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Diminished salivary cortisol response to mental stress predict all-cause mortality in general population

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ABSTRACT

Objectives: To characterize individuals with a diminished salivary cortisol response to mental stress, assess its association with all-cause mortality, and quantify the mediating effects of the most relevant and modifiable factors to identify potential target for prevention.
Methods: Data from MIDUS II study with a 16-year follow-up, were used to categorize 1129 participants as responders or non-responders based on the existence of increase in salivary cortisol under mental stress. LASSO-logistics analysis identified the most relevant factors. Cox regression models and restricted cubic splines evaluated the prognostic impact. Further analyses examined the mediating effects of identified factors on prognosis.
Results: After employing Inverse Probability of Treatment Weighting to adjust for demographic differences between groups, individuals with diminished cortisol responses were found to have higher levels of depressive symptoms ($p = 0.050$), increased inflammation (IL-6, 2.30 [1.41, 3.79] vs. 1.96[1.33, 3.31], $p = 0.011$), and were less likely to regularly exercise (74.3 % vs. 79.9 %, $p = 0.030$). IL-6 (OR: 1.25 [1.04, 1.52] , $p = 0.021$) and regularly exercising (OR 0.71 [0.51, 0.97], $p = 0.032$) emerged as significant modifiable factors in multivariate analysis. A notable prognostic association of diminished cortisol response with all-cause mortality (HR = 1.33 [1.01–1.76], $p = 0.046$) was observed, consistent across various subgroups and supported by non-linear model analysis. Approximately 13 % of the mortality risk associated with diminished cortisol response was mediated by increased IL-6 levels ($p = 0.043$).
Conclusion: Diminished salivary cortisol response is linked to an increased risk of all-cause mortality, significantly mediated by elevated IL-6. This study offers a new perspective on prognostic prediction while highlighting potential avenues for intervention.

1. Introduction

Cortisol, a stress hormone produced by the adrenal glands, plays a crucial role in safeguarding against adverse environmental threats or conditions [1]. Numerous studies have shown that a diminished cortisol response under mental stress is associated with a range of physical states, including body weight [2], coronary artery calcification [3], and shortened telomerase activity [4], as well as psychological conditions including childhood trauma experiences [5], burnout [6], suicide attempt [7], and socioeconomic status [8]. However, the existing research is fragmented, with a clear gap in the comprehensive analysis of factors that lead to the reduction or absence of cortisol response. Additionally, it remains unclear whether this pattern of cortisol change under mental stress is an indicator of poor future health outcomes.

When the human body encounters stress, an increase in cortisol assists in maintaining the energy supply and modulating cardiovascular functions to meet physiological demands. Research suggests that prolonged mental stress can elevate cortisol levels, resulting in decreased

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immunity [9] and metabolic alterations [10]. Variations in cortisol levels observed during awakening responses, circadian rhythms, and mental stress tests may provide more insights into the body's condition. For instance, a blunted cortisol response could indicate changes in sleep [11] and memory performance [12], suicide attempt [7,13], or even predict the presence of posttraumatic stress disorder [14]. There are quite a lot of factors have been linked to a blunted cortisol response in various studies, the problem is that probably due to the limited sample sizes and enrolled variables, these existing researches are fragmented and a comprehensive analysis remains unperformed.

On the other hand, although a diminished cortisol response has been found to be associated with a range of adverse physical states and psychological conditions, its relationship with long-term health outcomes, such as all-cause mortality, has yet to be explored. Only one study has linked a flatter cortisol decline throughout the day to a higher risk of all-cause mortality [15]. In fact, an enhanced cortisol response to mental stress is not necessarily advantageous. For example, increased cortisol reactivity to mental stress has been linked to detectable plasma levels of troponin [16] and more severe coronary artery calcification [3], and research by Matthew C. Morris [17] showed that heightened cortisol reactivity under low-stress conditions is associated with an increase in depressive symptoms over time.

In research investigating stress responses under mental stress, Interleukin-6 (IL-6) has emerged as the most sensitive inflammatory marker [18]. This cytokine is significantly associated with all-cause mortality and traditional cardiovascular risk factors [19,20], as well as many psychological conditions [21]. Prior studies have demonstrated that cortisol reactivity and IL-6 levels fluctuate in parallel with physical conditions [22]. Notably, Shuhei Izawa's study [23] indicates that elevated IL-6 levels are associated with diminished cortisol responses in the context of mental stress. Given their similarities, it is reasonable to hypothesize that variations in IL-6 levels may significantly influence the relationship between cortisol reactivity and adverse outcomes.

By leveraging the Midlife in the United States II (MIDUS II) cohort database and over a decade of follow-up data, we initiated this research with three progressively developed objectives: 1. to explore the core factors related to diminished cortisol response; 2. to determine the predictive value of cortisol non-response patterns for all-cause mortality; and 3. to investigate modifiable factors among the correlates that impact outcomes, utilizing mediation analysis to clarify their significance. We hypothesize that diminished cortisol response is associated with an increased risk of all-cause mortality, with IL-6 serving as a relevant and modifiable inflammatory factor mediating this association with adverse outcomes. This study aims to provide a deeper and more comprehensive understanding of the diminished salivary cortisol response phenomenon, offering a novel approach for prognostic assessments.

