

**The effects of perceived stress on biological parameters in healthcare professionals:
A systematic review**

Abstract

We synthesised evidence on biological correlates of psychological stress in hospital-based health care professionals (HCPs), and examined whether there was evidence of consistent biological changes. Electronic databases were searched for empirical studies; sixteen papers (0.6%) met the inclusion criteria. Evidence of a relationship between indices of psychological stress and biological parameters was limited and inconsistent. There was some evidence of a consistent relationship between NK cells and lymphocyte subpopulations. Considerable heterogeneity in the methods used was seen. . Future prospective studies examining the relationship between indices of psychological stress and NK cells, including lymphocyte subsets, is required.

Keywords

Systematic review, Psychological stress, Health care, Methodology, Emotions

Introduction

Aversive emotional experiences, hereafter referred to as psychological stress, have long been associated with biological perturbations in the functioning of the cardiovascular, endocrine and immune systems (Sterling, 2012). Research into the clinical relevance of these perturbations, both in terms of disease vulnerability and disease progression continues apace. Research in this area often focuses on a specific disease, or a specific 'at risk' population and health care professionals (HCPs) are among those populations to have attracted particular interest.

Psychological stress in HCPs could be regarded as being of special concern. While HCPs encounter a number of occupational stressors common to other professions (e.g., increased workload, organisational problems and conflict etc. (Pelletier, 2011) they also contend with unique stressors such as contact with patients who are suffering and dying (Girgis et al., 2009). These additional emotional stressors may contribute to their experience of stress. Indeed it is thought that levels of psychological stress may be higher in HCPs than in other occupational groups (Michie and Williams, 2003). The potential significance of this occupational group is further underscored by the possibility that the experience of stress in this group is likely to have effects that go

beyond the HCP themselves. For example, evidence suggests that stress and job 'burnout' among nurses is associated with increased patient mortality, reduced quality of care as measured by 'failure to rescue' (Aiken et al., 2002; Halm et al., 2005) and increased patient dissatisfaction (Leiter et al., 1998; Vahey et al., 2004).

The relationship between psychological stress and biological perturbations in HCPs was the subject of a recent systematic review and meta-analysis. The authors focused exclusively on occupational burnout as their measure of psychological stress and examined the literature concerning its relationship with biomarkers within the autonomic nervous system (blood pressure and heart rate, epinephrine, norepinephrine, aldosterone), HPA axis (cortisol in blood, saliva and urine, ACTH, SBDNF) and immune system (TNF- α , TGF- β , hs-CRP, neopterin, lymphocytes, T cells, B cells, NK cells, Cytokines, Fibrinogen, IL-4, IL-10, Saliva IgA), metabolism (cholesterol, glucose, HbA1c, triglycerides, body mass index, insulin), as well as hormones other than cortisol and antioxidants. 31 articles were included in the review investigating 38 different potential biomarkers covering many physiological processes. For cortisol awakening response measured in saliva, systolic blood pressure and diastolic blood pressure, the number and quality of studies enabled a meta-analysis to be carried out.

This analysis did not find a convincing relationship between any of these biomarkers and burnout. The review concluded that there was no evidence in support of an association between occupational burnout and any of the biological factors studied (Danhof-Pont et al., 2011).

Although the findings of Danhof-Pont and colleagues suggest that burnout is not associated with reliable biological changes in HCPs; it remains unclear whether the same is true of aversive emotional experiences that are not characterised as 'burnout' or indeed psychological stress that is unrelated to one's occupation. Furthermore, it is now well-established that the levels of psychological stress experienced by any occupational group are typically a product of both occupational and non-occupational stressors and the interplay between personal and professional roles can be complex and can impact on work life, general well being and health (Allen, 2000). For example, associations have been found between work-family conflict and stress-related health outcomes including psychological distress, depression, somatic complaints and alcohol abuse (Greenhaus et al., 2006; Amati et al., 2010). Accordingly, it is possible that a focus on burnout alone does not provide a comprehensive picture of the psychological

stress experienced by HCPs and this may have contributed to the null findings in the Danhof-Pont et al. review.

