Work Stress, Immune, and Inflammatory Markers

32

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Contents

Abstract

The links between workplace stress and ensuing ill-health have been well researched, but less study has focussed on the underlying mechanisms responsible for this association. Despite this, it is timely to synthesize what data are available on the association between workplace stress and dysregulated inflammatory and immune responses, which are likely implicated in several of the disease

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"endpoints" of workplace stress. We focussed our review on the main biomarkers and workplace stress theories in this field and considered collectively workplace stress as measured by the job-demand control, effort-reward imbalance, and organizational justice models that appear to be most related to the biomarkers CRP, NKCC, and sIgA. The limitations of research in this field and the possible pathways of improvement of such research are considered. The aim of this chapter is to provide the reader with an appreciation of the key confounds in this research area and to discuss what research is required to move this field of enquiry forward.

Keywords

Occupational stress · Immunity · Inflammation · Health

Introduction

In this chapter we review the relationship between workplace stress and markers of immunity and inflammation. Specifically, the effort-reward imbalance (ERI; Siegrist 1996), job demand control (JDC; Karasek 1979), job demand-resources (JD-R; Bakker and Demerouti 2007), and organizational justice (OJ; Elovainio et al. 2002) workplace stress models have dominated the small literature examining the relationship between workplace stress and immunity and will be the focus of this review. While there are other studies that have assessed the association of workplace stress with immune and inflammatory markers (see Nakata 2012, for a review), the disparate constructs and measures used in these studies to measure workplace stress compromise the ability to adequately synthesize the literature.

The immune response involves multiple biological systems, and there are several arms to the immune response, each with very specific functions. This review will focus on the most prominently studied immune measures within the workplace stress literature: cytokines, leukocytes and lymphocytes, and immunoglobulins/antibodies. We will start with a brief overview of the workplace stress models before providing the reader with some background on the various roles and functions of these markers of inflammation and immunity. The ensuing sections of the chapter will synthesize and critique the literature with an aim of answering the questions:

1. Is workplace stress related to inflammation and/or reduced immunity?
2. Which models of workplace stress are associated with these markers?
3. What are the complications or limitations within this research?
4. What research is required to move this field of enquiry forward?

Workplace Stress Models

Full descriptions of the workplace stress models are found earlier in this book. However, for those reading this chapter in isolation, we provide a brief overview to assist in the interpretation of the findings presented throughout the chapter.

The ERI model has its foundations in theories of social reciprocity. That is, employees expect to get as much out of their work as they put in, and when they perceive this exchange as unfair, such as when efforts exceed rewards, the individual experiences stress. The specific hypotheses of the ERI model are that each of efforts, rewards (e.g., salary, esteem, job security), and the dispositional/cognitive style "overcommitment" are related to poor health. Further, the interaction of efforts and rewards, or the ERI ratio, contributes a greater explanation to the incidence of poor health than any of the three constructs in isolation. Finally, the overcommitment hypothesis posits that those high in this disposition, which involves an over-investment in work and an inability to "turn off" from work, further amplify the experience of stress.

The JDC model has been tested in a variety of ways, but the main assumption is that job control buffers the impact of job demands on the experience of stress. Others have also looked to segment the model into quadrants of high and low control and high and low demand to assess which quadrants were most associated with poor health. The term "job strain" applies to persons higher in the JDC ratio or in the high stress/low control quadrant. The JDR model differs from the JDC in that the focus moves from control/autonomy to job and personal resources as potential buffers of job demands. The JDR model posits that high job resources are linked with positive or motivational outcomes including improved employee engagement whereas job demands are related with health impairment. This review will focus on the health impairment process.

The OJ model is less researched than the other models presented thus far, but it bears some resemblance to the ERI model given the underlying theme of "fairness" in the workplace. The OJ model focuses on procedural or distributive justice, and these are said to reflect organization- and person-level outcomes, respectively (Elovainio et al. 2002). The outcomes for those who believe their workplace is not "just" include changes in attitude, drops in productivity (Terzioglu et al. 2016), and an increased risk of ill health (Ndjaboué et al. 2012; Robbins et al. 2012).

Indicators of Immunity and Inflammation

Studies of workplace stress have used a variety of molecules housed within blood, mucous, and saliva to identify markers of immunity. In this section we focus our attention on indicators of immune and inflammatory activity and function, namely, lymphocytes and leukocytes, immunoglobulins, and cytokines.

