Available online at www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2015; 7(1): 15-22

ISSN- 0975 1556

Research Article

Health Burden of Job Stress among Junior Resident Doctors

Metwally F.M. [1], *Mahdy E.M.E.* [2], *Ahmed H.H.* [*3], *Abdul-Rahman M.A.*[2]

[1]*Enviromental and Occupational Medicine Department, National Research Centre, Egypt.*
[2]*Chemistry Department, Faculty of Science, Helwan University, Egypt.*
[3]*Hormones Department, National Research Centre, Egypt.*

Available Online: 1st January, 2015

ABSTRACT
The goal of the present study was to elucidate the impact of job stress on some biochemical indices of junior resident doctors at Ain Shams University Hospitals. Forty-eight junior resident doctors at Ain Shams University Hospitals (28 males and 20 females) in four departments (Obstetrics & Gynecology, Neurosurgery, Urology and Cardiolgy) as a case group and twenty-four non-resident doctors (11 males and 13 females) as a control group were enrolled in the current study. The choice of departments was on the bases of high job stress according to number of work hours/week. The participants ranged from 26 to 28 years of age with a mean of 27 years. Serum levels of cortisol, immunoglobulin G (IgG), highly-sensitive c-reactive protein (CRP-hs), cholesterol (Chol), triglycerides (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) were estimated for all participants. The results showed that serum cortisol, IgG, CRP-hs, Chol, TG, and LDL were significantly higher in junior resident doctors, while HDL was significantly lower in junior resident doctors when compared with junior non-resident doctors. The present study shed light on the health hazards of job stress due to increasing working hours among junior resident doctors.
Key words: Job stress; Resident doctors; Stress hormone; Inflammation; Lipid profile.

INTRODUCTION

Job stress can be defined as a situation where stressors (events or conditions in the work environment which have the capacity to result in stress) and stress responses (the individual's responses to a stressor that are deemed harmful to themselves) are present. The person–environment fit theory proposes that stress results from demands (e.g. difficulty of the job) that the person may not be able to meet[1]. However, according to Karasek's job demands-control model of job stress, the ability to control one's working environment is a confounding factor, and stress is most typically found when low control is combined with heavy job demands[2].

According to the UK Health and Safety Executive, a total of 13.8 million working days were lost to work-related stress, depression and anxiety[3]. Following a staff survey conducted by the UK Healthcare Commission, 33% of workers claimed to have felt unwell because of work-related stress. Furthermore, it was estimated that the job stress costs £300–£400 million per year[4].

Research into job stress in resident doctors working in hospitals indicates that this phenomenon is alarmingly widespread[5]. The first year practicing medicine is recognized as having high demands (degree of responsibility and task difficulty)[6], low control (decision authority and skill discretion), high effort (pace of work and physical and mental load), frequent stressful events[7] and novelty.

In general with regard to emotional outcomes[8&5] found that resident doctors displayed high levels of psychological distress and psychiatric morbidity as a result of job stress. Birch et al.[9] also reported high levels of stress in first year doctors as indicated by the proportion of doctors scoring on the anxiety subscale and depression scale[10].

In a study of 115 post-graduate doctors in their first 3 years of practicing, not only found that 76% met the criteria for burnout (a syndrome of depersonalization, emotional exhaustion, and a sense of low personal accomplishment.) but that there was also a strong association with burnout and self-reported suboptimal patient care[11].

The aim of this study was to investigate the insult of job stress on serum levels of some biochemical indices such as cortisol, immunoglobulin G (IgG), highly-sensitive C - reactive protein (CRP-hs), cholesterol (Chol), triglycerides (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) in resident doctors at Ain Shams University Hospitals.

Subjects and Methods

Forty-eight junior resident doctors at Ain Shams University Hospitals (28 males and 20 females) in four departments (Obstetrics & Gynecology, Neurosurgery, Urology and Cardiology) as a case group, and twenty-four non-resident doctors (11 males and 13 females) as a control group were participated in the present study. Choice of departments was on the bases of high job stress according to number of work hours/week. The participants ranged from 26 to 28 years of age with a mean of 27 years. Information was gathered on the participants' medical history, and participants were excluded if they had a history of psychological morbidity. The exclusion criteria

**Author for Correspondence*

Table 1: Comparison between the studied groups (case and control) as regards to demographic characteristics

	Case (N=48)	Control (N=24)	Test of sig.	P value
Age (years)	26.4±0.7	26.5±0.6	t=1.417	0.161 NS
Weight (Kg)	70.7±10.1	70.3±7.4	t=1.880	0.851 NS
Working hours/week	108.5±15.4	56.0±0.0	t=23.59	<0.001 HS
Sex				
Female	20 (41.7%)	13 (54.2%)	χ^2=1.00	0.316 NS
Male	28 (58.3%)	11 (45.8%)		

t=Independent t-test χ2=Chi square test NS=Non-significant HS=Highly significant

Table 2: Comparison between the different departments as regards to demographic characteristics

