

Cortisol Stress Hormones as a Psychobiological Mechanism in Coronary Artery Disease: A Critical Review

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ABSTRACT

Coronary artery disease (CAD) is the most common type of heart disease and affects the lives of 1 in 20 adults. CAD-associated healthcare costs are estimated to exceed \$200 Billion annually in the United States alone. Psychosocial stress, mental distress, depression, and fatigue are all linked to CAD. While the underlying mechanisms are not fully understood, the involvement of cortisol in inflammation in the pathophysiological process in CAD has been demonstrated. The literature has documented some modifiable risk factors for CAD, such as diet and exercise; however, the scope of information on stress as a modifiable risk factor is limited. This critical review paper analyzed four empirical studies published between 2019 and 2023, all of which reviewed the role of cortisol stress hormones in CAD. The results of all four studies revealed that cortisol levels are associated with CAD, though the direction and magnitude of the relationship varied between studies. An overview of each study is provided, including a review of the methodology used, a summary of the main findings, and a discussion of limitations.

Keywords: Coronary Artery Disease, CAD, Stress, Cortisol

It is estimated that coronary artery disease (CAD) affects 1 in 20 adults and accounts for 2 in 10 deaths of adults under the age of 65 years [1]. CAD is both the most common type of chronic heart disease, as well as the leading cause of death in the United States, accounting for 375,476 deaths in 2021 [1-3]. This cardiac condition is impacted by inflammation and falls into the category of chronic heart disease involving atherosclerosis of the coronary arteries. The hardening of the coronary arteries results from adhesions forming on the arterial walls [4]. Annual healthcare costs related to CAD exceed \$200 Billion in the United States [5]. Studying chronic cardiac conditions is considered a public health initiative that can help lessen the burden of these diseases on the healthcare system. CAD, while a significant cause of mortality and disability, is largely preventable [5]. As such, there has been dedicated research into the mechanisms underlying disease development and progression of chronic cardiac conditions like CAD in the past four decades [4,5].

Depression and psychosocial stress have been linked to CAD, though the underlying mechanism of this association is not well

understood [6]. There are both modifiable and nonmodifiable cardiovascular disease risk factors. Modifiable cardiac risk factors include stress, obesity, hypertension, diabetes, smoking, poor diet, sedentary lifestyle, and hyperlipidemia. Reducing modifiable risk factors has proven effective in reducing some of the healthcare burdens posed by CAD, both economic and disease-related [5]. There is limited evidence linking modifiable risk factors like depression and psychosocial stress to cortisol in CAD patients. However, cortisol involvement in atherosclerosis and inflammation is an emerging topic of interest in the literature [6]. The focus on modifiable risk factors has contributed to a decrease in CAD-related mortality despite increased spending related to cardiovascular disease due to increased cost of care and population aging [5-8].

Positive outcomes have emerged from interventions targeted at modifiable risk factors, resulting in increased interest in nonmodifiable risk factors. There is a growing body of literature that examines the biological mechanisms associated with CAD, including the link between cortisol and CAD. Previously understood as a cholesterol-storage disease, atherosclerosis is now viewed as an inflammatory condition [4]. The impact of

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chronic cortisol dysregulation has been the focus of research into inflammation and general cardiovascular disease [9-11]. This paper aims to review recent literature focused on the role of cortisol and CAD and the cardiovascular risk factors mediating that association. Four studies from the last five years will be critically reviewed to deepen the understanding of the relationship between cortisol and CAD.

Brain Structures Involved in Cortisol and Stress Response

Cortisol is a glucocorticoid stress hormone released as a normal physiological response to stress through the hypothalamic-pituitary-adrenal (HPA) axis [12]. The effects of cortisol in the brain are mediated through glucocorticoid receptors, which are found throughout the brain structure, but the effects are especially evident in areas with higher concentrations of these receptors, like the hippocampus [12,13]. Short-term stress leads to acute changes in cortisol levels, which modulate inflammation and lead to glucose metabolism to provide energy [10]. However, when an individual experiences chronic stress, it may result in a blunted cortisol stress response, contributing to widespread inflammation [6,10]. Sustained elevation of cortisol levels can negatively impact cardiometabolic changes in the body and is also linked to deleterious effects on different brain structures. A decreased brain volume has been found in individuals with chronically elevated cortisol levels. There are also significant implications for the medial prefrontal cortex [13].