2. Methods

2.1. Study design and participants

The MIDUS study is a national longitudinal cohort study designed to examine the effects of psychological, behavioral, and social factors on age-related changes in physical and mental health. The initial data were collected from a diverse sample of adults aged 34 to 84 in 1995–1996. Data collection methods in the MIDUS database primarily included telephone interviews and self-administered questionnaires, which captured demographic details, psychosocial data, and biomarkers. The MIDUS II project expanded upon the initial assessments by including an additional evaluation of biomarkers with 1255 participants in 2004–2009. Of these, a substantial majority ($N = 1208$) completed the mental stress testing protocols.

This study utilized data from MIDUS II aiming at exploring the influencing factors associated with diminished salivary cortisol change to mental stress, and its prognostic value for all-cause mortality. After excluding participants who completed only one mental stress task ($N = 18$) or the PASAT task ($N = 26$), those lacking available salivary cortisol data ($N = 27$), or those with extreme salivary cortisol values ($N = 8$, defined as data more than 2 standard deviations from the mean), the final sample size was determined to be 1129 (as shown in **Fig. S1**). Follow-up data were obtained from the MIDUS Mortality study, which tracks all deceased participants and the causes of their deaths up to 2022. All-cause mortality refers to the occurrence of death from any cause between the time of a participant's enrollment and the end of the follow-up period.

The study received approval from the institutional review boards at each participating MIDUS center, and all participants provided written informed consent.

2.2. Mental stress testing protocol

The mental stress testing protocol is outlined in Fig. 1. Initially, participants underwent an 11-min quiet baseline period, followed by two 6-min cognitive stress tasks, each succeeded by a 6-min recovery period. The tasks comprised the Stroop test and the mental arithmetic (MATH) test. Half of the participants ($N = 586$) first completed the Stroop test followed by the MATH test, while the sequence was reversed for the other half ($N = 578$).

During the Stroop test, words were presented on a computer screen in colors that were either congruent or incongruent with the text. Participants were tasked with pressing a keyboard key corresponding to the font color, not the word's color. In the MATH test, participants resolved various subtraction and addition problems displayed on the screen, which were followed by the word "equals" and an answer. Participants needed to press a key to indicate whether the given answer was correct or incorrect.

2.3. Saliva sample collection and salivary cortisol

Saliva samples were collected at four timepoints (as shown in Fig. 1). The focus of this study was primarily on Saliva Sample 1, which were collected prior to the baseline rest period and Sample 2, which were collected after the second mental stress task, 12 min after the completion of mental stress task 1. Saliva Sample 3 was collected after the subsequent stand test, and Sample 4 was gathered following a 30-min recovery period.

Saliva was collected using Salivette kits (Sarstedt, Rommelsdorf, Germany). The salivary cortisol levels were measured twice for each sample, and the average of these measurements was used to represent the cortisol levels at each time point. Based on whether there was an increase in salivary cortisol levels after mental stress, participants were categorized as either responders or non-responders.

2.4. Control variables

Marital status was categorized as either "married" or "unmarried," with the latter encompassing separated, divorced, widowed, and never-married statuses.

Body Mass Index (BMI) was calculated as weight in kilograms divided by the square of the height in meters.

Smoking status was determined based on whether an individual had smoked at least 100 cigarettes in their lifetime.

The Center for Epidemiologic Studies Depression Scale (CES—D) is a widely used tool to assess symptoms of depression. This questionnaire uses a 4-point Likert scale to evaluate depressive symptoms experienced over the past two weeks, with higher scores indicating more severe symptoms.

Fasting peripheral blood samples were collected from participants prior to completing the mental stress test for further analysis of IL-6, CRP (C-Reactive Protein), blood lipids, blood glucose, liver and kidney function, and other indicators.

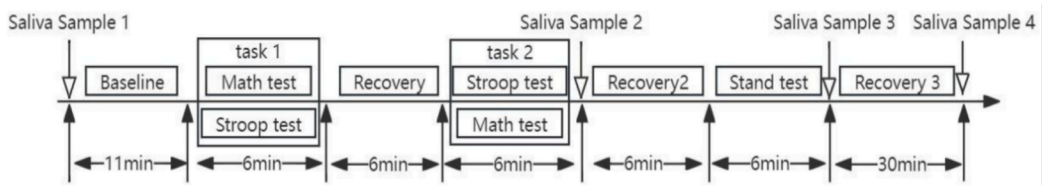

Fig. 1. Mental stress test protocol. Participants underwent an 11-min quiet baseline period, followed by two 6-min cognitive stress tasks, each succeeded by a 6-min recovery period. The tasks comprised the Stroop test and the MATH test. The saliva samples were collected at four timepoints. The focus of this study was primarily on Saliva Sample 1 and Sample 2.

Physical activity, quantified as the amount of exercise completed in the last week, was represented by the total metabolic equivalents (METs) per week, calculated as the product of metabolic equivalents and time.

2.5. Statistical analysis

Descriptive statistics were reported as follows: means ± standard deviation (SD) for continuous variables, median with interquartile range (IQR) for non-normally distributed variables, and frequency (percentage) for categorical variables. Univariate analyses were conducted to evaluate differences in clinical characteristics between responder and non-responder groups. Inverse Probability of Treatment Weighting (IPTW) was used to address discrepancies between these groups regarding age, sex, marital status, and BMI, thereby facilitating a more accurate comparison. Significant variables from univariate analyses,

Table 1
Comparisons of participants characteristics between saliva cortisol response and non-response groups.

