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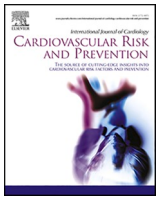

Association of stress hormones and the risk of cardiovascular diseases systematic review and meta-analysis

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ABSTRACT

Background: The roles of endogenous stress hormones (norepinephrine, epinephrine, and cortisol) in cardiovascular diseases have been discussed. However, the higher versus lower level of stress hormones in relation to cardiovascular risks remained uncertain.
Methods: We searched databases from their inception to 31, March 2023. We conducted a meta-analysis to estimate the effect of higher to lower level of stress hormones with random effect model. Subgroup and meta-regression analysis were done to clarify the heterogeneity.
Results: In total, 33 studies involving 43641 participants were included. With regard to cardiovascular disease risks, a higher risk for individuals with higher level of all stress hormones (risk ratio (RR), 1.63; 95 % Confidence intervals (CIs): 1.36, 1.97) was noted compared with lower level of all stress hormones. The meta-regression showed that as the follow-up year increased per year, the impact of higher level of all stress hormones on the risk of cardiovascular disease declined significantly (RR, −0.09; 95 % CIs: 0.15, −0.03, p = 0.006). A significantly higher risk of cardiovascular diseases for individuals with higher level of norepinephrine (RR, 1.68; 95 % CIs: 1.37, 2.06), with higher level of epinephrine (RR, 1.58; 95 % CIs: 1.10, 2.26), and with higher level of cortisol (RR, 1.60; 95 % CIs: 1.04, 2.26) were noted compared with a lower level of each stress hormone.
Conclusion: Higher levels of stress hormones were significantly associated with higher risks of cardiovascular diseases compared with lower levels of stress hormones.

1. Introduction

Cardiovascular diseases encompass a spectrum of conditions, including ischemic heart disease, stroke, heart failure, peripheral arterial disease, and other cardiac and vascular disorders [1]. According to Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019, cardiovascular diseases are the leading cause of global mortality and a major contributor to disability [2]. Notably, the World Health Organization highlights that cardiovascular diseases contribute to an annual total of 40.8 million disability-adjusted life years, encompassing 4.5 million years burdened by disability [2]. Furthermore, statistical data from 2020 reveals a global toll of 19.05 million deaths attributed to cardiovascular diseases and this surge in mortality is captured by an age-standardized death rate of 239.80 per 100,000 population [3]. A lot of risk factors such as tobacco, obesity, sedentary life style, high blood pressure, elevated blood glucose, high blood lipid level, and unhealthy dietary patterns, have been identified in relation to cardiovascular diseases [3]. However, among these numerous risk factors, stress is a non-negligible risk factor. Of particular significance, psychosocial factors have garnered attention for their autonomous association with

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coronary heart disease [4]. Stress, a prominent psychosocial factor, is implicated not only in the early stages of atherosclerosis but also in the precipitous onset of myocardial infarction and sudden cardiac death [5].

Notably recognized as "stress hormones," norepinephrine, epinephrine, and cortisol have emerged as pivotal components in this realm [6]. The functions of stress hormones include augmentation of vascular tone, instigation of cardiac and vascular remodeling, and regulation of renal sodium and water homeostasis [7]. The quantification of norepinephrine and epinephrine is typically achieved through serum and urine analysis, while cortisol levels are assessable via serum, urine, saliva, and even hair specimens [7]. In a general context, heightened concentrations of stress hormones directly correlate with an escalated magnitude of stress response [7]. One cohort study addressed that increased risk of incident cardiovascular events per doubling of urine cortisol; nonetheless, this risk elevation did not achieve statistical significance concerning norepinephrine and epinephrine [8]. Similarly, another cohort study indicated that urine levels of norepinephrine and epinephrine exhibited no discernible correlation with the incidence of coronary heart disease [9].

The implications of endogenous stress hormones (specifically norepinephrine, epinephrine, and cortisol) in the context of cardiovascular diseases have sparked considerable debate. However, the higher level versus lower level of stress hormones as well as the role of stress hormones as continuous variables in the context of cardiovascular disease risks remain uncertain. In light of these uncertainties, the primary objective of this study was to undertake a comprehensive systematic review and meta-analysis to clarify the association between stress hormones and cardiovascular diseases.