Lymphocytes and Leukocytes

The lymphatic system consists of the thymus, spleen, lymph nodes, and bone marrow. This system is responsible for producing and storing both lymphocytes (B and T cells), which are small white blood cells, and leucocytes which are white blood cells that identify and eliminate pathogens (bacteria, virus, or microorganism that can cause disease). B cells make antibodies that attack toxins and bacteria, whereas T cells can help destroy cancerous or infected cells. Natural killer cells

(NKC) are activated by cytokines known as interferons and act in response to tumor identification or persistent infection (3 days or more). Decreases in helper T cells (CD4+), and suppressor/cytotoxic T cells (CD8+), and an increase in the CD4+:CD8 + ratio have been associated with increased chronic stress (Kawakami et al. 1997). Helper-inducer (CD4 + CD29+) and suppressor-inducer (CD4+ CD45RA+) cells have also been considered in response to workplace stress. Some suggest that an increased proportion of CD8+ T lymphocytes with an effector-memory phenotype (CD27-CD28-) and a low CD4:CD8 ratio are features of an aging immune system and are key elements of the immune risk phenotype (Bosch et al. 2009).

Generally, in response to chronic stress, the number of circulating lymphocytes and leukocytes is expected to decrease, possibly in response to a depleted hypothalamic-pituitary-adrenal (HPA) axis response (Webster et al. 2002). Most researchers assessing the relationship of chronic stress with the number of circulating lymphocytes and leukocytes have hypothesized a negative relationship, with increased chronic stress suppressing this arm of the immune system and compromising the ability to protect the organism from invading pathogens and cancerous or infected cells.

Immunoglobulins

Immunoglobulins or antibodies as they are otherwise referred are produced by B cells and perform very specific actions to destroy antigens. The five main immunoglobulins are IgA, IgD, IgE, IgG, and IgM. IgA and IgG are further classified as IgA1 and IgA2 and IgG1, IgG2, IgG3, and IgG4. Immunoglobulins differ in their structure, features, targets, and distribution. Similar to lymphocytes and leukocytes, the expectation is that in response to chronic stress, the numbers of circulating immunoglobulins are reduced, leaving individuals at an increased risk of infection. Differences in the way the immunoglobulins respond to chronic stressors have been suggested, with IgG having a high "turnover rate" suggesting that a long-lasting stressor would not have a measurable impact on IgG levels until several days or weeks after exposure. Unlike IgG, sIgA has been used frequently in studies of acute stress and is known for its relatively quick response in circulating concentrations post-stressor.

Inflammatory Factors

Cytokines are proteins, specifically peptides, that are important in the communication and coordination of cell actions. Cytokines are important "immunomodulators"; they can both amplify and suppress immune and inflammatory responses and modulate the balance between humoral and cell-based immune responses to protect and repair the organism. Cytokines are synthesized by numerous cell types including B and T lymphocytes, macrophages, and endothelial cells; any given cytokine typically originates from more than one cell type.

Some debate exists about the classifications of cytokines as pro- or anti-inflammatory. While several cytokines such as interleukin (IL)-4 and IL-10 are involved in dampening inflammatory responses and tumor necrotic factor (TNF)-α and IL-6 are viewed as pro-inflammatory, there exists a wide spectrum of functions for most, if not all cytokines. To illustrate this point, most anti-inflammatory cytokines have some pro-inflammatory properties as well. Chronic stress has been linked to both increases and decreases in pro-inflammatory cytokines. For instance, several studies (see Tian et al. 2014, for a review) highlight the relationship of chronic stress with downregulation of pro-inflammatory cytokines in response to increases in markers of increased circulation counts of glucocorticoids, catecholamine, adrenocorticotropic hormone, and corticotropic-releasing hormone. In apparent contrast, a review of 330 studies assessing the relationship of various forms of chronic stress with pro-inflammatory cytokines reported an increase in these circulating cytokines compared to lower-stressed controls (Hänsel et al. 2010).

Potentially, these apparently divergent findings may be explained by the level or stage of chronicity of the stress experienced (Tian et al. 2014). That is, in the early stages of chronic stress, we see a downregulation of pro-inflammatory cytokines in line with an increase in HPA axis and sympathetic adrenomedullary system response, and then if the chronic exposure continues, we move to "HPA axis fatigue" where pro-inflammatory cytokines are increased due to the reduction in circulating glucocorticoids, catecholamines, adrenocorticotropic hormone, and corticotropic-releasing hormone.