Psychological stress and the biochemical components of thrombosis have been correlated, ultimately leading to a predisposition toward cardiovascular disease via coagulation pathways [14]. Neurohormonal changes mediated by the HPA axis, when compounded by stress reactions, can lead to changes in thrombotic activity [14]. Cortisol is a prothrombotic mediator which increases clotting. Changes in the presence of prothrombotic mediators, primarily increased circulation of these mediators in the blood, can increase an individual's risk of CAD [4].

Neurological Models Underlying the Relationship Between Stress and CAD

As previously explored, exposure to chronic stress can lead to dysregulation of the HPA axis and blunted cortisol responses. Repeated exposure to sustained, elevated cortisol levels can impact neurogenesis, synaptogenesis, and axon development [12]. Structural changes in the hippocampus associated with cortisol levels can lead to changes in neural structure, impact neuronal excitability in the hippocampus, and result in altered hippocampal function [12].

Dysregulation of the HPA axis is a primary psychoneurobiologic response to stressful stimuli. It has been proposed that this potential mechanism links stress with cardiovascular disease [7,15]. The HPA axis helps maintain homeostasis, adapting to environmental changes through a hormone cascade involving the hypothalamus, pituitary gland, and adrenal cortex. This cascade begins with the release of corticotropin-releasing factor (CRF) and vasopressin, which stimulate the production of adrenocorticotrophic hormone (ACTH) and prompt the pituitary to release cortisol [16]. The neurobiological link between cortisol and CAD is documented, though not well-understood. Research has examined whether there is evidence to support the model of HPA-axis involvement in the pathophysiology of CAD.

Further examination of the psychosocial factors that impact arteriosclerosis development may reveal additional biological pathways [17,18]. Research by Hamer et al. found that mental stress was correlated with calcification of the coronary arteries due to cortisol reactivity [19]. Another possible biological mechanism proposed by Lippi et al. and von Kanel et al. suggests that increased fibrinogen concentrations could be due to elevated cortisol levels leading to hypercoagulation [20,21].

Critical Review

The past five years have yielded several studies that examined the relationship between cortisol, stress response, and CAD. Since 2019, four critical studies have been published on this topic, and these are the ones that will be critically reviewed [7,17,22,23].

In the first article to be reviewed, Bergquist and colleagues underscored the importance of identification of risk factors to use as targets for therapeutic interventions [7]. The authors hypothesized that hair cortisol concentration (HCC) would be a valuable biomarker in evaluating the impact of chronic stress on the pathogenesis of CAD [7]. Hair cortisol concentrations were evaluated as a promising biomarker given the possibility of quantifying total cortisol secretion over several weeks, compared to serum, salivary, and urine cortisol samples, which are subject to diurnal cycles [7,16,24]. Prolonged cortisol reactivity can be measured through hair cortisol concentration (HCC), with each centimeter of hair length correlating with one month of cortisol production [7].

In their literature review, Bergquist et al. highlighted the body of literature supporting the impact of psychosocial factors on the pathogenesis of cardiovascular disease, which has yet to elucidate the underlying mechanisms of the relationship between stress and cardiovascular disease [7,15,25]. This study addresses the inconclusive results from previous studies that looked at cortisol levels as a means of connecting HPA axis dysregulation from chronic stress with CAD. Bergquist and colleagues postulated that the variation in prior findings may be the result of variation in biomarkers from acute versus chronic stress and cited it as a potential limitation [7]. This limitation informed the researchers' use of hair cortisol concentrations in their methodology, as it has been deemed a reliable way to measure repeated cortisol reactivity [7,26].

