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ORIGINAL ARTICLE

Associations between chronic work stress and plasma chromogranin A/catestatin among healthy workers

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Abstract

Objectives: Plasma chromogranin A (CgA) may play a critical role on linking work stress to health outcomes. The aim of our study was to investigate the associations between work stress and plasma CgA levels in healthy workers without chronic diseases.

Methods: The study included 260 healthy workers from EHOP study. Work stressors were assessed by the Chinese version of the 23-item ERI-Q questionnaire. Plasma CgA and catestatin levels were measured by ELISA kits. The demographic characteristics were collected from medical records.

Results: Among the final 260 subjects including 173 males (66.5%) and 87 females (33.5%), the average age was 37.6 ± 10.6 years old. Effort, overcommitment, and ERI were positively associated with plasma CgA level, respectively ($r = 0.267$, 0.319, and 0.304, all $p < .001$), while reward was negatively associated with CgA level ($r = -0.237$, $p < .001$). The workers with high effort, overcommitment, or ERI had significantly higher plasma CgA levels, while the workers with high rewards had significantly lower plasma CgA levels. The workers with both high overcommitment and high ERI had highest plasma CgA levels. In the linear regression analysis, after adjustment for confounders, effort, overcommitment, and ERI were respectively positively related to plasma CgA, while reward negatively related to plasma CgA. The associations between work stress and plasma catestatin was not significant. The ratio of CgA and catestatin was associated with work stress.

Conclusions: Work stress is associated with plasma CgA which may be play a crucial role on the pathway from chronic work stress to cardiovascular diseases.

KEYWORDS

catestatin, chromogranin A, effort–reward imbalance, work stress

Xin Liu and Weimin Dang are the co-first authors.

1 | INTRODUCTION

The role of work stress has received increased attention across a number of disciplines in recent years. Chronic stress experienced at work is considered a major health challenge for modern societies. China has experienced unprecedented growth over the past three decades. The present society is characterized by unstable jobs as a result of the excessive work to keep up with the rapid transformations in this age. This increases the risk of work stress and threatens the health of workers. There is a growing body of literature that recognizes the importance of work stress on health. These findings indicated that work stress was not only related to workers' behaviors and psychological health, but also related to physical health. The effort–reward imbalance (ERI) model, a lack of reciprocity between costs and gains at work, is one of the most widely used instruments of assessing work stress. According to ERI model, work stress increases the risk for adverse health outcomes. It was reported that effort–reward imbalance was more likely related to have unhealthy behaviors and psychological problems, such as more future sleep disturbances,[1] risky driving behaviors,[2] somatic symptoms,[3] psychological distress,[4] even suicidal ideation.[5,6] Effort–reward imbalance is associated with risk coronary artery disease,[7] transient ischemic attack,[8] and even mortality.[9] Work stress can increase the risk of cardiovascular disease by 50%, with increasing research focusing on the underlying mechanisms responsible for these associations.

One potential pathway mediating these associations involves the stress-related activation of the hypothalamus–pituitary–adrenocortical (HPA) axis with proceeding alterations in the secretion of its main effector hormone cortisol.[10-12] On the other hand, changes of autonomic nervous system activity including increased activation of the sympathetic nervous system and decreased vagal tone may also help to explain the increased risk for cardiovascular disease (CVD) to chronic work stress.[13] Inflammation and alterations in immune system,[14] as well as coagulation system,[15] has been shown to play a crucial role in a variety of stress-related diseases. The underlying mechanism linking work stress to health outcomes may be very complex and needs more researches. Chromogranin A (CgA) is attracting considerable critical attention recently.

CgA is co-stored and co-released with catecholamines from storage granules in the adrenal medulla1. Previous studies reported that high CgA plasma level was strictly associated with mortality risk after acute coronary syndrome as well as heart failure.[16,17] Catestatin is one of CgA-derived fragments through proteolytic processing, which is an endogenous multifunctional neuroendocrine peptide. There are a number of studies which have shown that catestatin is closely related to many cardiovascular diseases, such as hypertension,[18] acute coronary syndrome,[19] malignant arrhythmia in acute AMI stage,[20] and the severity of heart failure.[21] CgA and catestatin may play a critical role on cardiovascular disease and their plasma levels reflect the sympathetic tone and adrenomedullary system activity.

