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Hostility and Physiological Responses to Acute Stress in People With Type 2 Diabetes

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ABSTRACT

Objective: Hostility is associated with cardiovascular mortality and morbidity, and one of the mechanisms may involve heightened reactivity to mental stress. However, little research has been conducted in populations at high risk for cardiovascular disease. The aim of the present study was to assess the relationship between hostility and acute stress responsivity in individuals with Type 2 diabetes.

Methods: A total of 140 individuals (median age [standard deviation] 63.71 [7.00] years) with Type 2 diabetes took part in laboratory-based experimental stress testing. Systolic blood pressure, diastolic blood pressure, heart rate, plasma interleukin-6 (IL-6), and salivary cortisol were assessed at baseline, during two stress tasks, and 45 and 75 minutes later. Cynical hostility was assessed using the Cook Medley Cynical Hostility Scale.

Results: Participants with greater hostility scores had heightened increases in IL-6 induced by the acute stress tasks ($B = 0.082$, $p = .002$), independent of age, sex, body mass index, smoking, household income, time of testing, medication, and baseline IL-6. Hostility was inversely associated with cortisol output poststress ($B = -0.017$, $p = .002$), independent of covariates. No associations between hostility and blood pressure or heart rate responses were observed.

Conclusions: Hostile individuals with Type 2 diabetes may be susceptible to stress-induced increases in inflammation. Further research is needed to understand if such changes increase the risk of cardiovascular disease in this population.

Key words: Type 2 diabetes mellitus, hostility, interleukin-6, salivary cortisol, psychological stress.

INTRODUCTION

Hostility is a trait that is typically conceptualized as a negative cynical attitude toward others, with a propensity for anger or aggression (1). The impact of hostility on health has become increasingly well recognized. Several studies have identified hostility as an independent risk factor for all-cause mortality (2). In particular, hostility has been suggested to play a role in cardiovascular disease (CVD).

Results from a meta-analysis of prospective cohort studies indicate that hostility is associated with an increased risk of CVD in initially healthy populations, as well as poorer prognosis in patients with CVD (3). There is evidence that acute episodes of anger can trigger myocardial infarction and sudden cardiac death (4). In addition to cardiac events, hostility has been implicated in the long-term development of coronary atherosclerosis. Prospective associations between hostility and carotid atherosclerosis, as indexed by intima-media thickness, have been reported in both male and female samples (5,6).

Despite the growing evidence linking hostility to ill health, the underlying mechanisms involved are not well understood. One possibility is that the relationship is mediated through behavioral pathways. Hostility may lead to adverse health behaviors, such as poor diet, sedentary lifestyle, smoking, and excessive alcohol consumption (7), all of which are established risk factors for CVD. However, findings from most studies remain significant after adjusting for health behaviors (2,3). Thus, it may be that direct biological mechanisms are involved.

In epidemiologic studies, hostility has been linked with disturbances across multiple biological systems. High levels of hostility have been associated with

AUC = area under the curve, **BMI** = body mass index, **CAD** = coronary artery disease, **CI** = confidence intervals, **CVD** = cardiovascular disease, **DBP** = diastolic blood pressure, **HbA1c** = glycated hemoglobin, **HR** = heart rate, **IL-6** = interleukin-6, **SBP** = systolic blood pressure, **T2DM** = Type 2 diabetes mellitus

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autonomic dysfunction (8,9), inflammation (10,11), and increased platelet activation (12).

Acute mental stress testing is another research strategy that is used to investigate the biological concomitants of hostility. Mental stress testing involves the measurement of biological responses to acute challenges. This method allows detailed dynamic responses to be studied under controlled conditions, reducing the impact of other factors that may confound associations (13).

Most of research in the field has investigated cardiovascular responses to acute stress. Meta-analytic results indicate that heightened cardiovascular stress responsivity is associated with an increased risk of future CVD (14) and hostility has been associated with heightened cardiovascular stress responses in healthy participants (15).

CVD has been characterized as an inflammatory condition. Heightened inflammatory interleukin-6 (IL-6) concentrations have been prospectively associated with future CVD and poor outcomes in patients with existing CVD (16,17). In addition, positive associations between circulating IL-6 concentrations and hostility have been observed (10,11).

