

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

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Abstract

We synthesised evidence on biological correlates of psychological stress in hospital-based healthcare professionals, and examined whether there was evidence of consistent biological changes. Electronic databases were searched for empirical studies; 16 articles (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 natural killer cells and lymphocyte subpopulations. Considerable heterogeneity in the methods used was seen. Future prospective studies examining the relationship between indices of psychological stress and natural killer cells, including lymphocyte subsets, is required.

Keywords

emotions, health care, methodology, psychological stress, systematic review

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 healthcare 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 (Pelletier, 2011)), they also contend with unique stressors such as contact with patients who are suffering and dying (Girgis et al., 2009). These

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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 HCPs 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), hypothalamic–pituitary–adrenal (HPA) axis (cortisol in blood, saliva and urine, adrenocorticotrophic hormone (ACTH), serum brain-derived neurotrophic factor (SBDNF)) and immune system (tumour necrosis factor (TNF)- α , transforming growth factor (TGF)- β , high-sensitivity C-reactive protein (hs-CRP), neopterin, lymphocytes, T cells, B cells, natural killer (NK) cells, cytokines, fibrinogen, interleukin (IL)-4, IL-10, Saliva IgA), metabolism (cholesterol, glucose, HbA1c, triglycerides, body mass index, insulin), as well as hormones other than cortisol and antioxidants. Thirty-one 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 et al., 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 (Amati et al., 2010; Greenhaus et al., 2006). 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.

This 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, that is, not be restricted to occupation-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 1990 to end of 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 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher et al., 2009). The following electronic databases were searched using the strategies detailed in the protocol: MEDLINE, MEDLINE In-Process, PsycINFO, AMED (Allied and Complementary Medicine Database), BNI (British Nursing Index), Cochrane Library, Embase, Web of Science and 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 HCPs. These three sets of terms were combined using an ‘AND’ statement. The search terms were as follows:

1. ‘Stress’ or ‘burnout’ (and all related terms), ‘Work load’ or ‘job satisfaction’ (and all related terms)
2. ‘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)

3. ‘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 (K.D.) screened the titles and abstracts of the remaining references using an inclusion/exclusion form to determine which records were suitable for further assessment. Ten percent of these ($n = 273$) were also screened by a second reviewer (K.V.). 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.

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,

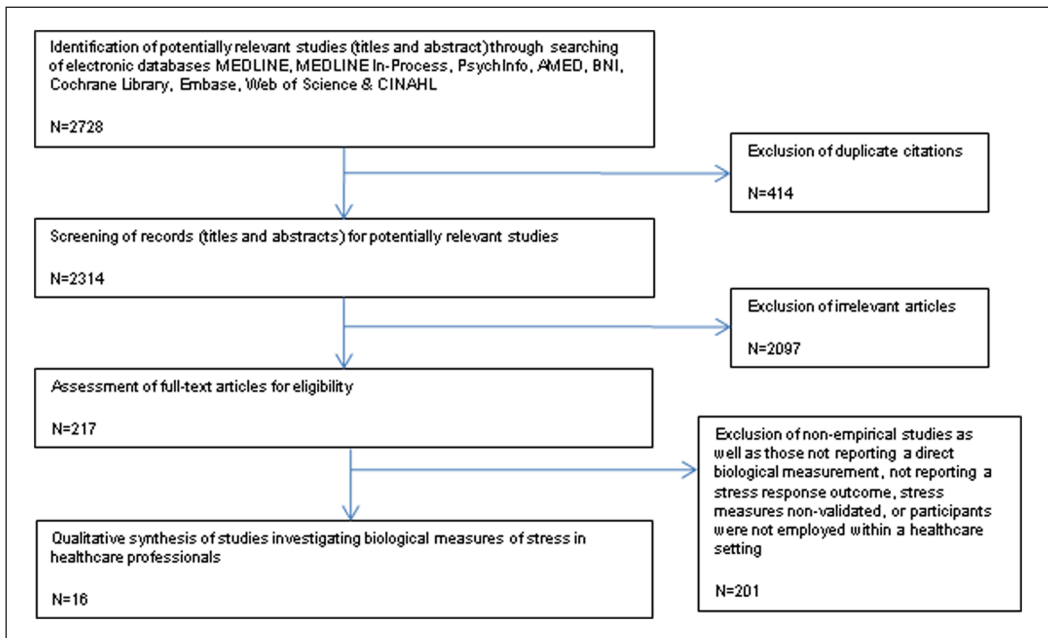


Figure 1. Flow diagram to illustrate the search and study selection process.