2. Materials and methods

2.1. Data sources and search strategy

This systematic review and meta-analysis were conducted with comprehensive keywords and strict definitions. The search process across prominent databases was guided by the Patient/Intervention/Comparison/Outcome (PICO) framework with adherence to the reporting standards set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Table A1). Two independent authors performed the initial search in the database of PubMed, Embase, and Cochrane Library screening for titles, abstract, and index terms in alignment with our keywords from the inception till the end of March 2023. In cases of discrepancies, consultation with a third author was carried out for resolution. The specific keywords employed in the search were as follows: (Stress Hormones) OR (cortisol) OR (epinephrine) OR (norepinephrine) AND (cardiovascular disease). The comprehensive search strategy, outlined in its entirety, is provided in Table A2. To ensure a thorough search strategy that aligned with our PICO criteria, no restrictions were initially imposed on language, publication year, or participant characteristics (including age). The systematic review's protocol, titled "Association of Stress Hormones and The Risk of Cardiovascular Diseases Systematic Review and Meta-Analysis," has been formally registered and is publicly available on PRSPERO under the identification number CRD42023444357.

2.2. Study selection

Our study focused on the primary outcome of cardiovascular diseases, encompassing a comprehensive composite of fatal and nonfatal conditions, including coronary artery disease, ischemic heart disease, myocardial infarction, stroke, cerebrovascular diseases, heart failure, and peripheral occlusive arterial diseases. The inclusion criteria were studies involving adult patients (participants≧18 years old) with or without previous cardiovascular diseases, studies with reports of the association of endogenous stress hormone (norepinephrine, epinephrine, cortisol) in urine, blood, saliva, or hair and the cardiovascular disease related outcome or cardiovascular mortality, studies reporting risk ratio (RR), odds ratio (OR), or hazard ratio (HR), observational studies including case-control and cohort studies and studies published in English. Exclusion criteria were animal studies, trials of medications, studies involving exogeneous stress hormones (eg. administration of medications including norepinephrine, epinephrine, or cortisol), review articles, case reports, conference abstracts, research letters, communications, letters, and non-English studies.

2.3. Data extraction

Five authors extracted the following data independently from each eligible study: the year of publication, the last name of the first author, the study region, the study type, the characteristics of the participants, adjusted variables, measurement of stress hormones and the levels, the cardiovascular outcomes, and the reported RR, OR, and HR by each group. Two authors exchanged their assigned portions to cross-check and verify the extracted data from each other.

2.4. Quality assessment

The Newcastle-Ottawa Scale assessment for nonrandomized studies was performed by two independent authors for assessment of study quality and discussion would be hold with the third author if any discrepancy. The details of the NOS for quality assessment were shown in Table A3-1 to Table A3-2.

2.5. Statistical analysis

We adopted the RR with 95 % CI for the analysis of the outcome in relation to the risk of cardiovascular diseases of each stress hormone. We compared the highest level versus the lowest level of each stress hormones and all together with random effect model using DerSimonian and Laird's methods, assuming that the true effect size was unknown and not the same. We also conducted the meta-analysis of continuous data (β-coefficients type) of stress hormones, which was transformed into the same unit in advance and which could only be compared by the same measurement of serum, urine, saliva, or hair, for the evaluation of change of cardiovascular diseases risk per unit of the stress hormone increase. The results were presented in forest plots, and the heterogeneity between studies were measured by Cochrane Q test and I^2 statistics. The value of I^2 statistics was defined low heterogeneity if it was below 25 %, moderate heterogeneity if it was below 75 %, and high heterogeneity if it was higher than 75 %. Because only dichotomous levels were studies in each study, to estimate the linear trend correlating the reference group and exposure dose of norepinephrine levels with the risk of cardiovascular diseases, we employed the Greenland & Longnecker method.

