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Prediction of Health Risk and Estimation of Associated Variables with Work Stress using Allostatic Load Index

Saleh Mai Sabry[1], Ali Ola[2], Badawy Nadia[1], Rizk Sanaa[1] and Gomaa Hend[1]

[1]Environmental and Occupational Medicine Department,
National Research Centre, Dokki, Giza, Egypt.
[2]Faculty of Pharmacy (Girls), Al-Azhar University, Cairo Egypt.
*Corresponding Author E-mail : nouranomer@gmail.com

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Allostatic load index (ALI) detects health risk due to stress at early stages. The best way for defining high risk threshold values of ALI biomarkers is not agreed upon. Environmental factors associating stress are also in need of further investigation. Methods: Study sample included 62 Egyptian workers. Biochemical, clinical and anthropometrical measures were done for calculation of ALI. Risk quartile method, cutoff point method and risk quartile of cutoffs (new) were used for determination of risk thresholds. Results: The new risk quartile of cutoffs method was able to detect the highest ALI, showed significant correlations with greater number of biomarkers and highlighted more predictors of allostasis. Predictors of stress included age and gender. Conclusions: Risk quartile of cutoffs is a recommended new method more appropriate for calculation of high risk threshold of ALI biomarkers.

Keywords: Allostatic Load Index; Biomarkers of Stress; Early Detection of Stress; High Risk Threshold; Stress Predictors; Work Stress.

The terms 'occupational stress', 'work stress', 'job stress' and 'work-related stress' are known to be interchangeable[1]. They refer to how persons go through mental and physical pressures to the extent that they may fail to achieve their career goals[2]. According to the WHO (2007)[3] work related stress is a matter of growing concern in developing countries. About 75% of the world's labor force -nearly 2400 million people- are localized in developing countries with only 5-10% of them (compared to 20-50% of the workers in industrialized countries) have access to adequate occupational health services. Nevertheless, stress is still a problem which is out of the scope of attention and is still far from being resolved. Unfortunately, very little specific national data on work-related stress is available for developing countries as well as for countries in transition. This could be attributed to poor recording mechanisms and non-recognition of the related outcomes in most of these countries.3 Similarly, among the Arab population, only few reports on clinical stress are available.[4]

In Egypt, some sporadic studies could give us an indication on the general condition regarding stress and its prevalence. In a cross sectional study carried by Shams and El-Masry (2013)[5] 69.4% of 98 anaesthesiologists working at Mansoura University Hospital in Egypt were encountering job stress. A redeployment process -after the concept of person-job (P-J) fit- was carried out to reduce workplace stress, provide security and improve performance of the human workforce at

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the Training and Capabilities Development Unit (TCD) in National Research Centre (NRC).[6] In this study forty two employees (12 males and 30 females) working at the different departments of TDC were asked to complete a survey to estimate their job satisfaction, some psychological stress parameters and to investigate some work-related factors. Results showed that 14.3% of the sample suffered from low job satisfaction, with 83% of them showing various psychological signs of distress. Loss of concentration and loss of sense of humor represented the most significantly prevalent signs among the non satisfied groups.[7] In the workshop “Let Your Job Be Your Friend’ that was held for researchers working at the NRC as a health education program for health promotion, feedback survey showed great acceptance for the intervention represented by 82% of the total participants which reflect the seriousness of stress issue in Egyptian working community.[8]

In order to reduce hazards of stress there should be some kind of adequate preventive measures against its harmful outcomes. In this context the present work suggested early detection of stressed workers at high risk of chronic diseases. A methodology relying on determination of some biochemical, clinical and anthropometric indicators with further calculation of their Allostatic load index (ALI)[9] was suggested. ALI is the quantitative measure of Allostatic load that proved to be a powerful predictor of stress and its outcomes.[10]

Allostatic load (AL) represents a multi-component assessment of long-term physiological changes occurring secondary to somatic responses to stress. The conceptualization of AL was first introduced by Sterling and Eyer during the 1980s and has gained lately a wide acceptance in the field of clinical research. It acquires many advantages as it detects the presence of stress in its early stages before reaching the stage of debilitation.[11] Moreover, the collective measure of AL can significantly predict risk for major health outcomes, including mortality which is a privilege over the individual biomarkers included in its calculation which are not always indicative on their own as stated by Seeman *et al*. (2002).[12]

