

Additional exploratory analyses focused on identifying potential demographic and lifestyle differences between the two groups that may account for the link between depressive symptoms and healing rate. Table 2 presents the results of these comparisons, which indicated that high and low dysphoric participants were similar on a large range of potentially confounding variables. Although p values were slightly above the 0.05 criterion, more low dysphoric participants reported consuming >20 alcoholic beverages per week (likelihood ratio = 3.4; $p = .068$), and high dysphoric group reported slightly fewer hours of sleep ($t_{(181)} = 1.91$; $p = .056$). Subsequent analyses indicated that high dysphoric participants also scored less favorably on other sleep indices, including having lower perceived sleep quality and more day-time

TABLE 2. Demographic and Behavioral Characteristics of Low Dysphoric (BDI-sf ≤7) and High Dysphoric (BDI-sf ≥8) Individuals

	Low Depressive Symptoms (n = 143)	High Depressive Symptoms (n = 40)	P^a (2-Sided)
BDI-sf	2.3 ± 0.2	10.1 ± 0.4	<.001
Demographics			
Age	20.2 ± 0.2	20.7 ± 0.4	.086
Gender (% female)	46.2	47.5	.88
Ethnicity			
African American	15.4%	15.0%	
White	74.8%	72.5%	
Other ethnic[b]	9.8%	12.5%	.89
Parental education (years)	15.3 ± 0.2	15.5 ± 0.5	.72
Parental household income (US$)[c]			
<35,000/year	21.4%	20.0%	
35,000–50,000/year	20.2%	13.3%	
50,000–100,000/year	40.5%	56.7%	
>100,000/year	17.9%	10.0%	.42
Health behavior indices			
Sleep (hours/night)	7.3 ± 0.2	6.9 ± 0.1	.058
Alcohol (drinks/week)	4.7 ± 0.8	3.2 ± 0.7	.23
Drinking ≥20 glasses/week	4.9%	0.0%	.064
Current smokers	18.2%	22.5%	.55
Smoking ≥2 packs/week	7.7%	5.0%	.54
Recreational drug use	10.2%	10.0%	.93
Caffeine (drinks/week)	6.1 ± 0.7	8.0 ± 1.6	.24
Exercise (hours/week)	2.4 ± 2.4	2.3 ± 4.2	.80
Body mass index (kg/m^2)	24.2 ± 0.4	24.4 ± 0.6	.82
Use of vitamins or other food supplements	36.7%	46%	.34
Serum albumin	4.05 ± 0.03	4.05 ± 0.05	.92
Tooth brushing (#/day)	1.97 ± 0.08	2.03 ± 0.08	.64
Dental floss use	28.7%	35.0%	.45

Data shown as mean ± standard error of the mean or percentages.

[a] Continuous variables were compared using a t test, proportions were tested using likelihood ratios.

[b] Asian (n = 6); Hispanic (n = 7); Native American (n = 1); and "other" (n = 5).

[c] Approximately 18% of participants in each group responded with "do not know"; 2% selected "no response."

sleepiness. However, these variables were not associated with healing rate, and adding those to the logistic regression Model 4 (Table 1) did not attenuate the observed association between dysphoria and wound healing.

Finally, in the light of evidence that smoking and excessive alcohol consumption influence immune function (61) and recovery from surgery (62–64), we also analyzed the data after the separate and collective exclusion of tobacco users (n = 38), participants who admitted to using recreational drugs (n = 8), and those who reported consuming ≥20 alcoholic beverages a week (n = 7). Applying these rigorous selection strategies did again not attenuate the observed association between dysphoria and wound healing.

