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The interplay of acute cortisol response and trait affectivity in associating with stress resilience

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Resilience is the cornerstone to mental health, and entails multiple biological and psychological mechanistic processes. However, the interplay of the psychobiological processes in shaping resilience is unclear. Here we report the results of testing whether an acute cortisol response and positive affectivity traits moderate the relationship between participants' five-year major life stress and current psychological symptoms. The participants comprised 147 individuals (93 females and 54 males, age = 24–45 years) without clinical diagnosis. Acute stress was induced using the Trier Social Stress Task. We found that both the cortisol response to anticipatory acute stress and positive affectivity moderated the stress–symptom relationship. Specifically, a positive relationship between life stress and current symptoms was only observed at low, but not high, levels of cortisol response and positive affectivity. Moreover, the moderating effect of cortisol response was only observed at a low level of trait positive affectivity. These results unravel how the biological and emotional processes of the stress response interact to shape resilience to major life stress.

Chronic stress causes overarching adverse consequences for mental health[1]. Past studies have suggested that major life stress predicted subsequent major depression[2], and associated closely with the onset of anxiety disorders, addiction and suicide[3,4]. On the other hand, individuals with high stress resilience are, by definition, more immune to negative stress-related mental health consequences[5]. Accumulating evidence suggests that resilience has both biological and psychological markers that could help identify individuals with differential vulnerability to chronic stress[6,7]. For example, individual differences in cortisol responses to chronic stress predicted depressive and anxiety symptoms[3].

Stress triggers multi-faceted biological responses, primarily by activating the hypothalamus–pituitary–adrenal (HPA) axis, which induces secretion of cortisol as part of the adaptation process to environmental challenges[8]. Cortisol triggers widespread downstream effects on biological and emotional systems[9]. For example, cortisol exerts important regulatory functions on the amygdala, hippocampus and prefrontal cortex, which may mediate its acute and long-term

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effects on affective response and regulation[5]. Importantly, existing evidence indicates that more pronounced cortisol responses to acute stress are associated with, and prospectively predicted, resilience to chronic life stress over a four-year period[10]. Moreover, the offspring of mothers with post-traumatic stress disorder (PTSD), who may possess increased risk for psychopathology, exhibited a reduced cortisol response to acute stress compared to offspring of non-PTSD mothers[11]. These findings collectively indicate cortisol response to acute stress is a biological marker of resilience to chronic stress[7].

On the psychological level, past evidence suggests that better mental health outcomes following chronic stress are associated with more positive affectivity[12], which refers to the trait of being joyful, interested and contented in life. Positive affectivity involves positive affect and positive emotion regulation strategies. A higher level of positive affect was previously found to 'buffer' the association between chronic life stress and affective symptoms among young adults, such that the positive relationship between chronic stress and affective symptoms was only observed among individuals with low positive affect, but not among those with high positive affect[13]. On the other hand, negative affect showed no significant moderating effect, suggesting that positive affect may be particularly important for maintaining good mental health under chronic life stress[5]. Furthermore, trait positive affect prospectively predicted fewer psychological symptoms six months later among adolescents coping with type-1 diabetes[14].

One positive emotion regulation strategy is positive reappraisal, or reframing, which entails the tendency to reinterpret adverse situations in positive or meaningful manners[15]. A greater tendency towards positive reappraisal prospectively predicted reduced lifetime likelihood of developing PTSD in combat veterans[16], and was associated with better psychosomatic adjustment after surviving a natural disaster[17]. Furthermore, among women newly diagnosed with cancer, both positive affect and positive reappraisal were associated with better self-reported quality of life[18].

Another positive emotion regulation strategy is positive refocusing, which involves steering one's attention away from the adverse event towards other positive stimuli[19]. A higher tendency towards positive refocusing was previously found to protect against both depression and anxiety symptoms[20]. Among patients with hypertension, positive refocusing at baseline predicted lower levels of depressive symptoms six months later[21]. Among young adults, greater use of positive refocusing was associated with better psychological adaptation to life adversity[22]. Therefore, positive affect, positive reappraisal and positive refocusing are strong candidate psychological markers for resilience to chronic stress. Although these traits are related, they are conceptually distinct from each other, as positive affect refers to one's chronic emotional status, whereas positive reappraisal and refocusing are two different emotion regulation strategies, respectively involving cognitive reframing of events and redirecting one's attentions.

Although existing evidence indicates that both the acute cortisol response and trait positive affectivity are candidate stress resilience markers, no study has investigated how they interact in relation to resilience to life stress. This is particularly important given that stress responses are multisystemic in nature and entail interacting, coordinated psychobiological processes[23]. To achieve this aim, we induced acute stress using the well-established Trier Social Stress Test (TSST)[24] on a sample of adults without major clinical diagnoses, to boost the generalizability of our findings to wider populations. Resilience was defined in relation to mental health outcome following major life stress, and individuals who maintained good mental health (fewer symptoms) despite experiencing life stress were considered resilient. Following this, variables that reduced the positive relationship between life stress and mental health symptoms were considered resilience markers[13]. Our primary hypothesis was that higher cortisol responses to acute stress and trait positive affectivity would reduce the positive relationship between major life stress and mental health symptoms. Our secondary hypothesis was that the moderating effect of cortisol response on the life stress–symptom relationship would further depend on trait positive affectivity.

Results

Descriptive demographic analyses

The data analyses included 147 participants (93 females and 54 males; see Supplementary Section 3 for the participant exclusion flow diagram). The mean age was 30.2 years (range = 24–45 years, standard deviation (s.d.) = 4.6 years). Participants reported 1.1 major life stress events on average (range = 0–7, s.d. = 1.3). Their mean Symptom Checklist-90 (SCL-90) total score was 37.8 (s.d. = 34.7). Age (Spearman's $\rho = 0.03$ and 0.04, $P > 0.66$) and sex (Mann–Whitney U test $Z = 1.60$ and 1.71, $P > 0.08$) had no significant association with the number of major life stress events, or with SCL-90 score.

Descriptive correlation analyses

Cortisol and positive affectivity correlations. See Supplementary Section 4 for the participants' mean and individual cortisol response trajectory. Controlling for the pre-TSST (T_2) cortisol level, anticipatory (T_3 minus T_2) and peak (T_4 minus T_2) cortisol responses showed no significant correlation with trait positive affectivity, including positive affect, positive reappraisal and positive refocusing (|Spearman's $\rho| < 0.08$, $P > 0.28$ and |Spearman's $\rho| < 0.11$, $P > 0.22$, respectively). The three trait measures showed significant correlations with each other: positive affect and positive reappraisal, Spearman's $\rho = 0.46$, $P < 0.001$; positive affect and positive refocusing, Spearman's $\rho = 0.20$, $P = 0.02$; positive reappraisal and positive refocusing, Spearman's $\rho = 0.37$, $P < 0.001$.

