Stress-Related Changes in Body Form: Results from the Whitehall II Study

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Objective: Stress is associated with body mass gain in some people but with body mass loss in others. When the stressor persists, some people adapt with their stress responses, whereas others do not. Heart rate variability (HRV) reflects autonomic variability and is related to stress responses to psychosocial challenges. It was hypothesized that the combined effects of stress exposure and autonomic variability predict long-term changes in body form.

Methods: Data of 1,369 men and 612 women from the Whitehall II cohort were analyzed. BMI, hip-to-height ratio, and waist-to-height ratio were measured at three time points over a 10-year period. HRV and psychological distress (General Health Questionnaire) were assessed.

Results: Men with high psychological distress were at risk of developing an increased waist-to-height ratio ($F = 3.4, P = 0.038$). Men with high psychological distress and low HRV were prone to develop an increased body mass and hip-to-height ratio (psychological distress: $F = 4.3, P = 0.016$; HRV: $F = 5.0, P = 0.008$). Statistical trends showed that women displayed similar patterns of stress-related changes in body form ($P = 0.061$; $P = 0.063$).

Conclusions: Assessing psychological distress and autonomic variability predicts changes in body form. Psychological distress was found to be associated with an increased risk of developing the wide-waisted phenotype, while psychological distress combined with low autonomic variability was associated with an increased risk of developing the corpulent phenotype.

Introduction

Many living organisms are able to change their phenotypes if their environment changes. This phenomenon is known from the field of evolutionary biology and is referred to as phenotypic plasticity (1). In detail, phenotypic plasticity is the ability of an organism to express different phenotypes depending on environmental factors. Phenotypic plasticity has been shown to depend on the genotype as well (2). In humans, phenotypic plasticity may manifest in an altered body form or in altered stress responses (3).

Body form may change in two divergent ways. Long-term exposure to a stressful environment has been found to be associated with the risk of body mass loss in some people and the risk of body mass gain in others. At the University College of London, perceived stress predicted body mass changes in first-year students: 55% of the students gained body mass, 12% of the students lost body mass, and 33% of the students displayed stable body mass over a 1-year follow-up period (4). In agreement with these findings, the Whitehall Study showed bidirectional effects of job strain on body mass; i.e., work stress predicted the risk of body mass gain in some and the risk of body mass loss in other people (5). Similar findings were obtained in the Enhancing Recovery in Coronary Heart Disease trial; among patients who experienced a myocardial infarction, one-quarter gained body mass, one-quarter lost body mass, and the remaining half showed only minor changes in body mass (6).

Stress responses may also change in two different genetically predisposed patterns once an individual has been exposed to an inhospitable environment (home, work, or neighborhood). Then subjects either maintain high stress responses to the same homotypic stressors or develop low stress responses. Repetition-induced stress response attenuation is referred to as stress habituation. Kirschbaum and colleagues showed in their classic human experiment on stress habituation that nonhabitutators maintain a high cortisol response.

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when repeatedly exposed to a psychosocial challenge, whereas habitu-
tators initially respond strongly to stress but develop attenuated stress responses over time (7).

The stress responses are coordinated by two main neuroendocrine sys-
tems: the hypothalamic-pituitary-adrenal (HPA) system and the auto-
nomic nervous system. As a biomarker of HPA activity, cortisol concen-
trations are mostly used. As a biomarker of the activity of the
autonomic nervous system, heart reactions are often used. Heart rate is
controlled by sympathetic and parasympathetic activity. Heart rate
reflects autonomic activity, and heart rate variability (HRV) reflects
autonomic variability. Thus, HRV is often used as an indicator of cor-
diag autonomic modulation (8). HRV is relatively simple to determine,
while cortisol measures require standardized conditions for assessment
(e.g., exact timing of sampling). Cortisol reactivity to mental chal-
lenge and autonomic variability were found correlated in a subset of
healthy participants of the Whitehall Study. As suggested by the data
of Kunz-Ebrecht and colleagues, high cortisol responses to psycholog-
ical stress are related to higher autonomic variability (9).