Dysphoria, Wound Healing, and Cortisol

All cortisol values were averaged over the five collection days. No association was observed between depressive symptoms and diurnal cortisol, expressed as the area under the curve (AUC) (R^2 = 0.002; $p > .10$). Also, no significant association was found between BDI-sf scores and cortisol levels at the different time points after controlling for gender, body mass index, and smoking status (lowest p = .08). However, regression analyses using the same covariates demonstrated a small negative association between BDI-sf and the average of all three morning levels (i.e., average of 8 AM, 9:30 AM, and 10:30 AM levels) (R^2 change = 0.029; $p < .05$). There was also an association with delta morning-evening cortisol (i.e., averaged morning values minus averaged evening values) (R^2 change = 0.038; $p < .01$), indicative of a flattened slope in participants who reported higher numbers of depressive symptoms. No significant differences in cortisol secretion (assessed as average AUC, mean values for individual time points, aggregated time points, or delta morning-evening) were found between slower and faster healing groups ($p > .20$). Moreover, adding these cortisol measures into the logistic regression analyses did not attenuate the observed association between dysphoria and oral wound healing (not shown). Replicating prior research (39,40), loneliness was also not associated with cortisol AUC. An association was, however, again found with the delta of averaged morning-evening cortisol, such that higher levels of loneliness were associated with less cortisol decline during the day (R^2 change = 0.042; $p < .01$) as well as lower average morning cortisol levels (R^2 change = 0.045; $p < .01$).

DISCUSSION

The present study investigated whether symptoms of depression and loneliness predicted the healing of a standardized palatal wound in a large sample of healthy young adults. Higher BDI-sf scores were associated with slower healing. High dysphoric individuals, identified as participants having a BDI-sf symptom score of ≥8, exhibited larger wound sizes, indicative of slower wound closure, and were over 3.5 times more likely to be classified as slow healers (i.e., slower than median healing rate). This substantial effect reflects a consistent pattern in the literature on wound healing, demonstrating a strong association between psychosocial distress and wound healing (4,18). Two additional features of the present study contribute to, and further strengthen, this literature: the use of a large sample size allowed for greater statistical control of potentially confounding factors than in previous studies; and our finding further establishes that the effects of psychosocial stress on dermal wound healing generalize to mucosal wounds (*cf*, 16). This generalization is of significance because a large proportion of surgical procedures involves damage to mucosal (e.g., oral, gastrointestinal, genitourinary) tissues, and the kinetics of mucosal wound healing are substantially different from dermal healing (48).

The association between dysphoria and wound healing was not attenuated after controlling for a number of demographic factors (e.g., gender, ethnicity) and health practices (e.g., alcohol, drug and tobacco use, sleep, oral hygiene). Moreover, direct comparisons of high versus low dysphoric individuals yielded no or only minimal differences on health-related and lifestyle variables. Although there is epidemiological evidence for associations between depressive symptoms and maladaptive health behaviors, our observations are largely in line with a recent meta-analysis, which indicates that depressive symptoms are likely to be only a minor predictor of health-promoting behaviors (65).

Optimal healing of wounded tissue involves a delicate trade-off between inflammation and rapid wound closure (49,50); inflammation is needed to clear debris and infection but this process may also cause damage that delays the healing process. In mucosal wounds, the balance is tilted toward low inflammation and rapid healing (48). Processes that facilitate inflammation also impair the rate of mucosal healing, and populations that exhibit enhanced inflammatory reactivity show a delay in mucosal wound healing (48,60). Interestingly, there is good evidence that, in clinically depressed and dysphoric populations, inflammatory activity is upregulated (38). It is therefore possible that such enhanced inflammatory activity contributed to the delay in mucosal wound healing observed in this study.

Glucocorticoids are important endocrine regulators of inflammation, and the present study investigated the possibility of an association between circadian cortisol release and oral wound healing. Glucocorticoids have long been known to have a detrimental effect on wound healing, knowledge that is largely based on observations in patients who experience prolonged increased glucocorticoid exposure, such as in Cushing's syndrome or as a result of dexamethasone treatment (29,66,67). Notwithstanding, the link between wound repair and glucocorticoid exposure is not straightforward. For example, glucocorticoid administration before or during surgery, including oral surgery, can have profound positive effects on many surgical outcomes, such as edema and pain (presumably by preventing excessive postsurgical inflammation) (68). Moreover, animal studies have shown that repeated acute stressors may facilitate wound healing (69). In the present study, an aggregate analysis (5-day average) of circadian cortisol release (e.g., AUC, morning levels, evening levels, delta morning-evening levels) was unrelated to mucosal wound healing. This suggests that, when within a normal range, interindividual variations in circadian cortisol levels do not have a major impact on the healing process. It remains possible, however, that analyses of intraindividual changes (70) or other aspects of HPA activity may yield relevant associations with healing. Examples are response to awakening (17), cortisol values at time of wounding (20,27), and tissue glucocorticoid sensitivity (38). Further, others have suggested that field studies may have substantial error variance, due to saliva collection methods and noncompliance, and thereby yield attenuated effect sizes (71,72).