This study used subjective measures of stress to examine the link between stress and CAD and to look at resilience as a factor relating to HCC and CAD. The researchers considered the sample included in prior studies, which were conducted on a small scale, and were limited in their ability to draw any conclusions about the directionality of the relationship between excess cortisol and cardiovascular disease [7]. Using a cross-sectional study design, Bergquist and colleagues analyzed a population recruited from an academic health clinical practice to test the hypothesis that there would be a stronger association with CAD when objective measurements of HCC to evaluate neuroendocrine stress reactivity compared to participants' evaluation of their subjective stress experience [7]. A total of 499 patients were recruited for the study from May to October 2017. From this group, twenty-four participants were included in the cohort (N = 24), constituting a representative sample of the patients seen in the study period. The only noted inclusion criteria was based on a participant's

willingness. Study participants were required to submit blood and hair sample collections and to complete some questionnaires. Given this requirement, individuals with insufficient hair volume were excluded from participating in the study.

Participants were placed into one of two groups based on their CAD status. The presence of CAD was determined by a confirmed history of CAD ($N = 4$), the presence of coronary arterial calcium CT score greater than zero ($N = 3$), or both. ($N = 2$). Inclusion in the non-CAD group required the absence of documented CAD history ($N = 6$) or a CT score of zero ($N = 9$). The mean age in the CAD group was 60.8 years ($N = 9$) and 51.1 years in the non-CAD group ($N = 15$). All nine individuals in the CAD group were male, while eleven were male in the non-CAD group, and four were female [7].

The measure of HCC involved the collection of one inch of hair, cut as close to the scalp as possible. Following retrieval, hair samples were washed and ground down before taking the HCC measurement. Exogenous factors that posed as potential confounders included hair-washing behaviors and history of hair treatments [27]. A questionnaire was used to collect information on the exogenous confounders. Information was collected on the frequency of hair washing and the use of hair dyes, bleaching products, curling products, or permanent straighteners in the preceding three-month period. Hair washing frequency, measured in times per week, was similar in the CAD and non-CAD groups, as were hair dyeing and bleaching behaviors. It was found that these differences between groups were not statistically significant [7].

Subjective measures were used to gather data on perceived stress and resilience. Bergquist and colleagues utilized the 10-item Perceived Stress Scale (PSS) and the 25-item CD-RISC questionnaire [7]. The PSS assesses stress in the last month via a self-report measure where individuals score life events as stressful on a scale of zero to four. Scores on this measure range from zero to forty, with increasing scores equating to higher levels of perceived stress. The CD-RISC questionnaire measures resilience in terms of ability to cope with stress. Total scores on the CD-RISC can range from zero to 100, with each item scored on a five-point scale. Higher scores on this measure are equated with greater resilience. Stress was also measured objectively using serum DHEA-S values, which are released from the adrenals during the stress response. DHEA-S is reported in micrograms per milliliter, with values ranging from 0.3 to 30 ng/ml [7].

Statistical analyses were performed on each variable (sociodemographic, stress, resilience, CAD prevalence, CAD risk factors), specifically utilizing a stepwise regression modeling approach. Poisson regression analyses were selected to overcome the overestimation of the relative risk of disease prevalence. The results indicated that 38% of participants had CAD, and mean PSS scores were lower in the CAD group than in the non-CAD group. HCC was also lower in the CAD group than in the non-CAD group. These results reinforce earlier findings by Nijm et al., which indicated that CAD patients exhibit a significantly blunted cortisol response when exposed to physical and psychological stress [28]. Furthermore, CAD patients were found to have flattened diurnal slopes due to elevated cortisol levels at bedtime and a higher 24-hour

secretion of cortisol [28]. Additionally, Bergquist and colleagues also found a significant relationship between HCC and CAD in the adjusted Poisson regression [7]. Once CAD risk factors were controlled for in the model, the risk of CAD increased 16-fold when dyslipidemia was present. There was no significant association between resilience variables and CAD, nor was a change in the relationship between HCC and CAD found when resiliency variables were included [7].