Autonomic variability (HRV) and cortisol responses to a psychoso-
cial challenge are linked with body form. Low HRV was found in
people displaying high body mass (corpulent phenotype) (10-13),
whereas high HRV was found in people displaying large visceral fat
(wide-waist phenotype) (14). High cortisol responses to psychoso-
cial challenges were found to be associated with the lean phenotype
exhibiting a large visceral fat mass (i.e., the lean-bu-wide-waist phenotype). The latter finding became evident in a milestone study
by Epel and colleagues. Women displaying different body forms were
repeatedly exposed to consecutive psychosocial challenges (15). Women with a high waist-to-hip ratio evaluated laboratory
challenges as more threatening and reported that they had experienced
more chronic stress in the past (15). These women with a high waist-
to-hip ratio secreted more cortisol during the first stress session than
women with a low waist-to-hip ratio. Furthermore, lean women with a
high waist-to-hip-ratio turned out to be nonhabituaors, as they contin-
ued to show the highest cortisol responses. These observational and
experimental findings support the hypothesis that the combination of
stress exposure and stress responses determines the risk of long-term
changes in body form. However, it is difficult to draw firm conclu-
sions from Epel’s experimental findings, as observations were cross-
sectional and require confirmation in longitudinal or prospective
analyses.

The combination of high stress exposure and high stress reactivity
has been shown by other researchers to predict the risk of athero-
sclerosis. First, in a subset of Whitehall Study participants, chronic-
ally stressed high responders to mental stress showed the highest
risk for developing coronary artery calcification (16). Second, Lynch
et al. found that those people who displayed a high cardiovascular
response to stress and who were born into poor families, received
little education, and had low incomes had the greatest atherosclerotic
progression of the carotid artery walls (17). Third, Everson et al.
reported that men with high job demands and a high blood pressure
response to an exercise challenge showed the greatest atherosclerotic
progression (18).

We used the longitudinal data set from the Whitehall II Study to investi-
gate how stress exposure (psychological distress measure) and auto-
nomic variability (assessed by HRV) affect body form in the long run.

**Methods**

**Study population**

Whitehall II is a large ongoing study investigating determinants of
health in British civil servants. In 1985, a cohort of 10,308 partici-
pants was initially recruited. Since this first phase of data collection,
questionnaires and clinical data have been assessed every 2 to 5
years. HRV was assessed in phase 5 (1997-1999), phase 7 (2002-
2004), and phase 9 (2007-2009). In phase 5, a total of 7,829 civil
servants participated. Of the 3,365 participants who had HRV mea-
sures, 1,384 participants had missing data on the main factors of our
analyses, leaving a final sample of 1,369 men and 612 women. There
was a slight participation bias, in that men included in our
analysis were about 0.5 years younger compared to men excluded
from our analysis (55.3 ± 0.2 vs. 55.8 ± 0.1 years; \(P = 0.009\)). How-
ever, there was no observable difference regarding the BMI of both
groups (25.9 ± 0.1 vs. 26.1 ± 0.1 kg/m²; \(P = 0.081\)). The same
applied to women. Women included in our analysis were younger
compared to women excluded from our analysis (55.7 ± 0.2 vs.
56.3 ± 0.2 years; \(P = 0.037\)), but there was no observable difference
regarding the BMI of both groups (26.4 ± 0.2 vs. 26.5 ± 0.2 kg/m²;
\(P = 0.762\)). Participants gave fully informed consent to participate in
the study, and ethical approval was obtained from the University
College London committee on the Ethics of Human Research.