There are a few studies reporting the correlations between psychological health and salivary CgA. The salivary CgA levels were significantly and positively correlated with total mood disturbance during menstrual cycle in women.[22] Among depressed patients, the levels of awakening salivary CgA significantly increased.[23] Previous studies mostly focused on salivary CgA level,[24-26] however, few focused on plasma CgA level, while plasma CgA are regarded as a valuable predictor of cardiovascular diseases. Saliva is convenient to retain samples. However, as we know, water in saliva accounts for more than 99%. There are many factors affecting salivary secretion, including internal and external factors, such as climate, age, food, medicine, health status and even mood. Therefore, the saliva composition is not constant enough. The sensitivity and specificity of the salivary biomarker need to be carefully considered. Reshma (2013) reported that the level of plasma CgA was significantly higher than that in saliva, and the former was dozens to hundreds of times higher than the latter.[27] The associations between plasma CgA and periodontal disease was also stronger than that between salivary CgA and periodontal disease.[27] For another biomarker cortisol, there is a similar situation. The level of cortisol in plasma is significantly higher than that in saliva.[28] Therefore, the diagnosis of hypercortisolism is mainly based on the level of plasma cortisol rather than the level of salivary cortisol. In the previous studies, salivary CgA were used widely in the mental health researches, while plasma CgA were used widely in the somatic diseases, such as cardiovascular disease, endocrine disease, and tumor.[25] There is little literature comparing the advantages or disadvantages between the salivary CgA and plasma CgA. Plasma CgA may be easier to measure accurately and more stable. Little is known about the influence of work stress on plasma CgA levels. We aimed to find the linking mechanism between work stress and cardiovascular disease, so we focused on the plasma CgA. The aim of our study was to investigate the associations between work stress and plasma CgA/catestatin levels in healthy workers without chronic diseases.

2 | METHODS

2.1 | Subjects

All the subjects came from the Emotion and Health among Occupational Population (EHOP) study which

was a registry study to explore the associations between emotional factors and physical health among Chinese occupational population.[29] There were 300 workers anticipated this study when they underwent physical checkups at the Peking University Third Hospital in August 2016. The 32 participants who had a history of chronic diseases or had abnormal results of this physical checkup, such as cardiovascular disease, cerebrovascular disease, hypertension, hyperlipidemia, diabetes mellitus, or immunological disease were excluded, and 8 participants with incomplete questionnaires were also excluded. The final sample was 260. This study was performed in accordance with the Declaration of Helsinki and was approved by the ethnic board of the Peking University Third Hospital. All the subjects provided their written informed consent.

2.2 | Questionnaires

Work stressors were assessed by the Chinese version of the23-item ERI-Q questionnaire developed by Li et al.[30] in accordance with Siegrist's ERI-Q which consists of three dimensions termed extrinsic effort (6 items), reward (11 items), and overcommitment (6 items). Response to each item in the extrinsic effort and reward category is scored on a 5-point scale, and each item in the overcommitment category is scored on a 4-point scale where higher value means higher degree. The total scores of each dimension reflects the degree of work stress. The ERI index was calculated using the following formula: ERI = 11 × effort/6× reward. The 23-item ERI-Q questionnaire was a valid and reliable instrument used widely in the world and in our previous studies. The Cronbach's alpha coefficient of extrinsic effort, reward, and overcommitment was 0.81, 0.87 and 0.79, respectively. The symptoms of anxiety and depression were measured with the Hospital Anxiety and Depression Scale (HADS), which was reported in our previous study.[29]

2.3 | Demographic characteristics

The demographic characteristics, such as age, gender, occupation, marriage, education, body mass index (BMI), were collected from medical records.

