Psychological stress and wound healing in humans: a systematic review and meta-analysis

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Psychological stress and wound healing in humans: A systematic review and meta-analysis ☆

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Abstract

Objective: The current review aims to synthesize existing knowledge about the relationship between psychological stress and wound healing. **Methods:** A systematic search strategy was conducted using electronic databases to search for published articles up to the end of October 2007. The reference lists of retrieved articles were inspected for further studies and citation searches were conducted. In addition, a meta-analysis of a subset of studies was conducted to provide a quantitative estimation of the influence of stress on wound healing. **Results:** Twenty-two papers met the inclusion criteria of the systematic review and a subsample of 11 was included in a meta-analysis. The studies assessed the impact of stress on the healing of a variety of wound types in different contexts, including acute and chronic clinical wounds, experimentally created punch biopsy and blister wounds, and minor damage to the skin caused by tape stripping. Seventeen studies in the systematic review reported that stress was associated with impaired healing or dysregulation of a biomarker related to wound healing. The relationship between stress and wound healing estimated by the meta-analysis was $r=-0.42$ (95% CI=−0.51 to −0.32) ($P<01$). **Conclusion:** Attention now needs to be directed towards investigating potential moderators of the relationship, mediating mechanisms underpinning the association, as well as the demonstration of a causal link by the development of experimental interventions in healthy populations.

Keywords: Psychoneuroimmunology; Punch biopsy; Stress; Suction blister; Transepidermal water loss; Wound healing

Introduction

Numerous studies show that stress is associated with increased mortality and morbidity across a range of conditions [1–3] and many studies highlight the impact of stress upon specific markers of immune functioning [4], but few have been able to connect the "micro" immune changes with "macro" changes in disease outcomes [4–6]. The recent utilization of wound healing as a primary outcome measure enables researchers to bridge this gap and investigate the impact of stress on an objective, concrete, and clinically relevant outcome, where the immune system plays a significant role [7]. Research investigating the determinants of wound healing has traditionally focused on clinical and biomedical factors (i.e., size of wound, dressing type, extent of pathology) associated with speed of healing [8–10]. However, recently the potential impact of psychosocial factors, including psychological stress, has been investigated. The objective of this review was therefore to systematically identify and synthesize existing knowledge about the relationship between psychological stress and wound healing.

A wound may be defined as a "disruption of normal tissue structure and function" [11] and can be categorized by its etiology, location, or duration. There are a variety of causes which give rise to many different types of wounds including

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surgery (planned intervention), trauma (i.e., burns or lacerations), pathological changes in the body (i.e., circulatory vessels associated with leg ulcers), as well as wounds related to pressure (i.e., pressure ulcers) [12]. Wounds frequently occur in the skin (cutaneous), although they can also occur in the mucosa (i.e., in the mouth, nose, digestive tract) [13]. Wounds are classified as "acute" if they progress through the stages of healing in the appropriate time. Alternatively, they are "chronic" if progression through the expected phases does not occur and healing is delayed [14].

Cutaneous wound healing is a complex process composed of interdependent and overlapping stages, namely, *clot formation*, *inflammation*, *proliferation*, and *remodeling* [15,16]. The initial postinjury phase is characterized by the formation of a fibrin clot followed by the inflammatory stage (within 1–3 days after injury) which is dominated by immune cells (i.e., neutrophils and macrophages) that destroy bacteria and debride the wound. These cells also release substances called cytokines which communicate between cells [17], specifically interleukin-1 (IL-1α, IL-1β), IL-6, IL-8, and tumor necrosis factor (TNF), and matrix metalloproteinases (MMPs) which are regulated by cytokines and digest factors during the healing process [18]. These substances are crucial if normal tissue repair is to progress. By Day 4, the proliferation phase begins whereby cells important in tissue regeneration (collagen-rich fibroblasts and epithelial cells) and vascularization (capillaries) migrate and replicate. Remodeling is the final phase of healing where cell numbers decrease and collagen fibers are remodeled to increase the strength of the wound. The repaired or scar tissue is not identical to the intact skin, but it is structurally and functionally adequate [19]. Cytokines and MMPs are important in this phase which may persist for weeks and months [7,16]. Healing in other tissue types follows a similar trajectory, although there are tissue specific differences, such as oral mucosal wounds healing more quickly with less scarring [20].

As can be seen from the above description, successful healing is dependent in part on a fully functioning immune system thus making it vulnerable to the myriad of factors which can impair immune performance. Since both acute and chronic psychological stress can modulate immune function [4], it becomes reasonable to consider that psychological stress might have an adverse effect on wound healing. As well as the variety of different clinical wounds described previously there are currently two experimental paradigms used by researchers to investigate wound healing in the laboratory. Specifically, inflicting a standardized wound to the skin or oral mucosa using a punch biopsy or alternatively creating suction blisters [16]. A third less invasive approach involves causing minor injury to the stratum corneum or outer layer of the skin by repeated application of cellophane tape. This damages the ability of the skin to regulate the movement of water in and out of the body known as its barrier function [21]. Recovery of the barrier can be measured by the level of transepidermal water loss (TEWL) [22]. This review aimed to investigate whether a common relationship with stress existed across different wound types and experimental models. There are a number of reviews in existence examining the relationship between stress and wound healing [23–26]; however, none is systematic in their methodology nor has attempted to quantify the relationship. The aims of this review are twofold: (i) to summarize existing research looking at the nature of the relationship between stress and wound healing in a systematic review and (ii) to quantify the size of the relationship in a meta-analysis of a subset of included studies.

Method

Procedure

The systematic review involved searching a range of computerized databases including AMED (Allied and Complementary Medicine), BNI (British Nursing Index), CINAHL (Cumulative Index to Nursing and Allied Health Literature), Cochrane Database of Systematic Reviews, EMBASE, MEDLINE, MEDLINE In-process and other Non-Indexed Citations, PsycINFO, and Web of Science (WOS). The databases were searched from their earliest date up to the end of October 2007. The review used a subject and text word strategy with (DISTRESS, STRESS, ANXIETY, DEPRESSION) AND (WOUND HEALING, ULCER, TRANSEPIDERMAL WATER LOSS) as the primary search terms. The search strategy was tailored for each database to ensure that it was comprehensive. The abstracts of the articles identified by the electronic search were examined to identify relevant articles which were retrieved for further inspection to ascertain whether they met the inclusion criteria. The reference sections of all retrieved articles were searched to identify further articles. A citation search was carried out on all included articles using the Social Science Citation Index. The methodology of the review attempted where applicable to adhere to the QUOROM statement regarding best practice for systematic and meta-analytic reviews [27].

Inclusion/exclusion criteria

Studies were included in the systematic review if they fulfilled the following criteria.

The measurement or condition of psychological stress

Studies were included if they contained original data investigating the impact of any form of negative psychological state, condition, or experience on the healing of a wound.

This enabled the review to reflect the existing heterogeneity in the interpretation of the term stress within psychoneuroimmunological research and its usage both as a stressor (e.g., academic examinations) and as a stress response (e.g., emotional distress) [28]. Thus, studies that compared groups of participants perceived to be experiencing a stressor with those who were not (e.g., carers vs. noncarers) were included as well as studies measuring self-reported emotional distress. Stress will be the umbrella term used in the review to cover all permutations of the concept of psychological stress and negative emotional experience.

Wound definition

A wound was broadly defined as a "disruption of normal tissue structure and function" [11].