**Anthropometric measures**

Body mass was measured in light clothes with an electronic scale;
height was measured using a stadiometer. BMI was calculated as
body mass (kilograms) divided by height (meters) squared. Waist
circumference was measured as the smallest circumference at or
below the costal margin. Hip circumference was measured at the
level of symphysis. Ratios were calculated for waist-to-hip, waist-to-
height, and hip-to-height (centimeters). Elevated values in BMI were
set at ≥25 kg/m²; for waist-to-hip ratio, elevated values were set
at ≥0.9 (men) or ≥0.85 (women) as suggested by the World Health
Organization (19). Anthropometric variables were combined into
phenotypes: (1) lean phenotype (BMI < 25 kg/m² and waist-to-hip
ratio < 0.9 [men] or < 0.85 [women]); (2) lean-but-wide-waist phenotype
(BMI < 25 kg/m² and waist-to-hip ratio ≥ 0.9 [men] or ≥ 0.85
[women]); (3) corpulent-but-narrow-waist phenotype (BMI ≥ 25 kg/m²
and waist-to-hip ratio < 0.9 [men] or < 0.85 [women]); (4) corpulent-
and-wide-waist phenotype (BMI ≥ 25 kg/m² and waist-to-hip ratio
≥ 0.9 [men] or ≥ 0.85 [women]). Of note, the waist circumference
measurement protocol used here differs from the measurement proto-
col suggested by the World Health Organization (midpoint between
the lower margin of the last palpable rib and the top of the iliac crest)
(19), which might have an impact on our definition of the wide-
waist phenotype. Because the incidences of phenotypes depend on
cutoff values, we used the analysis on the wide-waisted phenotype
only for the reason of better illustration. Our main results are based on
analysis of variance (ANOVA), for which these constraints do not
apply.

**Assessment of psychological distress**

Psychological distress was assessed using the General Health Ques-
tionnaire (GHQ-30). The GHQ-30 is widely used in many well-
being studies to detect individuals likely to have or be at risk of
developing psychiatric disorders (20). The GHQ-30 was validated
against clinical interview in Whitehall II. As described previously in
the Whitehall Study, standard scoring was utilized, assigning a value
Heart rate variability
We examined HRV as a proxy for autonomic variability. As described previously (22), supine 12-lead electrocardiograms were obtained at rest using SEER MC recorders (GE Medical Systems, Milwaukee, Wisconsin) over 5 minutes. Individual 10-second electrocardiograms were captured. Five minutes of beat-to-beat heart rate data at a frequency of 500 Hz were resampled to assess digitized recording of R waves. HRV was analyzed in the time domain (the SD of all intervals between R waves with normal-to-normal conduction [SDNN]) (22). In a categorical approach, high HRV was defined as a score of ≥ 5; high HRV was set at ≥ 50 percentile (34.7 SDNN for men and 34.0 SDNN for women) to split the sample into halves.

Covariates
We considered a wide range of covariates (Supporting Information Table S1), which were assessed at baseline:

- Ethnicity
- Still having periods (women)
- Self-reported birth weight
- Parameters of chronic distress/trauma and parental care during childhood
- Life satisfaction
- Parameters of chronic distress during study participation
- Socioeconomic position
- Exercise
- Nutrition
- Sleep duration
- Alcohol and nicotine abuse
- Use of medication
- Known diseases and general health

### Results

#### Subjects’ characteristics and their changes in body form

Participant characteristics are presented in Table 1. When analyzing the study population as a whole, both men and women showed on average an increase in body mass and waist and hip circumferences over time. Men, compared to women, had a higher waist-to-height-ratio (P < 0.001) and a lower hip-to-height-ratio (P < 0.001). Moreover, women experienced higher levels of psychological distress compared to men (P < 0.001). Because of these gender differences, we analyzed men and women separately.

When analyzing particular phenotypes (cross-sectional analysis at baseline), we found that 26% of men exhibited the lean phenotype, 15% displayed the lean-but-wide-waisted phenotype, and 11% the corpulent-but-narrow-waisted phenotype. The remaining participants exhibited a mixed phenotype with traits of the latter two phenotypes. In contrast, we found that 43.0% of women exhibited the lean phenotype.

#### Statistical analysis

Data analysis was performed using SPSS Statistics 23.0 software (IBM Corp., Armonk, New York). Descriptive statistics were given as mean ± SEM. Approximate normal distribution was clarified by Kolmogorov-Smirnov test. ANOVA for repeated measures was used to test differences in the variation of time with consideration of covariates. A χ² test was used to test differences in the distribution of categorical variables. In the categorical approach, GHQ-30 caseness was defined as a score of ≥ 5; high HRV was set at ≥ 50 percentile. Changes in anthropometric variables were calculated from phase 5 to 9. A general linear model was used to test differences between groups while adjusting for covariates. Age was considered as a covariate in most analyses. A P value (two-sided) of 0.05 was considered significant.