	Obstetric & Grnecology (N=12)	Cardiology (N=12)	Urology (N=12)	Neurosu-rgery (N=12)	Test of sig.	P value
Age (years)	26.7±0.4	26.2±0.4	26.6±0.8	26.6±0.6	F=1.6	0.198NS
Weight (Kg)	64.0±13.6	68.5±4.7	75.5±3.7	74.8±10.9	F=4.1	0.011 S
Working hours/week	125.9±0.3	84.1±0.3	112.1±0.3	112.0±0.0	F=5.917	<0.001HS
Sex						
Female	6 (50.0%)	5 (41.7%)	6 (50.0%)	3 (25.0%)	χ^2=2.057	0.561NS
Male	6 (50.0%)	7 (58.3%)	6 (50.0%)	9 (75.0%)		

F=ANOVA test χ2=Chi square test NS=Non-significant S=Significant HS=Highly significant

Table 3: Comparison between the studied groups (case and control) as regards to laboratory investigations

	Case (N=48)	Control (N=24)	Test of sig.	P value
Cortisol (µg/dl)	12.6±5.1	10.5±1.5	t=2.610	0.011 S
			χ^2=0.000	1.000 NS
IgG (mg/dl)	1331.9±86.5	1187.3±172.3	t=4.759	<0.001 HS
			χ^2=0.000	1.000 NS
CRP-hs (mg/l)	2.9±3.0	1.7±0.8	t=2.414	0.019 S
			χ^2=7.200	0.007 S
Cholesterol (mg/dl)	214.2±39.1	193.5±47.7	t=2.551	0.030 S
			χ^2=1.125	0.289 NS
Triglycerides (mg/dl)	107.4±38.3	69.3±13.5	t=6.174	<0.001 HS
			χ^2=3.273	0.070 NS
HDL (mg/dl)	50.5±7.3	54.5±7.1	t=2.211	0.030 S
			χ^2=1.029	0.310 NS
LDL (mg/dl)	146.9±40.1	125.2±42.5	t=2.127	0.037 S
			χ^2=0.000	1.000 NS

t=Independent t-test χ2=Chi square test NS=Non-significant S=Significant HS=Highly significant

included regular medication, recreational drug abuse, smokers or pregnant females. On recruitment, participants were provided with an information sheet, in addition to verbal information, to allow time to reflect prior to participating in this work. The protocol was approved by the Ethical Committee for medical research of the National Research Centre, Dokki, Giza, Egypt. Each participant in the two groups was subjected to full personal, occupational environmental and medical history with special emphasis on age, sex, weight, department, working hours/week and medical questionnaire about general health. Fasting blood sample was withdrawn from each participant on EDTA free centrifuge tubes, left to clot and then centrifuged at 1800 xg for separating serum.

Serum cortisol level was measured by ELISA method according to Check et al.[12]. Serum IgG level was estimated by turbidimetry method[13]. CRP-hs level was assayed using nephelometry[14]. Serum cholesterol (Chol) level was determined by enzymatic method according to Meiattini et al.[15]. Serum triglycerides (TG) level was measured by enzymatic method according to Fossati and Prencipe[16]. Serum HDL level was estimated by enzymatic method according to Burstein et al.[17]. Serum LDL level was quantitified enzymatically according to the method of Assmann et al.[18].

Statistical analysis

The results were computed and statistically analyzed using SPSS (Statistical Package for the Social Sciences) package system version 17.0. The quantitative results were expressed as means ± standard deviation (Mean ± SD) for normal distributed results, and as range and median for quantitative results with skewness. Qualitative results were

Table 4: Comparison between the different departments as regards to laboratory investigation

	Obstetric & Gynacology (N=12)	Cardiology (N=12)	Urology (N=12)	Neurosurgery (N=12)	Test of sig.	P value
Cortisol (µg/dl)	19.7±0.8	5.8±0.7	11.2±1.1	13.7±1.0	F=483	<0.001^{HS}
					χ^2=0.00	1.000^{NS}
IgG (mg/dl)	1221.0±36.9	1040.5±39.5	1186.5±40.0	1079.5±58.3	F=44.4	<0.001^{HS}
					χ^2=0.00	1.000^{NS}
CRP-hs (mg/l)	4.8±4.5	1.1±0.7	1.7±0.4	3.9±2.7	F=5.251	<0.001^{HS}
					χ^2=16.00	<0.001^{HS}
Cholesterol (mg/dl)	278.5±15.3	172.0±2.5	191.9±2.4	203.1±7.5	F=343	<0.001^{HS}
					χ^2=35.20	<0.001^{HS}
Triglycerides (mg/dl)	162.0±29.3	69.9±5.6	88.1±10.0	109.5±8.0	F=72.2	<0.001^{HS}
					χ^2=20.57	<0.001^{HS}
HDL (mg/dl)	41.5±2.7	56.0±4.7	52.0±5.7	52.5±6.2	F=18.6	<0.001^{HS}
					χ^2=6.26	<0.001^{HS}
LDL (mg/dl)	212.1±14.7	102.0±6.3	115.8±3.4	127.7±7.4	F=365.6	<0.001^{HS}
					χ^2=48.00	<0.001^{HS}