2.4 | Assays for blood sample

Fasting blood samples were collected from 8:00 to 10:00 after taking a rest of 20 min on the day of physical examination with one-time venous blood sampling needle. Blood samples were taken into chilled EDTA vacutainers containing 2500 IU/ml aprotinin, then immediately centrifuged at 3000 rpm for 10 min at 4°C, then finally stored at −80°C till analysis. Plasma CgA levels were determined by using ELISA kits (MyBioSource, San Diego, California, USA). Plasma catestatin levels were measured by the catestatin ELISA kits (Phoenix Pharmaceuticals, Burlingame, California, USA) according to the manufacturer's instructions.

2.5 | Statistical analysis

Continuous variables were given as mean ± SD; categorical variables were defined as percentage. Firstly, each work stress variable was divided into three groups (low, intermediate, and high groups) based on the tertiles according to the distribution of scores. Mean concentrations of plasma CgA and catestatin were compared among groups by Anova. Then, each work stress variable was used as continuous variables to explore the associations between each job stress variable and plasma CgA and catestatin by bivariate correlation analysis and multiple linear regression analysis. Each work stress variable was respectively entered into the multiple linear regression models where the model 1 was unadjusted, the model 2 was adjusted for age, gender, occupation, education, BMI, and the Model 3 additionally adjusted for anxiety and depression based on model 2. All tests of significance were two-tailed. Statistical significance was defined as $p < .05$. The statistical analysis was performed by SPSS statistical software (SPSS 20.0 for Windows; SPSS Inc, Chicago, IL, USA).

3 | RESULTS

Among the final 260 subjects, there were 173 males (66.5%) and 87 females (33.5%). They came from different occupational backgrounds (civil servants 33.4%, white collars 51.2%, blue collars 15.4%). The average age was 37.6 ± 10.6 years old, with an average BMI of 23.9 ± 3.3 kg/m^2. The average level of plasma CgA was 134.66 ± 92.90 ng/ml (6.0–430.50 ng/ml); the average level of plasma catestatin was 1.50 ± 0.54 ng/ml (0.37–4.62 ng/ml).

In bivariate correlation analysis, effort, overcommitment, and ERI were positively associated with plasma CgA level, respectively (r = 0.267, 0.319, and 0.304, all $p < .001$), while reward was negatively associated with plasma CgA level (r = −0.237, $p < .001$). There were no

significant associations between each work stressor and plasma catestatin. Table 1 presents the characteristics of the subjects by tertiles of CgA. The workers with high plasma CgA had higher work stress.

When workers were divided into three groups (low, intermediate, and high group) according to the tertiles of each work stressor scores, the workers with high effort, overcommitment, or ERI had significantly higher plasma CgA levels, while the workers with high rewards had significantly lower plasma CgA levels. The workers with both high overcommitment and high ERI had highest plasma CgA levels. There were no significant differences between groups as plasma catestatin levels were concerned (Table 2, Figures 1 and 2).

In the linear regression analysis, effort, overcommitment, and ERI were respectively positively related to plasma CgA, while reward negatively related to plasma CgA. After adjustment for age, gender, occupation, education, BMI, additionally anxiety and depression, the associations were still significant. However, the associations were not found between job stressors and plasma catestatin. The results were given in Table 3.

In our data, the plasma CgA was not related with plasma catestatin ($p = .939$). The ratio of plasma CgA and catestatin was associated with work stress ($r = 0.218$, -0.249, 0.275, and 0.279, all $p < .001$, for effort, reward, ovc, and ERI, respectively).

4 | DISCUSSIONS

In this present study, work stress indicators, such as effort, overcommmitment, and ERI, were significantly and positively associated with plasma CgA levels, while reward was inversely associated with plasma CgA levels, after adjustment for confounders even including anxiety and depression. There were no significant associations between work stressors and plasma catestatin. However, the ratio of plasma CgA and catestatin was associated with work stress.