Unmatched				Matched[a]		
	responder	non-responder	*p* value	responder	non-responder	p value
n	551	578		1125.85	1131.72	
Age,years	54.7 (10.7)	53.6 (12.4)	0.144	54.3 (10.6)	54.3 (12.5)	0.974
Sex,male,n (%)	**268 (48.6)**	**370 (64.0)**	**<0.001**	631.5 (56.1)	635.2 (56.1)	0.990
BMI	29.7 (6.4)	29.6 (7.0)	0.872	29.6 (6.5)	29.6 (6.8)	0.988
Married, n(%)	**383 (69.5)**	**334 (57.8)**	**<0.001**	721.1 (64.0)	723.2 (63.9)	0.961
Ever Smoked[b],n(%)	252 (45.7)	283 (49.0)	0.305	514.2 (45.7)	558.9 (49.4)	0.221
Dead,n(%)	96 (17.4)	121 (20.9)	0.155	**189.5 (16.8)**	**250.4 (22.1)**	**0.029**
Total METs,mL/kg	**720.0 [235.51806.0]**	**549.5 [0,1569.0]**	**0.012**	705.9 [191.81764.9]	583.4 [0,1620.0]	0.086
Regular Exercise,n(%)	**444 (80.6)**	**429 (74.2)**	**0.013**	**899.7 (79.9)**	**841.4 (74.3)**	**0.030**
History of hypertension,n(%)	186 (33.8)	214 (37.0)	0.278	382.7 (34.0)	424.6 (37.5)	0.226
History of diabetes,n(%)	66 (12.0)	72 (12.5)	0.877	131.9 (11.7)	143.3 (12.7)	0.635
History of heart Disease,n(%)	59 (10.7)	64 (11.1)	0.919	112.7 (10.0)	140.9 (12.5)	0.207
History of transient Ischemic Attack,n(%)	17 (3.1)	26 (4.5)	0.278	34.9 (3.1)	54.4 (4.8)	0.158
History of cancer,n(%)	80 (14.5)	69 (11.9)	0.233	165.7 (14.7)	136.1 (12.0)	0.194
History of depression,n(%)	113 (20.5)	106 (18.3)	0.398	244.2 (21.7)	192.0 (17.0)	0.047
CESD	**6.0 [2.0, 11.0]**	**7.0 [3.0, 13.0]**	**0.007**	**6.0 [2.0, 12.0]**	**7.0 [3.0, 12.0]**	**0.050**
PSS10	**21.0 [17.0, 26.0]**	**22.0 [18.0, 27.0]**	**0.011**	21.0 [17.0, 26.0]	22.0 [18.0, 26.0]	0.077
PSQI	5.0 [3.0, 8.0]	5.0 [4.0, 8.0]	0.159	5.0 [4.0, 8.0]	5.0 [3.0, 8.0]	0.740
CTQ-SF emotional abuse	6.0 [5.0, 9.0]	7.0 [5.0, 10.0]	0.070	7.94 (4.20)	8.09 (4.26)	0.572
CTQ-SF emotional neglect	8.0 [6.0, 12.0]	9.0 [6.0, 13.0]	0.161	8.0 [6.0, 12.0]	9.0 [6.0, 13.0]	0.292
CTQ-SF physical abuse	6.0 [5.0, 7.0]	6.0 [5.0, 7.0]	0.612	6.0 [5.0, 7.0]	6.0 [5.0, 7.0]	0.620
CTQ-SF physical neglect	6.0 [5.0, 8.0]	6.0 [5.0, 9.0]	0.244	6.0 [5.0, 8.0]	6.0 [5.0, 8.0]	0.353
HbAc,%	6.1 (1.3)	6.1 (1.1)	0.930	6.1 (1.3)	6.1 (1.1)	0.964
CHOL,mg/dL	185.7 (40.4)	186.4 (39.6)	0.754	186.5 (40.3)	185.9 (40.2)	0.801
LDLC,mg/dL	105.8 (36.0)	104.4 (34.1)	0.527	106.1 (36.2)	104.4 (34.1)	0.420
HDLC,mg/dL	**53.2 (17.1)**	**57.7 (18.5)**	**<0.001**	**54.4 (17.4)**	**56.8 (18.4)**	**0.026**
TRIG,mg/dL	138.2 (118.9)	125.8 (151.3)	0.130	133.8 (111.1)	128.7 (167.4)	0.568
CREA,mg/dL	0.87 (0.20)	0.89 (0.51)	0.404	**0.86 (0.20)**	**0.91 (0.50)**	**0.019**
CRP,mg/L	1.31 [0.64, 3.05]	1.46 [0.71, 4.09]	0.076	1.35 [0.65, 3.12]	1.44 [0.70, 4.06]	0.313
FPG,mg/dL	101.4 (25.0)	102.7 (31.8)	0.456	101.0 (25.6)	103.2 (32.9)	0.225
IL6, pg/mL	**1.96 [1.33, 3.22]**	**2.30 [1.42, 3.80]**	**0.004**	**1.96 [1.33, 3.31]**	**2.30 [1.41, 3.79]**	**0.011**
E-Selec, ng/mL	42.1 (21.7)	43.7 (22.7)	0.211	41.9 (21.7)	43.7 (22.4)	0.166
eGFR,mL/min/1.73m^2	**117.2 (39.8)**	**112.0 (39.8)**	**0.031**	115.3 (39.2)	112.9 (39.9)	0.322
ICAM, ng/mL	281.3(103.8)	293.2 (121.9)	0.079	279.3 (103.6)	292.1 (120.1)	0.058
Heart Rate,bpm	**70.1 (10.3)**	**71.6 (11.5)**	**0.021**	70.3 (10.3)	71.3 (11.6)	0.112
Average SBP,mmHg	**131.3 (16.2)**	**129.2 (17.8)**	**0.038**	131.1 (16.5)	129.8 (17.7)	0.218
Average DBP,mmHg	75.9 (9.9)	74.8 (10.7)	0.083	75.5 (9.9)	75.1 (10.6)	0.474

