Chapter 3

Psychosocial Job Stress and Immunity: A Systematic Review

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Abstract

The purpose of this review was to provide current knowledge about the possible association between psychosocial job stress and immune parameters in blood, saliva, and urine. Using bibliographic databases (PubMed, PsychINFO, Web of Science, Medline) and the snowball method, 56 studies were found. In general, exposure to psychosocial job stress (high job demands, low job control, high job strain, job dissatisfaction, high effort–reward imbalance, overcommitment, burnout, unemployment, organizational downsizing, economic recession) had a measurable impact on immune parameters (reduced NK cell activity, NK and T cell subsets, CD4+/CD8+ ratio, and increased inflammatory markers). The evidence supports that psychosocial job stresses are related to disrupted immune responses but further research is needed to demonstrate cause–effect relationships.

Key words: Psychosocial job stress, Immune system, Psychoneuroimmunology, Systematic review, Work environment

1. Background

A poor psychosocial work environment has been linked with a broad array of adverse health outcomes. Studies have demonstrated that prolonged exposure to psychosocial job stress increases the risk for coronary heart disease (1–3), hypertension (4), immune-related disorders (5), musculoskeletal disorders (6), depression (7, 8), poor mental health (9), and stress-related disorders (10), as well as adverse health behaviors such as alcohol dependence, substance misuse, physical inactivity, poor sleep, and obesity (11–14). To elucidate the mechanisms responsible for these effects, researchers have explored the relationship between psychosocial job stress and the immune system, the body's chief defense against numerous diseases.

Qing Yan (ed.), *Psychoneuroimmunology: Methods and Protocols*, Methods in Molecular Biology, vol. 934,
DOI 10.1007/978-1-62703-071-7_3,

Psychoneuroimmunology (PNI) studies have shown that exposure to psychological stress is associated with a variety of immune indicators (15, 16). Stress is known to activate the sympathetic nervous system leading to changes in peripheral adrenaline and noradrenaline secretions, while a variety of endocrine factors such as cortisol, prolactin, and growth hormone are altered through the hypothalamic-pituitary function. The immune system receives signals from the central nervous system and endocrine system to respond and adapt to the stimuli, i.e., stress. If stress is manageable, it may promote adaptation. However, if stress is persistent and difficult to manage, it can lead over time to wear and tear on the body and brain, consequently causing multiple physiological dysfunctions, i.e., allostatic load (17). Psychosocial job stresses are often related to the latter, which may lead to irreversible or incurable health conditions if stress cannot be managed (18, 19).

This chapter contains a systematic literature review specifically focused on psychosocial job stress and the immune response. First, the types of psychosocial job stressors studied in this area are listed. Second, the immunological indicators generally selected for studies of the relationship between psychosocial job stress and immunity and the primary functions and roles of these parameters are explained. Third, evidence will be provided about how psychosocial job stress may alter immune responses.

2. Method

A systematic review of all English articles using PubMed, PsychINFO, Web of Science, and Medline was conducted to identify all observational studies assessing the association between psychosocial job stress and the immune system. References from relevant reviews and articles ("snowball method") were also scrutinized. The search terms included: *job stress*, *occupational stress*, *work stress*, *job strain*, *job control*, *job demands*, *workload*, *job satisfaction*, *effort–reward imbalance*, *overcommitment*, *unemployment*, *burnout*, *overwork*, *social support at work*, *supervisor support*, *and coworker support* in combination with the selected immunological markers: *lymphocyte*, *natural killer (NK) cell*, *helper T cell*, *cytotoxic T cell*, *CD4*, *CD3*, *CD8*, *CD25*, *CD27*, *CD28*, *CD29*, *CD45RA*, *CD45RO*, *immunoglobulin (Ig)*, *IgA*, *IgG*, *IgM*, *IgD*, *IgE*, *cytokine*, *interleukin*, *inflammation*, *C-reactive protein (CRP)*, *complement component* as well as more general immunological terms: *immune system*, *immune function*, and *immunity*. Studies were included in our review if they were studies of workers and had immunological outcomes using blood, saliva, or urine. Overall, 56 studies were identified for the period ending August 2011 and the sample sizes of these studies ranged from 25 to 1,563.

3. Results

A list of psychosocial job stress measures frequently used in PNI research is presented in Table 1. As shown in this table, a number of subjective and objective measures have been used to define job stress. Some measures derive from theory-based models and measure subjective feelings about the job. Job stress may be also be defined objectively by work environment changes such as unemployment, organizational downsizing, and economic recession. Most studies are based on subjective feelings (how employees perceive job stress) as a measure of stress.

Table 2 shows the examples of immune (-related) indicators frequently investigated in job stress research. As shown in this table, functional and quantitative aspects of immune markers are measured. NK cell activity (NKCA) and lymphocyte transformation tests are typical functional parameters while measurement of lymphocyte subsets, immunoglobulins, and cytokine concentrations are classified as quantitative parameters.

Tables 3, 4, and 5 as well as Tables 6, 7, and 8 present the summary of the studies reviewed. Tables 3, 4, and 5 present the possible associations between psychosocial job stressors and cellular immune markers while Tables 6, 7, and 8 summarize the relationships between psychosocial job stressors, humoral immune markers, and cytokine concentrations. If a study found a statistically significant relationship, the association was indicated in Tables 3, 4, 5, 6, 7, and 8 as a positive (↑) or negative (↓) association. If the study measured immune parameters but found no significant associations, it was stated as non-significant (NS). There were 46 cross-sectional and 10 prospective studies of which 49 studies used blood, six used saliva, and one used urine samples. There were 27 studies from Europe (Norway, Sweden, Finland, Netherland, Germany, Switzerland, Belgium, Italy, and UK), 19 studies from Asia (Japan, Korea, Malaysia, Singapore, and China), four studies from the Middle East (Israel), three studies from Oceania (Australia and New Zealand), and three studies from the US.

4. Discussion

4.1. Job Strain and Immunity

The job demands-control (JDC) model (hereafter referred to as the job strain model) is one of the most influential job stress models in occupational stress research. Because it is spare, practical, and testable, it has been widely adopted in occupational health studies. According to Karasek, a limited number of job-related psychosocial risk factors (job control/decision latitude and job demands) can be combined in a simple theoretical framework (job strain)

Table 1
List of psychosocial job stress measures frequently used in job stress research

	Type of job stresses
Subjective stress measures	Job demands (*job strain model*) Job control (*job strain model*) Job strain (*job demands/job control*) Effort (*effort–reward imbalance model*) Reward (*effort–reward imbalance model*) Overcommitment (*effort–reward imbalance model*) Social support at work (*job strain model*) Supervisor support (*job strain model*) Coworker support (*job strain model*) Workload (*NIOSH generic job stress model*, etc.) Variance in workload (*NIOSH generic job stress model*) Job dissatisfaction Role conflict (*NIOSH generic job stress model*) Role ambiguity (*NIOSH generic job stress model*) Mental/cognitive demands (*NIOSH generic job stress model*) Interpersonal conflict Skill underutilization (*NIOSH generic job stress model*) Burnout (*Maslach*, *Shirom*)
Objective stress measures	Unemployment Job insecurity Organizational downsizing/restructuring Economic recession Overtime/overwork

that can be an important determinant of worker health (20). Job control refers to employees' control over their tasks and how those tasks are executed, while job demands are psychological stressors (e.g., time pressure, conflicting demands, reaction time required, work amount, degree of concentration required, etc.) in the work environment. The job strain model postulates that job stress becomes highest when job demands are high and job control is low. A number of studies have demonstrated that job strain predicts coronary heart disease (3), stroke (21), type 2 diabetes (22), musculoskeletal pain (23), depression (7), sickness absence (24), and poor psychological well-being (25).