Despite considerable research into associations between the effort reward imbalance (ERI) model and various health outcomes over the past 20 years, the underlying mechanisms responsible for the association remain unclear. One potential pathway mediating these associations involves the stress-related activation of the hypothalamus–pituitary–adrenocortical (HPA) axis with proceeding alterations in the secretion of its main effector hormone cortisol. Referring to the HPA axis, activation is often reflected in elevated cortisol concentrations. There were several studies showing increased cortisol levels[11,12] when work stress occurred. A recent meta-analysis has suggested a direct association between level of ERI and level of cortisol secretion.[31] However, a few studies observed reduced rather than increased cortisol excretion in association with stressful experience.[32] Marlene Penz et al. reported that there were prospective associations between ERI and cortisol, indicating a blunted cortisol

TABLE 1 Characteristics of the subjects with different levels of CgA

Variables	Low CgA	Intermediate CgA	High CgA	*p* value
Age (y)	37.46 ± 10.92	37.81 ± 10.16	37.44 ± 10.96	.967
Male (%)	57.5	69.8	72.4	.084
Occupation (%)				.823
White collars	8.1	11.6	9.2	
Civil servants	57.5	48.9	47.1	
Blue collars	14.9	15.1	16.1	
Businessmen	19.5	24.4	27.6	
Education (%)				.488
<12 y	27.6	27.9	37.9	
Bachelor's degree	35.6	31.4	26.5	
≥Master's degree	36.8	40.7	35.6	
BMI (kg/m^2)	24.33 ± 3.44	23.656 ± 2.99	23.59 ± 3.41	.271
Effort	11.90 ± 3.98	13.08 ± 4.60	15.20 ± 4.26	<.001
Reward	48.83 ± 6.62	47.21 ± 6.27	44.80 ± 7.97	.001
OVC	12.68 ± 2.91	13.48 ± 3.44	15.08 ± 2.81	<.001
ERI	0.47 ± 0.20	0.5274 ± 0.23	0.66 ± 0.26	<.001

Abbreviations: CgA, chromogranin A; OVC, overcommitment; ERI, effort–reward imbalance; BMI, body mass index.

TABLE 2 Differences of plasma CgA/catestatin between different groups

		Catestatin		CgA	
Variables	**Groups**	**Levels**	***p* value**	**Levels**	***p* value**
Effort	Low	1.51 ± 0.51	.838	108.59 ± 79.05	<.001
	Intermediate	1.53 ± 0.62		135.78 ± 93.67	
	High	1.48 ± 0.54		162.10 ± 98.96	
Reward	Low	1.44 ± 0.51	.245	153.86 ± 94.82	<.001
	Intermediate	1.58 ± 0.56		139.04 ± 101.61	
	High	1.49 ± 0.55		109.93 ± 76.14	
OVC	Low	1.50 ± 0.54	.937	105.59 ± 68.92	<.001
	Intermediate	1.52 ± 0.57		124.83 ± 91.88	
	High	1.49 ± 0.55		172.98 ± 102.40	
ERI	Low	1.51 ± 0.52	.352	110.15 ± 80.37	<.001
	Intermediate	1.56 ± 0.61		128.08 ± 92.16	
	High	1.44 ± 0.47		163.61 ± 97.51	
ERIxOVC	Low	1.53 ± 0.41	.839	95.10 ± 63.65	<.001
	Intermediate	1.51 ± 0.65		129.94 ± 89.69	
	High	1.47 ± 0.40		181.77 ± 103.08	

Abbreviations: OVC, overcommitment; ERI, effort–reward imbalance; CgA, Chromogranin A.