F=ANOVA test χ2=Chi square test NS=Non-significant HS=Highly significant

expressed as number (N) and percent (%). The used statistical tests were independent t-test for comparing the normal distributed quantitative results between the two groups and analysis of variance (ANOVA) for more than two groups. Likelihood ratio was used for comparing the qualitative results and Pearson's correlation coefficient was used to find out the statistical associations between the different quantitative variables. If the SD was more than 25% of the means, the non-parametric measures were used in form of Mann-Whitney U test for comparing the quantitative results between two groups, Kruskal Wallis test was used for comparing the quantitative results between more than two groups. Statistical analysis was considered to be significant at P-value <0.05.

Table 5: Correlation between working hours and weight, serum cortisol, IgG, CRP-hs, Chol, TG, HDL and LDL levels in the studied groups.

	Case group	
	r	P value
Weight	-0.053	0.721 ^{NS}
Cortisol	0.936	<0.001 ^{HS}
IgG	0.636	<0.001 ^{HS}
CRP-hs	0.423	0.002 ^{S}
Cholesterol	0.813	<0.001 ^{HS}
Triglycerides	0.785	<0.001 ^{HS}
HDL	-0.285	0.049 ^{S}
LDL	0.773	<0.001 ^{HS}

r=Pearson correlation NS=Non-significant S=Significant HS=Highly significant

RESULTS

Table (1) shows that working hours were significantly higher (P< 0.001) in case group compared to the control group. Both case and control group were homogenous for age, weight and gender.

Table (2) shows that working hours were significantly the highest in Obstetrics & Gynecology department group and significantly the lowest in Cardiology department. Different groups were homogenous for age and gender but not for weight.

Serum cortisol (P = 0.011 S), CRP-hs (P = 0.019 S), Chol (P = 0.030 S), and LDL (P = 0.037 S) levels showed significant increase in case group when compared to the control group (Table 3). Serum IgG and TG levels revealed highly significant elevation (P< 0.001 HS) in case group when compared to the control group. Meanwhile, serum HDL level showed significant decline (P= 0.030 S) in case group as compared to the control group.

Serum cortisol, IgG, CRP-hs, Chol, TG and LDL levels showed the highest significant elevation in Obstetrics & Gynecology department group while, they showed the lowest significant elevation in Cardiology department group (Table 4). However, serum HDL level revealed highest significant reduction in Obstetrics & Gynecology department group and the lowest significant reduction in Cardiology department group (Table 4).

Significant positive correlation was demonstrated between working hours and serum cortisol level in both control group r= 0.932 and case group r=0.936 and P value in both groups was <0.001 (HS). Similarly, working hours showed significant positive correlation with serum IgG level in both control group r= 0.751 and case group r= 0.636 and P value in both groups was < 0.001 (HS). Also, significant positive correlation was found between working hours and serum CRP-hs level in both control group r= 0.427 and case group r= 0.423 and P value in control group was 0.037 (S) and in case group was 0.002 (S). Moreover, working hours exihibited significant positive correlation with serum chol level in both control group r= 0.850 and case group r=0.813 and P value in both groups was <0.001 (HS). Furthermore, working hours revealed significant

positive correlation with serum TG level in both control group r= 0.939 and case group r =0.785 and P value in both groups was < 0.001 (HS). Finally, working hours displayed significant positive correlation with serum LDL level in control group r=0.848 and case group r= 0.773 and P value in both groups was < 0.001 (HS). In constrat, significant negative correlation was recorded between working hours and serum HDL level in both control group and case group r=- 0.285 and P value in both groups was =0.049 (S) (Table 5).

DISCUSSION

Junior physicians lack clinical experience, have difficulty in establishing the doctor–patient-relationship and often struggle with the administrative demands of their work[19]. Medical students and residents tend to be very dedicated to the demands of their profession and caring for patients[20]. However, some of them seem to be overcommitted in a way that they have difficulties to get away from patient issues and job demands, suffering from sleeping problems and neglecting social contacts. Overcommitted and stressed residents might have more difficulties establishing a good doctor–patient relationship, a factor which again contributes to feeling stressed[19]. Furthermore, stressed doctors have a negative influence on the atmosphere at their workplace; an unfavorable working atmosphere is again a factor for feeling stressed at work [21].