The job strain model is the most prevalent model used in studies of the psychosocial work environment and immunity and there are 12 studies reported to date (19, 26–36). One of the first studies that examined this relationship was from Sweden. In a sample of 49 workers with different occupations (air traffic controllers, waiters, physicians, etc.), Theorell et al. (1990) examined how job strain and workplace social support affected serum IgG levels and found

Table 2
Examples of immune (-related) indicators frequently used in job stress research

Indicators	Major roles/functions
Functional parameters	
Natural killer cell activity (NKCA)	NK cells are large granular cells possessing killer activity against certain tumor cells and virus-infected cells without prior sensitization. Reduced NKCA often indicates poor resistance to tumor cells and virus infected cells, leading to a higher cancer incidence and infection
Lymphocyte transformation test (mitogen stimulation)	A functional test of the ability of lymphocytes to respond to chemical substances called mitogens that encourage a cell to commence cell division triggering mitosis. There are several commonly used mitogens, i.e., phytohemagglutinin A (PHA), concanavalin A (ConA), and pokeweed mitogen (PWM); PPD (tuberculin), Candida antigen, and streptokinase-streptodornase. Lower value often indicates poor response to pathogens/antigens and reduced cellular immune function
CD4+/CD8+ ratio	An indicator for the status of the cellular immune system. The value depends on a balance of CD4+ and CD8+ T cells. The normal (non-clinical) range is between 0.60 and 220. Lower values are often found in HIV-infected patients and those with compromised immune system
Quantitative parameters	
Natural killer (NK) cells	Kill certain tumor and virus-infected cells. Lower counts may reflect poor resistance to tumor cells and virus-infected cells
B cells	Antibody (immunoglobulin, gammaglobulin) production. An extreme decrease of B cells is considered to be associated with suppression in production of immunoglobulins
T cells	Directly attack foreign antigens and regulate the immune system. An excessive increase of T cells is known to be associated with systemic inflammation, whereas a persistent decrease of T cells is related to immunodeficiency and psychological disorders such as depression
Cytotoxic T cells (CD8+)	Lysis of virus-infected cells, tumor cells, or allografted cells. Lower counts may reflect poor resistance to virus-infected cells and tumor cells
Helper T cells (CD4+)	Facilitate B cell proliferation and differentiation, immunoglobulin synthesis, assist cytotoxic T cells attacking antigens. An excessive increase in counts is associated with inflammation while a decrease of counts is found in HIV-infected patients
Memory T cells (CD4+ CD45RO+)	Subset of helper T cells that respond to previously encountered antigens. This cell can reproduce to mount a faster and stronger immune response than the first time the immune system responded to the antigens. Higher counts indicate inflammation while lower counts are often found in people exposed to hazardous chemical factors
Naive T cells (CD4+ CD45RA+)	Subset of helper T cells that have not yet encountered antigens. This cell responds to the newly encountered antigens and will turn into a reservoir of memory T cells

(continued)

Table 2 (continued)

Indicators	Major roles/functions
Immunoglobulin G, A, M (IgG, IgA, IgM)	Neutralize bacteria, viruses, and other environmental pathogens. Higher values may indicate primary infection or reactivation/reinfection to antigens
Interleukin (IL)-1	Proinflammatory cytokine primarily secreted by monocytes and macrophages. It stimulates B cells to produce antibody, NK cells to destroy foreign cells, resting T cells to produce more cytokines, and central nervous system to exert sickness behavior
Interleukin (IL)-4	Stimulates proliferation and differentiation of B cells into antibody-secreting cells
Interleukin (IL)-6	IL-6 is the major initiator of acute phase response by hepatocytes and a primary determinant of hepatic CRP production. It has both pro- and anti-inflammatory actions
Interleukin (IL)-10	Anti-inflammatory cytokine produced by T cells and inhibits the synthesis of IL-1 by macrophages and down-regulates expression of major histocompatibility antigens
Interferon (IFN)-γ	IFN-γ is primarily secreted by NK cells and T cells and has an ability to inhibit viral replication
Tumor necrosis factor (TNF)-α and -β	There are two types of tumor necrosis factors: TNF-α and TNF-β. TNF-β is cytotoxic against some tumors that can cause lysis and destruction of the cells. TNF-α stimulates the production of IL-6
Salivary IgA (s-IgA)	S-IgA is one of the antibodies that form a front line of defense in mucosal immunity and it is thought to be indicative of the functional status of the entire mucosal immune system. S-IgA deficiency represents a reduced level of protection for the body, and an increased risk of infection
C-reactive protein (CRP)	CRP is produced by the liver and the level of CRP rises when there is inflammation throughout the body. CRP rises up to 50,000-fold in acute inflammation, such as viral and bacterial infections. It has also been used as a very rough proxy for cardiovascular disease risk

that job strain was associated with an increase of serum IgG level but workplace social support attenuated its effect when job strain was at peak (33). This research group also examined the relationship between job strain and IgG and IgA in human service organizations, but failed to find significant associations between job strain and IgG or IgA (30). Studies from Japan and the Netherlands reported the relationship between job strain and lymphocyte subset counts (26–29). Among shift workers in the Netherlands, high job demands and high job control were related to decreases of CD4+ T cells and CD4+/CD8+ ratio (27). Three studies from Japan consistently reported that job strain was inversely related to counts of NK cells and CD4+ T cell subsets (26, 28, 29). More recent studies have focused on the relationship of job strain with inflammatory markers such as CRP, interleukin (IL)-6, tumor

Table 3
Association between psychosocial job stressors and cellular immune markers (functional markers)

First author	Country	Year	Sample (M/F)	Study design	Occupation	Exposure	NKCA	CD4+/ CD8+	LAA	LTT	Confounders
Arnetz	Sweden	1987	–/25W	L	Unemployed	Unemployment stress				↓	NM/NC
Arnetz	Sweden	1991	78M/246W	L	Blue-collar workers	Unemployment stress				↓	NM/NC
Endresen	Norway	1991	–/94W	CS	Bank employees	Job stress (communication, leadership, relocation, and workload)		NS		NS	NM/NC
Marriot	New Zealand	1994	45	CS	Meat factory workers	Unemployment stress		↓			NM/NC
Meijman	Netherlands	1995	24M/–	CS	Cargo handlers (shift workers)	High job demands		↓			NM/NC
Nakano	Japan	1998	45 (56) M/–	CS, CC	Taxi drivers vs. age-matched controls	Severe economic recession				↓	A
Nakamura	Japan	1999	42M/–	CS	Office workers	Burnout syndrome: Low personal accomplishments (LPA), high depreso-nalization (HD), high emotional exhaustion (HEE)	↓				A, Sm, Al, BMI

(continued)

Table 3
(continued)

First author	Country	Year	Sample (M/F)	Study design	Occupation	Exposure	NKCA	CD4+/ CD8+	LAA	LTT	Confounders
Lerman	Israel	1999	68M/111W	CS	Mixed population (69 postg raduate students, 48 laboratory technicians, 46 research associates, 16 other occupations)	Burnout syndrome: High total burnout (HTB), high emotional exhaustion (HEE), high chronic fatigue (HCF), high cognitive weariness (HCW)					S, A, Edu
Morikawa	Japan	2005	–/61W	CS	Nurses	High quantitative workload High conflict with physicians	↓				A
Di Donato	Italy	2006	40M/44W	CS	University and museum employees	Occupational stress	↓				NM/NC
Cohen	USA	2007	96M/104W	L	Unemployed	Unemployment stress (4 months)	↓				A, S, R, Ed, Sm, Med
Kawaguchi	Japan	2007	–/128W	CS	Nurses	High quantitative workload High variance in workload	↓				A, WkEx, WkSch, Sm
Okamoto	Japan	2008	59M/15W	CS	Emergency physicians	Overwork (long work hours)	↓				NM/NC
Boscolo	Italy	2009	88M/–	CS	University employees	High workload High job insecurity	↓				A, Sm, Al