The present review was designed to address these issues by widening the scope of the review to encompass a broader range of both occupational and non-occupational stress. Specifically, our aim was to review studies that would give us a more general picture of the aversive emotional experiences of people working in a hospital context, i.e., not be restricted to occupational related stress or burnout only. Accordingly, we focused our search on indices of psychological stress (including anxiety and depression) and did not distinguish between work-related and non-work related stress. We did, however, restrict our search to studies conducted with individuals working in hospital-based health care in order to limit the variability of the occupational environments being studied. We also did not include studies that examined 'stressors' such as inventories of stressful life events, with a view to capturing subjective emotional responses.

Methods

Search strategy

In order to examine the current evidence on biological correlates of psychological stress in HCPs, the review included all empirical studies containing original data involving the measurement of both indices of perceived psychological stress and reporting the direct measurement of one or more biological parameter. 'Psychological stress' was defined as any form of aversive emotional experience, including those captured through self-report instruments. Studies were eligible only if the stress measures employed had been validated. Only studies with HCPs employed within a hospital-based healthcare setting were included. The review covered published articles from the period 1990 – end July 2010 and was restricted to studies published in the English language as it was considered that the authors were not competent to review non-English publications.

A review protocol detailing all search strategies was developed in accordance with the PRISMA Statement (Moher et al., 2009). The following electronic databases were searched using the strategies detailed in the protocol: MEDLINE, MEDLINE In-Process, PsychInfo, AMED (Allied and Complementary Medicine Database), BNI (British Nursing

Index), Cochrane Library, Embase, Web of Science, CINAHL (Cumulative Index to Nursing and Allied Health Literature).

Three sets of search terms were used: one to target indices of psychosocial stress, one for biological outcomes and one for health care professionals. These three sets of terms were combined using an "AND" statement. The search terms were:

“Stress” or “burnout” (and all related terms)

“Work load” or “job satisfaction” (and all related terms)

“Cortisol” (and all related terms)

“Blood pressure” or “heart rate” or “galvanic skin response” (and all related terms)

“Immune system” or “immune cells” or “glucose” or “cytokines” (and all related terms)

“health personnel” or “hospital staff” (and all related terms)

Search terms were interpreted as broadly as possible to maximise the likely inclusion of relevant articles. Search results were exported to a Reference Manager (Thomson Reuters, California, USA) database. Duplicates were removed.

Inclusion and exclusion criteria

The first author screened the titles and abstracts of the remaining references using an inclusion/exclusion form to determine which records were suitable for further assessment. 10% of these (n=273) were also screened by a second reviewer (author KV). Level of agreement was 72.89%. Where there was disagreement the full text of the study was consulted and full agreement was achieved. At this stage records were excluded if it was clear they did not report the measurement of validated indices of psychological stress or biological parameters; if the participants were not based within a hospital setting; if there were no original data reported (e.g. a review article, editorial or comment piece); or if it was a duplicate study. Full-texts were then subjected to more detailed scrutiny using the same criteria. The reliability of inclusion/exclusion decisions was assessed by a second independent reviewer with articles retrieved in full and categorised in accordance with the inclusion/exclusion form. There was 95.24% agreement between the reviewers at this stage. Discrepancies were resolved by consensus. Figure 1 illustrates the search and study selection process.

INSERT FIGURE 1 HERE

Data extraction

Details of the main findings were extracted for comparison from each of the studies eligible for review. The data analysed were:

- Sample population and number of participants
- Study design
- Stress measures used
- Nature of stress under study (acute or chronic)
- Biological measures reported on
- Results of relevant analyses

The results of analyses performed in each study are summarized in Table 1. Details of the data extracted for each study is available as a supplemental file.