Specifically, a cutaneous wound was defined as a break in the epidermis or dermis that may be related to trauma, planned (e.g., surgery) or accidental (e.g., burn or injury), or to pathological changes within the body [29]. To capture the range of settings which have been assessed by researchers, surgical wounds which have been artificially closed by surgical processes (i.e., stitching) were included as well as experimental wounds (i.e., punch biopsy) allowed to heal naturally. In addition, studies which investigated the impact of stress upon the repair of the permeability barrier of the skin were included. These studies assess repair of the barrier by measuring TEWL from the skin. It is acknowledged that the disruption of the permeability barrier of the skin which occurs after repeated tape stripping does not result in a visible injury which would clinically be classed as a wound. However, inclusion of these studies is concordant with the definition of a wound as an event which disrupts the structure of the tissue (i.e., stratum corneum or outer layer of the skin [30]) and its function (i.e., regulation of water in and out of the body [21]) Furthermore, although the specific biological processes involved in the repair of the barrier response continue to be investigated [31], there is evidence that tape stripping also stimulates an inflammatory response [32], with the production of pro-inflammatory cytokines (i.e., TNF-α, IL-α, IL- β, IL-8) in the epidermis [31,33]. The review also included mucosal wounds, such as oral wounds resulting from dental surgery. The clinical studies were limited to those investigating wounds which were discrete entities as opposed to being part of a wider disease process such as eczema or psoriasis. The review excluded studies looking at internal wounds, such as duodenal or gastric ulcers, as these are influenced by a wide range of factors, such as the relationship with *Helicobacter pylori* infection, specific to their wound type [34].

The measurement of wound healing or a biological marker of healing

The review was not limited to studies measuring the physical size of the wound but also included those investigating biomarkers associated with wound healing taken from the wound site (i.e., cytokines) and those measuring healing complications (i.e., wound infection). This was to allow the review to accurately reflect the variety of healing measurements utilized by investigators.

Participants

Only studies with human participants were included since the stress paradigms used in animal studies, such as enforced social disruption [35] or periods of restraint [35,36], are qualitatively different to those used in studies using human participants.

Publication language

The review was restricted to studies published in the English language.

Interrater reliability

The articles were selected for inclusion in the review based upon the above criteria, using an inclusion and exclusion checklist. The reliability of the criteria was assessed by a second reviewer with a subsample of articles retrieved in full and categorized in accordance with the checklist. Where differences in judgment occurred these were resolved by discussion between the reviewers.

Classification of psychological stress

The stress paradigm of each study was not only categorized as either a stress stimulus (SS) or an emotional stress response (SR) but also in terms of its duration and course, using the taxonomy of stressors applied by Segerstrom and Miller [4] in a review of the relationship between stress and the immune system: acute time limited stressors (e.g., laboratory challenges), brief naturalistic real-life stressors (e.g., academic examinations), stressful event sequences (e.g., marital difficulties), chronic stressors which cause significant life changes where an end to the stressor is not foreseen, and distant stressors (e.g., childhood sexual assault). In addition, the assessment of stress by the number of life events experienced and participants' perceptions of their own levels of stress or "global stress appraisals" where no specific stressor is present, also utilized by Segerstrom and Miller [4], were also identified. Where studies incorporated both a stress stimulus and measured a self-reported emotional response, it was the interpretation (SS or SR) related to wound healing which determined categorization.

Study quality

To determine the quality of studies in the review and to inform the selection of studies to be included in a meta-

analysis, each paper was assessed by a standardized quality checklist [37]. Each study was assessed for the degree to which it satisfied the criteria (Yes=2, Partially=1, No=0, Not applicable=N/A) and a summary score was calculated by summing the items and dividing by the total score available thus excluding the items deemed nonapplicable. To aid understanding, the total score was converted into a percentage of marks available. In addition, to ensure that the list is sensitive to factors particularly relevant to this area of research, four specific items (see Table 2B) regarding the validity and reliability of measurement were added to the generic list (see Table 2A): direct measurement of healing (i.e., measurement of wound size itself rather than duration of healing from hospital notes); level of measurement of wound healing (i.e., interval/ordinal); evidence of methods to demonstrate the reliability of the measurement (i.e., measurement of wound by more than one assessor, duplicate laboratory tests of biomarkers of healing, or duplicate testing sites for measures of TEWL); whether assessors were blind to the stress status of the participant. The quality of each study was assessed independently and interrater reliability [38] was classed as substantial (Cohen's kappa=0.75) [39]. Discrepancies were resolved by discussion.

Data synthesis for meta-analysis of a subset of included studies

To assess the extent of the impact of stress on wound healing quantitatively, a meta-analysis was also conducted on a subset of the studies which measured the wound directly (i.e., not from information taken from medical notes [40–42]) and were of acceptable quality (scoring at least 1 or 2 on items in the generic quality checklist, excluding the sample size calculation item; see Table 2A). Studies were excluded if they measured healing only by biomarkers due to the heterogeneity of factors assessed [43–46] and if there was not enough information available to calculate an effect size directly from the published paper. Data was requested from these authors [47–49]; however, two studies were excluded as the authors could not be contacted [49] or could not access the required data to allow calculation of an effect size *r* [48]. In addition, one [50] of the intervention studies [47,50] was excluded from the meta-analysis because it did not provide evidence concerning the strength of the relationship between stress and wound healing, as the intervention failed to change levels of stress. Therefore, 12 studies were included in the meta-analysis.

The effect sizes were calculated using summary statistics and were then translated into Pearson's correlation coefficient *r* [with 95% confidence intervals (CIs)] using the Comprehensive Meta-analysis Software [51] to give an estimation of the magnitude of the relationship between stress and healing. Where studies had multiple outcomes (i.e., more than one measure of stress), the measurement used most frequently by other studies was selected to allow for more meaningful comparison between studies. If this was not applicable the most conservative estimate of the effect size was extracted. It is acknowledged that the studies may have had different follow-up time points when healing was assessed. The effect sizes were weighted by the sample size and a random-effects model was applied to avoid overestimation of the mean effect size [52] and allow generalization beyond the studies included in the meta-analysis. A random-effects model assumes that study samples are taken from populations with different effect sizes and therefore takes account of variability between, as well as within, the studies [53]. In particular, due to the heterogeneity of wound types it was judged unlikely for there to be one single true effect size but more likely a distribution of effect sizes. The summary *r* was considered to be statistically significant if $P<.05$ (two tailed). Additionally, in recognition of the variety of wound types included in the meta-analysis, a subgroup analysis was conducted, using the *Q* statistic for homogeneity [54] to assess whether there were significant differences in effect size dependent upon wound type. To identify publication bias, a funnel plot was drawn plotting effect size against standard error for each study and a classic fail-safe N analysis [55] was conducted.

Results

The electronic search strategy identified 2575 potentially relevant articles (see Fig. 1 for details of inclusion/exclusion of papers). Of these, 176 articles were retrieved in full, the remainder being excluded as they did not meet the inclusion criteria mainly due to their nonpsychological interpretations for the term stress (i.e., mechanical strain). Inspection of the retrieved articles resulted in 145 being excluded as the papers did not contain empirical data (88 studies), did not measure stress as the independent variable (11 studies), assessed other indices of "recovery" rather than specific measures of wound healing (25 studies), measured healing in a condition excluded from this review (gastric ulcer or skin complaint) (15 studies), or used animal models (six studies). A further eight studies which looked at the impact of complimentary therapies such as hypnosis [56] or therapeutic touch [57] on wound healing were excluded as either stress or healing was not measured. The remaining 23 studies included data which investigated the relationship between stress and wound healing. However, upon closer inspection a paper assessing the impact of schizophrenia on wound healing [58] was excluded because this was considered to be a separate psychiatric condition with distinct characteristics which may have a different relationship with healing to that of psychological stress. Therefore, 22 articles met the inclusion criteria, investigating stress and wound healing in a variety of tissue types and clinical and experimental settings.