Life stress and SCL-90 correlation. As expected, major life stress (Spearman's $\rho = 0.37$, $P < 0.001$) was associated significantly with the total SCL-90 score, even after controlling for daily hassle score (Spearman's $\rho = 0.30$, $P < 0.001$). Major life stress and daily hassle score correlated significantly with each other (Spearman's $\rho = 0.24$, $P = 0.004$).

Cortisol, positive affectivity and SCL-90 correlation. Controlling for the pre-TSST (T_2) cortisol level, anticipatory and peak cortisol responses showed no significant correlation with SCL-90 score ($P > 0.06$). Of the psychological variables of interest, positive affect negatively correlated with SCL-90 total score (Spearman's $\rho = -0.36$, $P < 0.001$). Positive reappraisal showed a trend of negatively correlating with the SCL-90 score (Spearman's $\rho = -0.14$, $P = 0.08$). Positive refocusing showed no correlation with the SCL-90 score ($P > 0.85$).

TSST effect

Cortisol. Linear mixed-effect analysis revealed a significant main effect of time ($F_{2, 288} = 41.90$, $P < 0.001$). A post hoc paired-sample t-test revealed a significant increase of salivary cortisol level from pre-TSST (T_2) to immediately after TSST (T_3) ($t_{144} = 8.65$, $P < 0.001$), which then showed a trend of increase again at 20 min after TSST (T_4) ($t_{144} = 1.91$, $P = 0.06$).

Profile of mood states. The total mood disturbance score computed from the Profile of Mood States (POMS) subscales showed a significant main effect of time ($F_{1, 146} = 41.25$, $P < 0.001$), indicating a significant increase of negative mood after TSST compared to before TSST.

Moderating the stress–symptom relationship

Cortisol. We found that the anticipatory cortisol response (T_3 minus T_2) significantly and negatively moderated the relationship between major life stress and SCL-90 score ($F_{1, 139} = 5.12$, bootstrapped confidence interval (CI) = −10.6462 to −0.9843, $P = 0.04$), while controlling for pre-TSST (T_2) cortisol level and daily hassle. Follow-up analysis revealed that, at a lower increase of cortisol during anticipatory stress,

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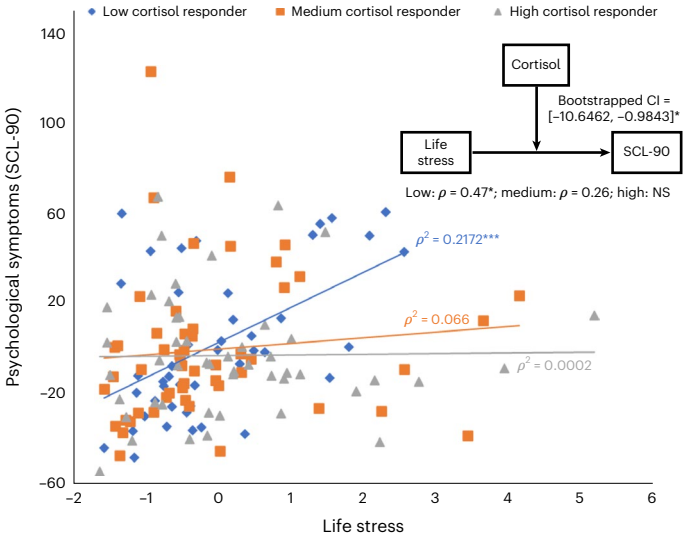

Fig. 1 | The moderating effect of anticipatory cortisol response to acute stress on the relationship between life stress and SCL-90 score. This moderating analysis was conducted using the PROCESS macro implemented in SPSS (pre-set Model No. 1). The test was two-sided. We conducted a Holm–Bonferroni correction procedure to adjust for the two types of cortisol response (anticipatory and peak) analysed. The anticipatory cortisol response (T_3 minus T_2) significantly and negatively moderated the relationship between major life stress and SCL-90 score ($F_{1,139} = 5.12$, bootstrapped CI = −10.6462 to −0.9843, $P = 0.04$), while controlling for pre-TSST (T_2) cortisol level and daily hassle. At a lower cortisol response, major life stress correlated positively with SCL-90 score (Spearman's $\rho = 0.47$, $P = 0.001$). This relationship became a positive trend at an intermediate level of cortisol increase (Spearman's $\rho = 0.26$, $P = 0.07$), and insignificant at a high level of cortisol increase ($P = 0.82$). The relationship is plotted separately for participants with low, medium and high levels of anticipatory cortisol response, divided according to 33% and 67% percentiles. Note that the *x* and *y* axes include negative values due to the intercept and nuisance variables being regressed out from the dependent and independent variables in the partial correlation analysis. ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$; NS, not significant.

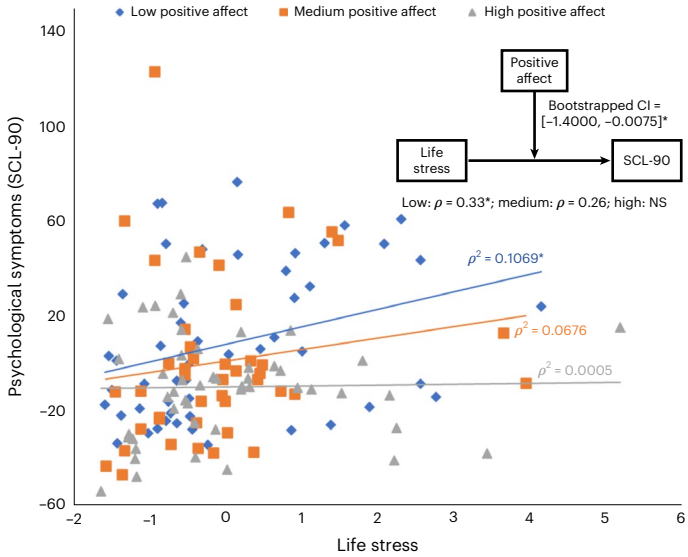

Fig. 2 | The moderating effect of trait positive affect on the relationship between life stress and SCL-90 score. This moderating analysis was conducted using the PROCESS macro implemented in SPSS (pre-set Model No. 1). The test was two-sided. As we analysed only one measure of positive affect, no multiple-testing correction was conducted. Positive affect negatively moderated the relationship between major life stress and SCL-90 score ($F_{1,139} = 2.71$, bootstrapped CI = −1.4000 to −0.0075, $P = 0.05$), while controlling for daily hassle. At a low level of positive affect, major life stress correlated positively with SCL-90 score (Spearman's $\rho = 0.33$, $P = 0.02$). This relationship became a positive trend at an intermediate level of positive affect (Spearman's $\rho = 0.26$, $P = 0.09$), and was insignificant at a high level of positive affect ($P = 0.71$). The relationship is plotted separately for participants with low, medium and high levels of positive affect, divided according to 33% and 67% percentiles. Note that the *x* and *y* axes include negative values due to the intercept and nuisance variables being regressed out from the dependent and independent variables in partial correlation analysis. ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$; NS, not significant.