Note: Median (IQR) is used for non-normally distributed data, mean ± standard deviation (mean (SD)) is used for normally distributed data, and n(%) is used for categorical variables.

Abbreviations: BMI, Body Mass Index;Toltal METs,Total Metabolic Equivalents per Week(METs×min);CESD, Center for Epidemiologic Studies Depression Scale; PSS10, Perceived Stress Scale; PSQI, Pittsburgh Sleep Quality Index;CTQ-SF:Childhood Trauma Questionnaire,it include emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect, comprising five subscales.; HbA1c, Glycated Hemoglobin; CHOL, Total Cholesterol; LDLC, Low-Density Lipoprotein Cholesterol; HDLC, High-Density Lipoprotein Cholesterol; TRIG, Triglycerides; CREA, Creatinine; CRP, C-Reactive Protein; FPG, Fasting Plasma Glucose; IL6, Interleukin-6; E-Selec, E-Selectin; eGFR, Estimated Glomerular Filtration Rate; ICAM, Intercellular Adhesion Molecule; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HR, Heart Rate.

[a] :Comparisons are performed after balancing demographic discrepancies including age, gender, and marital status by using IPTW (Inverse Probability Weighting).

[b] : Ever Smoked refers to having smoked more than 100 cigarettes in total.

along with basic demographic information, were further incorporated into a LASSO regression model. This model selected the most closely related factors to diminished salivary cortisol based on the lambda 1se criterion. The factors identified were then analyzed using a logistic regression model to determine the most related factors with the non-response change of salivary cortisol. Cox regression models, adjusted for varying numbers of potential confounders, were employed to explore the prognostic effects of the non-response salivary cortisol change pattern compared to the response pattern on all-cause mortality assessed over a 16-year follow-up period. The non-linear relationships were further analyzed using the restricted cubic spline (RCS) method. Due to potential collinearity, only most relevant and modifiable factors that significantly influence the prognostic impact of the non-response pattern were included into survival analysis to identify the core influencing factors. Mediation analyses were conducted to evaluate the mediating effect of the core factor, IL-6, on the relationship between salivary cortisol change pattern and all-cause mortality, with adjustment for age, sex, history of smoking, hypertension and diabetes, by using nonparametric bootstrap method with 10,000 simulations, implemented via the *mediation* package of R software. All statistical analyses were performed using SAS statistical software (version 9.4 TS1M6) and R software (version 4.13). A p-value of <0.05 was considered statistically significant.

3. Results

3.1. Participants characteristics and salivary cortisol change to mental stress

This study encompassed 1129 participants, averaging 54.2 years in age, with males comprising 43.5 % of the cohort (Table 1). The mental stress testing procedure is detailed in Fig. 1. Salivary cortisol was measured at four key time points: baseline, post-mental stress test, post-standing test, and during the recovery phase. Given the complex physiological responses induced by repeated stress stimuli, the study concentrated on cortisol levels at baseline and post-mental stress test. A total of 551 participants showed an increase in cortisol levels after the mental stress test, while 578 demonstrated a decrease. The cortisol response patterns are depicted in Fig. 2, where the responder group exhibited a peak followed by a gradual decline in a bell-shaped curve during recovery. In contrast, the non-responder group showed a continuous decline during the stress test with fluctuating levels thereafter.

Over a 16-year follow-up in the MIDUS 2 study, mortality rates were 17.4 % (96 individuals) in the responder group and 20.9 % (121 individuals) in the non-responder group. After balancing the discrepancies of age, sex, marital status and BMI with IPTW method, all-cause mortality rates were 16.8 % and 22.1 % for the responder and non-responder groups, respectively, showing a statistically significant difference ($p = 0.029$), suggesting that the differing salivary cortisol response patterns to mental stress might possess predictive value for long-term health outcomes.

3.2. Factors associated with diminished salivary cortisol response

Univariate analyses of participant characteristics between the responder and non-responder groups were presented in Table 1. There were significant differences in gender (male, 48.6 % vs. 64.0 %, $p < 0.001$), marital status (married, 69.5 % vs. 57.8 %, $p < 0.001$), exercise habits (regularly exercise, 80.6 % vs. 74.2 %, $p = 0.013$), CES-D scores (6.0 [2.0, 11.0] vs. 7.0 [3.0, 13.0], $p = 0.007$), interleukin-6 (IL-6) levels (1.96 [1.33, 3.22] vs. 2.30 [1.42, 3.80], $p = 0.004$), estimated glomerular filtration rate (eGFR) (117.2 ± 39.8 vs. 112.0 ± 39.8, $p = 0.007$), and high-density lipoprotein (HDL) levels (53.2 ± 17.1 vs. 57.7 ± 18.5, $p < 0.001$). After adjusting for demographic differences between groups using IPTW, those with a diminished cortisol response were more likely to exhibit severe depressive symptoms (CES-D scores, 6.0 [2.0, 12.0] vs. 7.0 [3.0, 12.0], $p = 0.050$), higher inflammation levels (IL-6, 1.96 [1.33, 3.31] vs. 2.30 [1.41, 3.79], $p = 0.011$), and were less likely to engage in regular exercise (79.9 % vs. 74.3 %, $p = 0.03$).