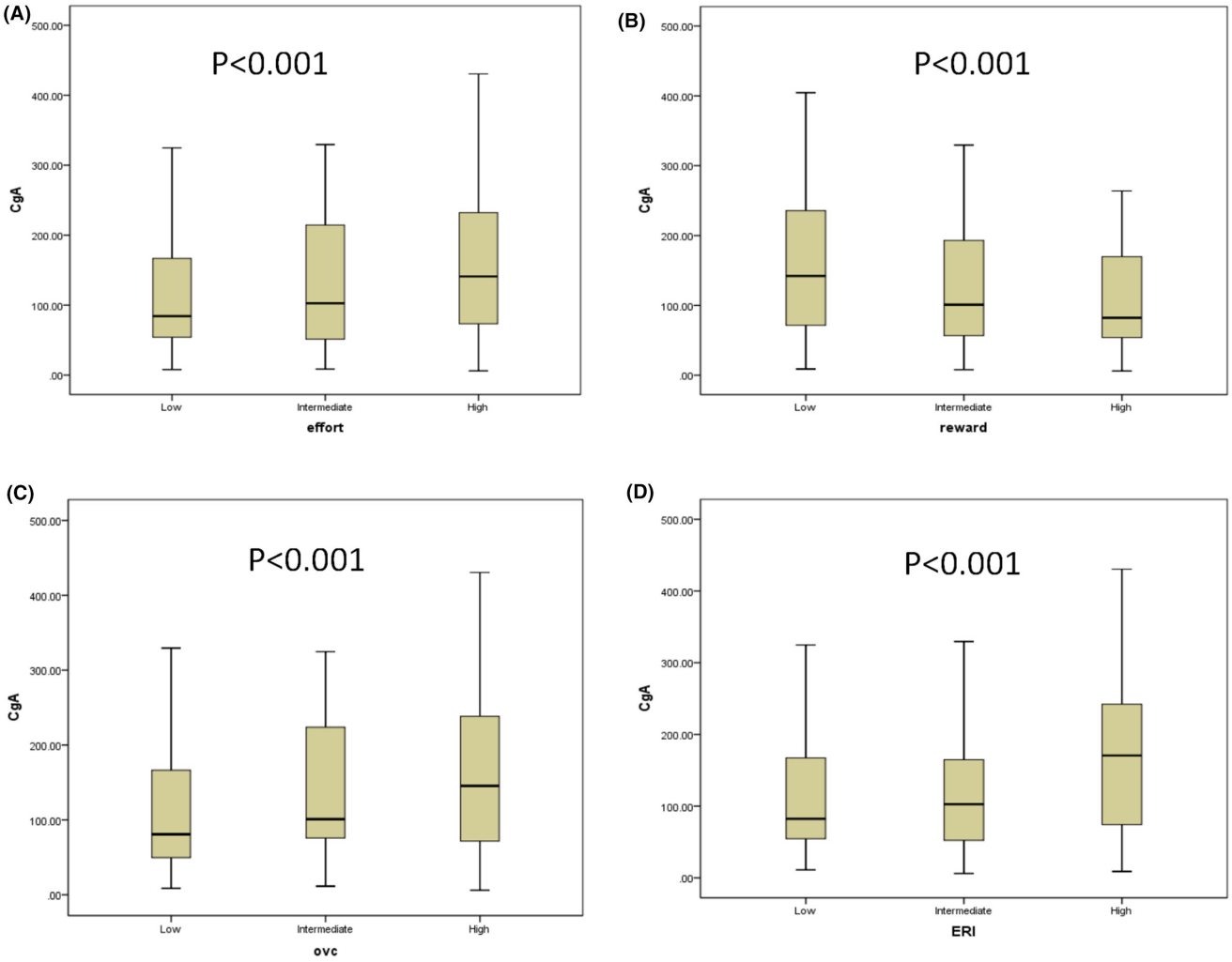

FIGURE 1 Box plot between different levels of work stress and plasma CgA. (A) The CgA levels of different efforts. (B) The CgA levels of different rewards. (C) The CgA levels of different OVC. (D) The CgA levels of different ERI