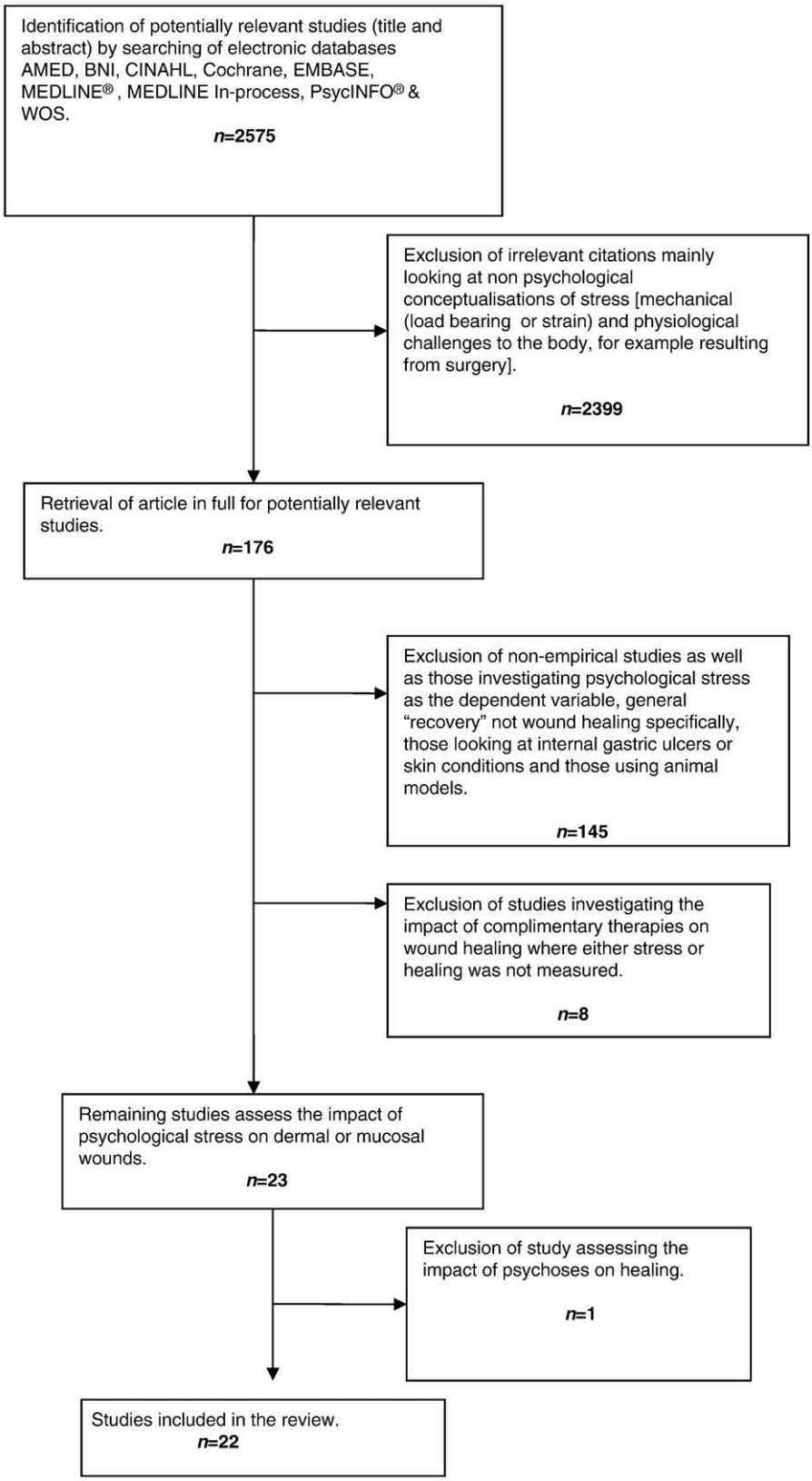

Fig. 1. Flowchart showing the process of selecting studies included in the review.

Table 1
Characteristics and main findings of studies included in the systematic review

A: Studies investigating clinical wounds.

Study	Sample	Design	Primary study aim	Classification/measurement of stress [stress stimulus (SS), stress response (SR)]	Healing measurement	Key findings
Broadbent et al. (2003) [46]	47 male and female patients with an inguinal hernia	Prospective Longitudinal Observational	To assess the relationship between psychological stress and worry, and wound repair of patients following routine surgery	SR Brief naturalistic stressor – Perceived Stress Scale – Worry Visual Analogue Scale – Mental Health Index	Levels of interleukin-1 (IL-1), interleukin-6 (IL-6), matrix metalloproteinase-9 (MMP-9) in wound fluid	(1) Perceived stress predicted lower levels of IL-1 in wound fluid (β=−0.44, P<.05), explaining 17% of the variance (2) Worry predicted lower levels of MMP-9 in wound fluid (β=−.38, P<.05), predicting 12% of the variance (3) Neither stress/worry predicted significant variance in IL-6 levels in wound fluid
Cole-King and Harding (2001) [65]	53 male and female patients with chronic wound of lower leg	Cross–sectional Observational	To assess the relationship between clinically significant depression and anxiety, and the healing of natural wounds	SR Chronic stressor – Hospital Anxiety and Depression scale (HADS)	– Rate of healing assessed by a clinician on a 5-point rating scale (1=*healing well* and 5=*not healing*) informed by the acetate tracings – The clinician was blind to anxiety and depression status	(1) Delayed healing was associated with a higher mean HADS score (P<.05) (2) 15/16 anxiety cases had delayed healing (P<.05) (3) 13/13 depression cases had delayed healing (P<.01)
Doering et al. (2005) [40]	72 male and female patients undergoing coronary artery bypass grafting	Prospective Longitudinal Observational	To assess the relationship between postoperative depressive symptoms and impaired wound healing	SR Brief naturalistic stressor. – Multiple Affect Adjective Check List	– Identification of wound complications (infection/healing problems [extra treatment/dressing changes, debridement/exploration of wound site]) from medical notes by research assistants (number not stated) blind to depression status.	(1) Patients with higher scores for depression symptoms at discharge were 3.7 times more likely than patients with lower scores to experience wound infections and wound healing problems 6 weeks after discharge (OR 3.71, 95% CI 1.15–12.0, P<.05)
George et al. (1980) [66]	38 male and female patients undergoing oral surgery	Prospective Longitudinal Observational	Effects of psychological factors (anxiety trait and state) on recovery from oral surgery	SR Brief naturalistic stressor Preoperative anxiety about surgical recovery was rated by participants on 2 rating scales (1–7) assessing concern about recovery and likelihood of complications The investigator also rated how concerned the patient seemed about recovery on a rating scale (1–7). *Trait anxiety* was rated by participants on 2 rating scales (1–7) measuring how tense/relaxed they were most of the time and how easily they got upset	– Healing of wound was rated by 1 researcher blind to self-ratings on levels of anxiety, on a 7-point rating scale (*poor* to *excellent*) 4 days postoperation – Severity of facial swelling was rated by the investigator on a 4-point rating scale (*none* to *severe*) 4 days postoperation – Duration of swelling was assessed by participants via postal questionnaire 2 weeks postoperation – Restriction of mouth opening 4 days postoperation	(1) No relationship between anxiety and overall healing. (2) Statistically significant association between trait anxiety and duration of facial swelling (r=0.30, P<.05) (3) Statistically significant association between anxiety about recovery and mouth opening restriction (r=0.29, P<.05)