A multivariate analysis employing a LASSO regression model (**Fig. S2**) pinpointed nine factors most relevant to the diminished salivary cortisol response pattern, including age, gender, marital status, IL-6, CES-D score, exercise habits, baseline salivary cortisol level, HDL, and heart rate. These variables were subsequently integrated into a multivariable logistic regression model (Table 2). Significant associations were found between the non-responsive cortisol change pattern and factors such as age, gender (female versus male: OR = 1.84, 95 % CI [1.38, 2.45], $p < 0.001$), marital status (married versus unmarried: OR = 0.67, 95 % CI [0.51, 0.89], $p = 0.005$), HDL, IL-6 (log-transformed

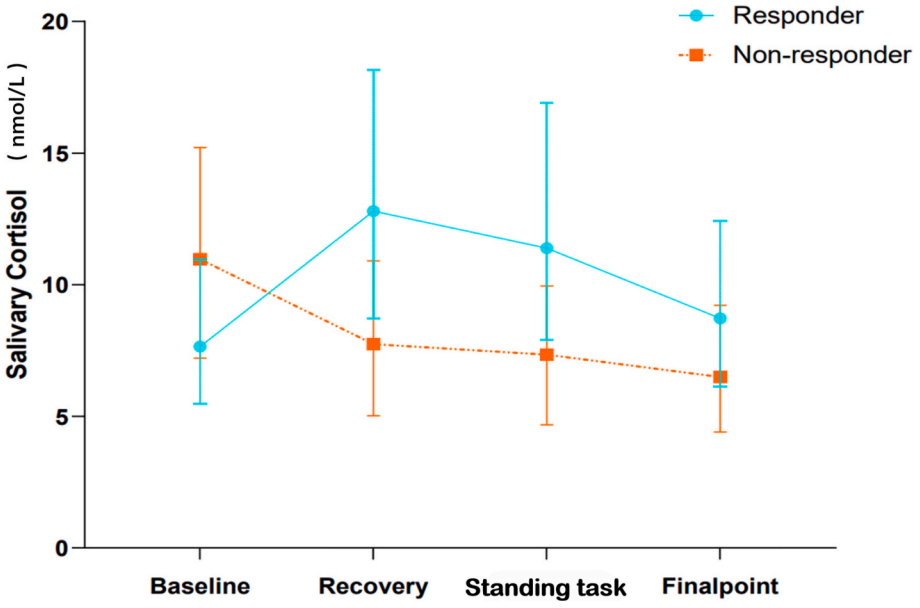

Fig. 2. The changes of salivary cortisol levels in the mental stress test.
This figure shows the changes of salivary cortisol level in the responsive and non-responsive groups at four timepoints during the mental stress test.

Table 2
Influence factors associated with diminished salivary cortisol change pattern using LASSO-logistics analysis.

Factors	OR	95 %CI	*p* value
Age, per 10 year increase	**0.78**	**(0.69, 0.88)**	**<0.001**
Sex, female versus male	**1.84**	**(1.38, 2.45)**	**<0.001**
Marriage status, married versus unmarried[a]	**0.67**	**(0.51, 0.89)**	**0.005**
IL-6[b]	**1.25**	**(1.04, 1.52)**	**0.021**
CESD[c]	1.12	(0.97, 1.30)	0.119
Regular excercise	**0.71**	**(0.51, 0.97)**	**0.032**
Baseline average salivary cortisol[d]	**2.64**	**(2.21, 3.16)**	**<0.001**
HDLC mg/dL, per 1 mg/dL increase	**1.65**	**(1.20, 2.26)**	**0.002**
Heart rate, per 10 bpm increase	1.12	(1.00, 1.27)	0.060

[a] : Unmarried state includes separated,divorced,widowed and never married.
[b] : Transform the data using a logarithmic transformation($\log_{10}$(IL-6)) to achieve a normal distribution.
[c] : Transform the data using a logarithmic transformation($\log_{10}$(CESD)) to achieve a normal distribution.
[d] : Transform the data using transformation($\log_2$(Baseline average salivary cortisol)) to achieve a normal distribution.

[$\log_{10}$(IL-6)]: OR = 1.25, 95 % CI [1.04–1.52], $p = 0.021$), regularly exercising (OR = 0.71, 95 % CI [0.51–0.97], $p = 0.032$), and baseline cortisol levels.

3.3. Prognostic value of diminished salivary cortisol response

As illustrated by the Kaplan-Meier survival analysis (**Fig. S3**), a diminished salivary cortisol response pattern is significantly associated with an increased risk of all-cause mortality ($p = 0.037$). Table 3 presents the results of survival analyses using Cox regression models. In the simple model (Model 1), the classification of non-responder group was significantly associated with increased all-cause mortality risk (HR = 1.33, 95 % CI [1.02–1.74], $p = 0.039$). After adjusting for age, gender, BMI, marital status, and smoking history, this correlation remained significant (Model 2: HR = 1.3, 95 % CI [1.01–1.75], $p = 0.041$). Model 3, which further adjusted for common laboratory markers and a history of significant chronic diseases, still demonstrated a significant prognostic value of the diminished salivary cortisol response pattern (HR = 1.33, 95 % CI [1.01–1.76], $p = 0.046$).