Excessive glucocorticoid action is associated with cardiovascular risk factors such as central obesity (18), insulin resistance (19), and hypertension (20). Cortisol is involved in regulating inflammation through activation of the glucocorticoid receptor, leading to inhibition of inflammatory cytokine production by monocytes (21). However, prolonged exposure to heightened cortisol levels may result in dysregulation of this system manifested through insufficient glucocorticoid signaling (21). Hostility has been associated with flattening of cortisol rhythms in some studies (22,23). Evidence indicates that low cortisol responders have significantly higher cytokine responses to acute stress (24). Thus, diminished cortisol levels may facilitate heightened inflammation associated with ill health.

Despite this evidence, few studies have investigated inflammatory and neuroendocrine mechanisms in relation to hostility, and most of research has been conducted with healthy samples. To our knowledge, only one small study has investigated acute stress responses in a sample at high risk for coronary events (25). In this study, more hostile individuals with advanced coronary artery disease (CAD) had heightened systolic blood pressure (SBP) and diastolic blood pressure (DBP) responses to mental stress tasks. Hostility was also positively associated with IL-6 and negatively correlated with cortisol concentrations during poststress recovery.

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease that is becoming increasingly prevalent globally (26). CVD is a major cause of mortality and morbidity in individuals with T2DM (27). Results from a meta-analysis of 102 prospective studies indicate that patients with T2DM have a two-fold excess risk of developing CVD compared with controls, independent of standard risk factors (28). This additional risk is largely unexplained. Therefore, it is possible that personality factors could potentially play a role in linking the conditions.

Hostility is not well researched in relation to T2DM. However, it has been associated prospectively with raised fasting glucose (29) and cross sectionally with insulin resistance (30), glycated hemoglobin (HbA1c), and prevalent T2DM (31). In addition, angry temperament has been linked with T2DM onset 6 years later (32). Taken together, it is plausible that hostility plays a role in T2DM and that it may contribute to the increased risk CVD in people with the condition.

Considering the excess risk of CVD in this population and the lack of research relating hostility and inflammatory and neuroendocrine stress responses, we investigated the relationship between hostility and SBP, DBP, heart rate (HR), IL-6, and cortisol responses to laboratory stress in a sample of individuals with T2DM. In epidemiologic studies, raised IL-6 levels have been prospectively associated with CVD development (16) and poorer outcomes in patients with CVD (17). Inflammation is involved in the pathogenesis of T2DM, and IL-6 and C-reactive protein are the most widely studied markers in the field. Meta-analytic results indicate that heightened IL-6 rather than C-reactive protein is a stronger predictor of subsequent diabetes in initially healthy samples (33) and that concentrations of IL-6 are elevated in patients with T2DM (34). We predicted that participants with greater hostility scores would have greater cardiovascular and IL-6 responses to acute stress. Neuroendocrine dysfunction is suggested to play a role in T2DM, and recent results from a comparative study of individuals with diabetes and healthy controls indicate that cortisol stress responsivity is blunted in T2DM (35). We predicted that more hostile individuals would have more diminished cortisol responses to stress.

METHODS

Participants

Participants in this study were recruited as part of a larger trial comparing individuals with Type 2 diabetes and healthy controls (35). We recruited 140 people aged 50 to 75 years with doctor-diagnosed Type 2 diabetes from diabetic outpatient and primary care clinics in the London area between March 2011 and July 2012. Enrollment was restricted to patients without a history or previous diagnosis of coronary heart disease, inflammatory diseases, allergies, or mood disorders. In the 7 days before testing, all participants were prohibited from taking anti-inflammatory or antihistamine medication. On the day of testing, we rescheduled participants if they reported colds or other infections. We instructed participants to avoid caffeinated beverages and smoking for at least 2 hours before the session and to avoid vigorous exercise and alcohol from the previous evening. All participants gave

full informed consent to take part in the study, and ethical approval was granted by the National Research Ethics Service.