Among the limitations of this study, participants needed sufficient hair volume to be included. Additionally, baseline risk for CAD was not accounted for in the population. Finally, a small sample size was used to conduct this research. Future research could build on this study, using similar methods in a larger population with baseline CAD risk being considered. Bergquist and colleagues' findings supported the finding that hair cortisol concentrations are related to chronic stress and CAD [7]. Given this association, more research is needed to address the limitations outlined and better evaluate the magnitude of the relationship between CAD and HCC. Despite the 1.1 to 1.6-fold increased risk of CAD to adults with work or private-life stress, limited studies have been conducted on the role that HCC has on cardiovascular disease [15,29]. The work by Bergquist et al. underscores the importance of continuing this research to understand the relationship better [7].

Research from Gecaite-Stonciene and colleagues examined the relationship between cortisol responses to stress, distress, and health-related quality of life in individuals with CAD [22]. Underscoring this research is the relationship between psychosocial stress and the pathophysiology of CAD, as prolonged stress exposure is a major risk factor in the development and progression of cardiovascular disease. Psychological variables have been known to impact the lives of patients with chronic cardiovascular conditions. However, little research has been conducted to examine the influence of such psychological variables on CAD patients' cortisol stress responses. The variables of interest included anxiety, depression, health-related quality of life, and fatigue. The authors document that HPA axis dysregulation, leading to the secretion of stress hormones like cortisol, can be a predictor of heart conditions like CAD.

The included literature review for the article cited Nijm et al., highlighting that CAD patients exhibited different cortisol responses to stress than their healthy counterparts. Blunted cortisol responses, as can be seen in individuals with CAD, have also been linked to several mental health conditions [6,10,28,30,31]. Gecaite-Stonciene and colleagues postulate that psychological and health-related factors may be linked to CAD via dysregulation of the HPA axis. The study aimed to investigate how cortisol is linked to stress, fatigue, mental distress, health-related issues, and quality of life [22]. The authors hypothesized that lower cortisol levels would be measured during the Trier Social Stress Test (TSST) when mental distress was elevated [22].

The study participants were recruited upon admittance to a rehabilitation program. A total of ninety-eight individuals were included, with a mean age of 52.92 ($SD = 7.17$). The population comprised 87.8% men ($N = 86$) and 12.2% women ($N = 12$). Fifty percent of participants were educated at the high school

level, while the other 50% held a college degree. Diagnosis at admission and medications taken were also collected. Baseline clinical data was collected from participants' medical records, including current and prior nicotine use and body mass index (BMI). Information regarding anxiety, depressive symptoms, fatigue, and trait anxiety was collected using self-report measures [22].

Gecaite-Stonciene et al. utilized a cross-sectional study to examine CAD patients 2-4 days after admission to a rehabilitation center (N=98) [22]. The Trier Social Stress Test (TSST) and Paced Auditory Serial Addition Test (PAUSAT) were used to collect cortisol samples. The TSST exposed participants to various sections, such as public speaking and arithmetic tasks. An alteration was made to the arithmetic task of the TSST, where the PAUSAT was used in place of the standard protocol. The PAUSAT required participants to listen to a voice recording, which dictated numbers from one to nine. After each number was presented, the participant had to sum the value of the new number with the preceding one and announce the response aloud. Salivary samples were collected at baseline before the task and again at ten, fifteen, twenty-three, and thirty-eight minutes. Commercial enzyme kits measured the cortisol levels in each sample collected. Fifteen outliers were excluded from the study before statistical analyses were run. The relationship between cortisol and mental distress, health-related quality of life, and fatigue was evaluated using univariate regression.

The results supported the study hypothesis, in part, though the findings were non-significant. There was, however, a significant increase in cortisol in response to TSST. Diminished cortisol levels were significantly associated with higher anxiety and Type D personality. Overall, cortisol levels were elevated at the points following baseline. The stress reactivity in patients with CAD continued past the completion of the TSST tasks and did not return to the participants' baseline levels [22]. Notably, the TSST measured acute and short-term stress responses rather than chronic stress using salivary samples [7,24].