A subgroup analysis of hormone measurement, mean age of participants, participants with and without cardiovascular history was conducted to estimate the pooled effect and to explain the heterogeneity. A meta-regression to identify the factors (mean age, percentage of different gender, and follow-up year) associated with the relationship of stress hormones and cardiovascular diseases was also administered. In order to assess the reliability of our findings, we conducted a sensitivity analysis by systematically excluding one study at a time and re-evaluating the combined estimates.

We assessed publication bias and small-study effects using funnel plots, and for those studies related to each stress hormone equal to or more than 10 articles, Egger's test Begg's test were conducted.

All the analysis was done using R 4.2.3. with the packages meta, metagen, metafor and ggplot2.

3. Results

3.1. Study characteristics and quality assessment

The search process was illustrated in Fig. 1. Originally, 26751 articles were identified. After exclusion of the duplicated studies, exclusion by screening title and abstract, exclusion by publication type, language, and other factors in accordance with our exclusion criteria, in total, 33 studies involving 43641 participants were included. The details and characteristics of the included studies were shown in Table A4 and Table A5. Among the 33 studies, 22 studies were adopted for highest versus lowest meta-analysis between stress hormones and cardiovascular risk (norepinephrine, 11 studies [10–20], epinephrine, 3 studies [10,12,16], cortisol, 8 studies [19,21–27]); 19 studies were adopted for stress hormones (as continuous variables/β-coefficients type) and cardiovascular risk (serum norepinephrine, 5 studies [14,28–31], serum epinephrine, 2 studies [28,31], serum cortisol, 7 studies [21,32–37], hair cortisol, 3 studies [38–40], salivary cortisol, 2 studies [41,42]).

The included studies were published from 1994 to 2021. Among these studies, the duration of follow-up ranged from 30 days to 16.5 years. The median age of participants ranged from 38.8-year-old to 74.1-year-old. As for the study type, we identified 5 case-control studies and 28 cohort studies. The outcomes of cardiovascular diseases included composite cardiovascular events, cardiovascular mortality, heart failure, cardiogenic shock, significant coronary artery stenosis, stroke, ischemic heart disease, coronary heart disease, and myocardial infarction.

The mean scores regarding to quality assessment of the Newcastle-Ottawa Scale for the included studies was 8.36 ± 0.74 (mean ± standard deviation) (Table A3-1 and Table A3-2). Most of the included articles had a quality score higher than 7 points, which was considered high quality.

3.2. Highest versus lowest meta-analysis

With regard to cardiovascular risk, the result revealed a higher risk for individuals with higher level of all stress hormones (RR, 1.63; 95 % CIs: 1.36, 1.97) compared with lower level of all stress hormones (Fig. 2). A higher risk for individuals with higher norepinephrine level (RR, 1.68; 95 % CIs: 1.37, 2.06) was noted compared with lower norepinephrine level (Fig. A1). A higher risk for individuals with higher epinephrine level (RR, 1.58; 95 % CIs: 1.10, 2.26) compared with lower epinephrine level was presented (Fig. A2). A higher risk for individuals with higher cortisol level (RR, 1.60; 95 % CIs: 1.04, 2.26) compared with lower cortisol level with evidence of heterogeneity ($p < 0.01$, $I^2 = 72$ %) was shown (Fig. A3).

We conducted a meta-regression of age, sex, and follow-up year in term of total cardiovascular disease risk to explain the heterogeneity (Table 1) The univariate meta-regression showed that as the mean age (year) increased, the impact of higher level of stress hormones on the risk of cardiovascular disease increased without significance. As the follow-up year increased per year, the impact of higher level of stress hormones on the risk of cardiovascular disease declined significantly (RR, −0.09; 95 % CIs: 0.15, −0.03). The proportion of women (%) did not modify the effect significantly (Table1.). The bubble plots were shown in Fig. A4 to Fig. S6. R^2 represented the amount of heterogeneity explained by the meta-regression. The subgroup analysis was also conducted by mean age group, geographical area, patient type, and outcome (Table 2). In sum, geographic area and different patient type could explain some degree of heterogeneity.