The role of cytokines in the human immune system is both complex and specialized. The role of cytokines as a "communicator" is further highlighted with the upregulation of C-reactive protein (CRP), a marker of inflammation, in response to signals from pro-inflammatory cytokines including TNF-α, IL-6, and IL-1.

Our brief description above is provided to give the reader a basic understanding of key principles to aid interpretation of the findings presented later in this chapter. Those interested in a more extensive review of cytokines are directed to McInnes (2017) and Tian et al. (2014). The review of the relationship of *workplace stress* with cytokines is less extensive than those provided by studies of *chronic stress*, but an advantage of narrowing the focus to employees is that employees represent a potentially more homogenous sample of somewhat healthy individuals given that they are actively employed.

Workplace Stress and Inflammatory Factors

In our review of the literature of workplace stress with cytokines and CRP, we identified seven papers using the ERI model, six papers using the JDC model, one paper using the JD-R model, and two papers using the OJ model (Table 1).

We located papers that used ten different markers of inflammation including ratios of pro-inflammatory to anti-inflammatory ratios, but most of the cytokines were only captured in one or two papers. The exception to this were the inflammatory markers CRP (12 papers), IL-6 (7 papers), and TNF-α (3 papers). The CRP

Table 1 Workplace stress and markers of inflammation

Marker	Stress model	Study	Effect size/findings
CRP	ERI	Bellingrath et al. 2009 104 females	ERI $r = 0.24$
		Mauss et al. 2015 $N = 3797$ (79.3% males)	ERI $r = -0.02$
		Almadi et al. 2013 204 males	ERI $r = -0.29^*$
		Hamer et al. 2006 92 males	ERI not associated with CRP levels at baseline
		Izawa et al. 2016 142 males	Higher effort related with higher CRP in young group only*
	JDC	Emeny et al. 2013 $N = 1027$ (68% males)	Job strain $r = 0.11$ (CVD group) Job strain $r = 0.08$ (non-CVD group)* Demands $r = 0.19$ (CVD group)* Demands $r = 0.03$ (non-CVD group) Control $r = 0.04$ (CVD group) Control $r = -0.10$ (non-CVD group)*
		Hemingway et al. 2003 $N = 283$ (59% males)	High versus low demands did not differ High versus low control did not differ
		Emeny et al. 2012	Job strain $r = 0.09^*$
		(P) Shirom et al. 2008 $N = 1121$ (66% males)	Job strain not prospectively related with CRP
		Tsai et al. 2014 825 males	High strain related to higher CRP in the under 35 age group only (odds ratio = 2.71)*
		Schnorpfeil et al. 2003 $N = 324$ (84% males)	Demands positively associated with CRP* Control negatively associated with CRP*
	OJ	(P) Elovainio et al. 2010 $N = 4409$ (73% male)	Lower perceived justice related with higher CRP prospectively in men* Perceived justice not related with CRP prospectively in women
		Herr et al. 2015 353 males	Low and high justice groups did not differ
IL-6	ERI	Bellingrath et al. 2010 $N = 55$ (62% female)	ERI $r = 0.30^*$ Overcommitment $r = 0.21$
		Bellingrath et al. 2013 $N = 46$ (63% females)	High ERI group higher IL-6 than low ERI group at baseline*. No difference in OC groups
	JDC	Emeny et al. 2013 $N = 1027$ (68% males)	Job strain $r = 0.04$ (CVD group) Job strain $r = 0.01$ (non-CVD group) Demands $r = 0.13$ (CVD group) Demands $r = -0.02$ (non-CVD group) Control $r = 0.10$ (CVD group) Control $r = -0.01$ (non-CVD group)
		Hemingway et al. 2003 $N = 283$ (59% males)	High versus low demands did not differ High versus low control did not differ
		Emeny et al. 2012	Job strain $r = 0.01$
	JDR	Falco et al. 2017 $N = 119$ (71% females)	Emotional demands $r = 0.19^*$ Control $r = -0.15$ Support $r = -0.03$
	OJ	(P) Elovainio et al. 2010 $N = 4409$ (73% male)	Lower perceived justice related with higher Il-6 prospectively in men*

(continued)

Table 1 (continued)