The use of salivary cortisol samples is one of the potential limitations of the study by Gecaite-Stonciene and colleagues [22]. The relationship between CAD and cortisol is typically looking at chronic stress, which salivary cortisol samples cannot reliably measure due to the rhythmicity of cortisol [7,24]. Additionally, this study did not compare patients with CAD to a control group. While the elevated cortisol levels were evidenced in the CAD patients and remained elevated after the conclusion of the stressful tasks, there is no comparison group to determine if this is typical of all patients or more prevalent in those with cardiovascular disease. This limitation offers a potential direction for future research. Researchers could repeat the study with a larger group and include a control group to compare the cortisol levels in CAD vs. non-CAD patients.

Research published in 2022 by Stomby and colleagues also examined the relationship between hair cortisol concentrations and CAD. The authors emphasize that there is a primary focus on preventing CAD through the control of modifiable risk factors like smoking, hypertension, dyslipidemia, and diabetes. Patients without the presence of modifiable risk factors, however, make up about fifteen percent of those admitted for ST-segment

elevation myocardial infarction (STEMI) and are at elevated risk of death following their cardiac event. Stomby et al. highlight the importance of finding other risk factors that contribute to CAD in patients without modifiable risk factors [23]. Given the focus of this research, the primary outcome studied was the link between CAD and hair cortisol concentrations [23].

The study by Stomby et al. involved a cross-sectional design involving participants from two prior studies: the Swedish Cardiopulmonary Bioimage Study (SCAPIS) and the Stressheart study [23]. A total of 203 patients were included in the Stressheart Study, and another 3,134 from the SCAPIS study were included as controls. Exclusion criteria for the CAD group from the Stressheart Study included hair length of less than one centimeter, advanced age greater than 65 years, and not speaking Swedish. For the control group, a history of cardiovascular disease, including CAD or a lack of provision of hair samples, excluded participants from the study. Participants from the CAD group (N = 203) had a mean age of 57.7 years (SD = 6.5). This group comprised fifty-six females (28%) and fifty-six current smokers. Other information, including previous cardiac events, BMI, and the presence of modifiable risk factors, was also provided for the group. The group without CAD (N = 3,134) was comprised of sixty-four percent females (N = 1,994) and had a mean age of 57.3 years (SD = 4.4).

Hair sampling required the collection of at least one centimeter of hair, which was analyzed using competitive radioimmunoassay (RIA). Participants in both the CAD and control groups answered questionnaires to collect demographic, risk factors, and diagnostic information. The median hair cortisol concentration in the CAD group was 75.2 (IQR = 167.1) compared to the median HCC of 23.6 (IQR = 35.0) in the non-CAD group. Statistical analysis revealed that the hair cortisol concentrations required logarithmic transformation since they were not normally distributed [23].

The results of this study confirmed a link between CAD and HCC. The data indicated that HCC was three times higher ($p < .0001$) in participants with CAD than in the non-CAD group. While seventy-one percent of individuals in the non-CAD group did not have any standard modifiable risk factors, only thirty-two percent of individuals in the CAD group had zero standard modifiable risk factors. The results of this study indicate that higher logarithmic HCC was associated with larger waist size, as well as a diagnosis of diabetes, hyperlipidemia, or hypertension. Females had lower logarithmic HCC than their male counterparts. Finally, logarithmic HCC was also associated with CAD, and there was an increased risk of CAD noted for smokers and those individuals with hypertension, hyperlipidemia, and diabetes [23]. Stomby and colleagues concluded that long-term cortisol elevation may be more related to the presence of modifiable risk factors than it is to CAD [23]. The authors found that around eighty percent of the association between HCC and CAD was indirect. Therefore, risk factors may mediate the association [23].

Some methodological limitations for this study were identified. First, data was gathered from two cohorts, expanding the possibility of systematic errors. Also, hair samples for individuals in the CAD group who were admitted for acute myocardial

infarction (AMI) were collected from the hospital. It is possible that the weeks leading to the cardiac event were more stressful, and therefore, HCC could have been higher as a result of that persistently elevated stress level. One final limitation is posed by the potential failure to diagnose CAD. Stomby et al. posed a solution for this as an option for further research [23]. Future studies could consider using diagnostic imaging to detect the presence of atherosclerotic plaques.