### Table 1 Characterization of the study population

|                      | Men (n = 1,369) |                      | Women (n = 612) |
|----------------------|-----------------|---------------------|-----------------|
|                      | Phase 5         | Phase 7             | Phase 9         | Phase 5         | Phase 7             | Phase 9         |
| Age (y)              | 55.2 ± 0.2      | 60.8 ± 0.2          | 65.7 ± 0.2***   | 55.7 ± 0.2      | 61.1 ± 0.2          | 66.2 ± 0.3***   |
| Body mass (kg)       | 80.9 ± 0.3      | 81.6 ± 0.3          | 81.4 ± 0.3***   | 70.0 ± 0.5      | 70.1 ± 0.6          | 70.9 ± 0.6***   |
| Height (cm)          | 176.6 ± 0.2     | 175.5 ± 0.2         | 175.2 ± 0.2***  | 162.9 ± 0.2     | 161.7 ± 0.2         | 161.4 ± 0.3***  |
| BMI (kg/m²)          | 25.9 ± 0.1      | 26.5 ± 0.1          | 26.5 ± 0.1***   | 26.4 ± 0.2      | 27.1 ± 0.2          | 27.2 ± 0.2***   |
| Waist circumference (cm) | 91.9 ± 0.3   | 94.0 ± 0.3          | 95.2 ± 0.3***   | 80.8 ± 0.5      | 83.5 ± 0.5          | 85.8 ± 0.5***   |
| Waist-to-height index | 0.521 ± 0.002  | 0.536 ± 0.002       | 0.544 ± 0.002***| 0.49 ± 0.0      | 0.52 ± 0.0          | 0.53 ± 0.0***   |
| Hip circumference (cm) | 99.6 ± 0.2   | 99.9 ± 0.2          | 100.9 ± 0.2***  | 101.3 ± 0.4     | 102.3 ± 0.4         | 104.1 ± 0.4***  |
| Hip-to-height index  | 0.564 ± 0.001  | 0.570 ± 0.001       | 0.576 ± 0.001***| 0.62 ± 0.0      | 0.63 ± 0.0          | 0.65 ± 0.0***   |
| Waist-to-hip ratio   | 0.922 ± 0.0     | 0.939 ± 0.0         | 0.941 ± 0.0***  | 0.80 ± 0.0      | 0.82 ± 0.0          | 0.82 ± 0.0***   |
| Psychological distressa | 2.7 ± 0.1   | –                   | –               | 4.0 ± 0.3       | –                   | –               |
| HRV (SDNN)b          | 38.2 ± 0.5      | –                   | –               | 36.3 ± 0.6      | –                   | –               |

Values expressed as mean ± SEM.

aAssessed by GHQ-30.

bHeart rate variability (SD of all intervals between R waves with normal-to-normal conduction).
phenotype, 2.6% displayed the lean-but-wide-waisted phenotype, and 34.6% the corpulent-but-narrow-waisted phenotype.

We next analyzed phenotypic plasticity (longitudinal analysis). In this approach, participants, who were initially lean in phase 5 were classified according to their changes in body form from phase 5 to 9 (Figure 1). We found that 59% of men who were initially lean in phase 5, stayed lean about 10 years later, while 21% of initially lean men developed the lean-but-wide-waisted phenotype and 7% developed the corpulent-but-narrow-waisted phenotype. For women, we found that 71% of those who were initially lean in phase 5 stayed lean about 10 years later. Eight percent of initially lean women developed the lean-but-wide-waisted phenotype, and 15% developed the corpulent-but-narrow-waisted phenotype. The remaining participants developed a mixed phenotype with traits of the latter two phenotypes.

Changes of body form depend on psychological distress and autonomic variability

For the purpose of better illustration, we first performed the longitudinal analysis using a categorical approach. To be more specific about the various covariates, we later show the longitudinal analysis based on ANOVA for repeated measures.