Allostatic load Index (ALI) is the score that indicates the state of allostasis in human bodies. It represents the interplay of inflammatory, neuro-endocrine and metabolic systems where the composite markers range from acute (primary mediators) to more long-term effects (secondary outcomes). There is a wide range of biomarkers that could be used for ALI calculation. Biomarkers vary between studies and their choice depends –in most cases- on the matter of availability of measures.

ALI is calculated according to the number of biomarkers lying in the highest risk quartile.[13] Risk quartiles could either be the upper or lower 25th percentile of the indicated biomarkers values within the population under study. The cutoff point can be also set to the highest or lowest 10% according to literature. It is also possible to use clinical cut-offs, but until now there are no universally agreed values for cut-offs.[14]

The present pilot study aims at calculating ALI in a convenient way that is able to predict population at health risk and associated factors to stress in the Egyptian working environment.

Subjects and Methods

A random sample of 62 adult workers and employees (18males and 44 females) was included in the study with age ranging from 25 to 59 years old. Thirty-five of them working at the different departments of the Faculty of Pharmacy (Girls), Al-Azhar University, Egypt and 27 individuals working at the pediatric oncology outpatient clinic, National Cancer Institute (NCI), Egypt. Inclusion criteria encompassed both genders, adults below 60 years old, working at either of the aforementioned places either as workers or employees. Exclusion was for individuals with missing measures, pregnant females and individuals suffering from cognitive or psychiatric problems. Ethical committee in the XXX approved the study and all volunteers agreed with consenting participation in the study.

For determination of AL, biochemical markers measured as primary mediators were serum cortisol, dehydroepiandrosterone-sulphate (DHEA-s), C-reactive protein (CRP) and total thyroxine (tT4). Secondary outcome biomarkers were total cholesterol (TC), HDL-cholesterol, LDL-cholesterol and triglycerides (TG). Systolic and diastolic blood pressure (SBP and DBP) and anthropometric measures; body mass index (BMI) and waist-to-hip ratio (WHR) were also measured as secondary outcomes.

Systolic blood pressure and diastolic blood pressure were calculated as the average of two seated blood pressure readings taken about one minute apart, using a mercury sphygmomanometer.[15] Value of WHR was calculated based on waist circumference (measured at its narrowest point between the ribs and iliac crest) and hip circumference (measured at the maximal buttocks).[16] For BMI, it was calculated from measured data as weight in kilograms divided by height in meters squared[15]. Total cholesterol to high density lipoprotein cholesterol (TC/HDL) and LDL were calculated as secondary mediators of AL. Biochemical assessments and calculations followed the procedure stated by Ali *et al*. (2016).[17]

All parameters chosen for calculation of Allostatic load index were chosen according to literature.[13,18] ALI was then calculated for the study population. For each biomarker, the high-risk threshold was calculated and each participant was assigned a point for each biomarker that was beyond the threshold. The high-risk threshold was defined as below the 25th percentile for DHEA-s and HDL and above the 75th percentile for all other markers according to each measurement's distribution within the population under study. The points were summed to generate the ALI, with a range from 0 to 13. According to similar research, an ALI of four or greater was used to define a high AL.[19-20]

ALI was also calculated after the cut point method where the high-risk thresholds are represented by the upper normal value for each marker. Additionally, in a third method, the high risk threshold was calculated as below the 25th percentile and above the 75th percentile regarding the cut points previously defined rather than the measurement's distribution within the population under study. High risk thresholds for the different parameters using the three methods of calculation are defined in table 1.

Concerning statistical analysis, the study is a cross sectional descriptive study where frequency distribution, student t-test and person correlation were performed. The statistical package for social sciences version 18 for windows (SPSS Inc., USA) was used.