Depressive symptomatology has broad dysregulating effects and, aside from the HPA axis, affects aberrantly on the autonomic nervous system and the immune system (37,38,73–75). The brain senses and responds to local inflammation (e.g., induced by wounding) via autonomic pathways (76,77), and dysregulation of these pathways may therefore affect the wound healing process. For example, recent studies have shown that heightened adrenergic activity delays wound healing (78,79). Likewise, the parasympathetic nervous system is an important regulator of inflammation (76,77). In light of reports showing associations between depression and lowered parasympathetic tone (75), it seems possible that reduced parasympathetic activation may contribute to local inflammation and thereby delay healing (50,76). Importantly, most of the mucosa, including the oral palate, is densely innervated by parasympathetic nerves (47,80). Thus, further research into the role of autonomic processes in wound healing seems warranted. Psychophysiologists have a number of measurement strategies available that facilitate such research. These strategies include the monitoring of autonomic activity and reactivity in laboratory and ambulatory settings, for example, by utilizing impedance and electrocardiography or by measuring plasma and urinary catecholamines (81,82). Other options include monitoring wound healing in patients with autonomic defects or in patients who use drugs that modulate autonomic functions.

The present study adds to a larger literature showing that depression and depressive symptoms are powerful predictors of physical health outcomes (4,34,36,37). The study also contributes to an ongoing debate on whether specific psychosocial factors, rather than a general "negative affectivity" factor, exert unique health effects (13). The present results

appear consistent with a specificity model: although loneliness and depressive symptom scores are correlated, no significant association between wound healing and loneliness was observed. Such specificity was not unexpected as dysphoria and loneliness have distinct experiential, behavioral, and genetic features and are therefore likely to affect health through partially distinct pathways (38). A comparable specificity has been reported for other health outcomes as well, such as cardiovascular health and human immunodeficiency virus progression, whereby social factors (e.g., loneliness, social support) and depressive symptoms are found to have unique contributions to developing pathology and mortality (33,41,83).

A number of limitations of the current study should be noted. For example, participants with known risk factors for delayed healing, such as increased age and metabolic and endocrine diseases (e.g., diabetes), were excluded and participants with decidedly unhealthy lifestyles were rare; e.g., the proportion of smokers was small (<20%, mostly light smokers) and alcohol consumption was modest for most participants. The weak associations between health behaviors and either wound healing or depressive symptoms may thus reflect a restriction of sample variance. The current study cannot answer how depressive symptomatology affects or interacts with other risk factors. Meta-analysis shows that the effects of stress on immune function are generally stronger in the aged (73), whereas studies also show that depressive symptomatology can aggravate risk factors such as diabetes. Thus, the effects of depressive symptomatology on healing may be larger in populations that exhibit other wound healing risk factors. Another limitation of the present study is that measurement of depressive symptoms was not accompanied by clinical interviews. Although the use of questionnaires to obtain an index for depression reflects a very common research strategy, it limits the understanding of what specific aspects of depressive symptomatology underlie the association with the wound healing (e.g., clinical classification, symptom intensity, the extent of comorbidity, and the duration of symptoms). Finally, it needs to be established to what extent the magnitude of the association between dysphoria and wound healing is preserved in samples not preselected on high and low depressive symptom scores.

Wound healing provides a compelling paradigm to test whether psychosocial factors can influence clinically relevant biological processes, and an important aspect of the current finding is therefore its potential clinical implications. A large fraction (at least 60%) of surgical procedures is elective, which provides a window of opportunity for presurgical interventions aiming at the modification of risk factors (84). Psychological interventions in the form of educating patients about postsurgical care are already a common element of presurgical care, and several meta-analyses have shown that the well-informed patient experiences less distress, uses less analgesics postoperatively (at the same time reporting less pain), and performs better on various other indices of recovery (5–12). Our results suggest that extending the focus of standard presurgical care to identify and treat the depressed patient, and even nondepressed individuals with increased depressive symptom scores, may benefit postoperative convalescence (*cf*, 85). Given the financial burdens of hospital care and work absenteeism, this could also prove cost effective.