Results

Study selection

The electronic search strategy identified 2728 records. Identification and removal of duplicates left 2314 records. The titles and abstracts of these references were screened and 2097 were excluded. This was primarily the result of the participants not being healthcare professionals (n=1605) and a lack of original data (n=450). Two hundred and seventeen full-text articles were assessed further for eligibility.

Assessment of the 217 full-text articles resulted in the exclusion of a further 201 studies which were non-empirical (n=39), did not report a biological measure (n=13), did not report a measure of psychological stress (n=58), used non-validated stress measures (n=39), or concerned participants not employed within a hospital environment (n=60). Some studies were excluded on the basis of more than one of these criteria. A further 16 studies were duplicates that had not been identified during the first round of exclusion, and 21 studies were classified as excluded for 'other' reasons. For example, excluded studies in the 'other' category included those where psychological and biological measures were investigated as confounders and as such were not analysed with respect to each other. Following this assessment 16 studies

remained (see Figure 1.) which met the inclusion criteria and contained empirical data on the relationship between indices of psychological stress and biological parameters in HCPs.

General findings

Details of all studies included in the review and a summary of the data extracted can be accessed as a supplemental file. Nearly all of the studies (n=14) were observational in design, either cross-sectional (n=11) or prospective (n=3). Two studies (Galantino et al., 2005; Kaspers and Scholz, 2004) were prospective experimental, and examined the relationship between self-report measures of stress and salivary cortisol during the course of intervention programmes (Mindfulness Meditation and Cognitive Behavioural Stress Management respectively).

The self-report measures of perceived stress employed by the studies included in the review varied, and comprised more unique scales than individual studies. The only scales common to more than one study were the Profile of Moods States (PoMS, n=3/16, (Fukuda et al., 2008; Galantino et al., 2005; Munakata et al., 2001)), and the Perceived Stress Scale (PSS, n=2/16 (Amati et al., 2010; Picardi et al., 2007)).

Just under half of the studies reviewed (n=7/16 (Amati et al., 2010; Bergman et al., 2008; De et al., 1999; Fukuda et al., 2008; Morikawa et al., 2005; Munakata et al.,

2001; Picardi et al., 2007)) found a significant relationship between a measure of psychological stress and some biological parameter. Studies focussed on the assessment of aspects of the endocrine, cardiovascular, immune system or a combination of these. We present the findings in relation to each of these physiological systems.

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Psychological stress in HCPs and the endocrine system

All studies which assessed the endocrine system, focused on the hormone cortisol. Indeed, cortisol was the most common biological parameter to be measured: assessed in 12 out of 16 papers included in this review. One study reported a significant association with change in salivary cortisol between morning and evening found to be positively correlated associated with change in the mean response to the 'State of Mood Questionnaire' over the equivalent timeframe (Bergman et al., 2008). However, similar analyses from other studies reviewed found no relationship between cortisol and other indices of psychological stress (see Table 2).

INSERT TABLE 2 AROUND HERE

Psychological stress in HCPs and the immune system

Seven studies explored the relationship between psychological stress and immunological parameters (Amati et al., 2010; De et al., 1999; Fukuda et al., 2008; Kawaguchi et al., 2007; Morikawa et al., 2005; Picardi et al., 2007; Seyed-Hosseini et al., 2007). Two studies analysed lymphocyte populations in whole blood. One of these looked at total number of lymphocytes as well as a wide range of lymphocyte subpopulations (Amati et al., 2010). This study found evidence for a relationship between total lymphocyte numbers and scores from both the PSS and General Health Questionnaire-12 (GHQ12) ($r=0.161$ $p<0.05$ and $r=0.175$ $p<0.05$ respectively). The evidence for a relationship between scores from the PSS and GHQ12 with individual subpopulations was mixed (see Table 1). Another study did not look at total lymphocyte numbers but focused instead on lymphocyte subpopulations (De et al., 1999). The subpopulations/ratios of subpopulations analysed were unique to each study so comparison of results was not possible.