Bosch	Germany	2009	478M/59W	CS	Factory workers	High effort Low reward High ERI High overcommitment Low job control High job demands	↓	A, S, Ms, Ed, Sm, Ex, Al, BMI, PC, Dp
Nakata	Japan	2010	165M/141W	CS	White-collar workers (trading and pharmaceutical companies)	Low job satisfaction	↓	A, Sm, Al, Ex, Edu, Sl, BMI, Med, Dep, Conf
Lee	Korea	2010	–/38W	L	Nurses	High objective stress High subjective stress	NS	A, Sm
Nakata	Japan	2011	165M/141W	CS	White-collar workers (trading and pharmaceutical companies)	Overtime (hours of overtime per month)	NS	S, A, Al, Ex, Edu, Sl, BMI, Med, Dp, Conf, Com, Occup, Jobsat
Nakata	Japan	2011	190M/157W	CS	White-collar workers (trading and pharmaceutical companies)	High effort Low reward High ERI High overcommitment	↓	A, Sm, Al, Ex, Edu, Sl, BMI, Med, Dp, Conf, Com, Occup, Caf

M men; *F* women; *CS* cross-sectional; *CC* case–control; *L* longitudinal; *ERI* effort reward imbalance; *NKCA* natural killer cell activity; *LTT* lymphocyte transformation test; *LAA* leukocyte adhesiveness/aggregation test; *A* age; *S* sex; *R* race; *Ed* educational level; *Ms* marital status; *Sm* smoking; *Al* alcohol consumption; *Ex* physical exercise; *Sl* sleep, *Anx* anxiety; *BMI* body mass index; *Med* medication usage; *Conf* interpersonal conflict at work; *BL* blood lead concentration; *HRT* hormone replacement therapy; *WkEx* work experience; *WkSch* work schedule; *PC* physical condition; *Occup* occupation; *Caf* caffeine intake; *Com* commuting time; *Jobsat* job satisfaction; *IC* income, *NM/NC* not mentioned or not controlled for
↓= decrease; ↑ = increase; NS = no significant change

Table 4
Association between psychosocial job stressors and cellular immune markers (NK, T and, B cells)

First author	Country	Year	Sample (M/F)	Study design	Occupation	Exposure	T cells	NK cells	B cells	Confounders
Endresen	Norway	1991	–/94W	CS	Bank employees	Job stress (communication, leadership, relocation, and workload)	NS			NM/NC
Marriot	New Zealand	1994	45	CS	Meat factory workers	Unemployment stress	NS	NS	NS	NM/NC
Kawakami	Japan	1997	76M/–	CS	Blue-collar workers (chemical company)	Low job control High job strain				A, Sm, BL
Nakamura	Japan	1999	42M/–	CS	Office workers	Burnout syndrome: Low personal accomplish-ments (LPA), high depresona-lization (HD), high emotional exhaustion (HEE)		↓		A, Sm, Al, BMI
De Gucht	Belgium	1999	17M/43W	CS	Nurses	High nursing stress	NS	NS		NM/NC
Nakata	Japan	2000	116M/–	CS	White-collar workers (power plant operators)	High job strain Low social support at work		↓		A, Sm
Bargellini	Italy	2000	39M/32W	CS	Physicians	Burnout: Low personal accomplishments (LPA), high depresonalization (HD), high emotional exhaustion (HEE)	↓			S, Sm, Occup, WkEx

Nakata	Japan	2002	231M/–	CS	White-collar workers (power plant operators)	Low job control				A, Sm, Al, Ex
Miyazaki	Japan	2003	98M/–	CS	Private company	Low social support		↓		A, Sm
Sakami	Japan	2004	71M/–	CS	Non-smoking firefighters	High quantitative workload	NS			A
Morikawa	Japan	2005	–/61W	CS	Nurses	High quantitative workload High conflict with physicians		NS		A
Miyazaki	Japan	2005	241M (142M)/–	CS	White-collar workers (manufacturing company)	High job demands combined with low social support at work	NS	NS		A, Al, Sm, Ex
Mommersteeg	Netherlands	2006	44M/50W 49 Cases/38 controls	CC	Participants recruited via websites	Burnout	NS	NS	NS	S, A, BMI matched (Med excluded)
Okamoto	Japan	2008	59M/15W	CS	Emergency physicians	Overwork (long work hours)		NS		NM/NC
Nakata	Japan	2010	165M/141W	CS	White-collar workers (trading and pharmaceutical companies)	Low job satisfaction		↓		A, Sm, Al, Ex, Edu, Sl, BMI, Med, Dep, Conf
Amati	Italy	2010	26M/75W	L	Nurses	Low job satisfaction	NS	↑	NS	NM/NC
Lee	Korea	2010	–/38W	L	Nurses	High objective stress High subjective stress	NS	NS	NS	A, Sm

(continued)

Table 4 (continued)

First author	Country	Year	Sample (M/F)	Study design	Occupation	Exposure	T cells	NK cells	B cells	Confounders
Bellingrath	Germany	2010	21M/34W	CS	School teachers	High ERI High over-commitment				A, Med, Dep, Sm
Nakata	Japan	2011	165M/141W	CS	White-collar workers (trading and pharmaceutical companies)	Overtime (hours of overtime per month)	NS	↓	NS	S, A, Al, Ex, Edu, Sl, BMI, Med, Dp, Conf, Com, Occup, Jobsat
Nakata	Japan	2011	190M/157W	CS	White-collar workers (trading and pharmaceutical companies)	High effort Low reward High ERI imbalance High overcommitment	NS	↓	NS	A, Sm, Al, Ex, Edu, Sl, BMI, Med, Dp, Conf, Com, Occup, Caf

M men; *F* women; *CS* cross-sectional; *CC* case–control; *L* longitudinal; *ERI* effort reward imbalance; *NKCA* natural killer cell activity; *LTT* lymphocyte transformation test; *LAA* leukocyte adhesiveness/aggregation test; *A* age; *S* sex; *R* race; *Ed* educational level; *Ms* marital status; *Sm* smoking; *Al* alcohol consumption; *Ex* physical exercise; *Sl* sleep; *Anx* anxiety; *BMI* body mass index; *Med* medication usage; *Conf* interpersonal conflict at work; *BL* blood lead concentration; *HRT* hormone replacement therapy; *WkEx* work experience; *WkSch* work schedule; *PC* physical condition; *Occup* occupation; *Caf* caffeine intake; *Com* commuting time; *Jobsat* job satisfaction; *IC* income; *NM/NC* not mentioned or not controlled for
↓ = decrease; ↑ = increase; NS = no significant change

Table 5
Association between psychosocial job stressors and cellular immune markers (CD4, CD25, CD27, and CD28 subsets)