Marker	Stress model	Study	Effect size/findings
			Perceived justice not related with Il-6 prospectively in women
IL-10	ERI	Bellingrath et al. 2010 $N = 55$ (62% female)	ERI $r = 0.30^*$ Overcommitment $r = 0.21$
IL-2	ERI	Bellingrath et al. 2010 $N = 55$ (62% female)	ERI $r = 0.01$ Overcommitment $r = 0.09$
IL-4	ERI	Bellingrath et al. 2010 $N = 55$ (62% female)	ERI $r = 0.13$ Overcommitment $r = 0.07$
	JDC	Miyazaki et al. 2005 241 males	Higher work social support related to lower IL-4* Demands not associated
IL-8	JDC	Emeny et al. 2013 $N = 1027$ (68% males)	Job strain $r = 0.05$ (CVD group) Job strain $r = -0.04$ (non-CVD group) Demands $r = 0.10$ (CVD group) Demands $r = -0.01$ (non-CVD group) Control $r = 0.02$ (CVD group) Control $r = 0.03$ (non-CVD group)
		Emeny et al. 2012 $N = 951$(66% males)	Job strain $r = -0.03$
IL-18	JDC	Emeny et al. 2013 $N = 1027$ (68% males)	Job strain $r = 0.08$ (CVD group) Job strain $r = -0.05$ (non-CVD group) Demands $r = 0.12$ (CVD group) Demands $r = 0.01$ (non-CVD group) Control $r = 0.04$ (CVD group) Control $r = 0.09$ (non-CVD group)
		Emeny et al. 2012 $N = 951$ (66% males)	Job strain $r = -0.03$
TNF	ERI	Bellingrath et al. 2009 104 females	ERI $r = 0.05$
		Bellingrath et al. 2010 $N = 55$ (62% female)	ERI $r = 0.11$ Overcommitment $r = 0.08$
	JDC	Schnorpfeil et al. 2003 $N = 324$ (84% males)	Control negatively associated with TNF*
INF- γ	JDC	Miyazaki et al. 2005 241 males	Not associated with social support Demands not associated
INF- γ: I-L4	JDC	Miyazaki et al. 2005 241 males	Positively associated with social support* Demands not associated
TNF: IL-10	ERI	Bellingrath et al. 2010 $N = 55$ (62% female)	ERI $r = 0.05$ Overcommitment $r = 0.08$
IL6: IL-10	ERI	Bellingrath et al. 2010 $N = 55$ (62% female)	ERI $r = 0.21^*$ Overcommitment $r = 0.08$

Note. *significant finding, (P) prospective design, *r* values for Bellingrath et al. 2009, 2010, 2013; Almadi et al. 2013; Mauss et al. 2015 were retrieved from the Eddy et al. (2016) meta-analysis where they had been transformed from the original measure of effect size

findings are evenly balanced with 10 of the 20 associations significant and suggest a positive association between increased workplace stress and circulating levels of CRP, especially when workplace stress is measured using the JDC model (7/11 significant associations). The exception is the Almadi et al. (2013) paper, which has the largest effect size, but suggests a negative relationship between ERI and CRP. It

is noteworthy that the large ($N = 4409$) prospective study reported that lower perceived justice was related to higher CRP and IL-6 in men, but not women (Elovainio et al. 2010).

The studies that assessed IL-6 include 2 significant associations out of the 17 comparisons with workplace stress, with the significant findings suggesting higher workplace stress is related with higher IL-6. Similarly, the relationship between workplace stress with TNF-α was weak with only one of the three papers reporting a positive association between variables.

While the findings suggest that most associations are weak and nonsignificant, the Eddy et al. (2016) meta-analysis of the relationship between ERI with cytokines and inflammatory markers suggests that when considered together, the result may be different. Specifically, the meta r from Eddy et al. (2016) was 0.08, $p = 0.04$, for these markers, suggesting that while the effect is small and only 2 out of the 13 individual associations rejected the null, when considered collectively, the association is significant.

Workplace Stress, Lymphocytes, and Leukocytes

In this review we located ten papers that assessed the relationship of workplace stress with leukocytes and lymphocytes (Table 2). Of the 18 markers used in these studies, most were studied on at least 2 occasions, with the exceptions being CD4%, CD8%, CD4 + CD45RA + %, lymphocytes%WBC, neutrophils%WBCC, and neutrophils/lymphocytes. Of these 82 associations, 19 were significant. Of the components of the workplace models, ERI was most likely to be associated with the lymphocyte and leukocyte markers with 5/16 (38%) negative associations. Next was job strain with 5/17 (30%) negative associations and then control 4/13 (30%), overcommitment 2/9 (22%), support 2/15 (13%), and, finally, demands 1/11 (9%).