In the categorical approach, we found that different combinations of psychological distress and autonomic variability led to different forms of phenotypic plasticity. Those men who displayed elevated levels of psychological distress as well as low autonomic variability showed the greatest increases in body mass ($P = 0.061$; Figure 2A) and hip-to-height ratio ($P = 0.063$; Figure 2B). Those women who reported high levels of psychological distress showed the highest increases in waist-to-height ratio ($P = 0.053$; Figure 3C).

In the ANOVA for repeated measures approach, we were able to confirm our findings from the categorical analysis in men. To consider a wide range of covariates, we first investigated the impact of covariates on body mass over time (Supporting Information Table S2), hip-to-height ratio (Supporting Information Table S3), and waist-to-height ratio over time (Supporting Information Table S4). We found that elevated levels of psychological distress and low autonomic variability were associated with an increased risk of developing the corpulent phenotype, i.e., high body mass (Table 2) and hip-to-height ratio, in men (Table 3). These effects were very robust after adjustment for a wide range of covariates (Tables 2 and 3). We also found that high levels of psychological distress were associated with an increased risk of developing the wide-waisted phenotype in men (Table 3). In all, those men who reported high levels of psychological distress were at risk of developing a high waist-to-height ratio. Those participants who developed the most corpulent phenotype (hip-to-height ratio, BMI) showed the combination of elevated levels of psychological distress and low autonomic variability. In contrast, women who reported high levels of psychological distress showed the highest increases in body mass (Supporting Information Table S5), while we could not detect an influence of psychological distress and autonomic variability on waist-to-height or hip-to-height ratios in women (Supporting Information Tables S6-S7).

Discussion

Using the Whitehall data set of 1,369 men and 612 women, we investigated how the factors of psychological distress and autonomic variability interact and how that interaction relates to changes in
body form during a 10-year period. We were able to show that those men who reported high levels of psychological distress were at risk of developing a large waist-to-height ratio, indicating the accumulation of visceral fat. The combination of high psychological distress and low autonomic variability identified those men who had the highest risk of developing a high body mass accompanied by a large hip-to-height ratio, indicating accumulation of subcutaneous fat. We also found statistical trends that women showed the same pattern.

Previous investigators have also reported that autonomic variability was strongly linked to body form. Low HRV has been found in people displaying high body mass (10,13), whereas high HRV was found in people displaying large visceral fat (14). Moreover, epidemiological evidence has demonstrated that individuals with low heart rate responses to psychosocial stress and low blood pressure responses to psychosocial stress are at risk of gaining body mass over the following decades (23,24). Experimental studies have suggested that low stress responses might be a key feature in participants with high body mass, who have reported low neuroendocrine, neuroenergetic, emotional, and cardiovascular responses to social or mental challenges in obesity (25,26). Here, we extend previous knowledge by showing that the combination of high psychological distress and low autonomic variability increases the risk of long-term body mass gain. We also found high psychological distress to be associated with an increased risk of developing visceral fat (increased waist-to-height ratio). As mentioned in the introduction, Epel and colleagues have shown that those subjects who maintained high stress responses when repeatedly challenged with a psychosocial stressor (i.e., the nonhabitators) exhibited more central fat (15). Given Epel’s findings, our data suggest that high stress exposure causes increases in visceral fat in nonhabitators.

Genetic predisposition is a factor that determines whether individuals habituate (and develop low stress responses) or do not habituate when they are exposed to an inhospitable environment. The endocannabinoid system in the prefrontal cortex plays a key role in stress habituation (27). If stressors cannot be defended successfully, then a learning process involving synaptic plasticity within the prefrontal...
cortex allows for attenuating of the amygdala’s response to the stressor (28,29). The maintenance of long-term plasticity at synapses is controlled by endocannabinoids (30) and glucocorticoids (31,32). The synaptic changes during stress habituation result in a lower response of the sympathetic nervous system and the HPA (7). Thus, whether individuals habituate when exposed to stress is determined by the characteristics of their endocannabinoid and glucocorticoid receptors.