First author	Country	Year	Sample (M/F)	Study design	Occupation	Exposure	Naïve CD4+ T cells	Memory CD4+ T cells	CD3+ CD25+ cells	CD4+ CD25+ cells	CD27+ CD28+ cells	CD27+ CD28- cells	CD27- CD28- cells	Confounders
Kawakami	Japan	1997	76M/–	CS	Blue-collar workers (chemical company)	Low job control High job strain		↓						A, Sm, BL
De Gucht	Belgium	1999	17M/ 43W	CS	Nurses	High nursing stress			NS	↑				NM/NC
Nakata	Japan	2000	116M/–	CS	White-collar workers (power plant operators)	High job strain Low social support at work	↓							A, Sm
Nakata	Japan	2002	231M/–	CS	White-collar workers (power plant operators)	Low job control		↓						A, Sm, Al, Ex
Bosch	Germany	2009	478M/ 59W	CS	Factory workers	High effort Low reward High ERI imbalance High overcommi tment Low job control High job demands					NS	↑	↑	A, S, Ms, Ed, Sm, Ex, Al, BMI, PC, Dp

M men; *F* women; *CS* cross-sectional; *CC* case–control, *L* longitudinal; *ERI* effort reward imbalance; *NKCA* natural killer cell activity; *LTT* lymphocyte transformation test; *LAA* leukocyte adhesiveness/aggregation test; *A* age; *S* sex; *R* race; *Ed* educational level; *Ms* marital status; *Sm* smoking; *Al* alcohol consumption; *Ex* physical exercise; *Sl* sleep; *Anx* anxiety; *BMI* body mass index; *Med* medication usage; *Conf* interpersonal conflict at work; *BL* blood lead concentration; *HRT* hormone replacement therapy; *WkEx* work experience; *WkSch* work schedule; *PC* physical condition; *Occup* occupation; *Caf* caffeine intake; *Com* commuting time; *Jobsat* job satisfaction; *IC* income; *NM/NC* not mentioned or not controlled for
↓ = decrease, ↑ = increase, NS = no significant change

Table 6
Association between psychosocial job stressors and immunoglobulins and complement components

First author	Country	Year	Sample (M/F)	Study design	Occupation	Exposure	IgG	IgM	IgA	s-IgA	Antibody titers	C3	C4	Confounders
Ursin	Norway	1984	38M/40W	CS	School teachers (W) Merchant navy students (M)	High job stress	NS	↓	NS			↓	NS	A, S, WkEx
Endresen	Norway	1987	–/34W	CS	Nurses	High psychological job stress Low job satisfaction	NS	↓	↑			↑		NM/NC
Theorell	Sweden	1990	39M/10W	CS	Various occupations (air traffic controllers, waiters, physicians, etc.)	Job strain	↑							NM/NC
Endresen	Norway	1991	–/94W	CS	Bank employees	Job stress (communication, leadership, relocation, and workload)	NS	NS	NS			NS	NS	NM/NC
Henningsen	USA	1992	–/40W	L	Nurses	Occupational stress				↑				NM/NC
Zeier	Switzerland	1996	158M/–	CS	Air traffic controllers	High work demands				↑				NM/NC
Ng	Singapore	1999	–/124W	CS	Nurses	High general stress				↓				NM/NC
Nakata	Japan	2000	116M/–	CS	White-collar workers (power plant operators)	High job strain	↑	↑	NS					A, Sm

Ohlson	Sweden	2001	8M/95W	CS	Human service organizations	High job strain	NS	NS			A, S, Ms, Ed, Sm, Al
Yang	Singapore	2002	–/132W	CS	Nurses	High professional stress		↓			Ms, WkEx
Herttig	Sweden	2002	–/31W	L	Nurses/medical secretaries	Downsizing Reorganization	↓				NM/NC
Clays	Belgium	2005	892M/–	CS	Various occupations (private companies, public administration, bank, insurance companies, hospitals)	Low social support			CV CP- HP-		A, Edu, Occup, Sm, BMI, Al, Med
Wright	Australia	2011	43M/55W	CS	Disability workers	Effort, ERI Overcommitment		↓			A
Masilaman	Malaysia	2011	52M/240W	CS	Teachers	High job strain Low social support		↓			NM/NC

M men; *F* women; *CS* cross-sectional; *CC* case–control; *L* longitudinal; *C3* complement component 3; *C4* complement component 4; *IL* interleukin; *IFN* interferon; *TNF* tumor necrosis factor; *TGF* transforming growth factor; *CRP* C-reactive protein; *hs* high sensitive; *ERI* effort reward imbalance; *A* age; *S* sex; *R* race; *Ed* educational level; *Ms* marital status; *Sm* smoking; *Al* alcohol consumption; *Ex* physical exercise; *Sl* sleep; *Anx* anxiety; *BMI* body mass index; *Med* medication usage; *Conf* interpersonal conflict at work; *BL* blood lead concentration; *HRT* hormone replacement therapy; *WkEx* work experience; *WkSch* work schedule; *PC* physical condition; *Occup* occupation; *Caf* caffeine intake; *Com* commuting time; *Jobsat* job satisfaction; *IC* income; *CV* cytomegalovirus; *CP Chlamydia pneumoniae*; *HP Helicobactor pylori*; *NM/NC* not mentioned or not controlled for
↓ = decrease, ↑ = increase, NS = no significant change

Table 7
Association between psychosocial job stressors and cytokines (IL-1β, IL-2, IL-4, IL-6, IL-10)

First author	Country	Year	Sample (M/F)	Study design	Occupation	Exposure	IL-1β	IL-2	IL-4	IL-6	IL-10	Urinary IL-8	Confounders
Nakano	Japan	1998	45 (56) M/–	CS, CC	Taxi drivers vs. age-matched controls	Severe economic recession		↓	↑				A
De Gucht	Belgium	1999	17M/43W	CS	Nurses	High nursing stress		NS					NM/NC
Theroell	Sweden	2000	102M/141W	CC	Case: Those who consulted caregiver Control: Age, sex matched controls	Low job satisfaction			↑W -M				A
Hemingway	UK	2003	168M/115W	CS	Civil servants	Low job control High job demands				NS			A, S
Sakami	Japan	2004	71M/–	CS	Non-smoking firefighters	High quantitative workload			NS				A
Miyazaki	Japan	2006	241M(142M)/–	CS	White-collar workers (manufacturing company)	High job demands combined with low social support at work			↑				A, Al, Sm, Ex
Mommersteeg	Netherlands	2006	44M/50W 49 Cases/38 controls	CC	Participants recruited via websites	Burnout					↑		S, A, BMI matched (Med excluded)
Fukuda	Japan	2008	–/118W	CS	Nurses	High nursing stress						↑	A

von Kanel	Germany	2008	55M/112W	CS	School teachers	Burnout syndrome: low personal accomplishments (LPA), high depresonalization (HD), high emotional exhaustion (HEE)			↓				S, A, AL, Sm, Sl, BP, Med, BMI, HR
Hintikka	Finland	2009	93M/132W 19 Cases/206 controls	CC, FU	General population without employment	Unemployment stress					↑		A, S, Ms, Ed, Sm, Ex, Al, BMI, PC, Dp
Amati	Italy	2010	26M/75W	L (12 mon)	Nurses	Low job satisfaction	↑				↑		NM/NC
Lee	Korea	2010	–/38W	L (8 mon)	Nurses	High objective stress High subjective stress	NS						A, Sm
Bellingrath	Germany	2010	21M/34W	CS	School teachers	High ERI High overcommitment		NS	NS	↑	↓		A, Med, Dep, Sm