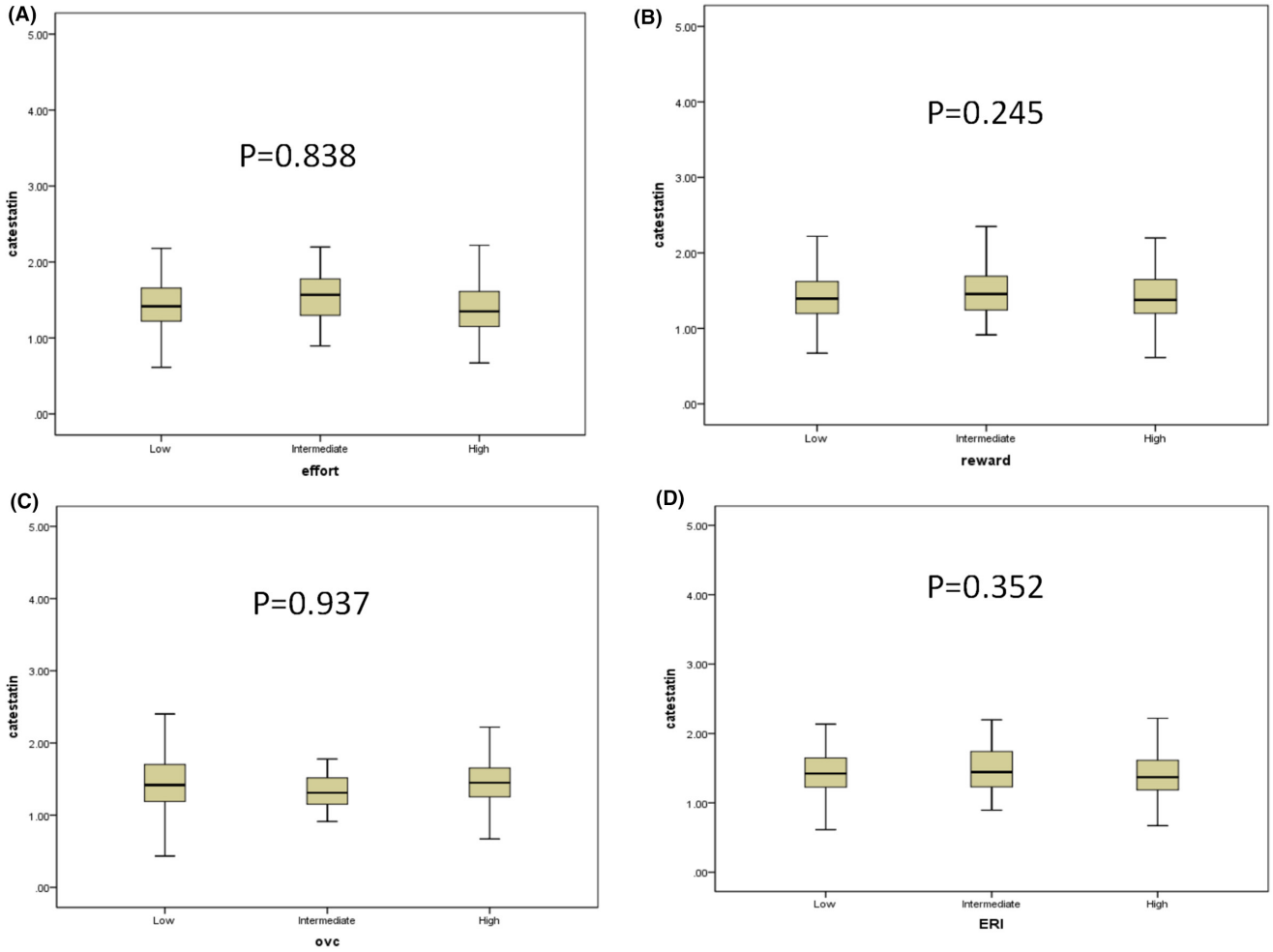

FIGURE 2 Box plot between different levels of work stress and plasma catestatin. (A) The catestatin levels of different efforts. (B) The catestatin levels of different rewards. (C) The catestatin levels of different OVC. (D) The catestatin levels of different ERI

TABLE 3 Associations between each work stress variable and plasma CgA/catestatin by multiple linear regression analysis