A total of 4 analyses investigated NK cell activity and perceived stress (Amati et al., 2010; Kawaguchi et al., 2007; Morikawa et al., 2005; Picardi et al., 2007) (see Table 3). Two of these analyses found a significant association with a reduction in NK cell activity being associated with perceived job strain (work quantity and physician conflict subscales on the Nursing Job Stressor Scale) (Morikawa et al., 2005) and psychological stress as measured by the PSS (Picardi et al., 2007). Three studies investigated cytokine

levels with respect to 4 different indices of psychological distress and found no association.

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Other immunological parameters investigated were surface antigens (Morikawa et al., 2005), lymphocyte transformation (Seyed-Hosseini et al., 2007), cytokine levels (Amati et al., 2010; De et al., 1999; Fukuda et al., 2008), and acute phase proteins (De et al., 1999). However, none of these studies found evidence for an association between these immunological parameters and the indices of psychological stress under investigation.

Psychological stress in HCPs and the cardiovascular system

Studies also investigated psychological distress in HCPs with respect to blood pressure and heart rate (Munakata et al., 2001), catecholamines (Kawaguchi et al., 2007), ACTH (Munakata et al., 2001), thyroid hormones and prolactin (Korompeli et al., 2009). Only blood pressure was significantly associated with the psychological stress measure in question (PoMS) for which it was found to correlate positively with vigour and negatively with scores for confusion (see Data Summary available as a supplemental file).

Discussion

The aim of this review was to synthesise the evidence on biological correlates of psychological stress in HCPs employed within a hospital environment. The findings revealed an area of research characterised by heterogeneity at the level of sampling (i.e., differences in the populations being studied), approaches to the measurement of stress, and the choice and measurement of biomarkers. Overall there is limited and inconsistent evidence for an effect of psychological stress on the activity of the endocrine, immune and cardiovascular systems in HCPs. Across studies investigating cortisol, NK cell activity, lymphocyte populations and other immunological parameters only a small number of analyses, often at the level of within-measure subscales, found evidence for a relationship (see Table 1). For example Morikawa et al. (Morikawa et al., 2005) did 21 different tests between job stress variables and immune variables and found 2 significant associations at the level of subscales of the nursing job stressor scale.

It is clear from our findings that there were substantial differences between studies with respect to the methodology employed in measuring stress and the biological indices measured. These variations make it difficult to draw conclusions across studies and this, in turn, made a quantitative synthesis of this evidence impractical. For

example, if we consider the two studies which looked at lymphocyte levels (Amati et al., 2010; De et al., 1999), while these studies both examined lymphocyte subpopulations, none of the subpopulations under investigated were common to both studies. Similarly, if we consider the studies which measured cortisol, which was the most commonly measured biological index, it was also the measure in which there was the greatest methodological heterogeneity. Studies which examined the relationship between cortisol and stress differed in the manner in which cortisol was measured (serum vs. saliva vs. urine), and the profile of release (morning, afternoon, change between morning and afternoon, release throughout the day). Of those reporting on salivary cortisol (n=5, see Table 2), the most common procedure, observed in 3 studies, was to collect 4 saliva samples over the course of a 12 hour period. However, exceptions were Galantino et al. (Galantino et al. 2005) who collected only one saliva sample during a meditation session, and Ganster et al. (Ganster et al. 2001) who collected one saliva sample following return from work 'at home'. As no two studies were alike meaningful comparison (i.e. calculation of an overall effect size) was not possible, even between subgroups of studies investigating similar exposures and outcomes.

Irrespective of concerns over heterogeneity of methodology, the majority of analyses in these studies yielded null findings. This may suggest, in keeping with the findings of Danhof-Pont and colleagues, that there is no association between psychological stress and biological indices in this population. However it could highlight that the methods currently being employed to investigate this topic are problematic. Indeed there are certain characteristics common to many of the studies reviewed that make it unlikely that a rigorous assessment of the relationship between distress and biological functioning has been undertaken thus far, including: the power of individual studies to detect an association, the cross-sectional nature of the study designs, the nature of the stress responses under investigation, and the characteristics of the sample population. The presence of these methodological issues suggest that any true association is unlikely to be detected.