major life stress correlated positively with SCL-90 score (Spearman's $\rho = 0.47$, $P = 0.001$). This relationship became a positive trend at an intermediate level of cortisol increase (Spearman's $\rho = 0.26$, $P = 0.07$), and was insignificant at a high level of cortisol increase ($P = 0.82$) (Fig. 1). The peak cortisol response (T_4 minus T_2) did not significantly moderate the relationship between major life stress and SCL-90 score (bootstrapped $P > 0.1$).

Positive affectivity. Positive affect negatively moderated the relationship between major life stress and SCL-90 score ($F_{1,139} = 2.71$, bootstrapped CI = −1.4000 to −0.0075, $P = 0.05$), while controlling for daily hassle. Follow-up analysis revealed that, at a low level of positive affect, major life stress correlated positively with SCL-90 score (Spearman's $\rho = 0.33$, $P = 0.02$). This relationship became a positive trend at an intermediate level of positive affect (Spearman's $\rho = 0.26$, $P = 0.09$), and insignificant at a high level of positive affect ($P = 0.71$) (Fig. 2).

A similar negative moderating effect was observed for positive refocusing ($F_{1,139} = 3.69$, bootstrapped CI = −5.3073 to −0.5542, $P = 0.04$), while controlling for daily hassle. Follow-up analysis revealed that, at a low level of positive refocusing, major life stress correlated positively with SCL-90 score (Spearman's $\rho = 0.52$, $P = 0.01$). This relationship became a positive trend at an intermediate level of positive refocusing (Spearman's $\rho = 0.19$, $P = 0.08$), and insignificant at a high level of positive refocusing ($P = 0.29$) (Fig. 3).

Positive reappraisal did not significantly moderate the relationship between major life stress and SCL-90 score (bootstrapped $P > 0.34$).

Moderated moderating effect

Positive affect. We further tested whether the moderating effect of cortisol on the life stress–symptom relationship was in turn moderated by trait positive affectivity. Moderated moderating analyses revealed that the moderating effect of cortisol was further moderated by positive affect ($F_{1,135} = 3.97$, bootstrapped CI = 0.0204 to 2.0364, $P = 0.05$). Specifically, the negative moderating effect of cortisol was only observed at a low level of positive affect ($F_{1,47} = 7.57$, bootstrapped CI = −21.5529 to −5.0381, $P = 0.005$), but not at an intermediate or high level of positive affect (bootstrapped $P > 0.35$) (Fig. 4a). Follow-up analyses revealed that at a low level of positive affect, major life stress correlated positively with SCL-90 score (Spearman's $\rho = 0.63$, $P = 0.01$) among those with a low cortisol response, showing a trend of correlating with the SCL-90 score (Spearman's $\rho = 0.39$, $P = 0.06$) among those with a medium cortisol response, and insignificantly among those with a high cortisol response (Spearman's $\rho = -0.18$, $P = 0.59$).

Positive reappraisal. In addition, the moderating effect of cortisol was further moderated by positive reappraisal ($F_{1,135} = 5.28$, bootstrapped CI = 0.5133 to 8.0221, $P = 0.04$). Specifically, the negative moderating effect of cortisol was observed at a low level ($F_{1,38} = 5.50$, bootstrapped CI = −21.5859 to −1.3569, $P = 0.04$) and an intermediate level ($F_{1,55} = 4.85$, bootstrapped CI = −19.7838 to −0.3268, $P = 0.04$) of positive reappraisal, but not at a high level (bootstrapped $P = 0.45$) (Fig. 4b). Follow-up analyses revealed that, at a low level of positive reappraisal, major life stress correlated positively with SCL-90 score (Spearman's $\rho = 0.704$, $P = 0.003$) among those with a low cortisol response, insignificantly (Spearman's $\rho = 0.35$, $P = 0.20$) among those with a medium

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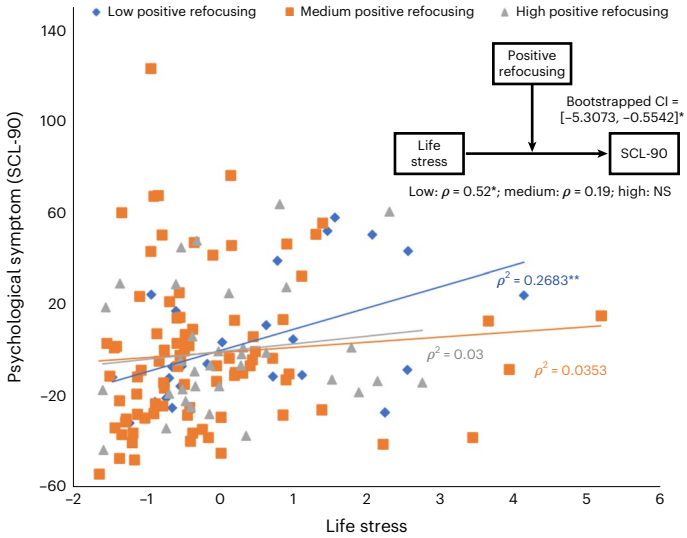

Fig. 3 | The moderating effect of trait positive refocusing on the relationship between life stress and SCL-90 score. This moderating analysis was conducted using the PROCESS macro implemented in SPSS (pre-set Model No. 1). The test was two-sided. We conducted a Holm–Bonferroni correction procedure to adjust for the two types of positive emotion regulation strategy (positive reappraisal and refocusing) analysed. Positive refocusing significantly and negatively moderated the relationship between major life stress and SCL-90 score ($F_{1,139} = 3.69$, bootstrapped CI = −5.3073 to −0.5542, $P = 0.04$), while controlling for daily hassle. At a low level of positive refocusing, major life stress correlated positively with SCL-90 score (Spearman's $\rho = 0.52$, $P = 0.01$). This relationship became a positive trend at an intermediate level of positive refocusing (Spearman's $\rho = 0.19$, $P = 0.08$), and insignificant at a high level of positive refocusing ($P = 0.29$). The relationship is plotted separately for participants with low, medium and high levels of positive refocusing, divided according to 33% and 67% percentiles. Note that the *x* and *y* axes include negative values due to the intercept and nuisance variables being regressed out from the dependent and independent variables in partial correlation analysis. ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$.

cortisol response, and negatively with SCL-90 score among those with a high cortisol response (Spearman's $\rho = -0.58$, $P = 0.03$). At an intermediate level of positive reappraisal, major life stress showed a trend of correlating positively with SCL-90 score (Spearman's $\rho = 0.48$, $P = 0.09$) among those with a low cortisol response, and insignificantly among those with a medium or high level of cortisol response ($P > 0.32$).