Considered collectively, there are substantially more null than statistically significant associations, and these are generally small effects. The most promising associations between workplace stress and leukocytes and lymphocytes would appear to be natural killer cell cytotoxicity with four out of seven associations with components of the JDC and ERI models across two studies. The Bosch et al. (2009) study is the only study to concurrently assess more than one job stress model with measures of inflammation or immunity. The findings highlight that the way in which workplace stress is assessed impacts whether associations are significant or not, with demands and control not associated and with ERI and support positively and negatively associated, respectively, with CD27-CD28-%. Similarly, the CD4:CD8 data is negatively related with ERI and control but with support positively associated with the CD4:CD8 ratio.

Workplace Stress and Immunoglobulins

In this review we located eight papers that assessed the relationship between workplace stress and immunoglobulins (Table 3). Of the three markers used in these papers, only sIgA and IgG were studied on two occasions. The relationship

Table 2 Workplace stress, lymphocytes, and leukocytes

Marker	Stress model	Study	Effect size /findings
CD4 + (helper T cells)	ERI	Bellingrath et al. 2010 $N = 55$ (62% female)	ERI $r = -0.04$ Overcommitment $r = -0.11$
	JDC	Kawakami et al. 1997 65 males	Demands $r = -0.03$ Control $r = 0.15$ Job strain $r = -0.07$ Supervisor support $r = -0.16$
	JDC	Nakata et al. 2000 116 males	Lower in high strain group*
CD4 + %	JDC	Kawakami et al. 1997 65 males	Demands $r = -0.11$ Control $r = 0.05$ Job strain $r = -0.05$ Supervisor support $r = -0.01$
CD8 + (suppressor/cytotoxic T cells)	JDC	Kawakami et al. 1997 65 males	Demands $r = -0.00$ Control $r = 0.16$ Job strain $r = -0.13$ Supervisor support $r = -0.20$
	JDC	Nakata et al. 2000 116 males	No difference between high and low strain groups
CD + 8%	JDC	Kawakami et al. 1997 65 males	Demands $r = -0.00$ Control $r = 0.16$ Job strain $r = -0.13$ Supervisor support $r = -0.20$
CD4 + CD45RA+ (suppressor-inducer T cells)	JDC	Kawakami et al. 1997 65 males	Demands $r = 0.04$ Control $r = 0.01$ Job strain $r = 0.03$ Supervisor support $r = -0.22$
	JDC	Nakata et al. 2000 116 males	Lower in high strain group*
CD4 + CD45RA + %	JDC	Kawakami et al. 1997 65 males	Demands $r = 0.01$ Control $r = -0.05$ Job strain $r = 0.06$ Supervisor support $r = -0.14$
CD4 + CD29+ (helper-inducer T cells)	JDC	Kawakami et al. 1997 65 males	Demands $r = -0.21$ Control $r = 0.31^*$ Job strain $r = -0.04$ Supervisor support $r = 0.14$
CD4 + CD29+ %	JDC	Kawakami et al. 1997 65 males	Demands $r = 0.13$ Control $r = 0.29^*$ Job strain $r = -0.27^*$ Supervisor support $r = 0.15$
NKC	ERI	Bellingrath et al. 2010	ERI $r = -0.05$ Overcommitment $r = -0.16$

(continued)

Table 2 (continued)

Marker	Stress model	Study	Effect size /findings
		$N = 55$ (62% female)	
		Nakata et al. 2011 N = 1747 (89% females)	ERI $r = -0.22^{*}$ (males) ERI $r = -0.11$ (females) Overcommitment $r = -0.15^{*}$ (males) Overcommitment $r = -0.02$ (females)
	JDC	Nakata et al. 2000 116 males	No difference between high and low strain groups
	JDC	Miyazaki et al. 2005 142 males	Demands not associated Support not associated
NKCC	ERI	Nakata et al. 2011 $N = 1747$ (89% females)	ERI $r = -0.12^{*}$ (males) ERI $r = -0.16^{*}$ (females) Overcommitment $r = -0.01^{*}$ (males) Overcommitment $r = -0.04$ (females)
	JDC	Nakata et al. 2000 116 males	Job strain $r = 0.173$ Demands $r = 0.25^{**}$ Social support $r = 0.18$
B cells	ERI	Nakata et al. 2011 $N = 1747$ (89% females)	ERI $r = -0.02$ (males) ERI $r = 0.02$ (females) Overcommitment $r = -0.02$ (males) Overcommitment $r = 0.11$ (females)
	JDC	Nakata et al. 2000 116 males	No difference between high and low strain groups
T cells	ERI	Nakata et al. 2011 $N = 1747$ (89% females)	ERI $r = -0.09$ (males) ERI $r = -0.12$ (females) Overcommitment $r = -0.01$ (males) Overcommitment $r = -0.03$ (females)
	JDC	Nakata et al. 2000 116 males	Lower in high strain group*
	JDC	Miyazaki et al. 2005 142 males	Demands not associated Support not associated
WBCC	ERI	Mauss et al. 2015 $N = 3797$ (79.3% males)	ERI $r = 0.02$