After a mailed survey of all 404 internal medicine residency program directors in the USA[22], concluded that nearly all programs in this sample had problem residents, in whom the most frequently reported difficulties were insufficient medical knowledge, poor clinical judgment, and inefficient use of time, with stressors and depression as the most frequently identified underlying problems. Young physicians have been reported to have a high level of chronic stress at work. The proportion of chronically stressed physicians is remarkably consistent over time[23].

In the current study, working hours were significantly higher in the case group than the control group. Additionally, working hours were significantly the highest in Obstetrics & Gynecology department group and were significantly the lowest in Cardiology department. These results are in agreement with those of some studies that have been shown that historically junior doctors' training involved long working hours with little sleep overnight[24] which was recognized to be hazardous to both the doctor's and patient's health[25]. The association between long working hours and illness occurs largely as a result of stress, as doctors try to maintain performance levels with increasing fatigue[26]. Stress results in emotional, behavioral and psychological reactions, such as anxiety, depression, increased consumption of alcohol, increased blood pressure and, in extreme cases, death, through suicide or cardiovascular disease[27]. It has been demonstrated that shift work is associated with an increased risk of cardiovascular disease[28] which is thought to be due to alterations in the circadian rhythm, following changes in the sleep-wake cycle[29]. Circadian adjustment takes time, being most rapid in the first 1–3 days[10] and during this period the subject experiences jet lag or desynchronizes. The most important consequence is a reduced quantity and quality of sleep[30] which has been linked to declines in both cognitive and psychomotor performance in junior doctors[24].

A study on prolonged duty hours and fatigue among gynecology and obstetrics residents in Venezuela showed that professionals, especially males, ingest stimulants, and that residents in this condition have unacceptably high rates of fatigue. The author adressed the need for work schedules that include periods of rest during 12-hour shifts[31].

Experimental research has shown that sleep debt negatively influences the carbohydrate metabolism and endocrine function, leading to impaired glucose tolerance and increased serum cortisol levels in the afternoon[32].

Cortisol was significantly higher in the case group compared to the control group. Cortisol recorded the most significant increase in Obstetrics & Gynecology department group and the lowest significant increase in Cardiology department group. In both the case and control groups, there was a significant positive correlation between working hours and serum cortisol level. These results are in agreement with the results of human and experimental studies that have been shown that the individual's expectation of coping with a stressful work situation has a great impact on cortisol secretion[33]. As when an event or situation is stressful, a cascade of hormonal changes occurs that appears to work either to motivate or to support coping with the stressor [34]. Almost type of stress stimulates the hippocampus to activate the hypothalamus to secrete corticotrophin releasing factor (CRF), which travels through the hypophysial portal system to the pituitary, stimulating the secretion of adrenocorticotropic hormone (ACTH). ACTH then travels through the systemic circulation to the adrenal cortex, where it induces release of the glucocorticoid cortisol[35]. As the body cycles through prolonged or repeated alarm reactions, receptors in the hippocampus become desensitized and damaged (it is unknown if the damage is permanent), leading to a feed-forward overproduction of cortisol[36]. The study of Fischer et al[37] revealed that the experienced intensive care nurses and physicians have lower cortisol levels and reactivity than their less-experienced colleagues.

Many studies found that levels of serum cortisol increased in cases of stress[38&39]. In 23 studies that addressing the association between cortisol in serum and the psychosocial working environment, nine showed a positive association[40]. The psychobiological research postulated that the pathways by which work stress influences ill health is mediated by the hypothalamic-pituitary- adrenal (HPA) axis which regulates the long-term adaptation of organism to stress. A positive association between the early morning cortisol levels in high strain subjects has been reported [41].

The results of the present study revealed that immunoglobulin G (IgG) showed significant elevation in the case group when compared with the control group. Immunoglobulin G (IgG) recorded the most significant increase in the Obstetrics & Gynecology department group

and the lowest significant increase in Cardiology department group. In both the case and the control groups there was a significant positive correlation between working hours and serum immunoglobulin G level. These results are in agreement with those of Theorell et al[42] who suggested that acute job strain increases serum IgG concentrations. The increase in serum IgG concentrations has also been found in subjects under academic stress[43]. Cross-sectional studies of job stress and immunoglobulins have been shown that there may be positive associations between job stress and immunoglobulin G[44]. For instance, in a study of teacher stress, objective indicators of work load such as proportion of weekly lessons in full class correlated positively with IgG level in plasma[45].

Psychological stress is known to alter the humoral and cellular immune system by stimulating the cerebral cortex and hypothalamic-pituitary-adrenal axis [46]. That is, corticotropin-releasing hormone and vasopressin released from the hypothalamus during the stress lead to the secretion of adrenocorticotropic hormone from the pituitary gland and glucocorticoid from the adrenal gland. Glucocorticoid can cause non-committed type 0 T-helper cells to transform into type 2 T-helper cells and can inhibit the development of type 1 T-helper cells, which is related to the cellular immune system[47]. The type 2 T-helper cells secrete cytokines, which induce the production of antibodies[48]. Thus the increased serum IgG level seen in the present study may be attributed to such stressors through the different actions of glucocorticoid on two different T-helper cells.