Positive refocusing. The moderating effect of cortisol was not significantly moderated by positive refocusing ($F_{1,135} = 0.82$, bootstrapped $P > 0.36$).

Discussion

In this Article we have revealed the effects of anticipatory cortisol response and trait positive affectivity on resilience to major life stress. Specifically, major life stress was positively correlated with participants' current psychological symptoms, but only among those with a low cortisol response to anticipatory stress, or with low trait positive affectivity. On the contrary, for individuals with medium or high levels of cortisol response or trait positive affectivity, the stress–symptom association reduced in a dose-dependent manner. We additionally discovered that the effect of cortisol response was further dependent on the level of trait positive affectivity. Specifically, positive association between major life stress and current symptoms was only observed at low levels of both cortisol response and positive affectivity. These results have unravelled the intricate interplay between the biological and trait affective processes in relation to major life stress resilience.

Emerging evidence indicates an association between individuals' anticipatory cortisol response to acute stress and their psychobiological outcomes following chronic stress. For example, one study found that the anticipatory cortisol response to the TSST mediated the effect of perceived stress and oxidative stress damage among women who cared for demented spouses, implicating a key role for the anticipatory cortisol system in underpinning the accumulative biological effects of chronic stress[25]. Moreover, the offspring of PTSD mothers, who were considered more vulnerable to developing stress-related psychological illnesses, exhibited a 'flattened' anticipatory stress response compared to offspring of non-PTSD mothers[11]. However, neither of those studies explicitly quantified the participants' resilience to life stress. Our results demonstrate that a high anticipatory cortisol response nullified the pattern of increased psychological symptoms after experiencing greater levels of major life stress, indicating a protective role of the high-reactive cortisol system when the individual prepares for encountering acute stress. It is known that anticipation prior to actual occurrence of the stressor effectively activates the HPA axis, which in turn induces coordinated biological and affective responses and allows the individual to better adjust to the stressful environment[26]. During acute stress, the elevation in cortisol levels increases alertness[27] and regulates energy metabolism and output[28], preparing the body to engage in an adaptive 'fight-or-flight' response and achieve better performance[29]. In the longer term, this better adaptation to acute stress due to a greater anticipatory cortisol increase was found to dampen the effect of peer victimization in increasing rumination and depressive symptoms one year later[30]. On the contrary, the blunted anticipatory cortisol response was associated with major depression[31], increased genetic risk for major depression[32], and schizophrenia[33]. Thus, converging evidence suggests that a potent anticipatory cortisol response to acute stress represents a biologically adaptive system that protects an individual from mental health damage following major life stress.

We did not find a significant effect of peak cortisol response on resilience. Past findings on this association were inconsistent. Peak cortisol change was not associated with oxidative stress damage among chronically stressed women[25], and was not related to a questionnaire measure of resilience among male students[34]. However, the peak cortisol change predicted a four-year trajectory of resilience among police officers[10]. Although multiple discrepancies in participant characteristics and resilience measurement preclude conclusions based on previous findings, our current results suggest that anticipatory and peak cortisol responses may have differential correlates with resilience to major life stress. This is consistent with the previously proposed separation of indirect activation of the HPA axis, which delivers stress anticipation signals, and direction activation of the HPA axis, which delivers stress reaction signals[35].

Consistent with existing evidence indicating the protective effects of positive affectivity trait on mental health following major life stress[13,21], we observed that both positive affect and positive refocusing 'buffered' the relationship between life stress and psychological symptoms. It has long been recognized that the ability to maintain a positive prospect during chronic stress is key to resilience[36]. In our study, positive affect and positive refocusing correlated positively with each other. On the one hand, the strategy of shifting one's attention away from aversive events towards other positive aspects of life may boost resilience by enhancing general positive emotions. On the other hand, based on past studies showing an association between trait positive affect and attention control[37], it could also be that individuals with higher trait positive affect are more able to (re)direct their attention to maintain focus on positive aspects, even under major life stress. Regardless, converging evidence suggests that positive affectivity, which is related to greater sensitivity to rewards and better capacity of attending to positive aspects, is a core characteristic of resilience to chronic stress.

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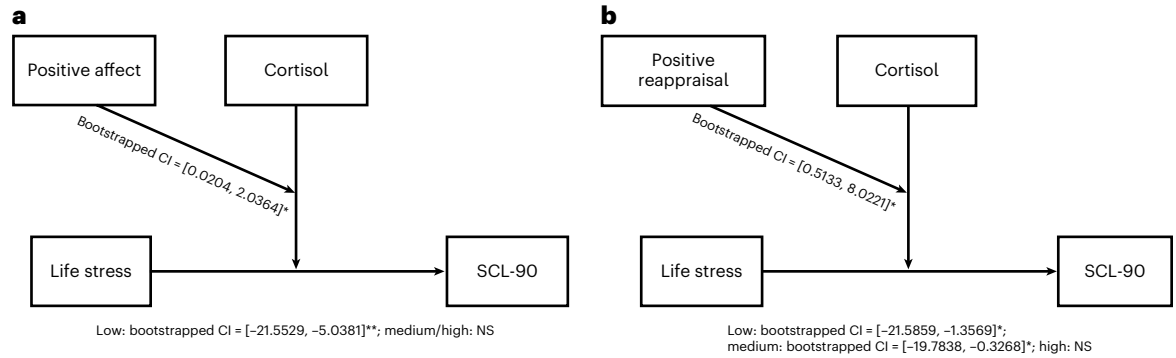