Table 1. High risk thresholds of biomedical markers of ALI

Biomarker	Highest (lowest) quartile after the risk quartile method	Highest (lowest) quartile after predefined cut points	Highest (lowest) quartile after risk quartiles of cut points
Serum cortisol	≥ 15.85 ug/dl	≥ 23 ug/dl	≥ 18.5 ug/dl
CRP	≥ 7.6 mg/l	≥ 8.2 mg/l	≥ 6.2 mg/l
tT4	≥ 12.4 ug/dl	≥ 13 ug/dl	≥ 11 ug/dl
TC	≥ 253 mg/dl	≥ 240 mg/dl	≥ 206 mg/dl
TG	≥ 231 mg/dl	≥ 150 mg/dl	≥ 139 for males and 115 for females mg/dl
LDL	≥ 171 mg/dl	≥ 120 mg/dl	≥ 122.5 mg/dl
TC/HDL	≥ 10.4	≥ 6	≥ 5.2 for males and 4.3 for females
BMI	≥ 38.1	≥ 30	≥ 27
WHR	≥ 1.5	≥ 0.9 for male and 0.85 for females	≥ 0.83 for male and 0.79 for females
SBP	≥ 150 mm Hg	≥ 140 mm Hg	≥ 135 mm Hg
DBP	≥ 100 mm Hg	≥ 90 mm Hg	≥ 87.5 mm Hg
HDL cholesterol	≤ 49.8 mg/dl	≤ 40 mg/dl	≤ 40 mg/dl for males and ≤ 47.5 for females
DHEA-s	≤ 1.02 ug/ml	≤ 0.59 for males and 0.4 for females ug/ml	≤ 1.2 for males and 1.8 for females ug/ml

DHEA-s=dihydroepiandrosteronesulphate. CRP= C-reactive protein, tT4=total thyroxine, TC=total cholesterol, TG-triglycerides, HDL=high density lipoproteins, LDL=low density lipoproteins, TC/HDL= total cholesterol to high density lipoprotein ration, SBP=systolic blood pressure, DBP=diastolic blood pressure, BMI=body mass index, WHR=waist to hip ratio, ALI=allostatic load index

RESULTS

Table 2 shows descriptive data of the study group as previously published by Ali *et al.* (2016).[17] Females (71%) exceed males (29%) and most of the study population are married (69.4%), don't have a second job (81%), live in urban residence (82%), work for more than five hours per day (76%) and work as employees (71%). Nearly quarter of the population (24%) under study show to be dissatisfied with their job or neither satisfied nor dissatisfied.

ALI (5.9, 3.6, 2.5) showed to be higher in the population working at faculty of pharmacy, Al-Azhar University compared to those working at the outpatient clinic in the NCI (4.6, 2.8, 2.1) upon using the three methods for AL calculation; the risk quartile method, the cut point method and the risk quartile of cut points method, respectively. AL assessment due to cut points and due to risk quartile of cut points have shown to be able to detect significant differences between population working at faculty of pharmacy Al-Azhar University and those working at the NCI at p values 0.042 and 0.002, respectively as compared to risk quartiles method (p=0.163). Calculation of risk threshold using the third method –first applied by the authors- proved to be the best in identification of the largest population under risk and was also able to differentiate between the different work places with greater degree of significance (p=0.002).

Correlation between each two methods for ALI calculation showed high significance at p<0.01. Tables 3 shows the correlation between ALI using risk quartile, cut points and risk quartile of cut points, respectively with the individual biomarkers comprising the ALI. Significant positive correlation is detected between ALI calculated after the quartile method TC/HDL (p=0.014) and BMI (p=0.014). Highly significant positive correlation is also detected with CRP (p=0.000) and TG (p=0.005). While highly significant negative correlation is shown between ALI and DHEA-s (p=0.009).

ALI due to cut points and ALI due to risk quartile of cut points showed similar correlations as ALI due to quartile method with the addition of significant positive correlation with age (p=0.001), total thyroxine (p=0.004) and LDL (p=0.048) for the former and age (p=0.000) and total thyroxine (p=0.02) for the latter.