M men; *F* women; *CS* cross-sectional; *CC* case–control; *L* longitudinal; *C3* complement component 3; *C4* complement component 4; *IL* interleukin; *IFN* interferon; *TNF* tumor necrosis factor; *TGF* transforming growth factor; *CRP* C-reactive protein; *hs* high sensitive; *ERI* effort reward imbalance; *A* age; *S* sex; *R* race; *Ed* educational level; *Ms* marital status; *Sm* smoking; *Al* alcohol consumption; *Ex* physical exercise; *Sl* sleep; *Anx* anxiety; *BMI* body mass index; *Med* medication usage; *Conf* interpersonal conflict at work; *BL* blood lead concentration; *HRT* hormone replacement therapy; *WkEx* work experience; *WkSch* work schedule; *PC* physical condition; *Occup* occupation; *Caf* caffeine intake; *Com* commuting time; *Jobsat* job satisfaction; *IC* income; *NM/NC* not mentioned or not controlled for

↓ = decrease, ↑ = increase, NS = no significant change

Table 8
Association between psychosocial job stressors and cytokines (IFN-γ, TNF-α, TGF-β) and inflammatory markers

First author	Country	Year	Sample (M/F)	Study design	Occupation	Exposure	IFN-γ	TNF-α	TGF-β	IFN-γ/L-4	TNF-α/ IL-4	TNF-α/ IL-10	CRP/ hsCRP	Confounders
Hemingway	UK	2003	168M/ 115W	CS	Civil servants	Low job control High job demands							NS	A, S
Grossi	Sweden	2003	–/63W 20 Cases/43 controls	CC	White-collar employees (social insurance offices)	Burnout syndrome		↑	NS				NS	A, BMI, HRT, Dep, Sm
Schnorpfeil	Germany	2003	272M/52W	CC	Airplane manufacturing plant	High job demands Low job control Low social support at work		↑					↑	A, S, Sm
Sakami	Japan	2004	71M/–	CS	Non-smoking firefighters	High quantitative workload	NS			NS				A
Shirom	Israel	2005	933M/630W	CS	Apparently healthy employees	Burnout syndrome							M–/ W↑	A, Sm, BMI, Ex, HDL, fasting glucose, BP, triglycerides, HRT, Dep, Anx
Shirom	Israel	2006	917M/622W	CS	Apparently healthy employees	Low job satisfaction							M↑/W-	A, BMI, Sm, Ex, HRT, Dep, Anx, HDL, fasting glucose, BP, triglycerides

Hamer	UK	2006	92M/– (non-smoking)	CS	Civil servants	High effort-reward imbalance				↑	A, BMI
Miyazaki	Japan	2006	241M (142M)/–	CS	White-collar workers (manufacturing company)	High job demands combined with low social support at work		↓			A, Al, Sm, Ex
Mommersteeg	Netherlands	2006	44M/50W 49 Cases/38 controls	CC	Participants recruited via websites	Burnout	NS				S, A, BMI matched (Med excluded)
Langelaan	Netherlands	2007	290M/–	CS	Managers	Burnout				NS	Sm, Ex
Sun	China	2007	634M/585W	CS	Various industries	High job strain				NS	A, S, Ed, M, AL, Sm, Ex
Shirom	Israel	2008	738M/383W	L (18 mon)	Apparently healthy employees	High workload Low perceived control Low social support at work				NS	A, S, Ed, Sm, Ex, BMI, Med, Dp, HRT (W)
von Kanel	Germany	2008	55M/112W	CS	School teachers	Burnout syndrome: Low personal accomplishments (LPA), high depresonalization (HD), high emotional exhaustion (HEE)	NS		↑	NS	S, A, AL, Sm, Sl, BP, Med, BMI, HR

(continued)

Table 8 (continued)

First author	Country	Year	Sample (M/F)	Study design	Occupation	Exposure	IFN-γ	TNF-α	TGF-β	IFN-γ/L-4	TNF-α/IL-4	TNF-α/IL-10	CRP/hsCRP	Confounders
Janicki-Deverts	USA	2008	1,093M/–	FU (5 years)	Various occupations (not reported)	Unemployment stress							↑	A, R, BMI, IC, Year 5 employment, Year 7 CRP
Hintikka	Finland	2009	93M/132W 19 Cases/206 controls	CC, FU	General population without employment	Unemployment stress							↑	A, S, Ms, Ed, Sm, Ex, Al, BMI, PC, Dp
Amati	Italy	2010	26M/75W	L (12 mon)	Nurses	Low job satisfaction	↑	NS						NM/NC
Lee	Korea	2010	–/38W	L (8 mon)	Nurses	High objective stress High subjective stress	NS	↓						A, Sm
Bellingrath	Germany	2010	21M/34W	CS	School teachers	High ERI High overcommitment		↑						A, Med, Dep, Sm

M men; *F* women; *CS* cross-sectional; *CC* case–control; *L* longitudinal; *C3* complement component 3; *C4* complement component 4; *IL* interleukin; *IFN* interferon; *TNF* tumor necrosis factor; *TGF* transforming growth factor; *CRP* C-reactive protein; *hs* high sensitive; *ERI* effort reward imbalance; *A* age; *S* sex; *R* race; *Ed* educational level; *Ms* marital status; *Sm* smoking; *Al* alcohol consumption; *Ex* physical exercise; *Sl* sleep; *Anx* anxiety; *BMI* body mass index; *Med* medication usage; *Conf* interpersonal conflict at work; *BL* blood lead concentration; *HRT* hormone replacement therapy; *WkEx* work experience; *WkSch* work schedule; *PC* physical condition; *Occup* occupation; *Caf* caffeine intake; *Com* commuting time; *Jobsat* job satisfaction; *IC* income; *NM/NC* not mentioned or not controlled for

↓ = decrease, ↑ = increase, NS = no significant change

necrosis factor (TNF)-α, and white blood cell (WBC) counts, as well as allostatic load indicators (19, 31, 32, 34, 35). Four out of five studies (19, 31, 32, 34) found that job strain was not related to these inflammatory markers. However, one study demonstrated that high job demands and low social support at work were significantly related to an increase of CRP while low job control was associated with elevated TNF-α (35). Hence, lymphocyte subsets appear to be a more sensitive immune marker to job strain than inflammatory markers.

4.2. Effort–Reward Imbalance and Immunity

In parallel to the job strain model which exclusively focused on the job task profile, Siegrist formulated the effort–reward imbalance (ERI) model (37, 38), which is known to hold a significant predictive power for adverse health outcomes (39, 40). This model postulates that job strain is not merely a product of employee efforts but results from an imbalance between the efforts spent and the rewards (money, career opportunities, esteem, respect, and job security) received. The model also considers a personal characteristic referred to as overcommitment. Overcommitment refers to a set of attitudes, behaviors, and emotions reflecting excessive endeavor in combination with a strong desire for approval and esteem. Reviews of the ERI model concluded that employees reporting overcommitment and exerting a high level of effort, but receiving a low level of rewards, may experience an increased risk of psychological and physical health disorders (39, 40).