In summary, Stomby et al. illustrated that certain modifiable risk factors mediate an indirect association between cortisol and CAD [23]. Patients with chronic elevation of cortisol may be more prone to cardiovascular risk factors and, therefore, are at a higher risk for cardiovascular disease. Future research directions may benefit from examining the link between inflammation and hair cortisol concentrations. Finally, longitudinal studies allow the investigation of causal relationships between CAD and elevated cortisol, as mediated by modifiable risk factors [23].

Using similar methods to Stomby et al. and Bergquist et al., Izawa et al. also investigated the onset of acute coronary syndrome (ACS), a type of CAD, and its association with cortisol levels [7,17,23]. In this study, cortisol was measured not only via hair cortisol concentration but also through fingernail concentrations. A notable difference in this research is the exclusive focus on middle-aged and elderly males [17]. The authors hypothesized that there would be higher HCC and fingernail cortisol levels in patients with ACS due to the impact psychosocial stress has on the onset of cardiovascular disease. Cardiac risk factors, like hypertension and dyslipidemia, and some psychosocial factors, like stress, were controlled for in this study [17].

As Bergquist and colleagues reported, Izawa et al. explained the use of hair cortisol concentrations as the more reliable option for measuring longer-term hormone levels [7,17]. Accumulating the stress hormone from the preceding weeks can lead to findings demonstrating chronic versus acute stress. Much like one centimeter of hair can illustrate the amount of cortisol secreted in a month, similar logic can be applied to using nail samples for cortisol. Nails grow at a rate of about one millimeter every ten days; therefore, sampling a millimeter section of fingernail could provide insight into the amount of hormone secreted over about ten days [17,32]. Research has shown that cortisol measured in fingernails may correlate with levels detected in salivary samples five months earlier [17,33,34]. Given the ease with which nail and hair samples can be collected, the authors opted to include this methodology.

Arteriosclerosis in coronary arteries can be impacted by psychosocial distress and chronic stress, which can lead to ACS presentation. The aim of the study by Izawa et al. was cited as an exploration of the onset of ACS and its relationship to cortisol levels measured in hair and nail samples [17]. The researchers utilized a case-control study of seventy-three men from Japan diagnosed with ACS by clinical history and ECG and plasma enzyme readings from a cardiologist. Participants were included in the study an average of 20.6 days (SD = 8.9) after the onset of acute coronary syndrome. The ACS group was compared to a control population of men aged 35-79 (N = 93). Inclusion criteria for both the study and control groups required that participants be males aged 35-79 years with no prior Cushing's

disease or adrenal dysfunction, no history of cardiovascular disease for controls or no recurrent acute coronary syndrome for patients, and no steroid medication use in the six months leading up to the sample collection. The mean age of participants in the control group (N = 93) was 59.6 years (SD = 9.2), which was not significantly different from the mean age of 60.5 years (SD = 9.4) in the ACS patient group ($p = 0.567$). Body mass index and obesity were also similar between the groups. Smoking status in the patient group was significantly higher than in the control group. Other significant differences between groups were found in education level, stressful events in the prior six months, HDL, and dyslipidemia [17].

Sociodemographic information was collected via a self-report questionnaire, including marital status, smoking history, educational level, working history, and hair and fingernail grooming behaviors. The other questionnaire used was a Japanese scale to measure stressful life events like death or change in employment status. The Social Readjustment Rating Scale uses a yes/no response format to assess the experience of twenty-eight different stressful events in the past six months. A total of 155 hair and 162 fingernail samples were tested for cortisol levels after excluding samples that fell outside of acceptable levels and ones that were subject to errors for technical or collection reasons [17].

Collection procedures for hair and fingernail samples were detailed in the paper's methodology. For patients with recent ACS onset, defined as taking place within less than six months at the time of sample collection, hair samples of up to six centimeters were cut as close to the scalp as possible. Fingernail samples were collected directly by participants following the process of growing out the nails for a period of two weeks. Fingernails from each digit were clipped directly into a resealable bag to ensure complete sample collection [17]. Cortisol hormone extraction replicated the methods Izawa et al. used, including washing the samples, gridding and centrifuging them, and then utilizing an enzyme immunoassay to determine hormone concentrations [17,33].