- study design,
- stress measures used,
- nature of stress under study (acute or chronic),
- biological measures reported on,
- results of relevant analyses.

Details of the data extracted for each study are 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 HCPs ($n = 1605$) and a lack of original data ($n = 450$). A total of 217 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. Excluded studies in the ‘other’ category included those in which 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 Gucht 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.

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 articles 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 1).

Psychological stress in HCPs and the immune system

Seven studies explored the relationship between psychological stress and immunological parameters (Amati et al., 2010; De Gucht 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) ($r = 0.161$ $p < .05$ and $r = 0.175$ $p < .05$, respectively). The evidence for a relationship between scores from the PSS and GHQ12 with individual subpopulations was mixed (see Online Supplementary Material). Another study did not look at total lymphocyte numbers but focussed instead on lymphocyte subpopulations (De Gucht et al., 1999). The subpopulations/ratios of subpopulations analysed were unique to each study so comparison of results was not possible.

A total of four 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 2). 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 four different indices of psychological distress and found no association.

Other immunological parameters investigated were surface antigens (Morikawa et al., 2005),

Table 1. Summary data from reviewed studies investigating cortisol.

| Study | Measurements | Results |
|---------------------------|--|--|
| Kawaguchi et al. (2007) | GHQ28 × cortisol in plasma | n = 128 r = -0.092 ns |
| Bergman et al. (2008) | Change in mean morning salivary cortisol and evening cortisol × change in perceived mood between morning and evening in men | n = 41 r = 0.50 p = 0.01 |
| Brant et al. (2010) | HADS × salivary cortisol | n = 36 Data not shown, all analyses ns. |
| Fukuda et al. (2008) | Nursing stress scale × urinary cortisol | n = 118 $F_{(1,115)} = 5.48, p = 0.021$ All other analyses ns |
| Galantino et al. (2005) | PoMS–Short Form × cortisol in saliva | n = 84 Data not shown, all analyses ns |
| Ganster et al. (2001) | Mental Health Index × cortisol in saliva | n = 105 mental health at time 1 × cortisol r = 0.12 ns mental health at time 2 × cortisol r = -0.11 ns |
| Kaspers and Scholz (2004) | Groups, as defined by salivary cortisol levels × amount of stress, coping quality or quantity, strain quality or quantity, amount or profile of physical complaints | n = 25 $F_{(14,22)} = 1.092, p = 0.415$ |
| Korompeli et al. (2009) | GHQ component of Standard Shiftwork Inventory × beginning to end of shift change in morning cortisol (in blood) × beginning to end of shift change in evening cortisol × beginning to end of shift change in night cortisol | n = 32 r = -0.13 ns r = 0.22 ns r = 0.02 ns |
| Munakata et al. (2001) | PoMS × plasma ACTH and cortisol | n = 18 Data not shown, all analyses ns. |
| Sertoz et al. (2008) | Serum cortisol × Beck Depression Inventory Serum cortisol × Beck Anxiety Inventory | n = 37 r = -0.051 p = 0.67 r = -0.075 p = 0.53 |

ACTH: adrenocorticotrophic hormone; GHQ = General Health Questionnaire; HADS = Hospital Anxiety and Depression Scale; PoMS = Profile of Mood States; ns: not significant.

lymphocyte transformation (Seyed-Hossein et al., 2007), cytokine levels (Amati et al., 2010; De Gucht et al., 1999; Fukuda et al., 2008) and acute phase proteins (De Gucht 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.

Table 2. Summary data from reviewed studies investigating NK cell parameters.

| Study | Measurements | Results |
|-------------------------|--|--|
| Amati et al. (2010) | PSS × NK activity GHQ12 × NK activity | n = 115 r = 0.150 ns NK activity r = 0.101 ns |
| Kawaguchi et al. (2007) | GHQ28 × NK cell activity | n = 128 r = -0.019 ns |
| Morikawa et al. (2005) | NK activity × Nursing Job Stressor Scale Perceived quantitative workload Perceived qualitative workload Perceived nursing role conflict Perceived conflict with nursing staff Perceived conflict with physicians Perceived conflict with patients Perceived conflict with dying | n = 61 r = -0.35 p < 0.05 r = -0.16 ns r = 0.02 ns r = -0.12 ns r = -0.26 p < .05 r = -0.15 ns r = -0.08 ns |
| Picardi et al. (2007) | NK cell cytotoxicity × perceived stress (as part of a multiple regression with NK cell cytotoxicity as the dependent variable and attachment-related anxiety as a covariable) NK cell cytotoxicity × perceived stress (as part of a multiple regression with NK cell cytotoxicity as the dependent variable and attachment-related avoidance as a covariable) | n = 61 β = -0.31 p ≤ .05 β = -0.30 p ≤ .05 |

GHQ = General Health Questionnaire; NK: natural killer; ns: not significant; PSS: Perceived Stress Scale.