Highly-sensitive C - reactive protein (CRP-hs) showed significant increase in the case group compared to the control group. CRP-hs recorded the highest significant elevation in Obstetrics & Gynecology department group and the lowest significant elevation in Cardiology department group. In the case and control groups a significant positive correlation between working hours and highly-sensitive C - reactive protein (CRP-hs) has been detedcted. These results agreed well with fewer studies which have been shown elevated concentrations of CRP in people with higher job demands[49&50]. Also, a study of Schnorpfeil et al. [51] demonstrated a positive association between job demands and serum CRP levels. Poor social support appeared to be related to high plasma levels CRP. These data suggest adverse social work conditions may be associated with increased inflammation as indicated by elevated plasma levels of CRP[51].

Acute stressor firstly evokes production of IL-6, which then signals the liver to synthesize and release C-reactive protein[52]. The acute phase response (APR) is responsive to stress and one aspect of the APR includes stimulation of acute phase proteins (APPs) such as C - reactive protein (CRP) released by the liver[53].

In the present study serum cholesterol (Chol) level showed significant rise in the case group when compared with the control group. Similar to the above mentioned parameters, Chol recorded the highest significant elevation in Obstetrics & Gynecology department group and the lowest significant increase in Cardiology department group. Significant positive correlation was detected between working hours and serum Chol level in both the case and control groups. These findings are in agreement with the study that has been demonstrated that men with a high job demand level showed high total cholesterol levels[54]. Also, in the study of Kang et al. [55] job stress has been found to be involved in the elevated serum cholesterol levels. It was suggested that acute lipid stress responsivity may reflect processes that contribute in the development of raised blood cholesterol levels[56].

In our study, serum triglycerides (TG) level revealed significant elevation in the case group compared to that in the control group. Also, TG showed the highest significant increase in Obstetrics & Gynecology department group and the lowest significant increase in Cardiology department group. In both the case and control groups there was significant positive correlation between working hours and serum TG level. These findings coincide with five out of eight studies that demonstrated increased serum concentrations of triglycerides in shift workers compared to day workers[57]. Also, in the study of Kang and his colleagues, job stress has been shown to be involved in the elevated serum triglycerides level[55]. The epidemiologic study of Knutsson and Boggild [58] reported that high triglyceride appears more often in shift workers than in day workers.

In the current study, low-density lipoprotein (LDL) serum level showed significant increase in the case group compared to that in the control group. Serum LDL level recorded the highest significant elevation in Obstetrics & Gynecology department group and the lowest significant elevation in Cardiology department group. In both the case and control groups there was significant positive correlation between working hours and LDL serum level. These results are in agreement with the results of some the study which reported that greater acute stress lipid responses predicted higher LDL-C several years later[56].

In general, during the periods of stress, the increased cortisol production facilitates triglycerides synthesis and stimulates very low density lipoprotein (VLDL) secretion by the liver[59]. Another possible explanation for stress-related changes in blood lipid concentrations is the changes in hem concentration during stress[60] whereby the acute loss of plasma volume within the intravascular space concentrates the nondiffusible blood constituents and, thereby, increases blood lipid concentration[61]. The third suggestion for the effect of stress on the plasma level of lipids is the metabolic effect of catecholamine spillover in response to acute psychosocial stress. The increased circulating level of norepinepherine (NE) - induce lipolysis and release of free fatty acids into the circulation[62] which, in turn, serve as a substrate for the resynthesis of TG and hepatic production of VLDL[63]. The increased NE production is associated with elevated plasma levels of Chol and LDL[64].

The present findings showed that high-density lipoprotein (HDL) were significantly decreased in the case group compared to that in the control group. Serum HDL level showed the most significant reduction in Obstetrics & Gynecology department group and the lowest significant decline in Cardiology department group. In the case and

control groups, significant negative correlation between working hours and HDL serum level has been detected. These results agreed well with those of the studies of Knutsson and Boggild[58] and De Backer et al.[65] which reported lower concentrations of HDL plasma level in shift workers than in day workers. The decreased HDL level could be explained as a result of the decreasing reverse cholesterol transport from the blood stream to the liver[66].
Some studies reported positive correlation between total Chol, TG or low-HDL levels and shift work [67]. Also, number of studies over several decades showed positive correlation between stress and LDL levels[68&69].
In conclusion, our study demonstrated that the adverse effects of increasing working hours on stress hormone, immune system and lipid profile of resident doctors. The present findings shed light on the involvement of job stress in the pathophysiology of immunsupression, inflammation and hypercholesterolemia among resident doctors. Threfore, there is a special need for constructing work schedules that include periods of rest during 12 –hours shift to modulate the insult of job stress on the public health.