Psychological Measures

We measured cynical hostility using the 10-item Cook Medley Cynical Hostility Scale (1). The Cynical Hostility scale is a widely used self-report measure of hostility, assessing cynical and mistrustful attitudes toward others, and has previously been related to physiological stress responses (15,25). The items (e.g., "I think most people would lie to get ahead" and "It is safer to trust no one") were scored using a binary (true/false) format. Total scores ranged from 0 to 10, with higher scores indicating greater hostility. The internal consistency (Cronbach α) of the scale was .80 in this sample. Depression was measured using the Center for Epidemiologic Studies Depression Scale, a standard measure of depressive symptomatology (36). The Cronbach α of the scale was .86 in this sample. Subjective stress was measured over the course of the laboratory session using a 7-point rating scale, with higher values indicating greater stress.

Other Measures

This study was part of a larger trial of physiological response to stress in people with diabetes and included other measures that are not described here (35). For the purposes of the present analysis, we measured household income as an indicator of socioeconomic status, and participants were categorized into low (<£20,000), medium (£20,000-40,000), and high (≥£40,000) income groups. Participant smoking status and medication use were also recorded. Medication was allocated to seven categories: oral diabetic medication (metformin, etc), insulin and other injected diabetic medication, aspirin, β-blockers, other hypertensive medication (angiotensin-converting enzyme inhibitors, calcium-channel blockers, etc), and statins.

Mental Stress Tasks

Mental stress was induced in the laboratory with two 5-minute behavioral tasks administered in random order. The first was a computerized version of the Stroop color-word interference task, which involved successive presentation of target color words (e.g., green and blue) printed in an incongruous color. The second task was mirror tracing, which involved tracing a star that could only be seen in mirror image using a mental stylus. When the stylus came off the star, a mistake was registered and a loud beep was emitted by the device (Lafayette Instruments Corp, Lafayette, IN). Participants were told that the average person could complete five circuits of the star in the allocated time. These tasks were selected because they have previously been shown to stimulate similar appraisals of involvement and engagement from participants across the social gradients and have been used in a number of previous studies in our laboratory (37).

Procedure

We tested participants individually in a light- and temperature-controlled laboratory. Sessions were held either in the morning or in the afternoon. At the beginning of the session, anthropometric measures were obtained using standardized techniques and body mass index (BMI) was computed. Participants were fitted with a finger cuff so that SBP, DBP, and HR could be continuously monitored using a Finometer device (TNO-TPD Biomedical Instrumentation, Amsterdam, Holland), and a venous cannula was inserted for the collection of blood samples. The participant rested for 30 minutes, and the last 5 minutes of data was averaged to constitute baseline cardiovascular values. At this time, a baseline blood sample was drawn, saliva was collected for the analysis of cortisol, and a subjective stress rating was obtained. We then administered the two 5-minute behavioral tasks. Five-minute recordings of SBP, DBP, and HR were made during each of the tasks, and subjective stress ratings and blood and saliva samples were taken immediately after the tasks. Monitoring of posttask recovery continued for 75 minutes. Further subjective stress ratings, cardiovascular measurements, and blood samples were obtained at 45 and 75 minutes posttasks. Additional saliva samples were obtained at 20, 45, and 75 minutes after the tasks.

Biological Measures

Blood samples were collected in EDTA tubes and centrifuged immediately at 2500 rpm for 10 minutes at room temperature. Plasma was removed from the tube and aliquoted into 0.5-ml portions and stored at −80°C until analysis. Plasma IL-6 was assayed using a Quantikine high-sensitivity two-site enzyme-linked immunosorbent assay from R&D Systems (Oxford, UK). The sensitivity of the assay ranged from 0.016 to 0.110 pg/ml, and the intra-assay and interassay coefficients of variation were 7.3% and 7.7%, respectively. Cortisol was assessed from saliva samples using a time-resolved immunoassay with fluorescence detection, at the University of Dresden. The intra-assay and interassay coefficients of variation were less than 8%.