We acknowledge the dedicated efforts of our co-workers and students who provided support with data management (Jason Davis, BA; Josja K. Eggen, MA), logistics and recruitment (April C. Logue, MA; Janet Schulte, MA), experimental procedures (Jason Davis, BA; Kelly Dillon, BA; Josja K. Eggen, MA; April C. Logue, MA; Rebecca Milliard, MA; Delandria Whitehouse). We are also grateful for the support provided by Drs. Janice Kiecolt-Glaser, Ronald Glaser, and Gary G. Berntson. Drs. Kavita Vedhara and Doug Carroll gave helpful comments on earlier drafts of this manuscript. The cortisol analyses were performed at The Ohio State General Clinical Research Center (with special thanks to Drs. Susan Moseley and William Malarkey).

REFERENCES

1. Centers for Disease Control and Prevention. Advanced data, from the vital and health statistics of the Centers for Disease Control and Prevention. Vital Health Stat 1998;300:1–16.
2. Contrada RJ, Leventhal E, Anderson JR. Psychological preparation for surgery: marshaling individual and social resources to optimize self-regulation. In: Meas S, Johnston M, Leventhal H, editors. International yearbook of Health Psychology. Vol. 3. New York: Wiley; 1994.
3. Vaeroy H, Juell M, Hoivik B. Prevalence of depression among general hospital surgical inpatients. Nord J Psychiatry 2003;57:13–6.
4. Kiecolt-Glaser JK, Page GG, Marucha PT, MacCallum RC, Glaser R. Psychological influences on surgical recovery. Perspectives from psychoneuroimmunology. Am Psychol 1998;53:1209–18.
5. George JM, Scott DS. The effects of psychological factors on recovery from surgery. J Am Dent Assoc 1982;105:251–8.
6. Munafo MR, Stevenson J. Anxiety and surgical recovery. Reinterpreting the literature. J Psychosom Res 2001;51:589–96.
7. Blumenthal JA, Lett HS, Babyak MA, White W, Smith PK, Mark DB, Jones R, Mathew JP, Newman MF. Depression as a risk factor for mortality after coronary artery bypass surgery. Lancet 2003;362:604–9.
8. Linn BS, Linn MW, Klimas NG. Effects of psychophysical stress on surgical outcome. Psychosom Med 1988;50:230–44.
9. Devine EC. Effects of psychoeducational care for adult surgical patients: a meta-analysis of 191 studies. Patient Educ Couns 1992;19:129–42.
10. Ludwick-Rosenthal R, Neufeld RW. Stress management during noxious medical procedures: an evaluative review of outcome studies. Psychol Bull 1988;104:326–42.
11. Mathews A, Ridgeway V. Personality and surgical recovery: a review. Br J Clin Psychol 1981;20:243–60.
12. Rosenberger PH, Jokl P, Ickovics J. Psychosocial factors and surgical outcomes: an evidence-based literature review. J Am Acad Orthop Surg 2006;14:397–405.
13. Watson D, Pennebaker JW. Health complaints, stress, and distress: exploring the central role of negative affectivity. Psychol Rev 1989;96:234–54.
14. Meyer T, Klemme H, Herrmann C. Depression but not anxiety is a significant predictor of physicians' assessments of medical status in physically ill patients. Psychother Psychosom 2000;69:147–54.
15. Kiecolt-Glaser JK, Marucha PT, Malarkey WB, Mercado AM, Glaser R. Slowing of wound healing by psychological stress. Lancet 1995;346:1194–6.
16. Marucha PT, Kiecolt-Glaser JK, Favagehi M. Mucosal wound healing is impaired by examination stress. Psychosom Med 1998;60:362–5.
17. Ebrecht M, Hextall J, Kirtley LG, Taylor A, Dyson M, Weinman J. Perceived stress and cortisol levels predict speed of wound healing in healthy male adults. Psychoneuroendocrinology 2004;29:798–809.
18. Sheridan JF, Padgett DA, Avitsur R, Marucha PT. Experimental models of stress and wound healing. World J Surg 2004;28:327–30. Epub 2004 Feb 17.
19. Cole-King A, Harding KG. Psychological factors and delayed healing in chronic wounds. Psychosom Med 2001;63:216–20.
20. Glaser R, Kiecolt-Glaser JK, Marucha PT, MacCallum RC, Laskowski BF, Malarkey WB. Stress-related changes in proinflammatory cytokine production in wounds. Arch Gen Psychiatry 1999;56:450–6.