Fig. 4 | The moderated moderating analysis results. a,**b**, The trait positive affect (**a**) and positive reappraisal (**b**) moderated the moderating effect of anticipatory cortisol response on the relationship between life stress and SCL-90. This moderated moderating analysis was conducted using the PROCESS macro implemented in SPSS (pre-set Model No. 3). The test was two-sided. We conducted a Holm–Bonferroni correction procedure to adjust for the two types of positive emotion regulation strategy analysed. In **a**, the moderating effect of cortisol is seen to be further moderated by positive affect ($F_{1, 135} = 3.97$, bootstrapped CI = 0.0204 to 2.0364, $P = 0.05$). The negative moderating effect of cortisol was only observed at a low level of positive affect ($F_{1, 47} = 7.57$, bootstrapped CI = −21.5529 to −5.0381, $P = 0.005$), but not at an intermediate or high level of positive affect (bootstrapped $P > 0.35$). In **b**, the moderating effect of cortisol was also moderated by positive reappraisal ($F_{1, 135} = 5.28$, bootstrapped CI = 0.5133 to 8.0221, $P = 0.04$). The negative moderating effect of cortisol was observed at a low level ($F_{1, 38} = 5.50$, bootstrapped CI = −21.5859 to −1.3569, $P = 0.04$) and intermediate level ($F_{1, 55} = 4.85$, bootstrapped CI = −19.7838 to −0.3268, $P = 0.04$) of positive reappraisal, but not at a high level (bootstrapped $P = 0.45$). ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$.

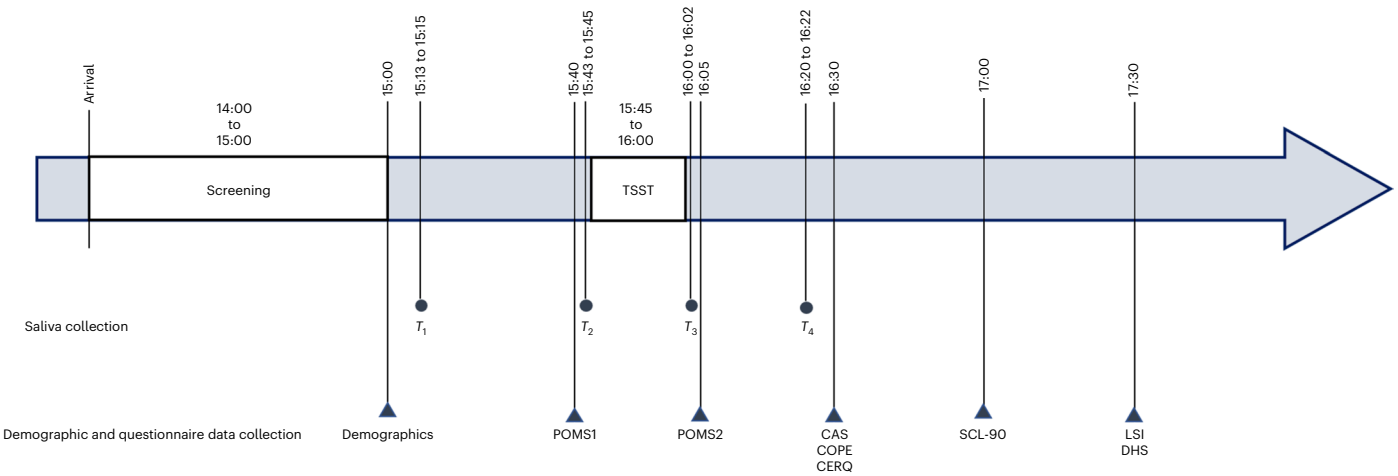

Fig. 5 | Study procedure timeline. The indicated times of the day were mostly fixed for each participant. Inter-participant timing shifts did not exceed 20 min. The timing intervals between different experimental phases were also fixed for each participant.

We did not find a significant moderating effect of positive reappraisal on the stress–symptom relationship, despite previous studies reporting such a link[16,18]. Many previous studies reporting a relationship between positive reappraisal/reframing and resilience were conducted on special populations, such as combat veterans[16], victims of a natural disaster[17] and newly diagnosed cancer patients[18]. It could be that better cognitive reappraisal/reframing ability is particularly important for mental health following certain types of life stress. The different mental health outcome measures may also account for the discrepancy. Although past studies assessed PTSD onset, psychosomatic disturbance and quality of life as outcomes, we comprehensively measured participants' psychological symptoms. It remains to be determined by future studies whether cognitive reappraisal/reframing may be differentially linked to resilience depending on the type of life stress and nature of health outcome.

We did not find significant correlation between positive affect and acute cortisol responses, contrary to the findings of previous studies[38]. Several discrepancies in the positive affect measure and nature of the acute stress task may explain the finding difference. The direct association between anticipatory cortisol response and SCL-90 score also did not reach the level of significance. This result was consistent with a previous study with a similar sample size, which found no significant relationship between mood symptoms and cortisol reactivity to the TSST[39].

The core results of our study are that the association between cortisol response and resilience is further dependent on trait positive affectivity. To the best of our knowledge, such an interactive effect of stress-related biological and trait affective processes on resilience has never been studied before, but is highly pertinent to understanding the integrated psychobiological systems underpinning resilience. In animals and humans, cortisol release following acute stress acts on glucocorticoid receptors in the brain, exerting a regulatory influence on cellular functions that may last beyond the timescale of the stressor[40]. The glucocorticoid receptors are densely located in the brain limbic circuitries involved in emotion regulation[41]. In addition, cortisol exerts an indirect influence on the brain reward system via modulating dopaminergic circuitries[5,42]. Therefore, a blunted cortisol response may cause maladaptive emotion processing and regulation functions within key neural circuitries. However, such deficiencies may be compensated by a high positive affectivity trait, possibly mediated by direct enhancement of dopaminergic functions, as well as functional interactions between the dopaminergic circuitries and limbic