A significantly higher risk for individuals with higher level of norepinephrine exposure compared with lower level of norepinephrine exposure was shown in the subgroup analysis in the younger group (RR,1.71, 95 % CIs: 1.35,2.17) but not in the older group (RR,1.69, 95 % CIs: 0.99,2.89) (Fig. A7). Meta-regression showed that the risk of cardiovascular diseases for higher level of norepinephrine was non-significant when modified by mean age(year), and follow-up year. As the proportion of women (%) increased, the impact of higher level of norepinephrine on the risk of cardiovascular disease increased without significance. Moderate heterogeneity remained even though we stratified the population by potential confounders of mean age, women proportion and follow-up year (Table A6). The funnel plot of the 11 studies showed asymmetry; the Eggers's test results indicated possible publication bias ($p = 0.009$); the Begg's test results indicated no evidence of

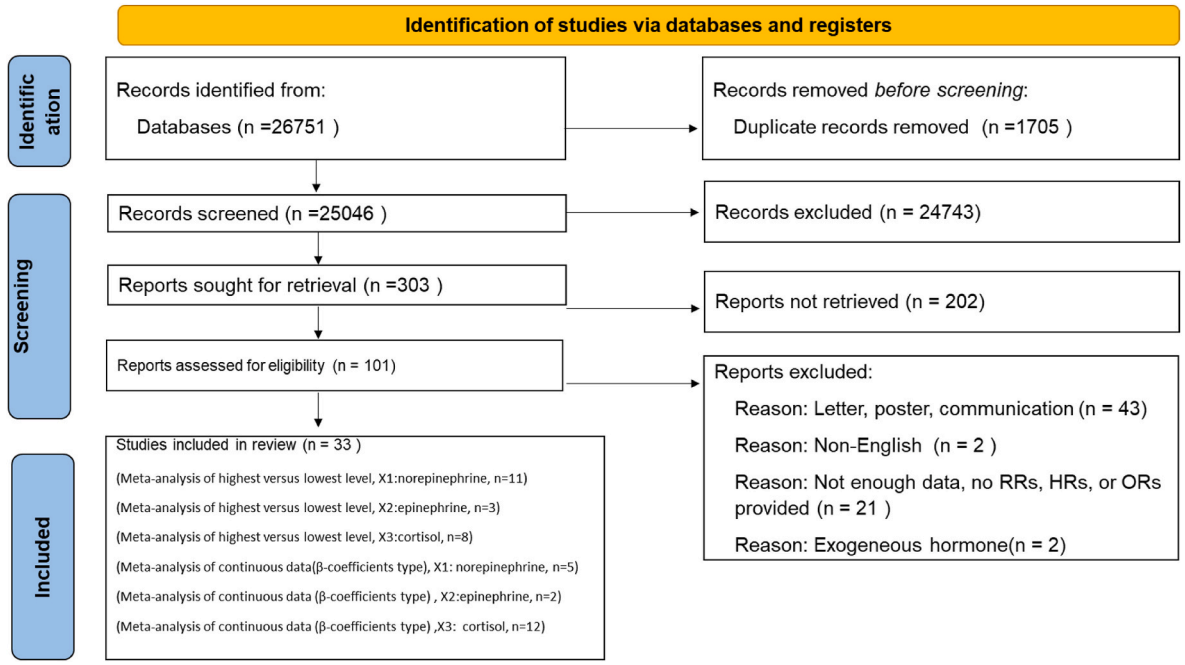

Fig. 1. Flowchart of the literature search for studies investigating association stress hormones (norepinephrine, epinephrine, and cortisol) and the risk of cardiovascular diseases.
Abbreviation: RRs, risk ratios. HRs, hazard ratios. ORs, odds ratios.