21. Broadbent E, Petrie KJ, Alley PG, Booth RJ. Psychological stress impairs early wound repair following surgery. Psychosom Med 2003;65:865–9.
22. Mercado AM, Padgett DA, Sheridan JF, Marucha PT. Altered kinetics of IL-1 alpha, IL-1 beta, and KGF-1 gene expression in early wounds of restrained mice. Brain Behav Immun 2002;16:150–62.
23. Kalin NH, Shelton SE, Engeland CG, Haraldsson HM, Marucha PT. Stress decreases, while central nucleus amygdala lesions increase, IL-8 and MIP-1alpha gene expression during tissue healing in non-human primates. Brain Behav Immun 2006;20:564–8.
24. Rojas IG, Padgett DA, Sheridan JF, Marucha PT. Stress-induced susceptibility to bacterial infection during cutaneous wound healing. Brain Behav Immun 2002;16:74–84.
25. Roy S, Khanna S, Yeh PE, Rink C, Malarkey WB, Kiecolt-Glaser J, Laskowski B, Glaser R, Sen CK. Wound site neutrophil transcriptome in response to psychological stress in young men. Gene Expr 2005;12:273–87.
26. Kiecolt-Glaser JK, Loving TJ, Stowell JR, Malarkey WB, Lemeshow S, Dickinson SL, Glaser R. Hostile marital interactions, proinflammatory cytokine production, and wound healing. Arch Gen Psychiatry 2005;62:1377–84.
27. Yang EV, Bane CM, MacCallum RC, Kiecolt-Glaser JK, Malarkey WB, Glaser R. Stress-related modulation of matrix metalloproteinase expression. J Neuroimmunol 2002;133:144–50.
28. Head CC, Farrow MJ, Sheridan JF, Padgett DA. Androstenediol reduces the anti-inflammatory effects of restraint stress during wound healing. Brain Behav Immun 2006;20:590–6.
29. Izadi K, Ganchi P. Chronic wounds. Clin Plast Surg 2005;32:209–22.
30. Rojas IG, Padgett DA, Sheridan JF, Marucha PT. Stress-induced susceptibility to bacterial infection during cutaneous wound healing. Brain Behav Immun 2002;16:74–84.
31. Padgett DA, Marucha PT, Sheridan JF. Restraint stress slows cutaneous wound healing in mice. Brain Behav Immun 1998;12:64–73.
32. Emery CF, Kiecolt-Glaser JK, Glaser R, Malarkey WB, Frid DJ. Exercise accelerates wound healing among healthy older adults: a preliminary investigation. J Gerontol A Biol Sci Med Sci 2005;60:1432–6.
33. Kiecolt-Glaser JK, McGuire L, Robles TF, Glaser R. Emotions, morbidity, and mortality: new perspectives from psychoneuroimmunology. Annu Rev Psychol 2002;53:83–107.
34. Hawkley LC, Cacioppo JT. Loneliness and pathways to disease. Brain Behav Immun 2003;17:S98–105.
35. Hawkley LC, Masi CM, Berry JD, Cacioppo JT. Loneliness is a unique predictor of age-related differences in systolic blood pressure. Psychol Aging 2006;21:152–64.
36. Uchino BN, Cacioppo JT, Kiecolt-Glaser JK. The relationship between social support and physiological processes: a review with emphasis on underlying mechanisms and implications for health. Psychol Bull 1996; 119:488–531.
37. Kiecolt-Glaser JK, Glaser R. Depression and immune function: central pathways to morbidity and mortality. J Psychosom Res 2002;53:873–6.
38. Hawkley LC, Bosch JA, Engeland CG, Marucha PT, Cacioppo JT. Loneliness, dysphoria, stress and immunity: a role for cytokines. In: Plotnikoff NP, Faith RE, Murgo AJ, Good RA, editors. Cytokines, stress and immunity. 2nd ed. Boca Raton: CRC Press; 2006.
39. Pressman SD, Cohen S, Miller GE, Barkin A, Rabin BS, Treanor JJ. Loneliness, social network size, and immune response to influenza vaccination in college freshmen. Health Psychol 2005;24:297–306.
40. Cacioppo JT, Hawkley LC, Crawford LE, Ernst JM, Burleson MH, Kowalewski RB, Malarkey WB, Van Cauter E, Berntson GG. Loneliness and health: potential mechanisms. Psychosom Med 2002;64:407–17.
41. Lett HS, Blumenthal JA, Babyak MA, Sherwood A, Strauman T, Robins C, Newman MF. Depression as a risk factor for coronary artery disease: evidence, mechanisms, and treatment. Psychosom Med 2004;66:305–15.
42. Allen NB, Badcock PB. The social risk hypothesis of depressed mood: evolutionary, psychosocial, and neurobiological perspectives. Psychol Bull 2003;129:887–913.
43. Heinrich LM, Gullone E. The clinical significance of loneliness: a literature review. Clin Psychol Rev 2006;26:695–718.
44. Cacioppo JT, Hughes ME, Waite LJ, Hawkley LC, Thisted RA. Loneliness as a specific risk factor for depressive symptoms: cross-sectional and longitudinal analyses. Psychol Aging 2006;21:140–51.
45. Boomsma DI, Willemsen G, Dolan CV, Hawkley LC, Cacioppo JT. Genetic and environmental contributions to loneliness in adults: the Netherlands twin register study. Behav Genet 2005;35:745–52.