REFERENCES

1. French JRP, Rogers W, Cobb S. Adjustment as person–environment fit. In: Coelho GV, Hamburg DA, Adams JE, editors. Coping and adaptation. New York: Basic Books. 1974; P 316–33.
2. Karasek RA. Job demands, job decision latitude, and mental strain: Implications for job redesign. Administrative science quarterly. 1979; 24: 285–308.
3. Health and Safety Executive. A total of 13.8 million working days were lost to work related stress, depression and anxiety in. 2006/07.
4. Hassan E, Austin C, Celia C, Disley E, Hunt P, Marjanovic S, Shehabi A, van Dijk LV, van Stolk C. Health and Wellbeing at Work in the United Kingdom. 2009.
5. Willcock SM, Daly MG, Tennant CC, Allard BJ. Burnout and psychiatric morbidity in new medical graduates. Medical Journal of Australia. 2004; 181: 357–60.
6. Schulz P, Kirschbaum C, Pruessner JC, Hellhamer D. Increased free cortisol secretion after awakening in chronically stressed individuals due to workload. Stress Medicine. 1998; 14: 91–7.
7. Van Eck M, Berkhof H, Nicolson N, Sulon J. The effects of perceived stress, traits, mood states, and stressful life events on salivary cortisol. Psychosomatic Medicine. 1996; 58:447–58.
8. Paice E, Rutter H, Wetherell M, Winder B, McManus I C. Stressful incidents, stress and coping strategies in the preregistration house officer year. Medical Education. 2002; 36: 56–65.
9. Birch D, Ashton H, Kamali F. Alcohol, drinking, illicit drug use, and stress in junior house officers in north-east England. The Lancet. 1998; 352: 785–6.
10. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatrica Scandinavica. 1983; 67:361–70.
11. Shanafelt T, Bradley K, Wipf J, Back A. Burnout and self reported patient care in an internal medicine residency program. Annals of Internal Medicine. 2002; 136:358–67.
12. Check JH, Ubelacker L, Lauer CC. Falsely elevated steroidal assay levels related to heterophile antibodies against various animal species. Gynecologic Obstetric Investigation. 1995; 40:139-40.
13. Price CP, Spencer K, Whicher J. Light-scattering immunoassay of specific proteins: a review. Annual of Clinical Biochemistry.1983; 20:1-14.
14. Price CP, Trull AK, Berry D, Gorman EG. Development and validation of a particle-enhanced turbidimetric immunoassay for C-reactive protein. Journal of Immunological Methods. 1987; 99:205-11.
15. Meiattini F, Prencipe L, Bardelli F, Giannini G, Tarli P. The 4- hydroxybenzoate/4- aminophenazone chromogenic system used in the enzymic determination of serum cholesterol. Clinical Chemistry. 1978; 24:2161-5.
16. Fossati P, Prencipe L. Serum triglycerides determined colorimetrically with an enzyme that produces hydrogen peroxide. Clinical Chemistry. 1982; 28: 2077- 80.
17. Burstein M, Schnolnic HR, Marlin R. Rapid method for the isolation of lipoprotein from human serum by precipitation with polyanions. Scandinavian Journal of Clinical & Laboratory Investigation. 1980; 40: 583-95.
18. Assmann G, Jabs HU, Kohnert U, Nolte W, Schriewer H. LDL-cholesterol determination in blood serum following precipitation of LDL with polyvinylsulfate. Clinica Chimica Acta. 1984; 140:77-83.
19. Jungbauer J, Kamenik C, Alfermann D, Brähler E. Wie bewerten angehende Ärzte rückblickend ihr Medizinstudium? Ergebnisse einer Absolvent enbefragung. Gesundheitswesen. 2004; 66: 51–6.
20. Rockenbauch K, Meister U, Schmutzer G, Alfermann D. Alumni of medical sciences and their life satisfaction. Gesundheitswesen. 2006; 68:176-84.
21. Karasek R, Theorell T. Healthy work: stress, productivity and the reconstruction of working life. New York Basic Books, New York 1990.
22. Yao DC, Wright SM. National survey of internal medicine residency program directors regarding problem residents. JAMA. 2000; 284:1099–104.
23. Buddeberg-Fischer B, Klaghofer R, Stamm M, Siegrist J, Buddeberg C. Work stress and reduced health in young physicians: prospective evidence from Swiss residents. International Archives of Occupational and Environmental Health. 2008; 82: 31–8.
24. Friedman RC, Bigger JT, Kornfeld DS. The intern and sleep loss. The New England Journal of Medicine. 1971; 285:201–3.
25. Lockley SW, Cronin JW, Evans EE, Cade BE, Lee CJ, Landrigan CP, Rothschild JM, Katz JT, Lilly CM, Stone PH, Aeschbach D, Czeisler CA. Effect of reducing interns' weekly work hours on sleep and attentional failures. The New England Journal of Medicine. 2004; 351: 1829–37.