Statistical Analysis

We averaged SBP, DBP, and HR into 5-minute means for baseline, the two tasks, and the two recovery periods. The two task trials were subsequently averaged. Plasma IL-6 values were normally distributed, but cortisol values were skewed and so were log-10 transformed before analysis. The pattern of cortisol over the laboratory session was analyzed using individual values, and also by computing cortisol area under the curve (AUC) with respect to ground using procedures described by Pruessner et al. (38).

Responses to mental stress testing were analyzed using repeated-measures analysis of variance. Subjective stress, cardiovascular variables, and IL-6 were analyzed across four trials (baseline, task, and 45 minutes and 75 minutes poststress), and cortisol was analyzed across five trials (baseline, task, and 20 minutes, 45 minutes, and 75 minutes posttask). Associations with hostility were analyzed using multiple regression. Multivariable linear regressions on baseline values of SBP, DBP, HR, and IL-6, and regressions on responses after stress were carried out. Cortisol was analyzed using individual values and AUC to investigate total cortisol output across the whole session. For analyses of associations with baseline values, hostility was entered into the regression models along with age, sex, BMI, smoking, household income, time of laboratory testing, oral antidiabetic medication, and β-blockers. These covariates were chosen because previous research has indicated that these factors might influence physiological function (37,39–41) and preliminary analyses indicated that these variables were correlated with the physiological responses assessed in this study.

Associations of hostility with stress reactivity and recovery involved regressions onto changes between baseline and task or posttask values and included the baseline level of the dependent variable as an additional covariate.

We conducted preliminary analyses to check whether other factors influenced the relationship between hostility and physiological function. We investigated whether there was a relationship between HbA1c and hostility as well as responses to stress. These analyses were nonsignificant and are therefore not presented in this article. We also investigated whether hostility interacted with sex, but found no significant associations with physiological responses, so interaction terms were not included in the final models. Most of the sample was obese, and we therefore investigated whether BMI interacted with hostility but found no significant associations with physiological responses. The present sample included 28 (20%) nonwhite individuals. Adding ethnicity as a factor to the analyses did not alter the results, so it was not included in the models described here. Depressed mood was also assessed in the study and was significantly correlated with hostility ($p < .001$). We investigated whether hostility interacted with depression, but found no significant associations with physiological responses. In addition, adding depression as an extra covariate did not affect the pattern of results. Therefore, depression was not included in the final models. As participants were taking medication at the time of testing, we assessed whether antidiabetic medication and β-blockers interacted with hostility. Hostility did not interact with antidiabetics, but we found a significant interaction between β-blockers and hostility for some of the cardiovascular responses. However, inclusion of this interaction term did not affect the pattern of physiological responses, so this variable was not retained for the final analyses.

Results are presented as unstandardized regression coefficients (B) with 95% confidence intervals (CIs) using continuous hostility scores as the predictor variable. Significant effects from the regression analyses are illustrated by comparing high- and low-hostility groups defined by a median spilt (cutoff ≥ 4) using analysis of covariance. All analyses were conducted using SPSS version 21 (SPSS, Chicago, IL).

RESULTS

Participant Characteristics

The sample consisted of 140 people (88 men and 52 women) with Type 2 diabetes. Participant characteristics are detailed in Table 1. Participants were aged 63.71 (7.00) years on average and were predominately white with relatively low incomes. BMI ranged from 19.2 to 47.80 kg/m^2, and the average BMI was in the obese range (BMI >30 kg/m^2). Levels of HbA1c were less than 6.5% in 29.9% of the sample, between 6.5% and 7.5% in 41%, and more than 7.5% in 29.1% of participants. Hostility scores averaged 3.77 (2.8) and were not related to age, sex, ethnicity, BMI, waist circumference, smoking, or medication use at the time of testing (p values > .136). However, there was an association with household income ($\chi^2 = 8.08$, $p = .018$). Hostility was greater among participants with household incomes less than £20,000 (mean = 4.2 [2.88]) and between £20,000 and 40,000 (4.01 [3.07]) than that among participants with incomes more than £40,000 (2.81 [2.22]).