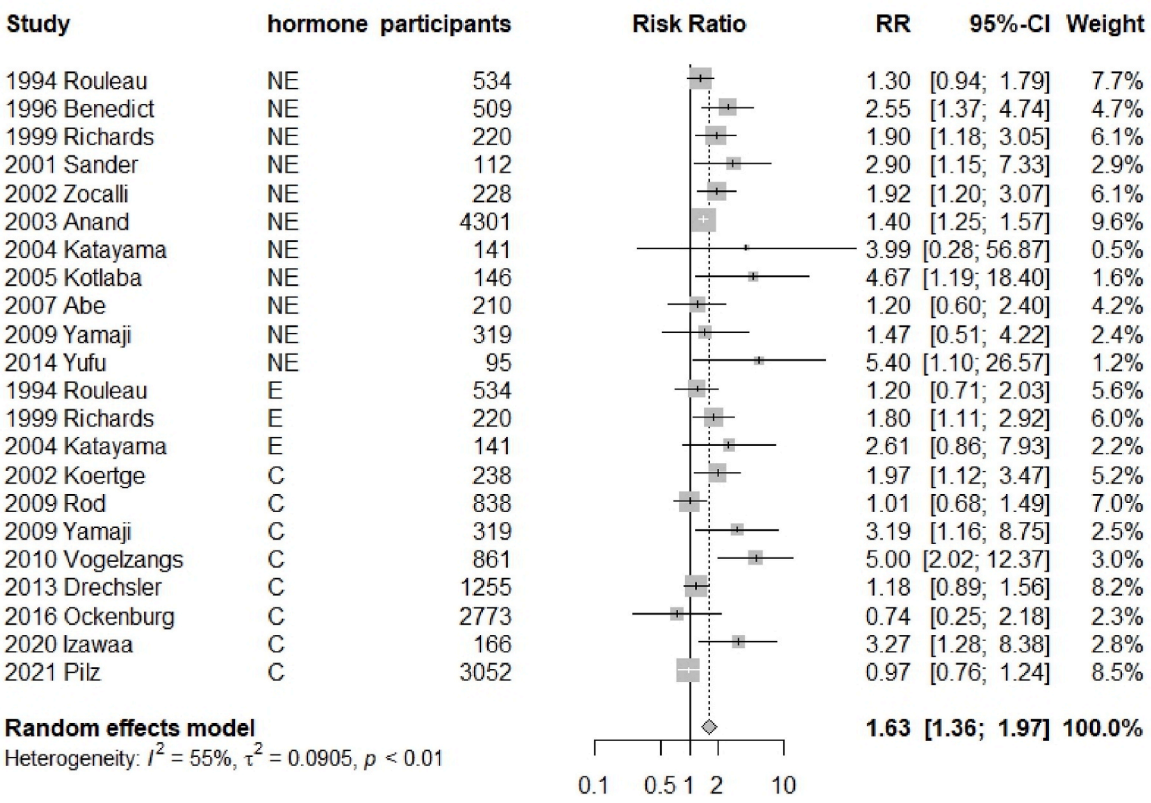

Fig. 2. Forest plot of highest versus lowest level of all stress hormones and the risk of cardiovascular diseases
Abbreviations: NE, norepinephrine. E, epinephrine. C, cortisol. RR, Risk ratios. CI, confidence interval.
Cardiovascular diseases included total cardiovascular disease, composite cardiovascular events, cardiovascular mortality, heart failure, cardiogenic shock, significant coronary artery stenosis, stroke, ischemic heart disease, coronary heart disease, and myocardial infarction.

Table 1
Summary table of meta-regression for the association of highest level to lowest level of all stress hormones and the risk of cardiovascular disease by mean age, percentage of women, and follow-up year of the study.

Meta Regression	Number of Estimates	Point Estimate (95%CI)	I^2 (%)*	p Value*
Mean age (year), per year increase	22	0.04 (−0.01, 0.09)	68.1 %	0.15
Percentage of men (%)	22	1.00 (reference)	NA	NA
Percentage of women (%)	22	−0.20 (−1.00, 0.60)	65.9 %	0.61
Follow-up year, per year increase	22	−0.09 (−0.15, −0.03)	29.3 %	**0.006**

Abbreviations: CI, confidence interval. RR, risk ratio.
*I^2 and p value related to meta regression analysis.

publication bias (p = 0.139) (Fig. A8.).