(continued)

Table 2 (continued)

Marker	Stress model	Study	Effect size /findings
	JDC	(P) Shirom et al. 2008 $N = 1121$ (66% males)	Demands not prospectively related with WBCC Control negatively related for males* Control not related in women Social support not related with WBCC
		Nakata et al. 2000 116 males	Lower in high strain group*
CD4:CD8	ERI	Bosch et al. 2009 $N = 537$ (90% males)	ERI negatively associated*
	JDC	Bosch et al. 2009 $N = 537$ (90% males)	Demands not associated Control negatively associated* Support positively associated*
	JDC	Kawakami et al. 1997 65 males	Demands $r = -0.05$ Control $r = 0.00$ Job strain $r = 0.03$ Supervisor support $r = 0.02$
CD27-CD28-%	ERI	Bosch et al. 2009 $N = 537$ (90% males)	ERI positively associated*
	JDC	Bosch et al. 2009 $N = 537$ (90% males)	Demands not associated Control not associated Support negatively associated*
Lymphocytes % WBCC	OJ	Herr et al. 2015 353 males	No difference between high and low justice groups
Neutrophils % WBCC	OJ	Herr et al. 2015 353 males	No difference between high and low justice groups
Neutrophils/lymphocytes	OJ	Herr et al. 2015 353 males	No difference between high and low justice groups

*$p < 0.05$

of various factors within the ERI, JDC, and OJ models was compared with immunoglobulins on 18 occasions. In seven instances these associations were significant and highlight that while the research in this area is sparse when compared with workplace stress and leukocytes, lymphocytes, and markers of inflammation, the results are more consistent. The most researched immunoglobulin was sIgA, with six studies assessing the marker of mucosal immunity. Four of these studies used the ERI model, while the other two used the JDC model. ERI was related with lower

sIgA in two investigations with the other two investigations reporting no association. Likewise, the findings from the two investigations that used the JDC framework were mixed; only one study suggested higher workplace control was related with *reduced* sIgA.

Investigations of the relationship of job strain with IgG concentration report both increased (Nakata et al. 2000) and reduced (Theorell et al. 1990) concentrations. This is not unusual; however, Nakata et al. (2000) cited several studies that have reported increases, decrease, and no association of various immunoglobulins in response to increased chronic stress. Potentially, the findings may be moderated by the chronicity of the stressor.

Considerations

Before embarking on a discussion of how best to interpret the evidence we have collated, some key points need to be considered. The following points not only will assist in interpreting the research that has been collected in the area to date but will also be used by those who seek to investigate the association of workplace stress with immunity and inflammation in the future.

Table 3 Workplace stress and immunoglobulins

Marker	Stress model	Study	Effect size/findings
sIgA	ERI	Bathman et al. 2013 66 males	ERI $r = -0.47^{*}$ Overcommitment $r = -0.27^{*}$
		Wright 2011 $N = 98$ (56% females)	ERI $r = -0.22^{*}$ Overcommitment $r = -0.04$
		Eddy et al. 2018 74 males	ERI $r = 0.01$ Overcommitment $r = 0.01$
		Yu et al. 2008 50 males	ERI not related Overcommitment not related
	JDC	Wright 2008 $N = 98$ (56% females)	Demands $r = -0.17$ Control $r = 0.24^{*}$
		Yu et al. 2008 50 males	Demands not related Control not related Support not related
IgG	JDC	Theorell et al. 1990 $N = 50$, 78% males)	Job strain $r = -0.23$ Adequacy of social support $r = -0.54^{*}$ Availability of social support $r = -0.24$
		Nakata et al. 2000 116 males	Job strain $r = 0.20^{*}$
IgM	JDC	Nakata et al. 2000 116 males	Job strain $r = 0.18^{*}$

$^{*}p < 0.05$

Does Affect Carry the Effect?