To date, several studies have used the ERI model in relation to immune parameters (41–45). In a sample of 537 German factory workers (89% men), Bosch et al. examined the link between ERI measures and CD4+/CD8+ ratio and late-differentiated (CD27−CD28−) CD8+ cytotoxic T cells (41). They found that reduced rewards were associated with a significantly lower CD4+/CD8+ ratio, and decreased rewards and heightened ERI were related to increased relative proportion and counts of late-differentiated cytotoxic T cells, suggesting that exposure to such chronic stress may promote immunosenescence (aging of the immune system). A study of German school teachers (34 women and 21 men) examined whether high ERI and overcommitment modulate the immune response after exposure to acute/stressful experimental tasks (an extemporaneous speech followed by mental arithmetic) (42). Authors hypothesized that those who perceived high job stress may maintain a poor immune status but their immune system can also be vulnerable when confronted with novel/acute stressors. The results revealed that the high ERI stress group at baseline had lowered CD4+ T cells, NK cells, and IL-10, and elevated TNF-α and IL-6 compared to the low ERI stress group, but immune responses to the subsequent acute experimental task were somewhat different for the high and low stress groups. Both high and low stress groups showed an increment of CD4+ T and NK

cells but an increase of these cells in response to acute stress in the high stress group was dampened compared to the response of the low stress group. In addition, those under low stress had an increased secretion of anti-inflammatory (IL-10) cytokine and a decreased secretion of pro-inflammatory (IL-2) cytokine after exposure to acute stress but those with high stress showed an opposite reaction, i.e., a decrease of IL-10 and an increase of IL-2, after exposure to acute stressors. This means that the immune responses of those with low stress at baseline could flexibly respond to additional stress exposure but those under high stress may not have adaptable immune response. Another study with a similar experimental protocol demonstrated that the ERI score was significantly and positively associated with high-sensitivity (hs) CRP after exposure to acute mental stress in a sample of 92 healthy working men (43). More recently, a study of white-collar employees reported that the counts of NK cells were inversely associated with effort and ERI and positively associated with reward scores but not with overcommitment in men; the reward score was positively associated with NKCC and inversely associated with B cells (44). A study of disability workers (at adult training and support services and community residential units) in Australia reported on the relationship between ERI and salivary IgA (s-IgA) and found that reward was positively associated with s-IgA while the ERI ratio was inversely related to s-IgA, suggesting the impairment of the oral mucosal host defense system (45).

All in all, ERI, especially reward seems to be a significant indicator of reduced immune function but prospective studies are necessary to allow causal conclusions.

4.3. Social Support at Work and Immunity

Social networks and support have been associated with a broad range of physical and mental outcomes, including cardiovascular disorders (46), hypertension (47), depression (48), sleep disorders (11), and all-cause mortality (49). According to Kahn and Antonucci, social support is characterized by affective support (i.e., loving, liking, and respect), confirmation (i.e., confirming the moral and factual "rightness" of actions and statements), and direct help (e.g., aid in work, giving information or money) (50). These various aspects of social support are usually highly interrelated. Studies reported during the 1990s suggested that emotional and tangible social support is related to a better immune function (51). Among the clinical population, higher social support has been reported to be protective against stress-induced immunosuppression. For example, among ovarian cancer patients, social support was significantly correlated with NKCA even after adjusting for cancer stage (52). Similarly, among breast cancer patients, the perception of higher quality emotional support from a spouse or intimate other and perceived social support from the physician was associated with higher NKCA (53). Moreover, in several studies,

social support was found to be a significant predictor of CD4+ T cell counts among human immunodeficiency virus (HIV) positive patients (54–56). A review of 81 studies on the relationship between social support and physiological processes concluded that social support is reliably related to beneficial effects in the cardiovascular, neuroendocrine, and immune systems (57).

Although social support has been identified as a significant candidate for alleviating stress-induced immunosuppression, not many studies have explicitly focused on the effects of workplace social support on immune outcomes. In the job stress research field, social support at work is often measured with regard to the source of support, i.e., support from supervisors or support from colleagues, although in many cases the sources of support are combined into one variable. Using search engines, 11 studies were identified that examined the relationship between social support at work and immunity (26, 28, 29, 33, 34, 36, 41, 58–61). Among these reports, seven studies (28, 33, 36, 41, 58–60) found significant beneficial effects of workplace social support on immune indicators such as increased CD4+/CD8+ ratio (41), NK cells (59), CD8+ T cells (28), IL-4 (60), and reduced late-differentiated (CD27−CD28−) CD8+ cytotoxic T cells (41), IL-6 (58), IgG (33), and s-IgA (36). It is important to note that these findings are consistent with the biological significance of the link between social support and immunity.

4.4. Job Satisfaction and Immunity

Job satisfaction, defined as the degree of pleasure a worker derives from his/her job, is one of the most widely studied constructs in occupational health psychology (62). Job satisfaction can be considered to be a global feeling about the job or as a related constellation of attitudes about various aspects or facets of the job. The former is often called global or general job satisfaction and the latter is called facet job satisfaction (63). It is often used as a summary measure of worker well-being because it captures not only micro-level daily interactions on the job but also macro-level factors related to selection into a job (64). Given its popularity, there is a considerable amount of literature that links job satisfaction with various health measures including mental and physical health status (65), health behaviors (66, 67), and sickness absences (68–71). A comprehensive meta-analysis based on 485 studies of job satisfaction and health reported that workers with low levels of satisfaction were more likely to experience anxiety, burnout, depression, cardiovascular disease, musculoskeletal disorders, and other physical illnesses, indicating that reduced job satisfaction is an important predictor of physical and psychological health (65). Some previous reports revealed that job satisfaction was positively associated with well-being over time (72, 73). Therefore, job satisfaction could be a key psychosocial determinant of worker health and well-being.

The connection between job satisfaction and health is widely acknowledged as mentioned earlier, but such findings are mostly based on subjective health outcomes derived from questionnaires or through self-report, and have not often been investigated through objective outcomes, especially immune measures. To date, only a handful of studies have attempted to examine the effects of job satisfaction on immunity (31, 58, 74–76). For example, a study of Norwegian female nurses ($n = 34$) found that a sum of facet-specific job satisfaction consisting of comfort, challenge, financial rewards, relations with coworkers, and resource adequacy and promotions, was significantly associated with decreased circulating IgA and complement component C3 but not with IgG or IgM (74). A large cohort study in Israel (917 men and 622 women) reported that facet-specific job satisfaction was inversely correlated with CRP in men ($B = -0.20$, $p < 0.05$) but not in women ($B = -0.10$, $p > 0.05$) (31). In contrast, global job satisfaction was inversely correlated with serum interleukin (IL)-6 in women but not in men in a sample of Swedish working people (141 women and 102 men) (75). A prospective study of job stress and immunity among nurses (75 women and 26 men) found that those who had undergone a decrease in job satisfaction over a 1-year period had increased levels of IL-1β, IL-6, and CD8+ CD57+ T cells, and a decreased level of interferon (IFN)-γ (58). More recently, Nakata et al. reported the relationship between job satisfaction and NKCA and lymphocyte subsets (T, B, and NK cells) among 306 healthy white-collar employees (76). Global job satisfaction, as measured by a 4-item scale, was significantly associated with NKCA and NK cell counts in women and positively related to NKCA but not NK cell counts in men; no significant association between job satisfaction and T or B cells was found in the study.

Taken altogether, these studies suggest that greater job satisfaction may have a positive impact on immune outcomes. However, the findings need to be interpreted cautiously because most studies were based on cross-sectional designs with a limited number of participants in some studies. An interesting question for future research is whether greater job satisfaction contributes to recovery/maintenance of NK cell immunity and host defense over time.

4.5. Unemployment, Job Insecurity, Economic Recession, Organizational Downsizing, and Immunity

As a result of globalization, increasing competition, and long-lasting global economic recession, people who are working under insecure and casual employment are increasing. Corresponding to such labor market status, unemployment, downsizing, restructuring, reorganization, and merging have become a common trend in modern work life. The loss of one's job as well as working under insecure conditions is highly stressful because, for most employed adults, work is a central part of one's life and identity and a major

source of income (77). Studies of unemployment suggest that unemployment is not only related to future premature morbidity and mortality of unemployed individuals but is also known to be a threat of their families' health (78). Similarly, downsizing and restructuring are health risks not only for employees who lose their job, but also for those who remained in employment (79–81). As such, employees in insecure jobs are repeatedly found to have higher stress-related health problems because job insecurity involves both the threat of job loss and uncertainty regarding future employment (82, 83). Although a number of studies have found adverse effects of unemployment, job insecurity, and organizational restructuring on health (79–86), there are only a limited amount of studies that specifically focused on the relationship between unemployment, job insecurity, and the immune system (87–95).