To further verify the reliability of this prognostic value, stratified analyses were conducted within subgroups differing by age, gender, BMI, exercise habits, and chronic disease status. Both unadjusted and adjusted survival analysis models, as depicted in Fig. 3, indicated that despite reduced statistical power due to smaller sample sizes in subgroups, the prognostic value of the diminished salivary cortisol change pattern did not show significant differences across groups.

The non-linear relationship between salivary cortisol changes (as a continuous variable) and all-cause mortality was further analyzed using RCS, as shown in **Fig. S4**. As the magnitude of salivary cortisol changes increased under psychological stress, the risk of death exhibited a continuous downward trend ($p_{\text{for trend}} = 0.086$).

3.4. IL-6 mediated association between non-response salivary cortisol change and mortality

To examine whether factors closely associated with the non-responsive change pattern in salivary cortisol are implicated in its prognostic impact, modifiable factors such as IL-6 and exercise habits were specifically targeted. To bolster the argument's rigor, total weekly exercise amounts were quantified to enhance the assessment of exercise habits. **Table S1** illustrates that in the univariate analysis, IL-6 significantly correlated with an increased risk of all-cause mortality (HR: 1.94, 95 % CI [1.63–2.29], $p < 0.001$). An increase in weekly exercise quantity significantly tends to improve prognosis (Q3 vs Q1: HR 0.67, 95 % CI [0.48, 0.93], $p = 0.017$). Notably, when adjustments for IL-6 or exercise habits were incorporated in Cox model 3, only IL-6 markedly influenced the predictive outcomes for cortisol response associated all-cause mortality. This finding suggests a potential strong collinearity between these two factors, warranting further analysis of mediation effects.

The mediation effect analysis of IL-6, as depicted in Table 4, confirmed that IL-6 indeed plays a significant mediating role ($p = 0.008$). Specifically, the increase in IL-6 mediated approximately 13 % ($p = 0.043$) of the association between diminished salivary cortisol response and all-cause mortality.

4. Discussion

In this large cohort study with extended follow-up, we found that participants exhibiting a diminished salivary cortisol response to mental stress were predominantly female, unmarried, displayed irregular exercise habits, and had higher levels of interleukin-6 and baseline salivary cortisol. Furthermore, salivary cortisol reactivity was inversely correlated with all-cause mortality, a relationship that is partially mediated by the elevation of resting IL-6. Our research provides a detailed profile of individuals with a diminished salivary cortisol response, introduces a novel approach for prognostic assessments, and offers insights into the mechanism and potential intervention target of this phenomenon.

Our study demonstrated that diminished changes in salivary cortisol under mental stress correlate with an increased risk of all-cause mortality. To the best of our knowledge, this is the first attempt to link salivary cortisol response to mental stress with long-term prognosis. While prior research has associated blunted or diminished changes with

Table 3
Prognostic value of diminished salivary cortisol on all-cause mortality using Cox regression models.

	Model 1			Model 2			Model 3		
	HR	95 %CI	*p* value	HR	95 %CI	*p* value	HR	95 %CI	*p* value
Non-responder versus responder	1.33	(1.02, 1.74)	**0.039**	1.33	(1.01, 1.75)	**0.041**	1.33	(1.01, 1.76)	**0.046**
Age,per 10 year increase				2.14	(1.88, 2.43)	**<0.001**	1.99	(1.72, 2.30)	**<0.001**
Sex female versus male				1.62	(1.21, 2.18)	**0.001**	1.55	(1.11, 2.16)	**0.011**
BMI,per 10 kg/m^2 increase				1.09	(0.87, 1.35)	0.457	0.93	(0.72, 1.19)	0.542
Marriage unmarried versus married[a]				1.36	(1.01, 1.82)	**0.041**	1.14	(0.84, 1.54)	0.394
ever smoked[b]				1.49	(1.13, 1.96)	**0.005**	1.43	(1.08, 1.90)	**0.013**
HDLC,mmol/L							0.85	(0.60, 1.22)	0.380
CHOL,mmol/L							0.90	(0.77, 1.04)	0.143
HbAc,%							1.19	(1.05, 1.34)	**0.006**
eGFR, per 10 mL/min/1.73m^2 increase							0.97	(0.93, 1.01)	0.182
Diagnosed Depression							1.61	(1.16, 2.25)	**0.005**
Diagnosed hypertension							1.39	(1.03, 1.86)	**0.031**
Diagnosed Diabetes							1.25	(0.82, 1.90)	0.302
Diagnosed Cancer							0.88	(0.61, 1.26)	0.484

[a] : Unmarried state includes separated, divorced, widowed and never married.
[b] : Ever Smoked refers to having smoked more than 100 cigarettes in total.