Holden-Lund (1988) [47]	24 male and female patients undergoing cholecystectomy	– Experimental – Randomised controlled trial – Intervention	To determine the effects of relaxation with guided imagery on the psychophysiological stress response and wound healing	SR Brief naturalistic stressor – A-state form of State Trait Anxiety Inventory (STAI) Intervention: Relaxation with guided imagery Control: Quiet period Protocol: 2 days preoperation participants completed STAI Intervention: Afternoon before operation participants were played RGI 20-min tape. Three tapes were played each postoperative day. Controls observed a 20-min quiet period	– Wound Assessment Inventory (WAI) developed for the study to assess key indicators of tissue inflammation in 3-day-old surgical wounds. It assessed 3 signs of inflammation (edema, erythema, and exudate) on a 4-point scale (0=*absent*, 3=*marked*). The WAI was applied by clinicians blind to group allocation of each participant. Interrater reliability was reported during development of WAI not for the study itself.	(1) Intervention group reported less state anxiety postsurgery than control group (F (1, 44)=6.24, P<.01) (2) Intervention group reported less erythema at wound margins (x^2=6.93, P<.01) compared to the control group
Scheier et al. (1999) [41]	309 male and female patients undergoing coronary artery bypass graft surgery	– Prospective – Longitudinal – Observational	To determine whether optimism (and other psychosocial factors including preoperative depression) predicts lower rates of rehospitalization after coronary artery bypass graft surgery	SR Brief naturalistic stressor – 10-item version of the Center for Epidemiologic tudies Depression Scale	– Wound infection causing rehospitalization reported by patients in follow-up interview and confirmed by physicians. Not reported whether interviewers were blind to level of depression.	(1) Depressed participants were more likely to be rehospitalized because of postoperative sternal wound infection, independently of optimism (OR 5.43, 95% CI 1.18–24.95, n=240)
Tarrier et al. (2005) [42]	50 (8 depression, 15 control). Male and female patients with burn injuries.	– Retrospective case controlled study – Observational	To determine whether patients with a comorbid psychiatric illness (depression or schizophrenia) took longer to heal and increased hospital stay	SR Brief naturalistic stressor – Preexisting clinical diagnosis of depression	– Amount of time until burn had healed assessed from medical notes by research assistant (number not stated) aware of diagnosis	(1) No significant difference between participants with a diagnosis of depression and control participants

B: Studies investigating experimental wounds grouped by wound type

Study	Sample	Design	Primary study aim	Classification/ measurement of stress	Wound type and healing measurement	Key findings
Transepidermal water loss after tape stripping of skin						
Altemus et al. (2006) [60]	36 (18) females with PTSD and 18 healthy controls	– Prospective – Longitudinal – Observational	To assess the impact of having PTSD on skin barrier function	SR Distant stressor Diagnosis of PTSD	– Tape stripping to disrupt skin barrier function – Recovery of skin barrier function after tape stripping on the skin of the forearm. Reliability/blindness to psychological status not reported.	(1) Skin barrier recovery was enhanced for the participants with PTSD compared to controls (71±6% vs. 56±3%, t=2.6, P<.05)

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Table 1 (*continued*)

B: Studies investigating experimental wounds grouped by wound type

Study	Sample	Design	Primary study aim	Classification/ measurement of stress	Wound type and healing measurement	Key findings
Altemus et al. (2001) [22]	46 (25 interview stressors) healthy females	– Quasi-experimental	Effect of 3 laboratory-induced stressors on 3 dermatological measures including skin barrier function	SS Acute time-limited stressor No psychological measurement	– Tape stripping to disrupt skin barrier function – Recovery of skin barrier function after tape stripping on the skin of the forearm. Reliability/ blindness to psychological status not reported. Did test from 2+ sites.	*Psychological stress* (1) Skin barrier recovery was delayed after the interview stressor (n=21, t=2.3, P<.05)
Garg et al. (2001) [61]	27 healthy male and female students	– Prospective – Longitudinal – Observational	To assess the relationship between psychological stress (academic exams) and skin barrier function	SS and SR Brief naturalistic stressor – Profile of mood states (POMS) – PSS	– Tape stripping to disrupt skin barrier function – Recovery of skin barrier function after tape stripping on the skin of the forearm. Reliability/blindness to psychological status not reported. Did test from 2+ sites.	(1) Skin barrier recovery was delayed during the high stress examination period compared to low stress vacation period [F (12, 2)=18.87, P<.001]. (2) There was a negative correlation between recovery of skin barrier function and changes in level of mood disturbance (POMS) at 3 h post tape stripping (r=−0.42; P<.05). When perceived stress was measured by the PSS the relationship was not significant (r=−0.33; P>.05).
Muizzuddin et al. (2003) [62]	55 healthy females (28 undergoing marital change)	– Prospective – Longitudinal – Observational	To assess the impact of self-perceived stress (marital dissolution) on skin barrier function	SR Stressful event sequence Life events – Self-perceived stress questionnaire (SPSQ) – Life Stressors and Social Resource Inventory form	– Tape stripping to disrupt skin barrier function – Recovery of skin barrier function after tape stripping on the skin of the cheek. Reliability/blindness to psychological status not reported. Did test from 2+ sites.	(1) There was a negative correlation between skin barrier recovery at 3 h (r=−0.64; P<.001) and 24 h post tape stripping (r=−0.74; P<.001) and stress SPSQ.
Robles (2007) [59]	85 healthy male and female students	– Experimental	To assess the impact of a brief laboratory stressor on skin barrier function	SS Acute time-limited stressor – STAI – Positive and Negative Affect Schedule (PANAS) – Perceived stress, control, and helplessness assessed post task	– Tape stripping to disrupt skin barrier function – Recovery of skin barrier function after tape stripping on the skin of the forearm. Reliability/blindness to psychological status not reported. Did test from 2+ sites.	(1) Skin barrier recovery was delayed by 10% at 2 h post skin disruption (r=0.29) in participants undergoing laboratory stress task.

Punch biopsy wound						
Bosch et al. (2007) [67]	193 healthy male and female students	– Prospective – Longitudinal – Observational	Assess the relationship between dysphoria and mucosal wound healing	SR Global stress appraisal Life events – Beck Depression Inventory–Short-Form (BDI-SF) – Impact of Events Scale – STAI – UCLA-R Loneliness scale	– 3.5-mm punch biopsy on oral hard palate – Wound size measured daily by a videograph using an intra-oral camera. Wound size was defined as the ratio between the area of a standardized template and the surface area of the wound measured by two researchers blind to the psychological status of the participant. Interrater reliability reported. – Classified as healed if closure >95%	(1) Participants with higher levels of dysphoria were more likely to heal slower than the median healing rate of 7 days (OR 3.57, 95% CI 1.58– 8.07; $P<.001$)
Ebrecht et al. (2004) [63]	24 healthy males	– Prospective – Longitudinal – Observational	To assess the relationship between perceived life stress and impaired cutaneous wound healing	SR Global stress appraisal. – PSS – General Health Questionnaire – UCLA Loneliness scale	– 4-mm punch biopsy from the upper arm. – The rate of healing was calculated as the difference in wound diameter at the base of the wound between the 7- and 21-day follow-ups. The wound was measured by high-resolution ultrasound scanner. Number of researchers scanning wound or blindness to psychological status not reported.	(1) The PSS at biopsy was negatively related to healing rate ($r=-0.59$, $P<.01$). (2) The General Health Questionnaire (GHQ) at biopsy was negatively related to healing rate ($r=-0.59$, $P<.01$)
Emery et al. (2005) [50]	28 healthy male and female older adults	– Experimental – Randomised controlled trial – Intervention	To evaluate the effect of a 3-month exercise program on wound healing, neuroendocrine function, and perceived life stress.	SR Global stress appraisal – PSS	– 3.5-mm punch biopsy wound on upper arm – Wound size measured by digital photograph at 1 week postwounding and 3 days per week until the wound was not visible. The outcome measure was a ratio between the area of a standardized black dot and area of the wound. Wound considered healed when wound-to-dot ratio was less than 10%. Wound assessed by 2 independent researchers blind to group assignment. Interrater reliability reported.	(1) Perceived stress did not change as a result of the intervention (2) Wound healing was significantly faster in the intervention group [29.2 (9.0) days] in comparison to the control group [38.9 (7.4) days] [F (1, 20)=7.64, $P<.05$]