	Model 1			Model 2			Model 3		
Variables	**B**	**Beta**	***p***	**B**	**Beta**	***p***	**B**	**Beta**	***p***
Catestatin									
Effort	0.002	0.017	.788	0.007	0.056	.378	0.014	0.116	.106
Reward	0.007	0.087	.163	0.004	0.046	.471	0.002	0.023	.748
OVC	0.003	0.018	.768	0.012	0.071	.269	0.024	0.142	.049
ERI	−0.094	−0.042	.497	0.017	0.008	.903	0.132	0.059	.425
CgA									
Effort	5.533	0.267	<.001*	6.272	0.310	<.001	3.669	0.181	.008
Reward	−3.078	−0.237	<.001*	−3.272	−0.256	<.001	−1.651	−0.129	.052
OVC	9.218	0.319	<.001*	9.328	0.328	<.001	5.796	0.204	.003
ERI	116.090	0.304	<.001*	126.489	0.338	<.001	78.076	0.209	.003

Note: Model 1: unadjusted model; Model 2: adjusted for age, gender, occupation, education, and BMI; Model 3: additionally adjusted for anxiety and depression based on model 2.

Abbreviations: CgA, Chromogranin A; OVC, overcommitment; ERI, effort–reward imbalance.

secretion in response to long-term work stress.[10] Except for cortisol, other indicators of immune function such as leukocytes, cytokines, and immunoglobulins were also investigated. A systematic review and meta-analysis of the effort–reward imbalance model of workplace stress with indicators of immune function by Pennie Eddy showed that greater ERI and overcommitment were both associated with lower immunity.[14] The association between mucosal immunity and ERI was stronger than the cytokine and leukocyte sub-groups. However, there were also studies reporting null associations between work stress and immunoglobulins.[33] These previous studies linking effort–reward imbalance at work with cortisol secretion produced divergent findings due to the varieties of study designs, workers sample, work stress duration, and cortisol measures. A more stable and precise biomarker is needed.

As we know, work stress can influence immunoendocrine responses not only through stimulation of the hypothalamic–pituitary–adrenocortical (HPA) axis but the sympathetic–adrenal–medullary (SAM) system as well. Chromogranin A has a longer half-life, is more stable and easier to handle than catecholamines, and could be an alternative marker for evaluating the SAM response.[34] CgA is a research hotspot in recent years. CgA is co-stored and co-released with catecholamines from storage granules in the adrenal medulla, or with the parathyroid hormone in response to hypocalcemia in the parathyroid gland.[35] Plasma CgA level reflects the sympathetic tone and adrenomedullary system activity. It has been well documented that plasma CgA was related with cardiovascular diseases. Chromogranin A (CgA) has shown promise as a biomarker for evaluating stress.[36]

In our study, work stress indicators such as effort, ERI and overcommitment were significantly related with plasma CgA, while rewards were negatively associated with plasma CgA. Plasma CgA probably played a crucial role on the pathway from chronic work stress to cardiovascular diseases. The findings are in accordance with our previous study which showed that anxiety was related with plasma CgA. There were also other previous studies confirming a correlation between salivary CgA level and anxiety or depression. Serfozo G found that the increased plasma CgA were associated with low social support and severe depressive symptoms in 23 patients with stable coronary heart disease.[37] Matsumoto T found that salivary CgA level significantly and positively correlated with total mood disturbance and four emotional subscales: tension-anxiety, depression-dejection, anger-hostility, and confusion in the late-luteal phase.[22] Robazza et al. (2018) found that elevation of CgA in orienteering athletes on the most difficult loops of the race in terms of both physical and psychological demands.[38]

Catestatin is an endogenous multifunctional neuroendocrine peptide which derived from CgA through proteolytic processing. It has been revealed catestatin is closely related to cardiovascular diseases. There were no previous studies investigating the alterations of catestatin during work stress. In this present study, we did not find the significant associations between work stressors and plasma catestatin. Our results were consistent with the study by Srithunyarat T, which reported that plasma catestatin did not differ significantly between stress group dogs that were unaccustomed to the animal hospital environment and control group dogs that were familiar with the handling and sampling procedures and the animal hospital environment.[39] But they found the dogs in the stress group had significantly higher saliva catestatin concentrations. Studies are needed to make clear whether catestatin may be useful as objective biomarker for stress.