Most of the studies reviewed have relatively small sample sizes; only 6 of the studies reviewed had a sample size greater than 100. In an area of research complicated by multiple levels of potential bi-directional interaction, sufficiently powered studies are vital. This is especially the case when dealing with potentially unreliable physiological measurements, such as measurements of cortisol. The most common procedure in the studies reviewed was to collect 4 saliva samples over a 12 hour period, a method that

relies on the participant for compliance with the study protocol. Therefore any error in cortisol measurement, will further obscure any true association.

Eleven out of 16 of the studies reviewed here were cross-sectional. It is, of course, not possible to examine causality in such designs. This issue is further compounded by the fact that most of the studies focused on an acute measure of stress (see below) but measured biological indices most likely to be effected by the cumulative effects of persistent or chronic stress (for example diurnal cortisol rhythm) (Pike et al., 1997). This is therefore an additional methodological factor likely to impact on the ability of these studies to observe an association between psychological distress and the chosen physiological variables.

Indeed, within the studies reviewed little consideration was given to the nature of the stress under investigation. We identified four types of studies: 1) acute measures of stress within cross-sectional studies (n=10); 2) acute measures of stress within prospective studies (n=4); 3) chronic measure of stress within cross-sectional studies (n=1); 4) chronic measures of stress within prospective studies (n=1). Only two studies (Fukuda et al. 2008; Kaspers and Scholz, 2004) investigated the effects of chronic stress on biological measures. Fukuda et al. (Fukuda et al., 2008) carried out a cross-sectional

study using a measure of chronic stress (Nursing Stress Scale) and found that participants categorised as experiencing 'high stress' had higher levels of urinary cortisol. In contrast, Kaspers&Scholz(Kaspers and Scholz ,2004) used both acute and chronic measures of stress in their prospective design (Trier Inventory for the Assessment of Chronic Stress, Nursing Stress Questionnaire, Hassles and Uplifts Scale, Allgemeine Depressions Skala) but found no relationship between cortisol levels and any self-report measures. Thus, the effects of chronic stress, in particular, remains an area worthy of further enquiry, especially in conjunction with those physiological factors most likely to be shaped by chronic stress.

A further potential limitation concerns the difficulty of collating evidence from highly varied populations in terms of type of hospital, type of ward and so on. Although our inclusion criteria were designed to include as many different occupational roles as possible, there is evidence that differences exist in the relationship between measures of psychological and biological functioning between staff from different types of wards (see Koh et al. 2002, for differences between emergency ward staff and general ward staff). While none of the studies reviewed reported having explicitly selected those participants experiencing higher levels of distress, it is likely that psychological

demands differ between sample populations and ideally evidence synthesis would utilise a more homogeneous sample. But given the small number of eligible studies available for review, such sample selection was not possible. Similarly there likely exists a recruitment bias that may exclude potential participants as a result of absenteeism or absence from work due to long-term sickness. Thus, the employees most likely to be vulnerable to the adverse consequences of psychological stress may have been the ones least likely to participate in the studies examined in this review, the so-called 'healthy worker effect' (Baillargeon, 2001).

A related issue concerns the need to delineate the effects of stress from the potentially confounding effects of shift work which, although may not have been made explicit, are likely to be inherent in the work of many HCPs and have been shown to interfere with basic biological function, work ability, social relationships, and psychophysical health (Kudielka et al. 2007). This, and the issue of the 'healthy worker effect', are additional issues that are likely to reduce the magnitude of any observed effect and may lead studies to underestimate the true association.