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Table 1 (*continued*)

Study	Sample	Design	Primary study aim	Classification/ measurement of stress	Wound type and healing measurement	Key findings
Kiecolt-Glaser et al. (1995) [64]	26 healthy female carers and controls	– Prospective – Longitudinal – Observational	The effects of stress, caused by caring, on wound healing	SS Chronic stressor – PSS	– 3.5-mm punch biopsy wound on forearm – Response to hydrogen peroxide foaming assessed daily after 7 days postwounding as an indicator that the wound had healed – Wound was photographed every 2–8 days until healed. Wound size was defined as the ratio between the area of a standardized dot and the area of wound measured by a researcher blind to group membership.	(1) Healing took significantly longer in carers (48.7 [2.9] days) than in controls (39.3 [3.0] days), ($P<.05$). (2) The size of the wound differed significantly between carers and controls at 9–14 days postwounding ($P<.05$)
Marucha et al. (1998) [68]	11 healthy male and female dental students	– Prospective – Longitudinal – Observational	To investigate the effects of academic exams on mucosal wound healing	SS Brief naturalistic stressor – PSS	– 3.5-mm punch biopsy on oral hard palate – Response to hydrogen peroxide foaming assessed daily after 5 days postwounding as an indicator that the wound had healed – Wound size was measured every day by a videograph using an intra-oral camera until healed. Wound size was defined as the ratio between the area of a standardized dot and the area of wound measured by researcher(s) (number not stated) blind to high or low stress period.	(1) Students took significantly longer to heal (mean 7.82 [S.E.M.=0.62] days) during the examination period compared to the vacation (mean 10.91 [S.E.M.=0.69] days) $F(1,10)=28.47$, $P<.001$ (2) Wound size over the first 5 days posthealing was significantly smaller during the vacation compared to the examination period [$F(1,10)=67.65$, $P<.001$].
McGuire et al. (2006[a]) [49]	17 female patients who underwent elective gastric bypass surgery. (11 for depression analysis)	– Prospective – Longitudinal – Observational	To assess the relationship between postsurgical pain intensity, depressive symptoms, and wound healing	SR Brief naturalistic stressor – BDI-SF	– 2.0-mm punch biopsy on upper arm – Wound size measured by digital photograph at 1, 2, 7, 10, 14, 17, 21, 24, and 28 days postwounding. Wound size was a ratio between the area of a standardized dot and the area of wound. Wound size assessed by 2 independent raters and interrater reliability reported.	(1) Depressive symptoms at time of surgery did not influence healing of punch biopsy wound

Suction blister						
Glaser et al. (1999) [43]	36 Healthy females	– Prospective – Longitudinal – Observational	Assess the relationship between perceived life stress and secretion of proinflammatory cytokines at wound site	SR Global stress appraisal Life events – PSS – PANAS – Psychiatric Epidemiological Research Inventory Life Events Scale	– Blister chamber model – Production of interleukin-1 alpha (IL-1α) and interleukin -8 (IL-8) in blister chamber wound fluid	(1) Higher stress was associated with lower production of IL-1α [$F(1,32)=5.73$, $P<.05$] and IL-8 [$F(1,32)=5.31$, $P<.05$] in the blister chamber fluid. (2) Women with low levels of both IL-1α and IL-8, in the blister chamber fluid, reported more perceived stress compared with those with higher levels [$F(1,27)=5.37$, $P<.05$] and negative affect [$F(1,27)=5.26$, $P<.05$].
Kiecolt-Glaser et al. (2005) [48]	42 Healthy married couples	– Experimental "cross-over" design	To assess how hostile marital behaviors modulate wound healing, local, and systemic proinflammatory cytokine production	SS and SR Acute time-limited. Stressful event sequence. – Hostility in couples' interpersonal behavior assessed using the Rapid Marital Interaction Coding System during a nonconfrontational interaction and during conflict – PANAS – Marital Adjustment Test.	– Blister chamber model – Recovery of skin barrier function at blister chamber wound. Healing was defined when the skin had recovered 90% of its barrier function.	(1) Couples' blister wounds healed more slowly following marital conflicts than after supportive interactions (HR 0.726, $P<.01$). The blisters took 1 day longer to heal after conflict. (2) Couples who were more hostile across both conditions had wounds that healed more slowly compared to less hostile couples (HR 0.598, $P<.05$).
Roy et al. (2005) [44]	4 Healthy males	– Prospective – Longitudinal	To identify stress-sensitive transcripts in wound site neutrophils during academic exams	SS Brief naturalistic stressor – BDI-SF	– Blister chamber model – Activation of neutrophil transcriptome in wound flid	(1) Neutrophil transcriptome was suppressed under stressful conditions (2) Time to heal was longer for all participants under stressful conditions
Yang et al. (2002) [45]	51 Healthy males and females	– Prospective – Longitudinal – Observational	To investigate whether stress (depressive symptoms) is sufficient to modulate MMPS and tissue inhibitors of metalloproteinase (TIMP) expression	SR Global stress appraisal. – BDI – Plasma cortisol – Plasma norepinephrine	– Blister chamber model – Levels of TIMP-1, MMP-2, MMP-8, and MMP-9 in blister chamber wound fluid.	(1) Depressive symptoms were not related to the expression of either MMP or TIMP in blister chamber wound fluid (2) Higher levels of plasma cortisol were associated with lower levels of MMP (3) Higher levels of norepinephrine were associated with higher levels of MMP-2 $F(1,34)=4.71$, ($P<.05$)

[a] This study used an experimental wound (standardized punch biopsy), although its population was undergoing a surgical operation.

The total number of participants taking part in the 22 studies was 1226, with a median of 36 (range 4 to 309). Nearly all [17] of the studies were observational in design, five [22,47,48,50,59] employed experimental or quasi-experimental designs of which two [47,50] conducted randomized controlled trials (RCTs) to test the impact of an intervention designed to reduce psychological distress and, in so doing, improve wound healing. Most studies assessed the relationship between psychological stress and healing by monitoring an acute experimentally induced wound in the skin [22,43–45,48–50,59–64]. Seven studies [40–42,46,47,65,66] assessed healing for a range of clinical wounds, six studied acute surgical wounds, and only one [65] assessed a chronic wound. The majority of studies observed healing of a cutaneous wound with only three assessing oral mucosal wounds [66–68]. Most studies assessed the wound directly, by quantitatively measuring size on a continuous scale [49,50,63,64,67,68], measuring transepidermal water loss from tape-stripped skin [22,59–62] or blister [48], and by judging the quality of healing on a discrete scale [47,65,66]. Four studies [43–46] assessed biomarkers (i.e., cytokines) associated with healing as the primary outcome measure and three used surrogate measures, such as healing complications extracted from participants' medical notes [40–42] (see Table 1A and B).