Statistical analyses involved chi-squared and independent t-tests to compare patients against non-ACS controls in the psychosocial, biological, and lifestyle factors categories. Hormone levels in the ACS group also underwent multivariate logistic regression analyses to categorize cortisol levels as low, medium, or high. Odds ratios were estimated following adjustments for psychosocial factors as potential confounders. This study revealed that cortisol levels were significantly higher in both hair and fingernail samples for patients compared to the control group. The elevated cortisol levels in hair and fingernail samples were associated with elevated ACS risk in patients, specifically in the "high" cortisol groups [17].

Some limitations to the study by Izawa et al. were noted. Sampling bias may have occurred, as patients were recruited from a hospital setting, and controls were recruited via an online survey [17]. Moreover, all participants were males in this study, which does not accurately represent the general population, given the hormonal differences between men and women. Future directions for this research could look at a larger population, expanding to male and female participants to decrease study bias [17].

Conclusion and Recommendations

Though the biological mechanisms underpinning cardiac conditions like CAD have received growing attention in the literature, the relationship between cortisol and CAD is not yet fully elucidated [11]. The impact of cortisol levels on cardiovascular risk has become the focus of an increasing body of research in recent years. This paper reviewed four studies from 2019 to 2023 exploring that relationship through different methods. All four articles reviewed found that cortisol levels were altered in patients with CAD.

The studies varied, however, in their methodologies for measuring cortisol. The studies by Bergquist et al., Stomby et al., and Izawa et al. used hair cortisol concentrations, which are more reliable in measuring persistent cortisol elevation [7,17,23]. The article by Gecaite-Stonciene et al. looked instead at salivary cortisol, which is more impacted by the diurnal nature of cortisol [22]. This variation in methodology could be responsible for the difference in findings between blunted cortisol responses in chronic stress and the elevated cortisol found in saliva following exposure to stressful stimuli. The results of the study by Bergquist et al. contradicted the findings of Izawa et al. and Stomby et al., finding that cortisol levels were blunted in patients with CAD [7,17,23]. Elevated cortisol levels in patient groups could be explained by elevated stress responses leading to the onset of cardiovascular conditions or cardiac events [17].

Several methodological limitations were consistent across this review's four empirical research studies. The first of these limitations is that cortisol changes are subject to diurnal fluctuations and that cortisol follows a particular circadian rhythm [7,24,]. Cortisol has previously been measured in blood, urine, and salivary samples, all affected by acute changes to short-term cortisol levels [7,35]. This makes measuring cortisol levels difficult and can lead to inconclusive results [7,29].

Additionally, many participants included in the studies were convenience samples. The samples are generally small and favor the inclusion of older individuals [7,13,16,17,22,23]. A focus of future research could include a broader range of ages rather than limiting to older adults. Furthermore, there is a need for more diverse representation in the research on this topic, as socioeconomic and demographic factors were largely absent from the studies. Heart disease prevalence in non-Caucasian populations is cited as a risk factor but was not controlled for in the research reviewed [36]. Attention should be paid to future research to diversify the included populations and specifically review the covariates like race, gender, socioeconomic status, and ethnicity.

Next, attention should be given to including modifiable risk factors as confounders. Controlling for these confounders could clarify the relationship between cortisol and CAD and any directionality in the relationship that could be elucidated. Lastly, measuring hair cortisol levels can reveal the amount of hormone secreted over several weeks or months. When sampling HCC in patients with CAD and other cardiovascular disease it is essential to consider the patient profile and expected stress levels leading up to a cardiac event [17]. Patients seen for CAD likely experienced an event like an acute myocardial infarction, which could mean that they were experiencing elevated stress levels before the event, which would be reflected in the HCC

[23]. The limitations presented offer an opportunity to expand on the research on this emerging topic and should be considered as possible future directions.

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