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 Online Supplementary Material). For example Morikawa et al. (2005) did 21 different tests between job stress variables and immune variables and found two significant associations at

the level of subscales of the nursing job stressor scale.

It is clear from our findings that there were substantial differences among 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 Gucht et al., 1999), while both these studies examined lymphocyte subpopulations, none of the subpopulations under investigation 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 1), the most common procedure, observed in three studies, was to collect four saliva samples over the course of a 12-hour period. However, exceptions were Galantino et al. (2005) who collected only one saliva sample during a meditation session, and 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 suggests that any true association is unlikely to be detected.

Most of the studies reviewed have relatively small sample sizes; only six 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 four 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 (e.g. 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 ($n = 1$) and (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. (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 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. However, 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 psycho-physical health (Kudielka et al., 2007). This and the issue of the 'health 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 Gucht 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 HCPs, 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

This study was conceived as a review of literature over a 20-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 articles 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 articles 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 and 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.

Conclusion

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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References

- Aiken LH, Clarke SP, Sloane DM, et al. (2002) Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. *JAMA* 288(16): 1987–1993.
- Allen TD, Herst DEL, Bruck CS, et al. (2000) Consequences associated with work-to-family conflict: A review and agenda for future research. *Journal of Occupational Health Psychology* 5(2): 278–308.
- Amati M, Tomasetti M, Ciuccarelli M, et al. (2010) Relationship of job satisfaction, psychological distress and stress-related biological parameters among healthy nurses: A longitudinal study. *Journal of Occupational Health* 52(1): 31–38.
- Baillargeon J (2001) Characteristics of the healthy worker effect. *Occupational Medicine-State of the Art Reviews* 16(2): 359–366.
- Baldwin PJ, Dodd M and Wrate RW (1997) Young doctors' health. 1. How do working conditions affect attitudes, health and performance? *Social Science & Medicine* 45(1): 35–40.
- Brant H, Wetherell M, Lightman S, et al. (2010) An exploration into physiological and self-report measures of stress in pre-registration doctors at the beginning and the end of a clinical rotation. *Stress: The International Journal on the Biology of Stress* 13(2): 155–162.
- Bergman B, Ahmad F and Stewart DE (2008) Work family balance, stress, and salivary cortisol in men and women academic physicians. *International Journal of Behavioral Medicine* 15: 54–61.
- Biondi M (2001) Effects of stress on immune functions: An overview. In: Ader R, Felton DL and Cohen N (eds) *Psychoneuroimmunology*, vol. 2. San Diego, CA: Academic Press, pp. 189–226.
- Danhof-Pont MB, Van VT and Zitman FG (2011) Biomarkers in burnout: A systematic review. *Journal of Psychosomatic Research* 70(6): 505–524.
- De Gucht V, Fischler B and Demanet C (1999) Immune dysfunction associated with chronic professional stress in nurses. *Psychiatry Research* 85(1): 105–111.
- Diefenbach A and Rautlet DH (2002) The innate immune response to tumors and its role in the induction of T-cell immunity. *Immunological Reviews* 188: 9–21.
- Fukuda H, Ichinose T, Kusama T, et al. (2008) The relationship between job stress and urinary cytokines in healthy nurses: A cross-sectional study. *Biological Research for Nursing* 10(2): 183–191.
- Galantino ML, Baime M, Maguire M, et al. (2005) Association of psychological and physiological measures of stress in health-care professionals during an 8-week mindfulness meditation program: Mindfulness in practice. *Stress and Health* 21(4): 255–261.
- Ganster DC, Fox ML and Dwyer DJ (2001) Explaining employees' health care costs: a prospective examination of stressful job demands, personal control, and physiological reactivity. *Journal of Applied Psychology* 86(5): 954–964.
- Girgis A, Hansen V and Goldstein D (2009) Are Australian oncology health professionals burning out? A view from the trenches. *European Journal of Cancer* 45(3): 393–399.
- Greenhaus JH, Allen TD and Spector PE (2006) Health consequences of work-family conflict: The dark side of the work-family interface. In: Perrewe P and Ganster DC (eds) *Employee Health, Coping and Methodologies*. Greenwich, CT: Elsevier Science/JAI Press, pp. 61–98.
- Halm M, Peterson M, Kandels M, et al. (2005) Hospital nurse staffing and patient mortality, emotional exhaustion, and job dissatisfaction. *Clinical Nurse Specialist* 19(5): 241–251.
- Hedges LV and Olkin I (1980) Vote counting methods in research synthesis. *Psychological Bulletin* 88: 359–369.
- Kaspers FA and Scholz OB (2004) Stress-induced increase in morning cortisol variance. *Stress and Health* 20(3): 127–139.
- Kawaguchi Y, Toyomasu K, Yoshida N, et al. (2007) Measuring job stress among hospital nurses: An attempt to identify biological markers. *Fukuoka Igaku Zasshi – Hukuoka Acta Medica* 98(2): 48–55.