The majority of studies adopted the response definition of stress (i.e., stress reflected individuals' subjective experiences and emotional responses to stress) rather than purely exposure to a stressful event. A variety of stressors were measured, the most popular (10 studies) being brief naturalistic stressors (i.e., surgical procedures and academic examinations) followed by global stress appraisals [43,45,50,63,67]. Less common were acute time limited stressors [22,48,59], chronic stressors [64,65], stressful event sequences (i.e., marital difficulties) [48,62], and distant stressors [60]. A variety of self-report measures were used to assess stress, with studies examining an experimentally induced wound most often measuring the level of global stress appraised by participants, frequently using the Perceived Stress Scale (PSS) [69]. Whereas studies assessing a clinical wound took a predominately mental health perspective measuring clinical and subclinical levels of anxiety and depression, using a variety of validated instruments (see Table 1A and B).

The overall quality of the studies varied from moderate to high, with 14 studies scoring above 70% and ratings ranged from 53.4% to 91.2% (mean 72.36%, S.D.=10.69) (see Table 2). The studies were most successful at having a clear objective, an appropriate design, and drawing conclusions supported by results. However, fewer studies comprehensively justified the analytic methods used, specifically not reporting whether data met parametric assumptions, and none reported a sample size calculation. Only one study [50] justified their sample size in terms of an effect size from a previous study. Nearly all studies attempted to control for factors which could confound the relationship between stress and healing (i.e., demographics, clinical factors, lifestyle). The comprehensiveness of the control varied across the studies with the punch biopsy paradigm controlling for a wider range of factors and the clinical studies being less well controlled. Specifically, few clinical studies controlled for a range of lifestyle factors (i.e., smoking, exercise, diet, alcohol consumption, sleep) which may mediate the relationship between stress and healing but also have an independent impact on wound healing, and three [47,65,66] did not control for clinical factors including comorbidity, [65,66] wound severity [65], or surgical complications [47]. Of the six clinical studies that used a discrete or indirect measurement of healing [40–42,47,65,66], two used one person to assess wound healing [65,66] and the rest did not demonstrate interrater reliability, although one [47] did report psychometric properties of their healing measurement during its development. Four studies [40,47,65,66] did state that their assessors were unaware of the psychological status of the participant. Where continuous measures were used, 14 out of 17 studies provided partial or no information regarding the reliability or biometric precision of their index of healing and 13 did not explicitly report whether those assessing healing were blind to the stress status of the participant (see Table 2B).

Main finding from the systematic review

The majority of studies (17/22) found that psychological stress was associated with impaired healing or dysregulation of a biomarker associated with wound healing across different clinical and experimental wounds in both cutaneous and mucosal tissue types and across heterogeneous interpretations of psychological stress (see Table 1A and B). The findings of the observational studies, which provide evidence of an association between stress and healing, are supported by one of the intervention studies [47]. Two studies [42,49] reported nonsignificant findings and one [60] found that a diagnosis of posttraumatic stress disorder (PTSD) augmented healing. Another [45] did not find a statistically significant relationship between depression and levels of MMPs in wound fluid; however, they did find a negative relationship with physiological measures of stress. The remaining study [50] found that exercise improved wound healing but not by altering levels of stress.

The meta-analysis

A subsample of 12 out of the 72 studies included in the systematic review was entered into a meta-analysis. None of the studies were excluded due to methodological limitations as measured by the quality checklist. The pooled effect size was $r=-0.37$ (95% CI=−0.51 to −0.22; $P<.01$), categorized as a medium effect size [70], showing that greater levels of psychological stress are associated with impaired wound healing. This value of r included the isolated finding [60] whereby a diagnosis of PTSD resulted in improved skin

barrier recovery. It was decided that there were legitimate grounds for excluding this finding from the final analysis, since it was the only study to assess a distant stressor and a response (PTSD) which is judged to be qualitatively different from the other studies in the analysis assessing more proximal and concurrent stressors. The pooled effect size, excluding this study [60], was r=−0.42 (95% CI=−0.51 to −0.32; P<01) (see Fig. 2). Examination of the forest plot shows that there was variation in the size of the effect and the breadth of the CIs. The effect sizes of the clinical and tape stripping studies varied from small to large [70], and the experimental punch biopsy wound studies (Refs. [40,56, 57,67,68]) were associated with medium to large effect sizes [70] (see Fig. 2). However, analysis of these wound types in a subgroup analysis found there to be no significant heterogeneity of effect size dependent upon wound type [Q value=0.41 P=.81; clinical wound: r=−0.45 (95% CI=−0.65 to −0.20); punch biopsy: r=−0.46 (95% CI=−0.61 to −0.27); tape stripping: r=−0.38 (95% CI=−0.54 to −0.20)]. Greatest weight in the analysis was given to studies [59,67] which had the largest sample sizes.

To assess whether this analysis has been influenced by publication bias, a funnel plot was drawn plotting effect size against standard error for each study. Inspection of the plot revealed that the studies were scattered symmetrically about the combined effect size indicating that the analysis had not been unduly influenced by publication bias and thus that the pooled effect size had not been significantly overestimated. Nevertheless, a classic fail-safe N analysis was also performed [55] which indicated that 278 "missing" studies would be required to negate the findings of the included studies.

Discussion

The primary aim of this review was to investigate the impact of stress upon wound healing in humans. The results reveal a robust negative relationship whereby stress is associated with impairment of healing and dysregulation of biomarkers associated with wound healing and this is broadly consistent across a variety of clinical and experimental, acute and chronic wound types in cutaneous and mucosal tissue. The relationship was evident across different conceptualizations and measures of stress. The size of the relationship between stress and wound healing estimated by this analysis is r=−0.42, classified as a medium effect size [70], suggesting that it may be of significance clinically as well as statistically. The extent of its impact indicates that it could be considered alongside other accepted factors affecting healing such as age [71], diabetes [25], and nutrition [72].

The findings are also concordant with studies assessing the relationship between stress and wound healing using animal models. A number of studies using a variety of animal species and stressors report that stress is associated with delayed healing [35,36,73]. Consistent with the human studies, this finding has been reported across different wound models, including punch-biopsy cutaneous wounds and tape-stripped skin [35,36,74,75]. It is interesting that a comparison of the size of the relationship found by this meta-analysis with that reported by a frequently cited animal study investigating the impact of restraint upon the time taken for a cutaneous punch biopsy wound in a murine wound model to heal [73] (r=−0.79 experiment 1, r=−0.94 experiment 2) indicates a stronger negative impact of stress upon wound healing. It can be speculated that the greater level of experimental control available in animal studies particularly in terms of the manipulation of the independent variable or stressor could allow for a more accurate measurement of the impact of stress upon healing. Alternatively, different processes may underlie the relationship, and a homogenous effect size across animal and humans would not be expected due to a number of factors including anatomical differences [76] and the nature of the stressor experienced.

Although there was broad consensus that stress was associated with impairment of wound healing, there were differences in conceptual interpretations of stress, methodology, and measurement between studies, which made comparison between studies problematic and diminished confidence in the accuracy of certain findings. In particular, the use of surrogate measures of healing (rehospitalization rates, inspection of clinical notes) by three clinical studies, and where direct assessment took place, the lack of objective standardized measures of wound healing (interval or ratio scale) relying instead on the more subjective judgment of a clinician or researcher to assess the process of healing. However, one study [65] did report that clinicians used quantitative tracings of the wound to inform their assessment. Furthermore, the clinical studies did not support their wound measurement by reporting interrater reliability, where appropriate, although the majority reported that assessors were blind to the "stress status" of the participants. The methodological and measurement heterogeneity across the studies may have also contributed to variance in effect sizes in the meta-analysis. Interestingly, clinical and tape-stripping studies were the only wound types to report nonsignificant findings [61,66] in the meta-analysis. In addition, it is worth noting that none of the tape stripping studies formally discussed the validity and reliability of their transepidermal water loss measurements, although one study [48] did state that procedural guidelines were followed. In summary, measurement error may have contributed to smaller observed effects in certain studies.