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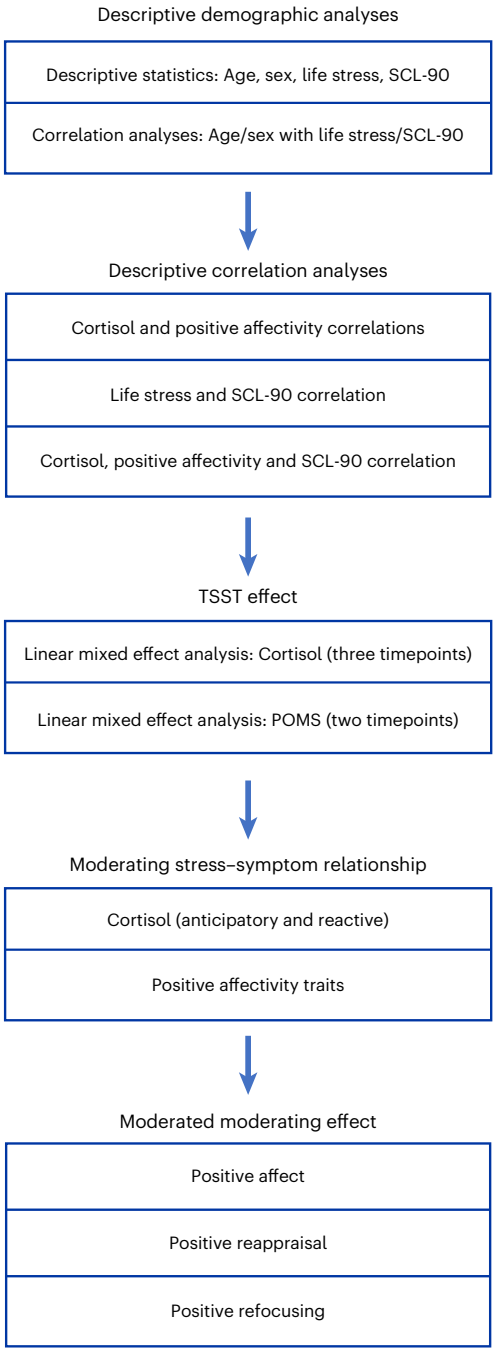

Fig. 6 | Data analysis plan. The data analysis pipeline.

networks[43]. The reason we did not observe a significant moderating effect of positive refocusing on the cortisol–resilience relationship is unclear. It could be that affective attention has a separate and parallel biological mechanism to the cortisol system. For example, a recent study showed that pharmacological challenge to the cholinergic system altered participants' affective attention function[44].

One recent review highlighted various confounding factors that may affect psychobiological responses to the TSST, including the acclimation period before TSST, time of day, mood measure (subjective versus objective) and TSST panel sex composition[45]. In this study, we adhered to the most standard TSST protocol by (1) having participants physically rest for over an hour after arriving at the laboratory, (2) delivering TSST at a mostly fixed time (15:45 to 16:00) across all participants, and (3) having both male and female panel members for each participant. Although we collected no objective affective response data, the expected mood changes in response to the TSST supported the validity of the self-reported mood measure.

Several limitations need to be noted. First, the current findings may not fully generalize to individuals who developed clinical conditions following major life stress. The averaged major life stress reported by participants was relatively low, which was expected for a non-clinical, relatively young sample, and the number of events may be higher for clinical samples. Second, we did not collect data about female participants' menstrual cycle or participants' body mass index, which could have impacted on participants' cortisol response profiles. Future studies may replicate our results while controlling for these variables. Third, in this study we tested the cortisol response and trait positive affectivity markers of resilience to major life stress. However, due to the cross-sectional nature of data, we could not be certain of the direction of influence, as it could also be interpreted as the psychological symptoms causing the difference in cortisol response[39]. Future prospective studies are necessary to test whether baseline cortisol response and trait affectivity may predict future mental health outcomes following major life stress. Fourth, our cortisol sampling timepoints may be too sparse to capture the detailed post-task cortisol change profile, although this was partly intended to reduce the effect of frequent cortisol sampling on mood state. Given our focus on anticipatory and peak cortisol responses, we also did not include cortisol sampling during the recovery phase. Future studies may replicate the current findings with more cortisol measurements, and with 'peak' timepoints tailored to the response profile of individual participants. Finally, our life stress questionnaire included relatively heterogeneous types of events; this was to capture participants' major life stress experiences as completely as possible. Future studies may focus on more specific types of event (for example, acute versus chronic) to investigate stress resilience at a finer scale.

In conclusion, we found that a higher anticipatory cortisol increase to acute stress, as well as trait positive affectivity, were associated with better mental health outcome following major life stress. Importantly, the relationship between cortisol response and resilience further depended on the level of trait positive affectivity. These results have implications for the identification of individuals with high psychobiological vulnerability to major life stress, and intervention for those individuals.

Methods

Participants

This study was approved by the Institutional Review Board of the University of Hong Kong. All participants provided written informed consent. One hundred and sixty-five participants were recruited via advertisement, printed and social media, and from the FAMILY Cohort[46], which is a participant registry containing ~30,000 local citizens. All participants had to be aged 24–45 years with at least a secondary level of education. Exclusion criteria included (1) current or past major physical or neurological conditions; (2) major psychological illnesses such as mood and anxiety disorders, schizophrenia and addiction; (3) any medication or other treatment received within two weeks before the study that might affect the endocrinological system; (4) (for females) pregnancy or breastfeeding. Psychological illnesses were assessed with the Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-CV). To rule out the potential confounding effect of intensive childhood trauma, we asked each participant to report any directly exposed or witnessed traumatic events in her/his lifetime, including those happening in childhood. Any participant who self-reported symptoms that met the diagnostic criteria for PTSD was excluded.

After stage-2 screening, 16 participants were screened out. One other participant was screened out due to abnormal cortisol change (>4 s.d. from total mean), and another was excluded due to a very high SCL-90 score of 210 (>4 s.d. from total mean), leaving 147 participants

in the data analysis (aged 24–45 years, 93 females, 54 males). Two participants' cortisol samples were used for protocol testing purposes, leaving 145 participants in the current cortisol-related analyses. This sample size is sufficient according to several previous studies investigating the association between cortisol response, positive affectivity and stress-related mental outcomes[11,14,34]. Post hoc power analysis based on ref. [11] revealed that our sample size achieved good power (>0.8).

Further details about the participants are included in Supplementary Section 2.

Procedure

Eligible participants were invited to join the experiment, which was always held in the afternoon between 14:00 and 18:00. Before the experiment, participants were reminded to (1) avoid food or beverage consumption within the past hour; (2) avoid intense physical activities or teeth-brushing within 2 h, (3) avoid caffeine intake or smoking on the day of the experiment; (4) avoid alcohol consumption within 24 h of the experiment.

Upon arrival at the laboratory, each participant completed the screening and demographic information-collection procedures, then provided the first saliva sample (T_1). They then rested for 30 min in a quiet room (room A), where they were provided with reading materials containing emotionally neutral content. This allowed the cortisol level to reach a resting baseline. Following the resting phase, the participant completed the first POMS and provided a second saliva sample (T_2), then was taken to another room (room B) for the TSST. Upon completion of the TSST, the participant was taken back to room A. The third saliva sample was collected (T_3) and the second POMS was completed. The participant then rested for 20 min before the fourth saliva sample was collected (T_4). After that, the participant completed the Chinese Affect Scale (CAS), Brief Cognitive Emotion Regulation Questionnaire (CERQ) and Brief COPE questionnaires, as well as the Symptom Checklist-90 (SCL-90), Daily Hassle Scale (DHS) and Life Stress Index (LSI) questionnaires. Following study completion, participants were debriefed, thanked and paid HKD$600 for time and travel compensation. Further details about questionnaire administration timing are included in Fig. 5 and Supplementary Section 2.