Mean values of ALI didn't show any significant difference upon grouping according to work related and socio-demographic variables considered in the study as shown in table 4. Upon recalculation of ALI according to cut point method, many factors are found to affect AL significantly. Such factors are the increased age (p=0.000), faculty of pharmacy at AL-Azhar University as working place (p=0.042), presence of chronic diseases (p=0.041), rural residence (p=0.049) and working for more than 10 years (p=0.02). Similarly, calculation of ALI according to risk quartile of cut points proved to be more able to highlight the

Table 2. Percentage distribution of the study variables as represented by Ali et al.[17]

Study Variables	Frequency(%)
Gender (n=62)	
Male	18(29%)
Female	44(71%)
Age (n=62)	
<40	27(44%)
=40	35(56%)
Work Place (n=62)	
Al-Azhar	35(56.5%)
NCI	27(43.5%)
Social Status (n=62)	
Married	43(69.4%)
Others	19(30.6%)
Other Job (n=61)	
Present	11(18%)
Absent	50(81%)
Chronic Diseases (n=62)	
Present	24(38.7%)
Absent	38(61.3%)
Residence (n=59)	
Urban	51(82%)
Rural	8(13%)
Daily Working Hours (n=60)	
= 5	13(21%)
> 5	47(76%)
Working Years (n=59)	
= 10	24(38.7%)
> 10	35(56.5%)
Job Nature (n=62)	
Employee	44(71%)
Worker	18(29%)
Job Satisfaction (n=62)	
<20	47(76%)
=20	15(24%)

variables that most probably predispose to stress. Highly significant differences appear between groups classified according to gender (p=0.007), age (p=0.000) and work place (p=0.002). Low working hours also affects ALI significantly at p=0.031.

DISCUSSION AND CONCLUSION

AL has proven to increase in relation to occupational stress among caregivers,[21] aircraft workers,[22] industrial workers[23] and similarly was the case in the present study. Yet, it attracted our attention in our study that risk thresholds calculated after the high-risk quartile method for TC (253mg/dl), TG (231 mg/dl), LDL (171mg/dl), TC/HDL (10.4), DBP (100 mm Hg), WHR (1.5) and BMI (38.1) highly jumped over the corresponding thresholds detected in similar studies as reported by Mauss and his colleagues (2015) 24 and even exceeded the normal ranges of the individual biomarkers. As reported, ranges of threshold values showed to be 177.9–249.0 mg/dl, 101.5–141.75 mg/dl, 116.0–137.3 mg/dl, 3.71, 71.2–95.0 mm Hg, 0.83–0.97, 25.2–28.5, respectively which are too much lower. Threshold for DHEA-s according to lowest risk quartile in our study was 1.02ug/ml that is also lower than the corresponding thresholds reported (13.3–51.5 µg/dl).24 These results reflected serious bad general health condition for our study population compared to others and rendered the mean value for AL deceiving and reflecting false indication of good state of health for some cases.

ALI was also calculated using the predefined cut points method previously used in similar studies.[25-28] In this methodology, the upper normal limit for each marker represents

Table 3. Pearson Correlation between ALI and the 13 individual biomarkers

Variables and Measures (N=62)		ALI due to risk quartile method	ALI due to cut points method	ALI due to risk quartile of cut points method
Cortisol	Pearson Correlation	0.249	-0.157	0.067
	P value	0.051	0.223	0.607
Dehydroepiandrosterone	Pearson Correlation	-0.331**	-0.456**	-0.400**
Sulphate	P value	0.009	0.000	0.001
C-Reactive protein	Pearson Correlation	0.490**	0.310*	0.388**
	P value	0.000	0.014	0.002
Total Thyroxine	Pearson Correlation	0.238	0.362*	0.318*
	P value	0.063	0.004	0.012
Total Cholesterol	Pearson Correlation	-0.040	0.232	0.206
	P value	0.760	0.069	0.109
Triglycerides	Pearson Correlation	0.352**	0.472*	0.482**
	P value	0.005	0.000	0.000
High Density Lipoprotein	Pearson Correlation	-0.241	-0.129	-0.170
	P value	0.059	0.317	0.186
Low Density Lipoprotein	Pearson Correlation	0.045	0.252*	0.225
	P value	0.730	0.048	0.078
Total cholesterol-to-high	Pearson Correlation	0.309*	0.377**	0.399**
density lipoprotein	P value	0.014	0.003	0.001
Systolic Blood Pressure	Pearson Correlation	0.112	0.117	0.180
	P value	0.385	0.367	0.161
Diastolic Blood Pressure	Pearson Correlation	0.060	0.114	0.154
	P value	0.645	0.377	0.232
Body Mass index	Pearson Correlation	0.310*	0.415**	0.400**
	P value	0.014	0.001	0.001
Waist-to-Hip Ratio	Pearson Correlation	-0.001	0.083	-0.026
	P value	0.991	0.522	0.842