Studies of the association between depression (Howren et al. 2009) and anxiety (Vogelzangs et al. 2013) with markers of immunity and inflammation also suggest associations between these constructs. The stress and coping model (Lazarus and Folkman 1984) suggests that it is not the stressor per se but rather the negative affect induced by the stressor that is responsible for ensuing ill-health. The consideration therefore is how, if at all, do negative affective states including depression and anxiety influence the relationship between chronic workplace stress and adverse physiological reactivity? Does it mediate the relationship as posited by the stress and coping model or is it that the relationship is moderated (amplified) in the subgroup of persons who report higher levels of negative affect? Unfortunately, the answers to these questions are not able to be answered at this point in time, but hopefully as researchers begin to assess these constructs both concurrently and prospectively, the underlying pathways from workplace stress to ill-health will be better understood.

Does "Level of Chronicity" Impact Findings?

As mentioned earlier in this chapter, there is good reason to suspect that the temporal location of when the physiological sample is taken from the period of chronic stress exposure may help explain the disparity that exists in the findings reported thus far. Specifically, the impact of HPA axis upregulation at the beginning of stress exposure results in downregulation of the immune and inflammatory response, but with HPA axis "exhaustion," we would expect an upregulation of the immune and inflammatory response. In short, those with chronic stress profiles are likely to have different immune and inflammatory profiles to those experiencing burnout. When these subgroups are not accounted for however, it is possible that a negative correlation for one subgroup may "cancel" the positive association of the other subgroup resulting in a false conclusion of no association between self-reported stress and physiological indices of immunity.

Much of the research has been cross-sectional in nature, and without consideration of the potential moderating impact of the duration or "chronicity" of the workplace stress, consequently it is difficult to tease apart these profiles. Considering both the self-reported and physiological indices of stress in combination may help to better identify subgroups of non-stressed, chronically stressed, and burned-out employees.

Functional Changes?

Although an association between high workplace stress with low concentrations (or counts) of the various immune and inflammatory markers may be statistically significant, in isolation, this information does not suggest that chronic workplace stress lowers immunity. Someone with the lowest or highest counts or concentration of a particular marker may not necessarily be outside the normal range for

that marker. In fact, even those that fall beyond these normal ranges (usually those in the top or bottom 2.5% in large normative data sets) may not represent an abnormal finding; after all, the entire sample was originally deemed "normal" and healthy.

It is also important to note that cell counts alone are not evidence of immune function. T-cell counts may be high in an individual, but the *functional* immune response may be dampened. For instance, in laboratory tests of functional immunity, T-cell function is measured by observing the response of the T cells to stimuli such as mitogens and antigens. These studies quantify T-cell proliferation and whether they produce cytokines. There are also a variety of other laboratory-based tests that assess the functionality of the immune and inflammatory markers described in this chapter, and interested readers are referred to Albert et al. (2018).

The final point in this section is that the cross-sectional approach used in most studies of the association of workplace stress with immunity does not allow for consideration of the *causal* association between workplace stress and lowered immunity. To infer a causal connection between A and B variables (i.e., A causes B), we need for A to occur before B, the dose of A to impact the magnitude of change in B (cross-sectional studies can't do this), and, finally, A to cause changes in B after controlling for other rival explanations.

Rival Explanations

Musculoskeletal injuries or infections may compromise the interpretation of the stress-immune/inflammation relationship. Traumatic injuries induce microcirculatory changes that involve the emigration of leukocytes and excessive amounts of pro-inflammatory mediators to the site. We have discussed earlier how the immune and inflammatory response is triggered by infection. Consequently, it's critical that researchers exclude participants who are unwell or injured. The problem, however, is that in the early stages of infection, for example, it is not always apparent to the individual that they are unwell. The same can be said for musculoskeletal injuries, with individual variations in what an individual would define as an "injury." In addition to exclusion, the researcher may also opt to statistically control for "health" based on self-reports from participants.

While both exclusion and statistical control of self-reports of health are useful, there is still likely to be some "noise" in the data, and this noise is amplified when research teams use disparate measures to account for health and injury. The different approaches to this problem impact the ability to synthesize the literature as the effect sizes are adjusted or not adjusted by covariates and exclusions. Moving forward, researchers should be prepared to give detailed information to participants on what constitutes exclusion, alongside clear definitions of injury and illness. It may also be prudent to follow up with participants at a short period post-collection to assess if they still fulfil inclusion criteria. In order to better articulate synthesis of findings across studies, researchers are also encouraged to report effect sizes for the associations they assess both with and without covariates.