TABLE 1. Participant Characteristics

Characteristics	
Age, M (SD), y	63.71 (7.00)
Sex, n (%), % men	88 (62.9)
Ethnicity, n (%), % white	112 (80)
Current smoker, n (%)	20 (14.4)
Body mass index, M (SD), kg/m^2	30.75 (5.72)
Waist, M (SD), cm	105.50 (13.49)
Household income, n (%)	
<£20,000 (approximately $33,286)	57 (42.9)
£20,000–40,000 (approximately $33,286–66,573)	38 (28.6)
>£40,000 (approximately $66,573)	38 (28.6)
Cook Medley Cynical Hostility (10 items), M (SD)	3.77 (2.8)
CES-D, M (SD)	11.85 (8.9)
HbA1c, M (SD), %	7.25 (1.42)
Oral antidiabetic, n (%)	109 (80.1)
Injectable antidiabetic and insulin, n (%)	15 (11.0)
β-Blockers, n (%)	16 (11.8)

M = mean; SD = standard deviation; CES-D = Center for Epidemiologic Studies Depression Scale; HbA1c = glycated hemoglobin.

Responses to Stress

Details of participants' subjective and biological responses to stress are presented in Table 2. We found significant main effects of trial for SBP, DBP, HR, IL-6, cortisol, and subjective stress levels (p values < .001). The tasks elicited substantial cardiovascular reactions, with an average rise of 23.27 (15.89) mm Hg in SBP and 12.51 (7.00) mm Hg in DBP. Although blood pressure (BP) returned toward baseline during the posttask period, both SBP and DBP remained elevated above baseline levels at 45 and 75 minutes after tasks. We found that HR also increased significantly in response to the tasks, with an average rise of 4.56 (4.67) beats/min. IL-6 increased after the tasks with a notable delay consistent with previous stress studies (42), reaching the highest values at 75 minutes posttask. The pattern of response was different for cortisol; levels fell significantly in response to the tasks with an average decrease of 1.29 (0.08) nM immediately posttask and 2.3 (0.13) nM 20 minutes posttask. There were marked individual differences in this stress response, with changes in cortisol ranging from 0.23 to −6.54 nM posttask and from −0.44 to −12.28 nM at 20 minutes posttask. Participants' subjective stress levels increased during the tasks and returned to low levels during recovery. There were no significant relationships between hostility and any of the subjective stress ratings (p values > .05).

TABLE 2. Subjective and Biological Responses to Stress

	Baseline	Task	20 min	45 min	75 min
Subjective stress	1.49 (0.08)[a]	4.49 (0.13)[b]		1.53 (0.08)[a]	1.43 (0.08)[a]
SBP, mm Hg	126.08 (1.16)[a]	149.35 (1.76)[b]		134.24 (1.74)[c]	137.05 (1.46)[d]
DBP, mm Hg	71.74 (0.87)[a]	84.25 (1.07)[b]		78.04 (1.27)[c]	79.51 (1.18)[d]
HR, beats/min	71.77 (1.04)[a]	76.33 (1.04)[b]		70.18 (1.04)[c]	70.15 (1.02)[d]
IL-6, pg/ml	2.08 (0.11)[a]	2.07 (0.11)[a]		2.18 (0.12)[a]	2.31 (0.12)[b]
Cortisol, nM	10.03 (0.47)[a]	8.74 (0.39)[b]	7.74 (0.34)[c]	6.89 (0.36)[d]	7.17 (0.49)[c]

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; IL-6 = interleukin-6.

Values are presented as means (standard deviation).

[a,b,c] Values in rows with different superscripts are significantly different from one another ($p < .05$).

Hostility and Biological Responses to Stress

There was no association between hostility and baseline levels of SBP, DBP, or HR (B values between −0.376 and −0.088 and p values > .113). Similarly, BP or HR responses to the task or recovery from the tasks were not related to hostility (B values between −0.0826 and 0.236 and p values > .113). There was no association between hostility and baseline plasma IL-6 concentrations (B = −0.015, CI = −0.095 to 0.064, p = .703). However, regressions on the change in IL-6 between baseline and 45 minutes posttask (B = 0.082, CI = 0.032-0.132, p = .002) and 75 minutes posttask (B = 0.076, CI = 0.021-0.131, p = .007) show larger increases in more hostile participants. These effects were independent of baseline IL-6, age, sex, BMI, smoking, household income, time of testing, β-blockers, and oral antidiabetic medications. The association between hostility and IL-6 levels over the laboratory session is illustrated in Figure 1, where participants in the study have been divided into high- and low-hostility groups. Greater hostility was associated with larger plasma IL-6 increases after stress.