One of the first studies that has dealt with unemployment and immunity was reported from Sweden (88). A study by Arnetz et al. evaluated the immunological impact of unemployment over a period of 12 months in women. In this study, two unemployment conditions (i.e., those who received traditional unemployment benefits only (Group A, $n=9$) and those who received the same benefits as Group A along with an opportunity to participate in a psychological program designed to counteract the negative psychosocial impact of unemployment and creating or finding new jobs (Group B, $n=8$)) were compared with a group of workers in stable jobs (Group C, $n=8$). At the 9- and 12-month follow-up periods (but not at 4- or 7-months), both unemployed groups had a significant decrease in their cellular immune response as measured by a lymphocyte transformation test, i.e., phytohemagglutinin A (PHA) and purified protein derivation of tuberculin (PPD), suggesting a functional decline of helper (CD4+) T cells. There were no significant differences between the groups regarding counts of lymphocyte subsets (CD4+, CD8+, NK, T, B, and total lymphocytes). The results indicate two important aspects of unemployment stress related to immunity. First, the effects of unemployment stress on cellular immune competence emerged after a period of time, even after a year, which indicates a long-lasting and time-lagged effect. Second, although it may largely depend on how psychological support was provided to the unemployed women in Group B, the effects of unemployment stress on immunity was not buffered by the psychological interventions used in this study. This research group later conducted a similar study of unemployment and immunity involving a larger sample of blue-collar workers ($n=354$, 75% women) with a longer follow-up period (2 years), and reported that unemployment was associated with a reduced response to PHA stimulation at the 12-month follow-up period but returned to baseline levels at the 20-month period (87). In the latter study, the authors have considered

whether locus of control and mastery (which measures self-control attitude, social support, work involvement, coping, mood, mental well-being, sleep, and depression) could modulate the impact of unemployment stress and concluded that coping style is the key factor that could modulate immune outcome against unemployment stress.

Another study that uncovered the relationship between unemployment and immunity has been reported from the United States using a case–control follow-up study design of 100 unemployed persons and 100 matched employed healthy controls followed over a 4-month period (91). This study design is unique in that 25% of the unemployed people were followed until they became re-employed, to determine whether re-employed people may be released from the unemployment stress that was anticipated to suppress immune function. As expected, those who were persistently unemployed had significantly lower NKCA compared to matched employed workers throughout all measurement occasions (months 1, 2, 3, and 4). However, those who were re-employed regained their NKCA levels by 44–72% within 1 month after reemployment, which were comparable NKCA levels to matched employed workers. The results indicate that the termination of the major stressor is an important factor in recovering NKCA. It is important to note that the difference in NKCA between the unemployed and employed was neither due to smoking status (because smokers were excluded from the analysis) nor percentage of NK cells in the blood. Taken together, the results showed unemployment stress seems to reduce the function of T and NK cells but not the counts of lymphocyte subpopulations.

The effect of unemployment stress on the immune system has also been tested in the context of inflammatory processes. Janicki-Deverts et al. examined whether unemployment history predicts future CRP levels among young working males in the United States (Coronary Artery Risk Development in Young Adults (CARDIA) study) (89). After controlling for age, race, BMI, baseline CRP, unemployment status (at year 5), and average income across the study period, baseline unemployment status was associated with an increase of CRP levels between 5 and 8 years later. More recently, Hintikka et al. compared the levels of IL-6 and hs-CRP between the unemployed and other study participants who consisted of 131 currently with jobs, 14 in sick leave, 52 retired, 3 students, and 6 voluntarily not working (90). Unemployment was associated independently with an increase of IL-6 in a sex- and age-adjusted linear regression analysis but the increase was attenuated after controlling for sex, age, marital status, economic hardship, education, smoking, alcohol consumption, somatic diseases, depression, and BMI, while hs-CRP was not related to unemployment. The prospective association between unemployment and these markers was weak but additional cross-sectional analyses

revealed that unemployment was associated with a fivefold greater odd for having an elevated inflammatory status. These findings may partly explain higher premature morbidity and mortality among involuntarily unemployed population.

With regard to job insecurity, Arnetz et al. examined the effects of different phases of unemployment, i.e., anticipation of job loss, actual job loss, and short- and long-term unemployment status with a lymphocyte transformation test using PHA (87). The study found that psychological stress was highest during the anticipatory phase although immunosuppression did not occur concurrently. Meanwhile, Boscolo et al. compared NKCA and lymphocyte subsets among workers with different levels of employment security and observed that young employees with a temporary/insecure employment status had a significantly reduced NKCA level compared to securely employed workers. However, no significant differences were found with regard to NK, T, and B cell subsets (93).

A study of Japanese taxi drivers evaluated the impact of the economic recession on the immune system using a case–control study design over 2 consecutive years (94). Immune responses to three different mitogens, PHA, concanavalin A (Con A), and Pokeweed mitogen (PWM) as well as levels of peripheral blood IL-2 and IL-4 levels were evaluated and compared between taxi drivers and age-matched controls in 1992 and 1993. In 1992, immune response to mitogens and cytokine levels were comparable between taxi drivers and controls (stably employed government researchers), however, in 1993, taxi drivers had significantly lower responses to mitogens as well as reduced IL-2 and increased IL-4 secretion. In 1992, there was no apparent economic recession, but in 1993 a major economic recession in Japan hit the taxi drivers drastically. The authors found that 76.4% of taxi drivers' income dropped from 1992 to 1993 whereas income in the control group increased from 1992 to 1993. The study also compared the immune responses of taxi drivers working under two different conditions: Those drivers who were permitted to work overtime (A-type) and those who were not permitted to work overtime (B-type). B-type taxi drivers exhibited a significantly lower response to all three mitogens and decreased IL-2 and increased IL-4 secretion than A-type taxi drivers. Because all taxi drivers' income was commission-based, a restriction of working time as in B-type condition, these drivers may find it difficult to attain a desirable income. In contrast, the A-type condition may have more flexibility in earning and control over time, which resulted in lower work-related stress levels in A-type drivers. In this case, it is notable that lower demands were associated with higher stress leading to immunosuppression suggesting that lower control over work demands resulted in increased stress levels.

There is one study which investigated the effects of organizational downsizing and reorganization on the immune response (95). Hertting and Theorell reported that after a reduction of 20% in personnel in the health care sector ($n = 31$, 80% nurses) during 1995–1997, serum IgG was significantly decreased in 1998 compared to 1997. The authors concluded that as a result of a long-lasting adaptation process, a flattened circadian cortisol rhythm may have contributed to physiological dysfunction leading to an inhibited IgG level.

On balance, these studies revealed that the objective work environment as represented by unemployment, job insecurity, economic recession, and restructuring/downsizing is a potentially significant factor that lead to deterioration in the immune system, which may help explain premature morbidity and mortality in workers who had undergone such events.