In the highest versus lowest level of epinephrine and the risk of cardiovascular disease meta-analysis, the funnel plot of the 3 studies showed uncertainty of asymmetry because there was no obvious trend due to few studies (Fig. A9.).

The heterogeneity could be partially explained by stratification of measurement of serum cortisol (Figs. A10–A12). Meta-regression showed that the risk of cardiovascular diseases due high level of cortisol was non-significant when modified by mean age(year) and the proportion of women (%). Also, a non-significance of decreased risk was shown by potential confounders of follow-up year. High heterogeneity remained even though we stratified the population by mean age and women proportion, and the follow-up year may explain some degree of heterogeneity (Table A7.). The funnel plot of the 8 studies showed asymmetry (Fig. A13.).

Sensitivity analyses showed that the overall results were not significantly affected by omitting any single study and the results were robust (Figs. A14–A16).

3.3. *Dose response meta-analysis*

In dose response meta-analysis, considering the numbers of researches, only studies related to norepinephrine were included. Finally, six studies reporting serum norepinephrine and cardiovascular disease risk were included. The risk ratio in the linear model (Fig. 3) indicated that the risk of cardiovascular disease significantly increased by 41 % when 1 nmol/L dose of norepinephrine was measured (RR, 1.41; 95 % CIs:1.10–1.81).

4. Discussion

In terms of cardiovascular risk, our analysis revealed a substantial 63 % increase in risk for individuals with higher levels of all stress hormones compared to those with lower levels. Additionally, an intriguing trend emerged as the duration of follow-up increased each year – the impact of elevated stress hormone levels on the risk of cardiovascular disease displayed a noteworthy decline, signifying a potentially time-dependent effect. When examining each stress hormone individually, specifically, the analysis indicated a 68 % elevated cardiovascular risk associated with higher norepinephrine levels, a 58 % heightened risk linked to higher epinephrine levels, and a 60 % increased risk connected to higher cortisol levels.

Throughout our comprehensive review, it became evident that while the utilization of stress biomarkers varied among different research studies, norepinephrine, epinephrine, and cortisol remained

Table 2
Summary of subgroup analysis for the association the association of highest level to lowest level of all stress hormones and the risk of cardiovascular disease by mean age groups, geographical areas, patient types, and outcomes.

Subgroup Analysis	Number of Estimates	Point Estimate (95%CI)	I^2 (%)*	p Value*
Overall	22	1.63(1.36,1.97)	55.0 %	<0.01
Subgroups				
Age groups				0.53
Not older age (mean age <65 year old)	14	1.39(1.27,1.51)	58.2 %	
Older age (mean age≧65 year old)	8	1.50(1.20,1.87)	55.2 %	
Geographical Areas				0.040
America	4	1.48(1.16,1.89)	56.5 %	
Oceania	2	1.85(1.32,2.60)	0.0 %	
Europe	8	1.23(1.06,1,43)	70.8 %	
Asia	7	2.12(1.43,3.15)	2.8 %	
Multiple	1	1.40(1.25,1.57)	–	
Patient types				0.002
Heart failure	6	1.42(1.28,1.57)	24.7 %	
Myocardial infarction	7	2.08(1.60,2.71)	0.0 %	
Stroke	1	2.90(1.15,7.33)	–	
Coronary artery disease	1	0.99(1.79,1.26)	–	
Acute coronary syndrome	1	0.97(0.76,1.24)	–	
Patients with chronic diseases	3	1.38(1.09,1.75)	66.3 %	
General population	3	1.23(0.87,1.72)	81.9 %	
Outcomes				0.09
Cardiovascular mortality	6	1.26(1.03,1.54)	77.6 %	
Heart failure	2	1.85(1.32,2.60)	0.0 %	
Composite cardiovascular events	11	1.37(1.25,1.50)	34.0 %	
Cardiogenic shock	1	2.61(0.86,7.93)	–	
Significant coronary stenosis	1	1.97(1.12,3.47)	–	
Acute coronary syndrome	1	3.27(1.28.8.38)	–	

Abbreviations: CI, confidence interval. RR, risk ratio.
*I^2 and p value related to subgroup difference.