In the analyses of cortisol, there was again no association with hostility at baseline (B = −0.002, CI = −0.016 to 0.011, p = .747). However, cortisol concentration at 20 minutes posttask (B = −0.017, CI = −0.027 to −0.006, p = .002), 45 minutes posttask (B = −0.018, CI = −0.032 to −0.005, p = .010), and 75 minutes after tasks (B = −0.023, CI = −0.037 to −0.009, p = .002) was lower in more hostile individuals after adjustment for covariates. The association between hostility and cortisol was further examined using the cortisol AUC measure. There was an inverse association between hostility and cortisol AUC (B = −26.69, CI = −41.39 to −11.98, $p < .001$). The difference in cortisol levels between participants with high and low hostility scores is illustrated in Figure 2. Cortisol levels declined across the laboratory session in both groups. However, higher hostility was associated with a significantly greater decrease in cortisol output over the testing period.

Intercorrelation Between IL-6 and Cortisol

In light of the associations between hostility and IL-6 and cortisol responses to stress, we assessed the intercorrelations between IL-6 and cortisol. The change in IL-6 in responses to the tasks at 45 and 75 minutes was significantly negatively correlated with cortisol AUC (r = −0.35 and −0.38, p values < .001) and with all individual cortisol measurements over the laboratory session (r values between −0.19 and −0.29, all p values < .05).

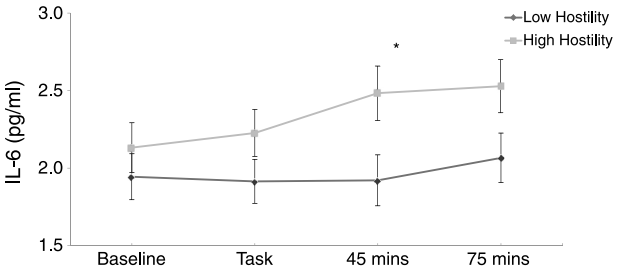

FIGURE 1. IL-6 stress responses for high-hostility (light gray line) and low-hostility groups (dark gray line) during baseline, speech and mirror tasks, and recovery. Values are adjusted for age, sex, BMI, smoking, household income, β-blockers, and oral antidiabetic medications. Error bars indicate standard error of mean. IL-6 = interleukin-6; BMI = body mass index.

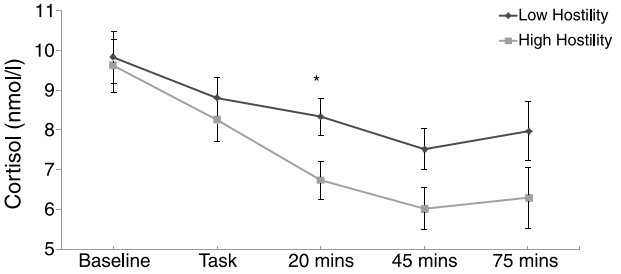

FIGURE 2. Cortisol stress responses for high-hostility (light gray line) and low-hostility groups (dark gray line) during baseline, speech and mirror tasks, and recovery. Values are adjusted for age, sex, BMI, smoking, household income, β-blockers, and oral antidiabetic medications. Error bars indicate standard error of mean. BMI = body mass index.

DISCUSSION

This study investigated the relationship between hostility and cardiovascular, inflammatory, and neuroendocrine responses to acute stress in people with T2DM. We predicted that participants with greater hostility scores would be more responsive to stress. The main finding is that greater hostility was associated with elevated IL-6 responses to acute stress. By contrast, cortisol output after stress was diminished to a greater extent in more hostile individuals. These associations were independent of baseline values, age, sex, BMI, smoking, household income, antidiabetic medications, and β-blockers. Contrary to prediction, we did not observe any associations between hostility and BP or HR responses.