Hits and Misses

There are various methods available to the researcher when seeking to identify measures of inflammation and immunity from the samples they collect. Traditionally enzyme-linked immunosorbent assay (ELISA) techniques have been used, and while this approach is still appropriate, new testing technology such as the SIMOA platform (Quanterix, Lexington, MA, USA) provides a higher level of precision for the detection of specific molecules (Rivnak et al. 2015). In essence, some markers of inflammation and immunity are harder to detect in blood than others and may be at an increased risk of imprecise reporting when using older technology. As newer testing methods become more viable and affordable, transitioning from ELISA to SIMOA testing may provide greater clarity on the underlying mechanisms between the association of workplace stress and lowered immunity. This argument is compelling given that the SIMOA technology has a 1000-fold greater sensitivity of detection of blood-based molecules compared with traditional assays (Fischer et al. 2015).

Cytokine Imbalance

Of the 15 studies that assessed the association of workplace stress with measures of inflammation, only 1 assessed cytokine imbalance. Cytokine imbalance refers to the ratio of pro-inflammatory to anti-inflammatory expression. A potential issue with assessing the pro- or anti-inflammatory markers in isolation may be best understood by the following example: When compared to the group, an individual is ranked high on both pro- and anti-inflammatory markers and is consequently categorized most "at risk." When the ratio is computed however, this individual is not "at risk"; it is more likely that those with lower or higher ratios are more at risk. Due to a dearth of data, there is little evidence to support this premise in the workplace stress literature. However, investigations of depression and cytokine expression are accumulating evidence in support of this prediction (Kim et al. 2007). Bellingrath et al. (2010) reported significant relationships between ERI and both anti-inflammatory (IL-6, $r = 0.30$) and pro-inflammatory (IL-10, $r = 0.30$) cytokines, but given the statements above, perhaps the most important finding was the relationship of ERI with the measure of cytokine imbalance (IL-6:IL-10, $r = 0.21$). Given these promising findings, future researchers are encouraged to compute measures of cytokine imbalance alongside standard measure of pro- and anti-inflammatory markers.

Conclusions

The aim of this chapter was to answer some key questions about whether workplace stress was related with markers of inflammation and immunity and, additionally, which specific workplace stress models were most associated with these markers. The results of the review reveal that inflammatory markers were most assessed (16 papers, 10 markers of inflammation), followed by leucocyte and lymphocyte

numbers (8 papers, 18 markers) and immunoglobulins (8 papers, 3 immunoglobulins). The JDC (ten papers, $N = 7028$), ERI (eight papers, $N = 4977$), and OJ (two papers, $N = 4744$) models were generally used to assess workplace stress followed by the JD-R model (one paper, $N = 119$).

The findings suggest that for the measures of inflammation, CRP was positively associated with workplace stress, especially when workplace stress was assessed using the JDC and OJ models. Other important findings in this section include the significant positive relationship between IL-6 and IL-10 with ERI.

The association of workplace stress with leukocytes and lymphocytes was quite diverse. While many markers of this branch of the immune system were collected, the overall N for each association was relatively modest as a majority of these associations were only assessed by ≤ 2 studies. Most of the findings suggested no association between variables, with the most promising markers being NKCC and CD4:CD8.

The immunoglobulins were the least researched markers of immunity, but each of sIgA, IgG, and IgM shared associations with workplace stress. sIgA was the most assessed and was associated with elements from both the JDC and ERI models. The small N precludes definitive conclusions on these associations, but given the large effect sizes and consistency of findings, these immunoglobulins appear to represent promising options for workplace stress researchers.

Considered collectively, workplace stress as measured by the JDC, ERI, and OJ models appears to be most related to CRP, NKCC, and sIgA. For the reasons outlined earlier, more research, preferably prospective in design, on the relationship of ERI with cytokine imbalance may also prove useful in understanding the pathways from workplace stress to ill-health.

In short, the understanding of the relationship between workplace stress with altered immune and inflammation factors is compromised by a literature largely cross-sectional in nature. Further factors inhibiting definitive conclusions include the disparate ways that workplace stress has been measured alongside the impact of injury, illness, and the duration of chronic stress upon markers of immunity and inflammation. A coordinated international effort coupled with more sophisticated research design will help to resolve many of these problems and assist in understanding if and how altered immune and inflammatory responses are associated with workplace stress and ill-health.

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