4.6. Burnout and Immunity

Burnout is a chronic affective state characterized by persistent exhaustion, cynical work attitude, diminished competence, reduced energy, increased irritability, impaired sleep, and concentration problems that can occur irrespective of the type of profession (96). According to Maslach and Jackson, burnout consists of three main interrelated concepts, i.e., emotional exhaustion, depersonalization (cynicism), and reduced personal accomplishments, none of which overlap with any other concepts such as depression or anxiety, and which is conceptually distinct from a temporary state of fatigue (97). Burnout has been considered as an independent risk factor for mental disorders such as depression (98–100) as well as physical disorders, i.e., cardiovascular disease (101, 102), type 2 diabetes (103), and gastroenteritis (104). It is also considered as a strong risk factor of prolonged sickness absences (105–107) that may be connected with loss of productivity.

As burnout is a result of chronic work-related stress, occupational health researchers have explored the psychophysiological mechanisms of burnout. Several researchers have specifically focused on the immune responses to burnout and a total of eight studies have been reported to date (108–114). Bargellini et al. reported that physicians with low scores on personal accomplishment (which is one of three subcomponents of burnout) showed significant decreases in total lymphocytes, CD3+ T, CD4+ T, and CD8+ T cells as compared with physicians with higher scores (108). Nakamura et al. used the Maslach Burnout Inventory (96) among male office workers and found that depersonalization but not personal accomplishment or emotional exhaustion was inversely associated with NKCA (110). A study by Lerman et al. used a leukocyte adhesiveness/aggregation test as a non-specific marker of inflammation and reported that university employees with high burnout symptoms showed an increased leukocyte adhesiveness/aggregation (111). They also reported that subcomponents

of burnout, i.e., emotional exhaustion, chronic fatigue, and cognitive weariness, were all significantly associated with leukocyte adhesiveness/aggregation. More recently, researchers have started to focus on the relationship between burnout and inflammatory cytokines/proteins because accumulating evidence suggests a direct relationship between burnout and arteriosclerotic diseases (115). In a large sample of healthy men and women, Toker et al. found that burnout was positively associated with hs-CRP in women but not in men (112). In contrast, no significant difference in CRP was found between burned-out employees and a control group among managers of a Dutch Telecom Company (114). In white-collar female employees in Sweden, those participants with high burnout exhibited higher plasma levels of TNF-α than counterparts with lower burnout scores but there were no significant differences in CRP and TNF-β levels between the two groups (113). Among school teachers in Germany, higher levels of total burnout symptoms were associated with a lower level of IL-4 and higher TNF-α/IL-4 ratio while lack of accomplishment was associated with diminished IL-4 and heightened TNF-α/IL-4 ratio (116). In more severe cases of burnout, Mommersteeg et al. reported that the burnout group had an increased production of anti-inflammatory cytokine IL-10 released by monocytes but not by T cells (109). The study did not find significant differences between the burnout group and healthy controls with regard to proinflammatory cytokines gamma interferon and TNF-α or counts of T, B, and NK cells.

In sum, burnout seems to be associated with immune parameters to some extent but further explorations are needed to find robust and sensitive immune markers for burnout.

4.7. Other Psycho-Social Job Stress and Immunity

Apart from job strain and ERI models, earlier studies have focused on certain type of jobs that were considered to be inherently stressful such as air traffic controllers (117), teachers (118), nurses (74, 119–122), and bank employees (123). Several studies focused on s-IgA (117, 119–121) and other studies focused on serum/plasma immunoglobulin G, A, and M (33, 74, 118). However, the associations between psychosocial job stress and the immunoglobulin markers were inconsistent between these studies. With regard to s-IgA, for example, Zeier et al. found that exposure to job stress caused increased s-IgA among air traffic controllers (117). In contrast, two studies in nurses reported a decrease of s-IgA due to a high nursing stress (120, 121), while in an 8-month longitudinal study, nurses with higher objective stress showed consistently higher s-IgA than their lower stress counterparts (124). The relationship between job stress and serum/plasma immunoglobulin levels seems also to be contradictory. Some studies reported that job stress increases IgG (28, 33), IgM (28), or IgA (74) levels,

while other studies suggested that job stress reduces IgG (95) or IgM (74, 118) levels, or impact on IgG and IgA levels (30).

With regard to cellular immunity, eight studies have reported on the relationship between psychosocial job stressors and lymphocyte subsets and NKCA. Two studies from Italy reported that university employees with high levels of occupational stress, high anxiety levels, and job insecurity had reduced NKCA (93, 125). Among Japanese physicians, overwork was associated with decreased NKCA and CD4+ T cell counts (126). Similarly, two studies of Japanese nurses reported that high quantitative workload and frequent conflict with physicians were inversely associated with NKCA (127), while high quantitative workload and high variance in workload were inversely correlated with NK cell counts (61). A study which focused on overtime (amount of time beyond normal working hours) and cellular immunity reported that overtime was inversely associated with a decrease in NK cell counts in white-collar male and female workers (128). However, there are several studies that found an insignificant relationship between quantitative workload and cellular immune indicators. A study in an electric equipment manufacturing company reported that quantitative workload and mental demand was not independently related to counts of CD3+ T, CD4+ T, and CD8+ T cells among male employees (129). Similarly, no direct association between quantitative workload and T or NK cell counts were found in male white-collar workers (60). Inconsistent findings in these studies may be related to differences in intensity and length of stress exposures (acute vs. chronic), timing of blood sampling, differences in psychosocial job stress instruments used, and confounding factors considered.

Regarding urinary immune indicators, a study focused on nurses compared the level of urinary IL-8 between acute and chronic care (control group) departments and found that those in the acute care department exhibited higher stress and increased urinary IL-8 compared with the control group (130). Because urine sampling is non-invasive and painless, authors concluded that urinary IL-8 may be a convenient immune marker for stress assessment among nurses.

5. Future Directions and Conclusions

The relationship between psychosocial job stress and immunity has only been explored during the past few decades, and is therefore still in a developing phase within the discipline of PNI. In consideration of this fact, future studies should elaborate on the following

methodological shortcomings. First, to strengthen the cause and effect relationship, prospective studies with multiple waves are needed. As listed in Tables 3, 4, 5, 6, 7, and 8, most investigations have been based on cross-sectional or case–control study designs. Although some studies used a prospective approach, they suffer from small sample sizes or high dropout rates, which make it difficult to generalize the results. Second, a number of confounding factors need to be taken into account in future studies. In earlier studies, confounders which modify dependent and independent variables, such as sociodemographic (age, sex, race, education, etc.) factors, health behaviors (smoking, sleep, alcohol consumption, exercise, caffeine, diet, etc.), physical/mental health status (comorbid disorders, body mass, etc.), and medication usage (antihypertensive or anti-depressive drugs, oral contraceptive use, etc.) are not always taken into account. It is also true that the immediate state before the blood sampling, i.e., how long participants slept the night before, timing (morning vs. night, beginning or end of the weekday) and condition (fasting vs. non-fasting blood sampling), menstrual cycle (women), and other exposures related to work (hazardous substances, radiation, etc.) need to be considered since they can have a direct impact on immune measurements. Third, it is essential to use well-established job stress measures with high validity and reliability; it is also important to use measures which cover various and broad aspects of working conditions. Stress measures should be carefully selected because some job stress measures may not be suitable for certain groups, occupations, and jobs. Fourth, immune indicators which measure both functional and quantitative aspects may be useful to measure systemic immune response to job stress. It is also desirable to find sensitive non-invasive (saliva or urine) measures that reflect job stress. These issues should be considered when one is designing a study regarding job stress and immunity.

In this review, we find that job stressors are associated with various immune parameters indicating disrupted immune functioning. The relationship between job stress and NK cell immunity was found to be robust but the relationships with other immune markers were less clear cut because of methodological issues raised above. A continued effort is needed to establish a cause and effect association between job stressors and immunity.

Acknowledgements

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the US National Institute for Occupational Safety and Health.

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