IL-6 responses to stress were significantly elevated in participants with T2DM with greater hostility ratings. This result corroborates previous work from our group in which IL-6 was elevated after acute stress in more hostile patients with CAD (25). Only one other study has investigated inflammatory stress responses in relation to hostility. Brummett et al. (43) examined the effects of hostility on IL-6 responses to an emotional recall stressor in 525 healthy participants, but found no association.

This discrepancy in findings may reflect variation in the study population. The current investigation and the study by Brydon et al. (25) assessed IL-6 responsivity in two high-risk phenotype samples, whereas Brummett et al. (43) used a healthy participant group. It may be that heightened inflammatory stress responses are only associated with hostility in groups with an increased propensity for CVD. Further studies will be required to assess the impact of the study population on the presence of an association between hostility and inflammation. Nevertheless, the results of the current analysis suggest that more hostile individuals with T2DM may be susceptible to stress-induced inflammation.

We observed no relationship between hostility and cardiovascular responses to stress in this T2DM sample. This result is paradoxical as a considerable body of evidence indicates that heightened cardiovascular stress responsivity is associated with hostility in healthy individuals (15,44–46). Indeed, in our previous analysis of patients with CAD, greater hostility was associated with increased SBP and DBP responses to laboratory stress (25). The lack of association seen in the present analysis cannot be attributed to the intensity of stressor used, as both subjective stress ratings and cardiovascular measures increased significantly in response to the task. It is unlikely that the current study was underpowered to detect cardiovascular effects. We used the same laboratory procedure as our study of 34 patients with CAD (25), and associations have been reported in other analyses with much smaller sample sizes than the present study (44). Our analysis also took account statistically of medications, and a number of previous studies have found no effect of β-blockers on cardiovascular responses to stress (47). However, we cannot rule out the possibility that the null association observed was attributable to medication, as the participants with T2DM continued to take β-blockers and antidiabetic medications at the time of testing.

We found that cortisol output after stress was attenuated in participants with T2DM with greater hostility scores. The observed inverse relationship between cortisol AUC and hostility is consistent with the findings of our previous analysis in which cortisol levels were reduced poststress in more hostile participants with CAD (25). It is plausible that decreased cortisol levels may have facilitated the elevated IL-6 responses observed in more hostile participants in both studies. However, this relationship has not been consistently observed. In a study of 52 healthy men, high levels of hostility were associated with heightened cortisol responses to an anagram task, but only in those who simultaneously experienced harassing comments from the experimenter (46). The task used in the present analysis was designed to elicit general stress responses, whereas the task in the study by Suarez et al. (46) was designed to provoke hostile reactions, and this may account for the diverging findings.

Our results observed in a laboratory environment offer the possibility that the negative impact of hostility on health could be mediated, in part, through stress-related dysregulation of the neuroendocrine and inflammatory systems. Cortisol levels declined significantly throughout the laboratory session in all participants, which may be indicative of neuroendocrine dysfunction in individuals with T2DM. Elevated cortisol levels assessed from single plasma (48) and 24-hour urinary-free samples (49) have been associated with higher plasma glucose concentrations and insulin resistance (48,49), and T2DM is a recognized complication of long-term cortisol excess as seen in Cushing syndrome (50) and in glucocorticoid-treated patients (51). Recently, high levels of hair cortisol have been correlated with 3.2-fold increased risk of T2DM in a community sample (52). There is emerging evidence that diurnal cortisol secretion may be altered in individuals with T2DM. In a recent study of 3508 community-dwelling individuals, we showed that T2DM was associated with a flatter slope in cortisol across the day (53). Although in a subsample of the Multi-Ethnic Study of Atherosclerosis, individuals with T2DM exhibited a blunted cortisol awakening response relative to controls (54).