46. Boomsma DI, Cacioppo JT, Slagboom PE, Posthuma D. Genetic linkage and association analysis for loneliness in Dutch twin and sibling pairs points to a region on chromosome 12q23-24. Behav Genet 2006;36:137–46.
47. Bosch JA, Ring C, de Geus EJC, Veerman ECI, Amerongen AV. Stress and secretory immunity. Int Rev Neurobiol 2002;52:213–53.
48. Szpaderska AM, Zuckerman JD, DiPietro LA. Differential injury responses in oral mucosal and cutaneous wounds. J Dent Res 2003;82:621–6.
49. Szpaderska AM, DiPietro LA. Inflammation in surgical wound healing: friend or foe? Surgery 2005;137:571–3.
50. Martin P, Leibovich SJ. Inflammatory cells during wound repair: the good, the bad and the ugly. Trends Cell Biol 2005;15:599–607.
51. Hawkley LC, Browne MW, Cacioppo JT. How can I connect with thee? Let me count the ways. Psychol Sci 2005;16:798–804.
52. Beck AT, Beck RW. Screening depressed patients in a family practice: a rapid technique. Postgrad Med 1972;52:81–5.
53. Beck AT, Steer RA, Garbin MG. Psychometric properties of the Beck depression inventory: twenty-five years of evaluation. Clin Psychol Rev 1988;8:77–100.
54. McGuire L, Kiecolt-Glaser JK, Glaser R. Depressive symptoms and lymphocyte proliferation in older adults. J Abnorm Psychol 2002;111:192–7.
55. Glaser R, Robles TF, Sheridan J, Malarkey WB, Kiecolt-Glaser JK. Mild depressive symptoms are associated with amplified and prolonged inflammatory responses after influenza virus vaccination in older adults. Arch Gen Psychiatry 2003;60:1009–14.
56. Russell D, Peplau LA, Cutrona CE. The revised UCLA loneliness scale: concurrent and discriminant validity evidence. J Pers Soc Psychol 1980;39.
57. Spielberger C. Manual for the state-trait anxiety inventory (form Y). Palo Alto: Consulting Psychologists Press, Inc; 1983.
58. Horowitz M, Wilner N, Alvarez W. Impact of event scale: a measure of subjective stress. Psychosom Med 1979;41:209–18.
59. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.
60. Engeland CG, Bosch JA, Cacioppo JT, Marucha PT. Mucosal wound healing: The roles of age and gender. Arch Surg 2006;141:1193–7.
61. Sopori M. Effects of cigarette smoke on the immune system. Nat Rev Immunol 2002;2:372–7.
62. Silverstein P. Smoking and wound healing. Am J Med 1992;93:22S–4S.
63. Tonnesen H, Kehlet H. Preoperative alcoholism and postoperative morbidity. Br J Surg 1999;86:869–74.
64. Benveniste K, Thut P. The effect of chronic alcoholism on wound healing. Proc Soc Exp Biol Med 1981;166:568–75.
65. Yarcheski A, Mahon NE, Yarcheski TJ, Cannella BL. A meta-analysis of predictors of positive health practices. J Nurs Scholarsh 2004;36:102–8.
66. Shibli-Rahhal A, Van Beek M, Schlechte JA. Cushing's syndrome. Clin Dermatol 2006;24:260–5.
67. Gordon CB, Li DG, Stagg CA, Manson P, Udelsman R. Impaired wound healing in Cushing's syndrome: the role of heat shock proteins. Surgery 1994;116:1082–7.
68. Holte K, Kehlet H. Perioperative single-dose glucocorticoid administration: pathophysiologic effects and clinical implications. J Am Coll Surg 2002;195:694–712.
69. Kinsey SG, Prendergast BJ, Nelson RJ. Photoperiod and stress affect wound healing in Siberian hamsters. Physiol Behav 2003;78:205–11.
70. Adam EK, Hawkley LC, Kudielka BM, Cacioppo JT. Day-to-day dynamics of experience-cortisol associations in a population-based sample of older adults. Proc Natl Acad Sci U S A 2006;103:17058–63.
71. Kudielka BM, Broderick JE, Kirschbaum C. Compliance with saliva sampling protocols: electronic monitoring reveals invalid cortisol daytime profiles in noncompliant subjects. Psychosom Med 2003;65:313–9.
72. Strazdins L, Meyerkort S, Brent V, D'Souza RM, Broom DH, Kyd JM. Impact of saliva collection methods on sIgA and cortisol assays and acceptability to participants. J Immunol Methods 2005;307:167–71.
73. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol Bull 2004;130:601–30.
74. Zorrilla EP, Luborsky L, McKay JR, Rosenthal R, Houldin A, Tax A, McCorkle R, Seligman DA, Schmidt K. The relationship of depression and stressors to immunological assays: a meta-analytic review. Brain Behav Immun 2001;15:199–226.
75. Berntson GG, Cacioppo JT. Heart rate variability: stress and psychiatric conditions. In: Malik M, Camm AJ, editors. Dynamic electrocardiography. New York: Futura; 2004.
76. Tracey KJ. The inflammatory reflex. Nature 2002;420:853–9.
77. Steinman L. Elaborate interactions between the immune and nervous systems. Nat Immunol 2004;5:575–81.
78. Eijkelkamp N, Engeland CG, Gajendrareddy PK, Marucha PT. Restraint