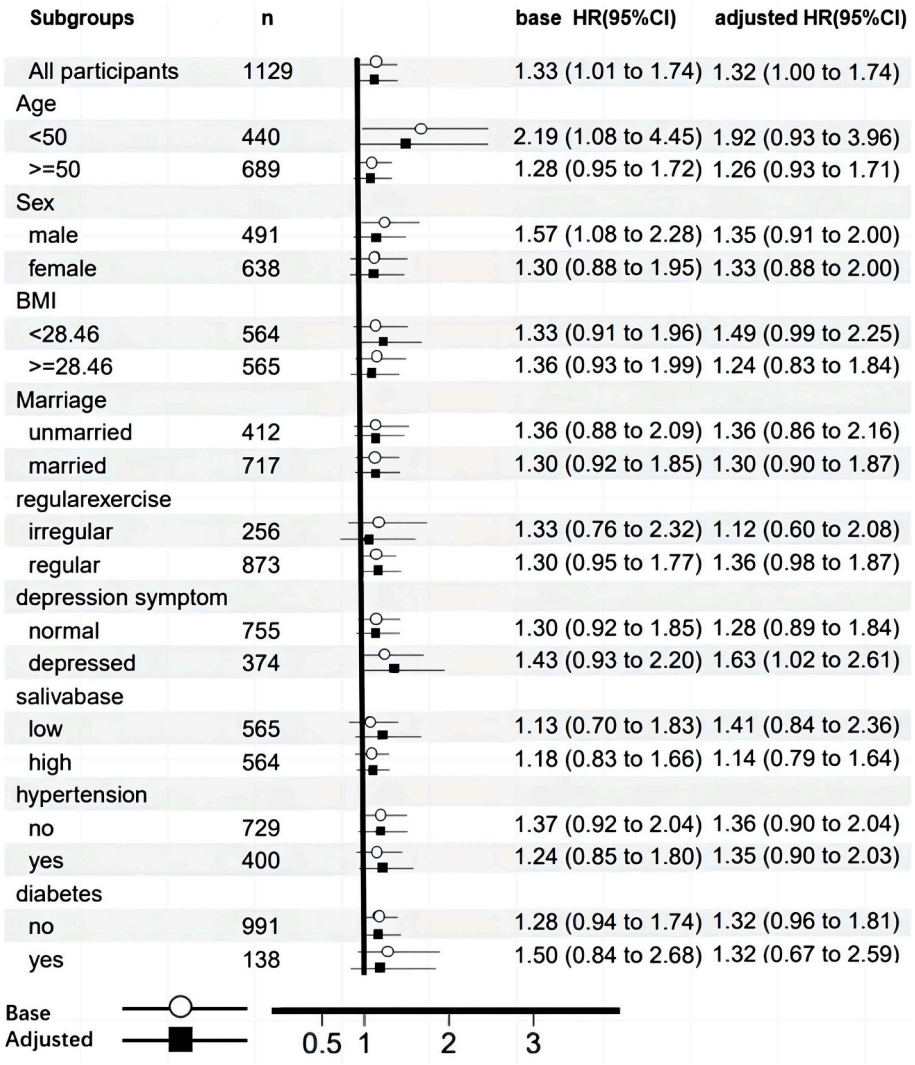

Fig. 3. Forest plot of Cox survival analysis for all-cause mortality in subgroups.
This forest plot is to further verify the reliability of the association between the pattern of salivary cortisol changes under psychological stress and prognosis. The results indicate that the prognostic outcomes among the subgroups are relatively stable, suggesting that the pattern of salivary cortisol changes has a reliable impact on prognosis.

Table 4
Mediation effect of IL-6 on the association between non-response pattern and all cause mortality.

	Estimate	95 % CI Lower	95 % CI Upper	p-value
Total Effect	0.04445	0.0029	0.09	0.036 *
ACME	0.00585	0.00123	0.01	0.0076 **
ADE	0.0386	−0.00322	0.08	0.0714
Proportion	13 %	0.97 %	76 %	0.043 *

Note: Mediation effect of IL-6 analyzed with the adjustment for age, sex, history of smoking, hypertension and diabetes.
ACME:average causal mediation effect; ADE:average direct effect.

poor physical and psychological states such as shortened telomerase activity [4], depression [24], suicide intent [7] and socioeconomic status [8], these studies did not explore their prognostic value due to limitations in sample size and follow-up duration. Our finding could be indirect supported by the researches on circadian rhythms has shown that a flatter diurnal cortisol slope is associated with an increased risk of health conditions [25] and all-cause mortality [15]. However, it should be noted that excessively elevated cortisol levels under stress may also indicate adverse functional states, such as stress-induced myocardial damage [16] and more severe depressive symptoms [17]. This could be attributed to differences in the study populations. In this large cohort focusing on the general population, we have conducted various sensitivity analyses to guarantee the correctness of our conclusion.

Our findings align with previous researches that younger age [5], depression [24], inflammation [26] and high baseline cortisol levels related to blunted cortisol reactivity under mental stress. However, widely reported trauma experiences [5,27] did not exhibit significant differences in the current research. After compiling demographic data, individual habits, psychological factors, laboratory results, and comorbid chronic conditions, we identified exercise habits and IL-6 as the two most closely related modifiable factors associated with the non-response change pattern. This finding aligns with the observations made from Manuel Mücke et al. [28] that in their meta-analysis, cortisol reactivity was found to be attenuated by higher physical activity or better fitness, and Shuhei Izawa et al. [23] revealing that elevated IL-6 levels are associated with diminished cortisol responses under mental stress.