Peripheral glucocorticoid regulation is critical for the maintenance of homeostasis, and cortisol plays a pivotal role in many physiological processes relevant to diabetes. Cortisol directly triggers hepatic gluconeogenesis, promotes lipolysis, and the release of fatty free acids into the circulation and the accumulation of triglycerides in adipose tissue. It directly reduces insulin sensitivity and decreases insulin secretion by acting through glucocorticoid receptors, which are expressed on pancreatic β-cells (55). Another way in which neuroendocrine dysfunction may play

a role in diabetes is through circadian disruption. Circadian rhythms are regulated at the hypothalamic level by the suprachiasmatic nuclei. It has been suggested that disturbances in circadian rhythms may act on T2DM through the alteration of glucose metabolism. Indeed, recent experimental work indicates that circadian disruption heightens both fasting and postprandial plasma glucose levels through inadequate pancreatic insulin secretion (56).

Despite the literature highlighting the role of neuroendocrine dysfunction in T2DM, little research has assessed dynamic physiological stress responses in this population. The participants in the present study were part of a larger trial comparing biological responses to stress in individuals with T2DM and healthy controls (35). Results from this trial indicate that participants with diabetes have blunted cortisol responses to stress compared with healthy individuals. The current study suggests that greater levels of hostility exaggerate disturbances in neuroendocrine function in this population.

Cortisol is also involved in the regulation of inflammation and chronic exposure to psychosocial stress results in increased cortisol secretion (57). Cortisol typically has an inhibitory effect on proinflammatory cytokine production. However, long-term heightened cortisol concentrations may result in dysregulation of this system manifested through insufficient glucocorticoid signaling (21). In this case, reduced cortisol levels may have a permission effect on inflammatory markers. In the current investigation, hostility was inversely associated with cortisol output over the laboratory session. Other evidence indicates that high cortisol responders have significantly smaller cytokine responses to acute stress (24). Our findings suggest that more hostile people with T2DM show insufficient glucocorticoid signaling to inhibit inflammatory responses under stress due to decreased hormone release. This decreased cortisol production may have contributed to the heightened IL-6 stress responses observed in more hostile participants.

The acute changes observed in this study offer the possibility that inflammation may be one of the mechanisms through which hostility confers an increased risk for ill health. Although we found no association between hostility and baseline IL-6 in our sample, large cohort studies have reported a relationship (10,11). Post hoc power calculations (data not shown) revealed that the present study was under powered to detect basal differences in IL-6, which might explain why the association between IL-6 and hostility only emerged when induced by stress. In epidemiologic studies, raised IL-6 levels have been prospectively associated with CVD development (16) and poorer outcomes in patients with CVD (17). Inflammation also plays a role in the pathogenesis of T2DM. Heightened circulating IL-6 levels are predictive of T2DM development in initially healthy samples (33), and concentrations are elevated in patients with T2DM (34).

It is possible that hostility might potentially contribute to increase the risk for CVD in people with T2DM through dysregulated stress-related inflammatory pathways. In this way, hostility may contribute to insulin resistance and dyslipidemia, as elevated IL-6 concentrations inhibit AMP-activated protein kinase, an enzyme involved in insulin-stimulated fatty acid oxidation, down-regulating gene transcription of proteins involved in insulin-stimulated glucose transport and lipid uptake in adipose tissue (34). However, prospective studies will be required to test this pathway.

The present study is not without limitations. The participants were patients with T2DM without a history of coronary heart disease recruited from the London area, and most were of white European origin. Therefore, the results may not apply to other groups. Most of the participants were taking medications at the time of testing. Analyses took account statistically of medications; however, an effect of medication on stress reactivity cannot be excluded. The study was cross sectional in nature, so it is not possible to infer causality. Longitudinal research is needed to elucidate the degree to which trait hostility and changes in hostility over time are associated with inflammatory, neuroendocrine, and cardiovascular processes, as well as negative health outcomes in people with T2DM. Finally, the study was limited by use of a self-report measure to assess hostility. The assessment of observable hostile behavior could provide a different perspective in understanding the relationship between hostility and stress reactivity.

Despite these considerations, the results suggest that responses to stress are dysregulated in more hostile individuals with T2DM. We observed greater IL-6 stress responses and diminished cortisol output over the laboratory session in more hostile diabetic individuals, independent of covariates. It is possible that heightened stress-induced inflammation may increase the risk for CVD in this population. However, further studies are required to confirm this pathway.

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