26. Spurgeon A, Harrington JM, Cooper CL. Health and safety problems associated with long working hours: a review of the current position. Occupational and Environmental Medicine. 1997; 54:367–75.
27. Park J, Kim Y, Hisanaga N. Work-related cerebrovascular and cardiovascular diseases (WR-CVDs) in Korea. Ind Health. 2011;49:3-7.
28. JDC Report. Implications for health and safety of junior doctors' working arrangements. London: BMA 2000.
29. Winget CM, Deroshia CW, Markley CL, Holley DC. Review of human physiological and performance changes associated with desynchronosis of biological rhythms. Aviation**,** Space**,** and Environmental Medicine. 1984;55: 1085–96.
30. Akerstedt, T. Psychological and psychophysiological effects of shift work. candinavian Journal of Work, Environment & Health. 1990; 16: 67–73.
31. Flores F. Jornada prolongada y fatiga en médicos residentes del gineco-obstetricia: Hospital Central de Maracay, Venezuela, [dissertação]. Maracay, Universidad de Carabobo, Facultad de Ciências de la Salud 1994.
32. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet. 1999; 354; 1435–9.
33. Wong IS, Ostry AS, Demers PA, Davies HW. Job strain and shift work influences on biomarkers and subclinical heart disease indicators: a pilot study. J Occup Environ Hyg. 2012; 9:467-77.
34. Neary JP, Malbon L, McKenzie DC. Relationship between serum, saliva and urinary cortisol and its implication during recovery from training. Journal of Science Medicine Sport. 2002; 5:108-14.
35. Steptoe A, Cropley M, Griffith J, Kirschbaum C. Job strain and anger expression predicts early morning elevations in salivary cortisol. Psychosomatic Medicine. 2000; 62: 286–92.
36. Sapolsky RM, Kry LC, McEwen BS. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. Endocrine Reviews; 1986; 7:284- 301.
37. Fischer JE, Calame A, Dettling AC, Zeier H, Fanconi S. Experience and endocrine stress responses in neonatal and pediatric critical care nurses and physicians. Critical Care Medicine. 2000; 28: 3281–8.
38. Meyerhoff JL, Oleshansky MA, Kalogeras KT, Mougey EH, Chrousos GP, Granger LG. Neuroendocrine responses to emotional stress: Possible interactions between circulating factors and anterior pituitar hormone release. Circulating Regulatory Factors and Neuroendocrine Function. 1990; 274: 91-111.
39. Robert MB, Matthew NL. Physiology 4 th ed. Mosby Inc, 1998. Rockenbauch K, Meister U, Schmutzer G, Alfermann D. Lebenszufriedenheit von AbsolventInnen der Medizin. Eine empirische Untersuchung zum Vergleich der Lebenszufriedenheit von AbsolventInnen mit Gleichaltrigen sowie zur Aufklärung des factors Lebenszufriedenheit (Alumni of medical sciences and their life satisfaction). Gesundheitswesen. 2006; 68:176–84.
40. Hertting A, Theorell T. Physiological changes associated with downsizing of personnel and reorganisation in the health care sector. Psychother Psychosom. 2002; 71: 117–22.
41. Alderling M, Theorell T, de la Torre B, Lundberg I. The demand-control model and circadian saliva cortisol variations in a Swedish population based sample (The PART study). BMC Public Health. 2006; 6: 288-95.
42. Theorell T, Orth-Gomer K, Eneroth P. Slow-reacting immunoglobulin in relation to social support and changes in job strain: a preliminary note. Psychosomatic Medicine. 1990; 52: 511–6.
43. Glaser R, Mehl VS, Penn G, Speicher CE, Kiecolt-Glaser JK. Stress associated changes in plasma immunoglobulin levels. International Journal of Psychosomatic. 1986; 33: 41–2.
44. Hansen AM, Larsen AD, Rugulies R, Garde AH, Knudsen LE. A review of the effect of the psychosocial working environment on physiological changes in blood and urine. Basic Clin Pharmacol Toxicol. 2009; 105:73-83.
45. Mykletun RJ. Teacher stress. Personality, work-load and health. Rapport Nr RF 71/88. Academic thesis. Bergen, Norway, University of Bergen, Institution of Psychology. 1988
46. Ader R, Felten DL, Cohen N. Interactions between the brain and the immune system. Annual Review of pharmacology and toxicology. 1990; 30: 561–602.
47. Decker D, Schondorf M, Bidlingmaier F, Hirner A, von Ruecker AA. Surgical stress induces a shift in the type-1/type-2 T-helper cell balance, suggesting down-regulation of cell-mediated and up-regulation of antibody-mediated immunity commensurate to the trauma. Surgery. 1996; 119: 316–25.
48. Del Prete G, Maggi E, Romagnani S. Human Th1 and Th2 cells: functional properties, mechanism of regulation, and role in disease. Laboratory Investigation. 1994; 70: 299–306.
49. Almadi T, Cathers I, Hamdan Mansour AM, Chow CM. The association between work stress and inflammatory biomarkers in Jordanian male workers. Psychophysiology. 2012; 49:172-7.
50. Clays E, De Bacquer D, Delanghe J, Kittel F, Van Renterghem L, De Backer G. Associations between dimensions of job stress and biomarkers of inflammation and infection. Journal of Occupational & Environmental Medicine. 2005; 47: 878- 83.
51. Schnorpfeil P, Noll A, Schulze R, Ehlert U, Frey K, Fischer JE. Allostatic load and work conditions. Social Science& Medicine. 2003; 57: 647–56.
52. Gabay C, Kushner I. Acute phase proteins and other systemic responses to inflammation. The New England Journal of Medicine. 1999; 340: 448-54.
53. Black PH, Garbutt LD. Stress, inflammation and cardiovascular disease. Journal of Psychosomatic Research. 2002; 52: 1–23.
54. Xu W, Hang J, Gao W, Zhao Y, Cao T, Guo L. Association between job stress and newly detected