In contrast, comparison between the experimental punch biopsy wound studies [49,50,63,64,67,68] was facilitated by the fact that the wounds in these studies were of a standard size with reduced measurement variability. Indeed, most punch biopsy studies demonstrated the reliability and validity of their measurements. For example, four reported that wound size was measured by a member of the research team blind to participants' distress scores [50,64,67,68]. In

Table 2

A. Quality checklist results relating to generic items for studies included in the systematic review

Study	Question or objective sufficiently described	Study design evident and appropriate	Method of subject/comparison group selection or source of information/input variables described and appropriate?	Subject (and comparison group, if applicable) characteristics sufficiently described?	If interventional and random allocation was possible, was it described?	If interventional and blinding of investigators was possible, was it reported?	If interventional and blinding of subjects was possible, was it reported?
Altemus et al. (2001) [22]	2	2	1	2	n/a	n/a	n/a
Altemus et al. (2006) [60]	1	1	1	1	n/a	n/a	n/a
Bosch et al. (2007) [67]	2	2	2	2	n/a	n/a	n/a
Broadbent et al. (2003) [46]	2	2	2	2	n/a	n/a	n/a
Cole-King and Harding (2001) [65]	2	1	1	1	n/a	n/a	n/a
Doering et al. (2005) [40]	2	2	1	2	n/a	n/a	n/a
Ebrecht et al. (2004) [63]	2	2	2	1	n/a	n/a	n/a
Emery et al. (2005) [50]	2	2	2	2	1	2	n/a
Garg et al. (2001) [61]	2	2	2	2	n/a	n/a	n/a
George et al. (1980) [66]	1	2	1	2	n/a	n/a	n/a
Glaser et al. (1999) [43]	2	2	2	2	n/a	n/a	n/a
Holden-Lund (1988) [47]	2	2	2	2	1	2	0
Kiecolt-Glaser et al. (2005) [48]	2	2	2	2	n/a	n/a	n/a
Kiecolt-Glaser et al. (1995) [64]	2	2	1	2	n/a	n/a	n/a
Marucha et al. (1998) [68]	2	2	1	2	n/a	n/a	n/a
McGuire et al. (2006) [49]	2	2	2	2	n/a	n/a	n/a
Muizzuddin et al. (2003) [62]	2	1	1	2	n/a	n/a	n/a
Robles (2007) [59]	2	2	2	2	n/a	n/a	n/a
Roy et al. (2005) [44]	2	1	1	1	n/a	n/a	n/a
Scheier et al. (1999) [41]	2	2	2	2	n/a	n/a	n/a
Tarrier et al. (2005) [42]	2	2	2	2	n/a	n/a	n/a
Yang et al. (2002) [45]	2	1	2	1	n/a	n/a	n/a
Total	42/44	39/44	35/44	39/44	2/4	4/4	0/2

Study	Outcome and exposure measures well defined and robust to measurement bias? Means of assessment reported?	Was a sample size calculation reported? [a]	Analytic methods described/justified and appropriate? (e.g., testing of parametric assumptions)	Some estimate of variance is reported for the main results?	Controlled for confounding?	Results reported in sufficient detail?	Conclusion supported by results?
Altemus et al. (2001) [22]	2	0	1	2	1	2	2
Altemus et al. (2006) [60]	1	0	1	1	1	2	2
Bosch et al. (2007) [67]	2	0	1	2	2	2	2
Broadbent et al. (2003) [46]	2	0	2	2	2	1	2
Cole-King and Harding (2001) [65]	1	0	1	2	1	1	2
Doering et al. (2005) [40]	1	0	1	2	2	2	2
Ebrecht et al. (2004) [63]	2	0	2	2	2	2	2
Emery et al. (2005) [50]	2	1	1	2	2	2	2

Garg et al. (2001) [61]	2	0	1	2	1	2	2
George et al. (1980) [66]	1	0	1	1	1	1	1
Glaser et al. (1999) [43]	2	0	1	2	2	2	2
Holden-Lund (1988) [47]	2	0	1	1	1	1	1
Kiecolt-Glaser et al. (1995) [64]	2	0	1	1	2	1	2
Kiecolt-Glaser et al. (2005) [48]	2	0	1	2	2	1	2
Marucha et al. (1998) [68]	2	0	1	2	1	2	2
McGuire et al. (2006) [49]	2	0	1	1	2	2	2
Muizzuddin et al. (2003) [62]	1	0	1	1	1	1	1
Robles (2007) [59]	2	0	1	2	2	2	2
Roy et al. (2005) [44]	2	0	1	0	1	1	2
Scheier et al. (1999) [41]	2	0	1	2	2	2	2
Tarrier et al. (2005) [42]	2	0	2	2	1	2	2
Yang et al. (2002) [45]	2	0	2	2	1	2	2
Total	39/44	1/44	26/44	36/44	33/44	36/44	41/44

B: Quality checklist results relating to specific wound measurement related items for studies included in the systematic review

Study	Direct measurement of healing [b]	Level of direct measurement of healing [c]	Demonstration of reliability of healing measurement (i.e., by two independent researchers) [d]	Assessors blind to psychological status of participant [e]	Overall % of available score for both generic and specific checklist items
Altemus et al. (2001) [22]	2	2	1	0	73.3
Altemus et al. (2006) [60]	2	2	0	0	53.4
Bosch et al. (2007) [67]	2	2	2	2	90.0
Broadbent et al. (2003) [46]	2	2	0	1	80.0
Cole-King and Harding (2001) [65]	2	1	0	2	60.0
Doering et al. (2005) [40]	0	n/a	0	2	67.9
Ebrecht et al. (2004) [63]	2	2	1	0	76.7
Emery et al. (2005) [50]	2	2	2	2	91.2
Garg et al. (2001) [61]	2	2	1	0	80.0
George et al. (1980) [66]	2	1	0	2	56.7
Glaser et al. (1999) [43]	2	2	1	1	80.0
Holden-Lund (1988) [47]	2	1	1	2	66.7
Kiecolt-Glaser et al. (1995) [64]	2	2	1	2	80.0
Kiecolt-Glaser et al. (2005) [48]	2	2	1	0	70.0
Marucha et al. (1998) [68]	2	2	1	2	76.7
McGuire et al. (2006) [49]	2	2	2	0	80.0
Muizzuddin et al. (2003) [62]	2	2	1	0	56.7
Robles (2007) [59]	2	2	1	0	76.7
Roy et al. (2005) [44]	2	2	1	0	56.7
Scheier et al. (1999) [41]	0	n/a	1	0	71.4
Tarrier et al. (2005) [42]	0	n/a	0	0	67.9
Yang et al. (2002) [45]	2	2	1	1	80.0
Total	38/44	35/38	19/44	19/44	Mean (S.D.) 72.36 (10.69)