Although heterogeneity in both study participants and the methodology used, make interpretation difficult, the findings regarding psychological stress and NK cells were among the most consistent. This is in agreement with an established literature on the

effects of psychological stress on NK cells in the general population (Biondi, 2001; Kiecolt-Glaser et al., 1987). We found evidence that perceived stress was associated with decreased number of NK cells (De, V et al. 1999) and reduced NK cell activity (Kawaguchi et al. 2007; Morikawa et al. 2005; Picardi et al. 2007). NK cells are known to have an important role in the defence against viral infection (Vivier et al. 2011) and nascent tumours (Diefenbach and Raulet, 2002) and could therefore represent an important mechanistic link underlying previously reported relationships between psychological stress and poor health outcomes. For example, it has been shown that male doctors have a higher proportional mortality ratio for viral hepatitis, liver cancer, and cirrhosis while female doctors have a higher ratio for cancer of the pancreas (Baldwin et al. 1997). In view of the tumour surveillance role of NK cells, these findings may provide insight into the biological mechanism underlying the increased risk of cancer and cancer-related mortality in HCPs. This review also found evidence that psychological stress in hospital-based HCPs is associated with alterations in lymphocyte populations. It would, therefore, be of interest to investigate the prevalence of autoimmune diseases in HCPs, given that autoimmune diseases arise from dysfunction in lymphocyte recognition of self-antigens (Yanaba et al., 2008).

Implications for future research

The major constraint of the scope of this review concerned the high degree of heterogeneity in the employed methodologies between studies. In the wider context of the literature on the occupational health of healthcare professionals, this lack of consensus on the future direction of research will likely hamper progress with groups focusing efforts in differing directions with no expanding base on which to build future proposals. Specifically we would recommend that future research seeks to address the contribution of chronic stress to perturbation in biological parameters, especially NK cells which seem the most potentially fruitful avenue of enquiry. There are also a number of fundamental methodological issues common to many of the studies reviewed here; small sample sizes mean that studies are insufficiently powered, common measurements such as cortisol are prone to measurement error, studies are cross-sectional in design and do not take account of the nature of the stress under investigation, or the characteristics of the sample population. These issues prevent conclusions from being drawn regarding the lack thereof or otherwise of an association between psychological and physiological factors. Studies in this area should ensure they are sufficiently powered and minimise measurement error as far as is possible. Further work should also control for the composition of the population under study (e.g. type of work, shift patterns etc.), and seek to define the association

between psychological stress and physiological health (e.g. autoimmune disorders), ideally using prospective experimental designs, appropriately powered.

Limitations of the current review

The current study was conceived as a review of literature over a twenty year period (1990-2010). Resource constraints have prevented subsequent updating of the searches. Thus a potential limitation of this review is that there may be more recent papers that could contribute to the evidence. An additional limitation concerns the lack of quantitative analysis by meta-analysis. This was not possible due to the high degree of heterogeneity in the studies reviewed. Ideally this review would have used a more narrow criteria for papers to be included, allowing for homogeneity within the psychological scale used, the physiology under investigation, the population sample and so on. However the very limited number of studies with these characteristics in common prevented this. Similarly there were not sufficient common characteristics between groups of studies to allow for subtype analysis. This means that our analysis has been limited to a technique known as 'vote-counting' (Hedges & Olkin, 1980). Vote-counting can only speak to whether there is any evidence for an effect or not. It is problematic because it relies on statistical significance in order for a study to be 'counted', rather than producing a measure of overall magnitude reflecting all

combined effect sizes. Similarly vote-counting does not allow for different weighting to be attributed to different studies, for example to account for differences in sample size.

Conclusions

There is evidence of considerable heterogeneity in the methods used to measure both psychological stress and biological perturbations in hospital-based HCPs. We propose that this area of research could benefit from greater consistency in the approaches used; the use of prospective designs and a focus on chronic experiences of stress. As the field stands currently there is limited and inconsistent evidence for an association between psychological stress and biological parameters. However our analysis of the studies reviewed suggests this may be due to current research lacking the ability to detect a true association rather than a genuine lack of relationship.

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