In our study, what we found was that plasma CgA levels were increased among workers with high work stress, but plasma catestatin levels were not significantly different between groups, although catestatin is one of CgA-derived fragments through proteolytic processing. However, the ratio of plasma CgA and catestatin was associated with work stress. CgA-to-catestatin conversion procession might be one of explanations for this phenomenon at present. Ottesen et al found CgA was hyperglycosylated in the failing myocardium in their animal studies, and acute heart failure patients with low CgA-to-catestatin conversion had a worse outcome compared with the patients with higher CgA-to-catestatin conversion in clinical studies.[40] A mechanism for posttranslational protein modification, processing of glycosylated proteins, could be impaired by sugar groups blocking the binding of proteases to cleavage sites. Little is known about the CgA-to-catestatin conversion under stress, further studies are needed.

There are some advantages in our study. Firstly, we focused on plasma CgA. The salivary CgA has been considered as a stress-related biomarker and used in previous studies. There is little literature comparing the advantages or disadvantages between the salivary CgA and plasma CgA. Saliva is convenient to retain samples, but the saliva composition is not constant enough. Previous study showed the level of plasma CgA was significantly higher than that in saliva. Plasma CgA may be easier to measure accurately and more stable. Secondly, we found the associations between work stress and plasma CgA were still significant after additionally adjusted for anxiety and depression. This means that long-term work stress, even if it does not cause anxiety and depression, will also lead to the increase of CgA level. The increase of CgA level is closely related to many cardiovascular diseases, which may also be an important mechanism

for the increased risk of cardiovascular diseases caused by work stress. This is an important finding which may be not consistent with a general stress model in which it is said that under the load of work stress, there is a stress response, which leads to unhealthy mental condition and the changes of biomarkers. Thirdly, we explored not only the associations between work stress and plasma CgA, but also the associations between work stress and plasma catestatin. In our data, we found work stress was associated with CgA, but not with catestatin. The ratio of CgA and catestatin was associated with work. This implies CgA-to-catestatin conversion procession might be one of explanations for this phenomenon. These data will help us to understand the mechanism linking work stress and cardiovascular diseases. Lastly, the subjects in our study were healthy without chronic diseases which may influence the levels of plasma CgA/catestatin.

Several limitations of this study need to be addressed. Firstly, the assessments of work stress were just for one time. As work status is flexible, multiple repetitive assessments may help to evaluate the levels of work stress more accurately. Secondly, as our study was cross-sectional, we could not draw a cause–effect conclusion. Thirdly, this was also only one center study. The study sample size was relatively small. We will carry out large sample, multicenter studies in the future.

5 | CONCLUSIONS

In summary, the present study showed that work stress indicators such as effort, ERI and overcommitment were significantly related with plasma CgA, while rewards were negatively associated with plasma CgA. Plasma CgA may shown promise as a biomarker for evaluating work stress. Plasma CgA probably played a crucial role on the pathway from chronic work stress to cardiovascular diseases. Chronic stress experienced at work is considered a major health challenge for modern societies. Even among the relatively healthy workers, high levels of effort, ERI, and overcommitment have adverse physical effects indicated by CgA. It is necessary to take favorable measures to reduce work stress.

DISCLOSURE

Ethical approval: The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The study was approved by the Institutional Review Board of Peking University Third Hospital. *Informed consent*: The written informed consent to participate in the study was obtained from all participants. *Registry and the registration no. of the study/trial*: N/A. *Animal studies*: N/A. *Conflict of interest*: The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTION

W.X.X. conceived the ideas; X.L., W.M.D and W.X.X. collected and analyzed the data; H.L., Y.L. and Y.S. collected the data; X.L, W.M.D., W.X.X. led the writing.

DATA AVAILABILITY STATEMENT

Data available on request from the authors. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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