consistently representative and prominently employed markers [43]. Our review encompassed 11 studies investigating norepinephrine [10–20], 3 studies examining epinephrine [10,12,16], and 8 studies exploring cortisol [19,21–27] in relation to the comparison of higher and lower stress hormone levels. Similarly, within the context of continuous variables and β-coefficients, our review included 5 studies measuring serum norepinephrine [14,28–31], 2 studies measuring serum epinephrine [28,31], 7 studies measuring serum cortisol [21, 32–37], hair cortisol was measured in 3 studies [38–40], and 2 studies measuring salivary cortisol [41,42]. It is evident that the body of literature examining each stress hormone individually remains somewhat limited.

It is noteworthy that the measurement methods for norepinephrine and epinephrine primarily involved serum and urine samples, while cortisol measurement exhibited greater variation, encompassing serum, urine, hair, and saliva samples [44]. It's important to highlight that during our rigorous review process, certain studies involving urine-based measurements of norepinephrine, epinephrine, and cortisol were excluded due to inconsistencies in the measurement units, which underlines the meticulous approach we employed to ensure data quality and comparability [8,9]. These observations underscore the need for further research and comprehensive investigations, ideally with standardized measurement approaches, to contribute to a more robust understanding of the intricate interplay between stress hormones and

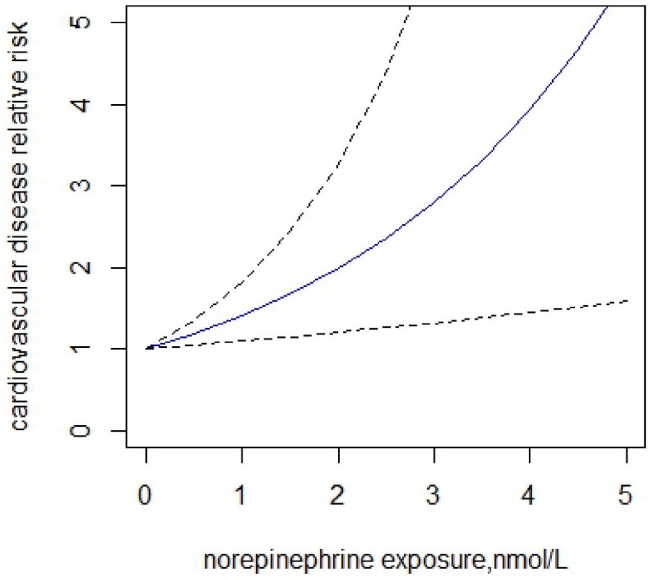

Fig. 3. The linear association of serum norepinephrine and cardiovascular disease.
Heterogeneity: $I^2 = 56$ %; $p = 0.0451$.

cardiovascular disease risk.

The meta-regression analysis exploring the relationship between the highest and lowest levels of all stress hormones and cardiovascular disease risk unveiled a noteworthy and statistically significant trend: a decrease in cardiovascular disease risk with prolonged follow-up time. While no specific research could directly elucidate the potential confounding factors behind this trend, it is reasonable to infer that as time progresses, the previously established risk inferred from laboratory data might gradually diminish. This logical deduction underscores the dynamic nature of cardiovascular risk assessment over extended periods. Additionally, our subgroup analysis provided compelling insights. A majority of the studies encompassed patients with heart failure and myocardial infarction, with relatively fewer involving the general population. Notably, the type of patients included in each study significantly contributed to the observed heterogeneity within our analysis, further emphasizing the importance of patient characteristics in influencing outcomes.

The potential role of catecholamines and cortisol in the pathogenesis of hypertension and their implication in cardiovascular diseases has been underscored by various studies [6,44]. The identification of novel causal risk factors, including elevated morning plasma cortisol, holds promise for refining cardiovascular risk prediction and fostering the development of innovative treatments to mitigate cardiovascular disease-related mortality [36]. However, most prior studies of catecholamines and cardiovascular health outcomes were based on cross-sectional data [8]. Thus, our meta-analysis was with great value for the investigation of stress hormones and cardiovascular diseases among general population or patients already had cardiovascular diseases.