Interestingly, although both exercise habits and IL-6 are associated with prognosis and the non-response cortisol change pattern and physical exercise has been proven to reduce inflammation levels [29], only IL-6 demonstrated a high degree of collinearity with cortisol change in the prognostic analysis. Mediation analysis revealed that IL-6 acts as a

mediator in the relationship between changes in cortisol and the increased risk of mortality, indicating that salivary cortisol changes and IL-6 may share a common pathway in the association between the phenotype and adverse outcomes. This pathway could potentially be driven by a specific mechanism influencing both factors simultaneously or represent two sequential manifestations of the same process. However, this cannot be determined based solely on the data.

As is known, aseptic chronic inflammation plays a crucial role in the adverse prognostic mechanisms of mental disorders such as depression and anxiety [30] as well as in somatic diseases and cardiovascular outcomes [31]. Inflammatory markers like IL-6 [32] and tumor necrosis factor-alpha [33] are known to increase under acute mental stress. Considering the anti-inflammatory effects of cortisol in physiological processes, it is reasonable to observe that IL-6 has considerable overlap with the salivary cortisol response in the associations with psychological and physiological aspects [34], and both tend to fluctuate in parallel with physical conditions [22]. IL-6 promotes chronic inflammation [35], which is associated with various health issues and impairs immune function, making the body more susceptible to infections and somatic diseases [36], thereby exhibiting differences in cortisol reactivity. On the other hand, it can influence the hypothalamic-pituitary-adrenal (HPA) axis [37], potentially altering cortisol secretion patterns. From this perspective, it seems more plausible that changes in salivary cortisol patterns are secondary to variations in IL-6. However, further research is needed to explore the validity of this hypothesis.

The significance of our findings lies in the following aspects: Firstly, considering the improvements in cortisol response to mental stress and inflammation levels that psychological therapy can bring [38], these results indicate the potential role of psychological therapy in mitigating the adverse prognostic risks associated with diminished cortisol response [39]. Furthermore, the identification of IL-6 as a key mediating factor provides insights into the underlying mechanisms and suggests the feasibility of using anti-inflammatory treatments to enhance related outcomes. In fact, anti-IL-6 therapies have already shown promising results in improving cardiovascular outcomes [40].

The strengths of this study include a robust sample size, extensive long-term follow-up, and a comprehensive analysis of various factors related to diminished salivary cortisol responses. This research is the first to demonstrate the significant predictive value of this change pattern for all-cause mortality, thereby introducing a novel approach for prognostic assessments. However, it also has several limitations. First, the predictions are based solely on salivary cortisol measurements from one mental stress test. The physiological and psychological states of individuals might fluctuate over long-term follow-ups. Second, the baseline saliva samples in this study were collected before the start of the resting period, differing from some studies where saliva is collected after a full rest period [41]. However, the baseline salivary cortisol collected using this approach may more accurately reflect participants' typical daily states. Third, this study employed a combination of the MATH and STROOP tasks. However, there is limited literature confirming whether these tasks can elicit a sufficient salivary cortisol response. Additionally, cortisol samples were collected immediately after the second mental stress task, 12 min after the completion of the first task. Despite this, the response group in our study showed an increase of approximately 5.78 nmol/L in cortisol, which aligns closely with findings from studies utilizing the standardized TSST (Trier Social Stress Test) protocol [42,43]. Moreover, based on previous research, a single mental stress task is sufficient to induce a significant cortisol response [44]. Fourth, although this study has a relatively large sample size compared to similar research, it is still limited by the number of participants, which restricts our ability to conduct sufficiently powered statistical analyses of specific causes of death. Fifth, due to the observational nature of this study, we cannot establish a causal relationship between diminished cortisol responses and adverse outcomes. Lastly, the study predominantly involved middle-aged Americans with an average age of 54.18 years, limiting the generalizability of our findings. Validation in more diverse populations is required to extend these conclusions.

In conclusion, our research revealed that a diminished salivary cortisol response under mental stress is associated with an increased risk of all-cause mortality. Elevated IL-6, as one of the main modifiable factors relevant to the non-response change pattern, mediated the relationship between this pattern and prognosis. These findings introduce a novel approach for early risk identification and prognostic assessments, offering insights into the underlying mechanisms and potential intervention target. Further research is warranted to generalize these findings in more diverse populations and to explore more specific mechanism underlying this phenomenon.

Ethics statements

The study received approval from the institutional review boards at each participating MIDUS center, and all participants provided written informed consent.

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CRediT authorship contribution statement

Han Yin: Software, Resources, Methodology, Formal analysis, Data curation, Writing – review & editing, Writing – original draft. **Zihan Gao:** Visualization, Data curation, Writing – review & editing, Writing – original draft. **Mengyang Jia:** Investigation, Formal analysis, Data curation. **Cheng Jiang:** Visualization, Validation, Software, Data curation. **Yuanhao Wang:** Supervision, Software, Resources. **Dahui Xue:** Project administration, Methodology, Investigation, Formal analysis. **Jingnan Huang:** Supervision, Software, Conceptualization. **Huhao Feng:** Project administration, Methodology, Investigation. **Nana Jin:** Software, Formal analysis, Data curation. **Jingjin Liu:** Validation, Supervision. **Lixin Cheng:** Formal analysis, Data curation. **Qingshan Geng:** Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Han Yin reports statistical analysis was provided by Shenzhen People's Hospital. Qingshan Geng reports a relationship with Peking University Shenzhen Hospital that includes: non-financial support. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2024.112031.

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