combined dyslipidemia among Chinese workers: findings from the SHISO study. J Occup Health. 2011; 53:334-42.
55. Kang MG, Koh SB, Cha BS, Park JK, Baik SK, Chang SJ. Job stress and cardiovascular risk factors in male workers. Preventive Medicine. 2005; 40: 583- 8.
56. Steptoe A, Brydon L. Associations between acute lipid stress responses and fasting lipid levels 3 years later. Health Psychology. 2005; 24: 601-7.
57. Lasfargues G, Vol S, Cace`s E, Le Cle´siau H, Lecomte P, Tichet J. Relations among night work, dietary habits, biological measures, and health status. The International Journal of Behavioral Medicine. 1996; 3: 123–34.
58. Knutsson A, Boggild H. Shift work, risk factors and cardiovascular disease: review of disease mechanisms. Reviews on Environmental Health. 2000; 15: 359-72.
59. Mosca M, Aggarwal B. Sleep duration, snoring habits, and cardiovascular disease risk factors in an ethnically diverse population. J Cardiovasc Nurs. 2012; 27:263-9.
60. Allen MT, Patterson SM. Hemoconcentration and stress, a review of physiological mechanisms and relevance for cardiovascular disease risk. Biological Psychology. 1995;41: 1-27.
61. Bachen EA, Muldoon MF, Matthews KA, Manuck SB. Effects of hemoconcentration and sympathetic activation on serum lipid responses to brief mental stress. Psychosomatic Medicine. 2002; 64: 587-94.
62. Arner P. Human fat cell lipolysis: biochemistry, regulation and clinical role. Best Practice & Research Clinical Endocrinology & Metabolism. 2005; 19:471-82.
63. Hjemdahl P, Linde P. Adrenergic control of blood flow and lipolysis in human adipose tissue. In: Refsum HM, editor. Alpha-adrenoreceptor blockers in cardiovascular disease. London: Churchill Livingstone. 1985; p151-64.
64. McCann BS, Magee MS, Broyles FC, Vaughan M, Albers JJ, Knopp RH. Acute psychological stress and epinephrine infusion in normolipidemic and hyperlipidemic men: effects on plasma lipid and apoprotein concentrations. Psychosomatic Medicine. 1995; 57: 165-7.
65. De Backer G, Kornitzer M, Dramaix M, Peeters H, Kittel F. Irregular working hours and lipid levels in men. In: G Schling, H Mo¨ rl (eds) Expanding horizons in atherosclerosis research. Springer, Berlin. 1987; pp 217–24.
66. Raveh O, Pinchuk I, Fainaru M, Lichtenberg D. Kinetics of lipid peroxidation in mixture of HDL and LDL, mutual effects. Free Radical Biology and Medicine. 2001; 31: 1486–97.
67. Karlsson B, Knutsson A, Lindahl B. Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27,458 people. Occupational and Environmental Medicine. 2001; 58: 747–52
68. Bosma H, Stansfeld SA, Marmot MG. Job control, personal characteristics, and heart disease. Journal of Occupational Health Psychology. 1998; l 3:402-9.
69. Kivimäki M, Leino-Arjas P, Luukkonen R, Riihimäki H,Vahtera J, Kirjonen J. Work stress and risk of cardiovacular mortality: prospective cohort study of industrial employees. British Medical Journal. 2002; 325:857-60.