A compelling meta-analysis has demonstrated an augmented risk of cardiovascular diseases among individuals facing work-related stress [45]. Despite recognizing the role of central mediators and stress responses in the context of stress hormones, the precise mediation mechanisms underlying the resulting cardiovascular disease outcomes remain incompletely characterized [46]. Plausible mechanisms connecting stress hormones and cardiovascular diseases encompass a spectrum of acute and chronic stressors such as anxiety, depression, fear, abuse, and low socioeconomic status as initial triggers [47,48]. These stressors subsequently activate our autonomic nervous system, orchestrating the

sympathetic nervous system and the sympatho-adrenomedullary system to respond to stressors, leading to the secretion of norepinephrine and epinephrine in response [45,49]. These stress hormones exert direct cardiostimulatory effects via β1-adrenergic receptors and pressor effects through α1-adrenergic receptors [49]. An alternative pathway is the activation of the hypothalamic-pituitary-adrenal axis in response to stressors, resulting in the secretion of cortisol. Subsequently, cortisol interacts with glucocorticoid receptors in the vasculature, influencing blood pressure regulation, endothelial cell function, and the expression of inflammatory markers such as nitric oxide, angiotensin II, and endothelin I [50]. In concert, these stress hormones contribute to an elevated risk of cardiovascular diseases [44].

There were several strengths in our studies: (1) This is the first systematic review and meta-analysis to clarify the association of stress hormones and the risk of cardiovascular diseases. (2) our analysis delved deep into the involvement of norepinephrine, epinephrine, and cortisol within the pathogenesis of cardiovascular diseases. (3) we performed the subgroup analysis, encompassing geographical area, hormone measurement, different age groups, patient types, and study outcomes, considering the multifaceted factors that might influence the relationship between stress hormones and cardiovascular diseases. (4) our utilization of meta-regression, exploring mean age, proportion of women, and follow-up year, serves to enrich our comprehension of the complex interplay between stress hormones and cardiovascular diseases, providing more context to our results. However, our study also acknowledges certain limitations that warrant consideration: (1) there were a scarcity of studies examining each stress hormone. (2) high heterogeneity was noted among observational studies. (3) the varying units of measurement for different stress hormones introduce difficulties in aggregating and comparing results across studies, potentially influencing the overall findings. (4) the data and the studies were insufficient to do the dose-response meta-analysis. (5) Except for the three stress hormones analyzed in our study, there are additional stress hormones—dopamine, metanephrine, and normetanephrine—that were not included in our analysis. Future investigations focusing on these stress hormones are warranted. Finally, it is possible that the timing of sample collection affects the observed changes in stress hormone levels, especially for cortisol, which has a natural diurnal variation. However, while the collection time impacts the absolute values, it does not affect the relative levels (dichotomous, trichotomous, quartiles). Given the limited number of studies, a more extensive subgroup analysis considering the time of collection is needed in future research. Additionally, the method of sample collection—whether by blood, urine, or hair—affects the characterization of stress hormone changes. Acute changes are more likely to be reflected in blood samples, while chronic changes may be more accurately represented in urine and hair samples. These are significant limitations of our study.

5. Conclusion

In conclusion, our study delivers compelling evidence suggesting a significant association between higher stress hormone levels and an increased risk of cardiovascular diseases. It also highlights the need for further research to unravel dose-response dynamics and address the limitations inherent in our study.

CRediT authorship contribution statement

Szu-Ying Tsai: Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Jui-Yun Hsu:** Investigation, Methodology, Software. **Ching-Huang Lin:** Data curation, Formal analysis, Investigation, Validation. **Yen-Chun Kuo:** Data curation, Formal analysis, Validation. **Chi-Han Chen:** Data curation, Formal analysis, Visualization. **Hsing-Yuan Chen:** Data curation, Formal analysis, Validation. **Shu-Jung Liu:** Validation, Methodology, Project administration. **Kuo-Liong Chien:** Conceptualization, Methodology, Project administration, Supervision.

Declaration of competing interest

The authors declare no potential conflicts of interest.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2024.200305.

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