stress impairs early wound healing in mice via alpha-adrenergic but not beta-adrenergic receptors. Brain Behav Immun 2007;21:409–12.
79. Pullar CE, Grahn JC, Liu W, Isseroff RR. Beta2-adrenergic receptor activation delays wound healing. FASEB J 2006;20:76–86.
80. Cornelissen AM, Maltha JC, Von den Hoff HW, Kuijpers-Jagtman AM. Palatal mucoperiosteal wound healing in the rat. Eur J Oral Sci 1999; 107:344–51.
81. de Geus EJ, Willemsen GH, Klaver CH, van Doornen LJ. Ambulatory measurement of respiratory sinus arrhythmia and respiration rate. Biol Psychol 1995;41:205–27.
82. Willemsen GH, De Geus EJ, Klaver CH, Van Doornen LJ, Carroll D. Ambulatory monitoring of the impedance cardiogram. Psychophysiology 1996;33:184–93.
83. Antoni MH. Stress management effects on psychological, endocrinological, and immune functioning in men with HIV infection: empirical support for a psychoneuroimmunological model. Stress 2003;6:173–88.
84. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. Am J Surg 2002;183:630–41.
85. Holden-Lund C. Effects of relaxation with guided imagery on surgical stress and wound healing. Res Nurs Health 1988;11:235–44.