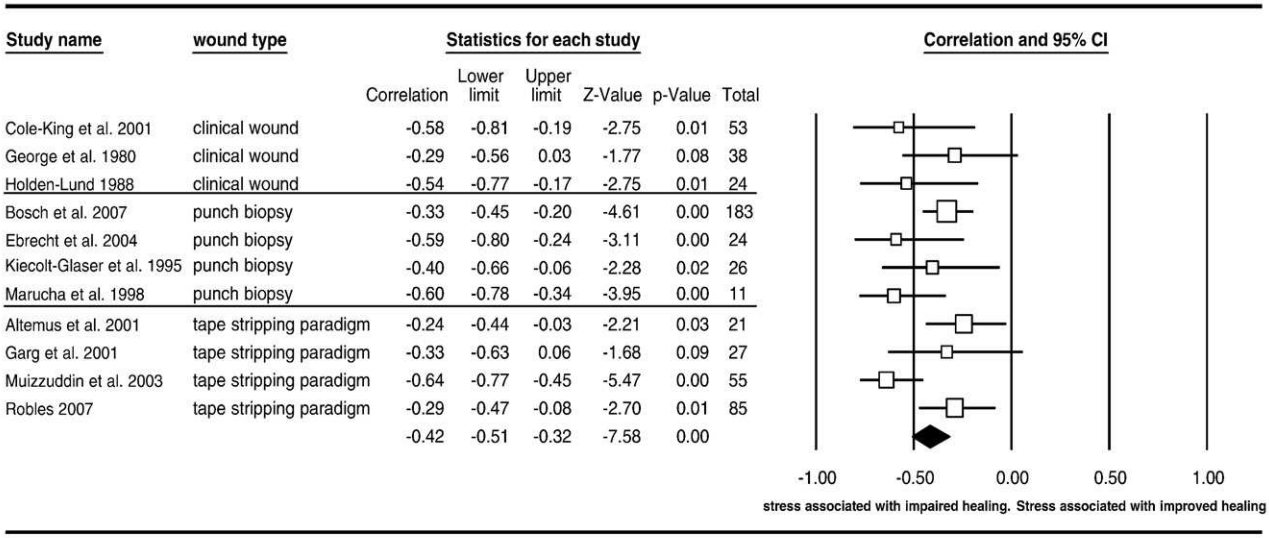

Fig. 2. Stress and wound healing.

addition, three studies demonstrated the reliability of the wound measurement by having two independent raters and providing acceptable correlations of interrater reliability [49,50,67]. Perhaps as expected, the studies using the punch biopsy and experimental wound models in general were also better controlled than the clinical studies, controlling for a wider variety of factors by experimental design and statistical analysis. The more recently published studies [59,67] are more rigorous in their level of control related in part to their larger sample sizes which allow greater statistical opportunity for adequate control. Therefore, the better measurement and control within these studies enhance the validity of their findings.

A number of explanations can be put forward to understand why a minority of the studies did not find stress to be associated with impaired wound healing. One study [60] was unique in reporting that stress improved the speed of skin barrier recovery. However, this was the only study to examine PTSD and it could be argued that the experience of PTSD is qualitatively different from other conceptualizations of stress, since evidence exists that the physiological stress response differs in comparison to chronic stress [77,78] and therefore may have a different relationship to wound healing. Another [49] reported that depression was not associated with the healing of a punch biopsy wound. As acknowledged by the authors, the study may have been underpowered due to the small sample size. In contrast, the absence of a significant association between depression and time to heal by another study [42] may have been due to a lack of precision in the measurement of healing (i.e., healing was determined from medical notes rather than by assessing the wound itself). Finally, an exercise intervention [50] did succeed in improving wound healing but this was not mediated via a change in stress levels. Although there is evidence that stress is reduced by exercise [79], it could be that other physiological changes, resultant from exercise, were beneficial to healing. Also, the sample exhibited low levels of stress at baseline making it more difficult for the intervention to have an identifiable effect.

The larger number of studies using experimental wound models may indicate the greater number of obstacles which exist when using a sample with a clinical wound. Valid and reliable measurement of a clinical wound may be complicated by the fact that wounds may not be a standard size. Surgical wounds are closed using a variety of techniques and access to the wound may not be possible without disturbing clinical dressings. For example, one study [49] used a punch biopsy wound in a surgical sample because quantitative measurement of the actual surgical wound was thought not to be viable. A further limitation

Notes to Table 2:

N/A=not applicable.

[a] To simplify the assessment, this item was amended from the original checklist item “sample size appropriate”. The scoring applies to the degree to which the study has met the requirements of that item (Yes=2, Partially=1, No=0, Not applicable=N/A). For further details see published checklist [37].

[b] 2=Direct measurement of healing, 0=indirect measurement of healing (a score of 1 is not available for this item).

[c] 2=Ratio/interval data, 1=ordinal, 0=nominal.

[d] 2=Clearly reported procedures carried out to demonstrate the reliability of the measurement of wound healing, 1=some procedures carried out but description unclear, 0=no procedures reported to demonstrate reliability of measurement of wound healing.

[e] 2=Clearly reported that assessors of wound healing were blind to psychological status of participant, 1=ambiguity as to status of the assessor, 0=assessor of wound healing not blind to psychological status of participant.

concerns the fact that, in clinical samples, it is more difficult to control factors, such as morbidity and medication. Although control could be improved by more stringent sample selection, this may hinder recruitment and limit generalizability and ecological validity of findings. Considering these obstacles, it is unlikely that clinical studies will have the methodological rigor of the experimental wound models studies and therefore their findings need to be assessed not in isolation but in the context of the wider literature using experimental wound models. That is, the strength of their findings is augmented by the existence of the experimental wound research.

Limitations

This review is limited by the relatively small number of published studies compared to other recent reviews of the psychoneuroimmunological literature such as the 89 studies reviewed by Miller and Cohen [80] assessing psychological interventions and immunity, and the 319 studies reviewed by Segerstrom and Miller [4] investigating the association between stress and immunity. Potentially relevant papers may have been missed due to the exclusion of non–English-language papers, although the results of the funnel plot suggest that the review was not significantly affected by publication bias. In addition, this review is automatically limited by the lack of randomized controlled trials, to demonstrate a causal link between stress and wound healing. A greater number of studies would have allowed further analysis of potential moderators of the reported relationship between stress and wound healing (i.e., age, comorbidity), as well as the impact of specific methodological factors (i.e., measurement quality, level of methodological and/or statistical control of confounders) in the meta-analysis. Sample sizes did vary, and alongside the measurement difficulties discussed previously may have contributed to the wider CIs around the effect sizes of some studies included in the meta-analysis (see Fig. 2). In particular, the experimental punch biopsy studies typically had smaller samples, albeit that small sample size is a feature of psychoneuroimmunological research [80]. Although we attempted to look at potential biological and behavioral pathways underlying the relationship between stress and wound healing, the data were insufficient to draw meaningful conclusions and therefore are not included in the present review.

Conclusion and future research

A primary strength of this review lies in its breadth and inclusivity, bringing together findings using a variety of experimental and clinical settings, and wound types. The negative impact of stress is consistent despite this heterogeneity. Future studies adequately powered and controlled are required to explore potential biological and behavioral pathways mediating the association between stress and wound healing as well as examining further factors which may moderate the relationship such as age, social support, duration of stress, or the measurement of a particular "type" of negative affect (i.e., perceived stress, anxiety, depression, or loneliness). Moreover, to establish a causal relationship between stress and healing, it will be necessary to conduct more experimental research, ideally RCTs, which manipulate stress, (i.e., development of interventions to reduce psychological stress) using validated measures of both stress and healing [81]. Causality should be established in healthy populations with experimentally induced wounds before intervention in the healing of clinical wounds is justified. The use of animal models can also contribute to the establishment of causality as they allow more complex experimental designs with greater control to be conducted. Research needs to continue to observe the impact of stress on the healing of clinical wounds, particularly chronic wounds to see whether the impairment of healing associated with stress reported by a single study in this review [65] can be replicated. In addition, clinical studies could be improved by developing more reliable measures of wound healing with proven validity. In this way, it could then be possible to translate experimental research findings into clinical settings and future interventions designed to improve wound healing in patient populations.

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