Task and materials

The Trier Social Stress Test. The TSST is a widely used laboratory paradigm to induce acute stress to participants[9,24]. The TSST consists of three successive phases: (1) anticipation/preparation, (2) speech and (3) mental arithmetic, each lasting for 5 min. Before the anticipation phase, the participant was instructed to imagine s/he was attending an interview for her/his 'ideal job', during which they would need to deliver a 5-min free speech to demonstrate to a panel of 'expert examiners' that s/he was the best candidate for the job. The anticipatory/preparatory phase started immediately after the instruction, during which the participant prepared for the speech alone. In the subsequent speech phase, the participant delivered the speech to a panel of three 'judges' (always one male and two females, all dressed in white laboratory gowns) who remained emotionless and speechless unless the participant was unable to speak for the full 5 min. If the latter happened, the 'chief' judge would ask one or several prompt questions (for example, 'What do you consider to be your main merit for this job?'). Dummy camera and audio devices were pre-installed in the room to enhance the perceived vividness of the job interview. Following the speech phase, the participant was asked to perform a mental arithmetic task involving sequentially subtracting 17 from 2,023. The participant needed to speak out the answer loudly after every calculation, and had to start over again from the beginning if they made a mistake.

Salivary cortisol. Salivary cortisol samples were collected using the Salivette Cortisol Kit (Sarstedt, cat. no. 51.1534.500). For each sample collection, the participant was instructed to chew a cotton swab for 60 s to fully soak the swab with saliva. The swab was then placed into the Salivette tube, and saliva samples were retrieved from the tube by centrifugation at 3,000*g* for 5 min. Quantification of cortisol concentration was performed with liquid chromatography-tandem mass spectrometry analysis (LC-MS/MS), which is considered a highly accurate and sensitive method of analysing salivary cortisol[47].

Salivary cortisol was collected at four timepoints before and after the TSST. The first sample (T_1) was collected shortly after the participant completed the screening and demographic information-collection procedures. Half an hour later, the second sample was collected immediately before the participant received instructions for the TSST (T_2); this was considered to be the baseline level. The third sample was collected immediately after completion of the TSST (T_3). The fourth sample was collected 20 min after completion of the TSST (T_4) (Fig. 5). Because the salivary cortisol response to acute stress has a typical delay of around 15–20 min (ref. [48]), we considered the contrast T_3 minus T_2 as reflecting anticipatory stress (corresponding to the instruction/preparatory phase), whereas the contrast T_4 minus T_2 was considered the peak stress response[25]. Based on recent reviews and meta-analyses[23,45,48], we placed T_3 and T_4 at +0 and +20 min post-TSST to capture both anticipatory and peak cortisol responses. All salivary cortisol collections happened between 15:00 and 16:30, to minimize the confounding effect of diurnal cortisol variations.

Questionnaires. The LSI assesses the experience of major life events, derived from the Life Stress Assessment[49] and the Life Events Checklist for DSM-5 (ref. [50]) (Supplementary Section 1). Participants indicated whether they had personally experienced the event or witnessed the event happening to others, in the past five years. Because witnessing is generally considered as causing weaker stress-related mental damage than experiencing oneself[51,52], we gave a score of 1 for every personal experience of a life event, and 0.5 for every witnessing of the event. For each event, the participant was also asked to provide details about the event's frequency and duration, as well as a brief description of the event. For witnessing events, only those happening to the participant's close friend or family member counted. All answers were independently reviewed by a panel of five judges (one clinical psychologist with more than 30 years of experience, two junior professorial-level academicians with more than 5 years of experience in stress-related research, one occupational therapist with more than 5 years of experience, and one junior research assistant in charge of collecting responses from the participant) to evaluate whether the event fulfilled the criteria for major life stress. The evaluation was based on multiple types of information about the event, such as duration, intensity, recurring frequency, relationship of involved other parties with the participant, and detailed nature of the event. Any discrepancy in rating was resolved through discussion. An event would score only if all panel members agreed on it. Further details about life stress assessment are included in Supplementary Section 2.

The DHS contains 63 items that assess daily stress and annoyance over the past month[53]. Because minor hassles and stress in daily life may also induce temporary psychological symptoms, we also incorporated this variable in the study[54]. Participants indicated the frequency of occurrence for each item. This scale had two subscales: the covert hassles subscale, containing 42 items (for example, inner concerns, internal consistency = 0.88), and the overt hassles factor, containing 21 items (for example, environmental hassles, internal consistency = 0.80) (ref. [53]). The two subscales were pooled together to produce a total score.

The SCL-90 (ref. [55]) has 90 items that measure psychological symptoms over the past week across ten dimensions: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism and additional. This scale performed well in detecting patients with mental disorders[56] and in measuring subclinical psychological symptoms

among community samples[57]. The Cronbach's alpha in our sample was 0.936. A total score was calculated using the sum of all subscales to quantify mental symptoms. Further details are included in Supplementary Section 2.

The CAS assesses trait positive and negative affects[58]. All items are rated on a five-point Likert scale (1 = very slightly or not at all, 5 = extremely). In this study, we focused on the positive affect subscale, which contains ten items and has an internal consistency of 0.9 (ref. [58]).

The CERQ assesses nine strategies of cognitive control over emotion[59]. All items are rated on a five-point Likert scale (1 = (almost) never, 5 = (almost) always). In this study, we focused on the positive refocusing subscale, which measures the tendency to think about positive experiences rather than the actual negative event. The internal consistency of the positive refocusing subscale is 0.86 (ref. [59]).

The COPE measures 14 problem- and emotion-focused strategies when coping with adversity[60]. All items are rated on a four-point Likert scale (0 = I haven't been doing this at all, 3 = I've been doing this a lot). In this study, we focused on the positive reframing subscale, which refers to the tendency to reappraise the negative situation more positively, through changing perspectives or digging positive aspects (that is, positive reappraisal). The positive reappraisal subscale has a reasonable internal consistency of 0.64 (ref. [60]).

The POMS assesses five transient negative emotion states (tension, anger, fatigue, confusion and depression) and two positive emotion states (vigour and esteem)[61]. All items were rated on a five-point Likert scale (0 = not at all, 4 = extremely). The mean internal consistency among the subscales is 0.942 (ref. [62]). A total mood disturbance score was computed by summing the scores for the positive and negative emotion states, and subtracting the former from the latter.