* P value Less than 0.05 ** p value less than 0.001

the high-risk threshold except for HDL and DHEA-s where the lowest normal limit is the risk threshold. Upon calculation of AL mean according to this second method, higher value of ALI for the study population (3.26) was detected and its value approached results of Schnorpfeil and his colleagues[22] for their study performed on aircraft workers in Germany (3.15) and work done by Li[23] on industrial workers in China (2.5-3.15). Moreover, ALI according to cut point method significantly differentiated –in their mean values- between sample groups according to age, work place, residence, presence of chronic diseases and working years. Additionally, the cut point method for AL assessment showed significant correlations with larger number of individual markers used for ALI calculation than the quartile method which is another point of advantage for the former over the latter. Yet, one drawback for the cut point method is that it determines threshold after pathological values of the incorporated markers that –in fact- signifies the actual presence of disorders or pathogenic state while the main aim after AL assessment is the health risk assessment and prediction of hazardous outcomes which should predict diseases and not diagnose them.

A third method for ALI calculation was suggested by the present work in order to overcome

Table 4. Comparing means for Allostatic load Index (ALI) according to studied socio-demographic and work-related variables of the study population

Study Variables	ALI (mean±SD)	ALI due to cut points (mean±SD)	ALI due to risk quartile of cut points (mean±SD)
Gender			
Male	2.0±0.8	3.22±1.83	4.39±1.58**
Female	2.5±1.3	3.27±1.58	5.70±1.72**
Age			
<40	2.1±1.3	2.44±1.40**	4.41±1.69**
=40	2.5±1.2	3.89±1.55**	6.03±1.51**
Work Place			
Al-Azhar	2.5±1.1	3.63±1.7*	5.91±1.58**
N CI	2.1±1.3	2.78±1.45*	4.56±1.74**
Social Status			
Married	2.3±1.2	3.05±1.65	5.07±1.71
Others	2.5±1.2	3.74±1.56	5.89±1.82
Other Job			
Present	2.4±1.1	3.91±1.70	5.55±1.64
Absent	2.3±1.2	3.10±1.62	5.22±1.79
Chronic Diseases			
Present	2.7±1.2	3.79±1.67*	5.75±1.54
Absent	2.1±1.2	2.92±1.55*	5.05±1.87
Residence			
Urban	2.4±1.2	3.06±1.52*	5.20±1.67
Rural	2.1±0.8	4.25±1.83*	5.50±1.60
Daily Working Hours			
= 5	2.5±1.1	3.92±1.89	6.08±1.55*
> 5	2.3±1.2	3.00±1.46	4.96±1.63*
Working Years			
= 10	2.3±1.5	2.62±1.61*	4.88±1.90
> 10	2.4±1.0	3.60±1.48*	5.57±1.60
Job Nature			
Employee	2.4±1.3	3.14±1.59	5.34±1.80
Worker	2.3±1.1	3.56±1.76	5.28±1.74

* P value Less than 0.05 ** p value less than 0.001

constrains on the aforementioned methods. The suggested method considered the threshold below the 25th percentile and that above the 75th percentile with respect to the upper normal limit. Conceptually, this method for calculation is sought to predict the cases most likely to reach behind the normal range as well as those already breaking the limits.