- Kiecolt-Glaser JK, Glaser R, Shuttleworth EC, et al. (1987) Chronic stress and immunity in family caregivers of Alzheimer's disease victims. *Psychosomatic Medicine* 49(5): 523–535.
- Koh D, Yong Y, Ng V, et al. (2002) Stress, mucosal immunity, upper respiratory tract infections, and sickness absence [2]. *Journal of Occupational and Environmental Medicine* 44(11): 987–988.
- Korompeli A, Sourtzi P, Tzavara C, et al. (2009) Rotating shift-related changes in hormone levels in intensive care unit nurses. *Journal of Advanced Nursing* 65(6): 1274–1282.
- Kudielka BM, Buchtal J, Uhde A, et al. (2007) Circadian cortisol profiles and psychological self-reports in shift workers with and without recent change in the shift rotation system. *Biological Psychology* 74 (1): 92–103.
- Leiter MP, Harvie P and Frizzell C (1998) The correspondence of patient satisfaction and nurse burnout. *Social Science & Medicine* 47(10): 1611–1617.
- Michie S and Williams S (2003) Reducing work related psychological ill health and sickness absence: A systematic literature review. *Occupational and Environmental Medicine* 60: 3–9.
- Moher D, Liberati A, Tetzlaff J, et al. (2009) Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *British Medical Journal* 339: b2535.
- Morikawa Y, Kitaoka-Higashiguchi K, Tanimoto C, et al. (2005) A cross-sectional study on the relationship of job stress with natural killer cell activity and natural killer cell subsets among healthy nurses. *Journal of Occupational Health* 47(5): 378–383.
- Munakata M, Ichi S, Nunokawa T, et al. (2001) Influence of night shift work on psychological state and cardiovascular and neuroendocrine responses in healthy nurses. *Hypertension Research: Clinical and Experimental* 24(1): 25–31.
- Pelletier KR (2011) *Healthy People in Unhealthy Places*. New York: Delacorte Press.
- Picardi A, Battisti F, Tarsitani L, et al. (2007) Attachment security and immunity in healthy women. *Psychosomatic Medicine* 69(1): 40–46.
- Pike JL, Smith TL, Hauger RL, et al. (1997) Chronic life stress alters sympathetic, neuroendocrine, and immune responsiveness to an acute psychological stressor in humans. *Psychosomatic Medicine* 59(4): 447–457.
- Sertoz OO, Binbay IT, Koylu E, et al. (2008). The role of BDNF and HPA axis in the neurobiology of burnout syndrome. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 32(6): 1459–1465.
- Seyed-Hosseini S, Morteza K, Ali P, et al. (2007) A study on relationship between job stress and lymphocyte transformation test in nurses. *Journal of Biological Sciences* 7(2): 333–337.
- Sterling P (2012) Allostasis: A model of predictive regulation. *Physiology & Behavior* 106(1): 5–15.
- Vahey DC, Aiken LH, Sloane DM, et al. (2004) Nurse burnout and patient satisfaction. *Medical Care* 42(Suppl. 2): 1157–1166.
- Vivier E, Raulet DH, Moretta A, et al. (2011) Innate or Adaptive Immunity? The Example of Natural Killer Cells. *Science* 331(6013).
- Yanaba K, Bouaziz JD, Matsushita T, et al. (2008) B-lymphocyte contributions to human autoimmune disease. *Immunological Reviews* 223: 284–299.