The timeframes of CAS, CERQ and Brief COPE were all set to be 'In general' to specifically capture the trait characteristics in those domains.

Statistical analysis

Data analyses were performed using SPSS v.26. Data normality was checked using the Kolmogorov–Smirnov test. Cortisol level changes and daily hassle score were non-normal, and a natural logarithm (ln) transformation was applied to those measures. To correct for residual deviation from non-normality and outlier effect, we conducted Spearman (rather than Pearson's) correlation analysis, which computed ρ (rather than r) values as the correlation coefficient[63].

A data analysis pipeline is included in Fig. 6. Descriptive correlation analyses were conducted among cortisol response, major life stress, SCL-90 total score, trait positive affectivity (positive affect, positive reappraisal and positive refocusing) and daily hassle score. For correlation analyses involving cortisol response, the baseline pre-TSST (T_2) cortisol level was controlled for as a covariate, because baseline level may affect the amplitude of subsequent cortisol level changes. For correlation analyses involving major life stress, daily hassle score was controlled for as a covariate. The purpose of the correlation analyses was to provide an overview of relationships among key variables.

To test whether the TSST caused significant cortisol responses and mood changes, we performed linear mixed modelling analyses on cortisol level and POMS score before and after the TSST, with time as the within-subject factor (cortisol: T_2, T_3 and T_4; mood: T_2 and T_3). The significant main effect of time was further evaluated using a post hoc paired-sample t-test.

To test whether a higher cortisol response reduced the relationship between major life stress and SCL-90 score, we conducted a moderating analysis using the PROCESS macro implemented in SPSS (pre-set Model No.1), utilizing a bias-corrected bootstrapping (5,000 times) approach[64]. The independent variable was life stress, the outcome variable was SCL-90 score, and the moderator was cortisol response (anticipatory or peak), controlling for pre-TSST (T_2) cortisol level and daily hassle score.

To test whether greater positive affectivity (positive affect, positive reappraisal, positive refocusing) reduced the relationship between major life stress and SCL-90 score, we similarly conducted a moderating analysis as above, except that the moderator was positive affectivity traits.

All significant moderating effects were further evaluated using simple-effect Spearman's full partial correlation analyses, where nuisance variables (T_2 cortisol, daily hassle) and intercept were regressed out from both dependent and independent variables before computing the correlation. During follow-up analyses and graph plotting, we split the continuous moderating variables into low, medium and high groups based on 33.33% quantiles.

Finally, to test whether the moderating effect of cortisol change was also dependent on positive affectivity trait, we conducted moderated moderation analyses using PROCESS (pre-set Model No.3). The model set-up was identical to that used for testing the simple moderating effect of cortisol, except that a second moderator (that is, positive affectivity trait) was added, and we tested whether it had a second-order moderating effect on the cortisol moderating effect.

All statistical thresholds were set at $P < 0.05$ (two-tailed). As we analysed two types of cortisol response (anticipatory and peak) and two positive emotion regulation strategies (positive reappraisal and positive refocusing), we conducted a Holm–Bonferroni correction procedure within these categories of testing for the key moderation and moderated moderation analyses.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this Article.

Data availability

Data included in this work are provided in the Supplementary Information. Source data are provided with this paper.

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Author contributions

R.S. contributed to study design, data analysis and interpretation, and drafting and revision of the manuscript. I.S.C.M. contributed to data collection, data analysis and interpretation, and drafting and revision of the manuscript. C.L. contributed to data collection, analysis and manuscript revision. S.-Y.Y., W.K.H., S.X.L., F.Y.L. and Y.K.W. contributed to study conceptualization and manuscript revision. T.M.C.L. contributed to study conceptualization, study design, data interpretation and manuscript revision.

Competing interests

The authors declare no competing interests.

Additional information

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☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used.
Data analysis	Data analysis was carried out using SPSS v. 26.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The data included in this work are shared as Supporting Information-Additional Supplementary Files and Supporting Information-Source Data.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☐ Life sciences ☒ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	Quantitative experimental data were collected. All participants performed a laboratory stress-induction task. Physiological and mood measures before and after the task were collected. Psychological trait measures were collected using questionnaires.
Research sample	The sample (N=147, 93 females) was drawn from a large representative public health cohort pool. The mean age was 30.12 years (range = 24-45 years). We selected a sample of adults without major clinical diagnosis, to boost the generalisability of our findings to wider populations. We included participants within the age range of 21-45 years because age is an important factor affecting stress resilience and psychobiological responses, so we limited the age to relatively young adults to reduce heterogeneity.
Sampling strategy	We conducted convenience sampling using a large public health cohort pool based on participation availability and screening outcome. The sample size was deemed sufficient according to the effect sizes provided by several previous studies investigating the association between cortisol response, positive affectivity and stress-related mental outcomes (Mikolajczak et al., 2008; Danielson et al., 2015; Lord et al., 2015). Post-hoc power analysis based on Lord et al. (2015) revealed that our sample size achieved good power (>0.8).
Data collection	Data were collected using computer and pen and pencil. No one was present aside from the participant and the experimenter. The experimenter(s) were blind to study hypotheses.
Timing	Data collection started from September 2020, and finished at April 2022.
Data exclusions	Sixteen participants were screened out due to issues with mental or physical health. One other participant was screened out due to abnormal cortisol change (>4SD from total mean), and another was excluded due to very high SCID-90 score of 210 (>4SD from total mean).
Non-participation	No participant dropped out or declined participation.
Randomization	Participants were not allocated to distinct experimental groups.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	All participants were carefully screened using DSM-5 Disorders- Clinician Version to ensure they had no past or present diagnosis of major psychiatric illness. All participants reported no past or present major physical illness. We included 147 participants in total (93 females, aged 24-45 years old, mean age=32.2 years).
Recruitment	Participants were drawn from a large representative public health cohort pool (total N=20,000) in the Hong Kong local

Recruitment	community. Some level of bias may arise due to individual difference in willingness or availability to participate. As participants were recruited through direct telephone contact of a public health cohort pool, and through advertisement, printed and social media, it was possible that bias derived from over-representation of individuals who were interested in or willing to participate in research studies. This is a common issue in psychology research that is very difficult to avoid for studies involving adult participants drawn from community samples. Our relatively large sample size partly alleviated this issue.
Ethics oversight	Institutional Review Board of the University of Hong Kong All participants provided written informed consent. Participants were paid HKD$600 for time and travel compensation.

Note that full information on the approval of the study protocol must also be provided in the manuscript.