Empirically, such conceptual assumption –according to our study- has proved a great deal of acceptance since the AL mean (5.32) calculated after the suggested methodology exceeded that of the other two methods; the quartile method (2.4) and the cut point method (3.26) which means it was able to detect more population under risk and showed to be more sensitive in identification of AL. The new methodology was also able to detect significantly some predisposing factors of stress like age (p=0.000), gender (p=0.007), workplace (p=0.002) and daily working hours (p=0.031) (table 4). Besides, highly significant correlations (p<0.01) in the positive direction between ALI calculated after the risk quartile of cut points and the other well-known methods (the quartile and the cut point methods) was also detected which emphasizes that the method is perfectly able to assess AL.

Regarding associated factors of stress, ALI mean values for Al-Azhar university using the three methods of calculation showed to be higher than that of NCI workers means, non-significantly upon using the quartile method for AL assessment and significantly (p=0.042, p=0.002, respectively) upon using the cut point method and the risk quartile of cut points method which ensures the worse health conditions of the former (population working at faculty of pharmacy (Girls), Al-Azhar university) over the later (population working at the outpatient clinic in NCI). Significantly higher AL (p=0.02) was also detected by using the cut point method for AL assessment upon population working for more than 10 years, while AL assessment after risk quartile of cut points detected significantly (p=0.031) increased ALI within population with less than five working hours per day. Loss of positive affect and decreased self esteem at the work place could introduce to bad health and initiation of stress[29]. Unfortunately, due to few research studies in this field and limited insights from research on AL assessment no similar data are available in literature concerning these studied variables for comparing results[24]. Work-related variables like effort-reward imbalance,[30] work safety,[31] job control,[23] job demands[32-33] and burnout[34] represent factors that proved direct association with AL in previous studies and could provide explanations for our findings upon testing them. Thus further predictors are needed to be investigated in Egypt and other developing countries.

Socio-economic status as reported by De Castro *et al*.[31] and Lipawicz *et al*.[35] together with age and gender also represent important predictors of stress and health deterioration. Some socio-demographic variables were tested –in the present work- as predisposing factors of stress.

In agreement with many research trials, a direct association between high AL and increased age[13,23,36] was detected. AL was 2.5 for the higher age group (=40 years) and 2.1 in the lower age group upon ALI calculation using the quartile method. Highly significant difference (p<0.01) was also detected between the two age groups upon using the cut point method and the risk quartile of cut points method showing worse AL state for the older aged group. Adverse effect of age on AL could be attributed to the fact that AL measures the cumulative biological risk normally increased with age as stated by Crimmins *et al*.[37]

Regarding gender, means of ALI showed to be higher in females (2.5) compared to males (2.0). Worse state of AL in females was also emphasized upon recalculation of ALI using the risk quartile of cut points method where highly significant difference (p=0.007) was detected between AL mean of females (5.7) and males (4.4). These results are in contrast with Schnorpfeil *et al*. 22 and Li 23 who recorded positive association between AL and the male gender and may indicate sever life conditions and health state for women in Egypt.

Presence of chronic diseases also showed to be associated with high AL (2.7) compared to population free from chronic diseases (2.1) upon using the quartile method. Similarly was the case upon using the cut point method for AL assessment but not in case of using the risk quartile of cut points method. These results are in agreement with the reported significantly increased AL with decreased physical health for Latino day workers in USA as stated by De Castro *et al*.[31] the decreased self-rated health recorded by Naswall *et al.*[38] in Sweden and the increased physical complaints as detected by Juster and Lupien[39] in Canada.

In conclusion, the quartile method for ALI calculation was defective as it escaped population suffering from chronic diseases and those who recorded pathological readings in critical health risk biomarkers like BMI, TC, SBP, DBP, … etc. The cut point method, on the other hand, skipped those who are most likely to break from the normal range and recorded readings very near to the upper or lower normal limit of the different biomarkers included in AL assessment. Eventually, the third method suggested by the present work was able to overcome the flaws of the other two methods and to provide a more acceptable prediction of the future health state and risk of stress among the study population. Hence, performing more studies testing the suggested method for calculation of high risk threshold of the different biomarkers upon ALI calculation using risk quartile of cut points to prove its efficiency is highly recommended. Age and gender are the most associated factors with health risk due to chronic stress.

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