Importantly, habituation is a specific process, allowing adaptation to the same stressor; the capability to respond to a novel heterotypic stressor is still preserved (33). With heterotypic stressors from different stressful environments, diversity in phenotypes can occur. It could be that a person who habituated to homotypic stressors at home would not habituate to heterotypic stressors at work, as those stressors would not induce a high cortisol response necessary to promote the habituation process. Thus, in complex environments, phenotypes may display both subcutaneous and visceral fat accumulation (3). It is likely that the participants investigated here belong to a nonhomogeneous study population, consisting of habituators and nonhabitua tors. Complex environments acting on nonhomogeneous populations produce a particularly high degree of phenotypic diversity.

Of course, our analysis is not free from limitations. One limitation is that we only found statistical trends in the analysis of women. Our sample of women was much smaller than our sample of men; thus, it lacked statistical power to detect the hypothesized effects. A low statistical power could also be due to the fact that the methods used were not accurate enough. The assessment of the subcutaneous and visceral fat by gold standards such as computed tomography or magnetic resonance imaging, as well as measuring the functional body composition (34), the assessment of the body mass by the weighting of the participants without light clothing, and the evaluation of the diet by a more specific analysis (e.g., healthy nutrition index) would have increased the statistical power. Another limitation is that the GHQ-30 questionnaire measures psychological distress, and thus we could not assess the real stress burden participants were exposed to. Participants may display low values in the GHQ-30
TABLE 2 BMI over time in 1,369 men

| Dependent variable | Inner-subject effects |
|--------------------|------------------------|
| Time               | F = 16.8; P = 0.001    |
| Time × age         | F = 8.1; P = 0.001     |
| Time × psychological distress at phase 5 | F = 6.3; P = 0.003b |
| Time × HRV at phase 5 | F = 4.8; P = 0.011c |

ANOVA for repeated measures with BMI at phases 5, 7, and 9 as dependent variable; age, HRV at phase 5, and psychological distress (GHQ-30) at phase 5 as independent variables.

The inner-subject effect "time × psychological distress" remained significant after separate adjustment for the following covariates: age, life satisfaction (F = 5.6; P = 0.003), MET mild exercise (F = 5.5; P = 0.004), alcohol dependence (F = 5.6; P = 0.005), alcohol smoking (F = 6.0; P = 0.004), rheumatic arthritis drugs (F = 5.8; P = 0.005), general health index (F = 4.3; P = 0.018), long-standing illness (F = 5.2; P = 0.008), incident diabetes (F = 6.7; P = 0.002), hypertension (F = 5.4; P = 0.007), and smoking categorical, antihypertensive drugs, cardiovascular (CVD) medication, angiotensin converting enzyme (ACE) inhibitors, anxiolytics, diuretics, nitrate medicine, rheumatic arthritis drugs, general health index (F = 5.8; P = 0.005), any long-standing illness, hypertension. These covariates were considered in the analyses in footnotes b and c.

The inner-subject effect "time × HRV" remained significant after separate adjustment for the following covariates: age, life satisfaction (F = 5.0; P = 0.010), MET mild exercise (F = 4.6; P = 0.013), sleep duration (F = 4.9; P = 0.010), alcohol dependence (F = 4.2; P = 0.019), cigarette smoking (F = 4.3; P = 0.018), rheumatic arthritis drugs (F = 4.2; P = 0.019), general health index (F = 4.3; P = 0.017), any long-standing illness (F = 4.8; P = 0.011), incident diabetes (F = 5.4; P = 0.006), hypertension (F = 3.9; P = 0.026).

TABLE 3 Hip-to-height and waist-to-height ratios over time in 1,369 men

| Dependent variable | Inner-subject effects |
|--------------------|------------------------|
| Time               | F = 1.0; P = 0.367     |
| Time × age         | F = 5.6; P = 0.004     |
| Time × psychological distress at phase 5 | F = 4.3; P = 0.016bc |
| Time × HRV at phase 5 | F = 5.0; P = 0.008bc |

ANOVA for repeated measures with hip-to-height or weight-to-height ratio at phases 5, 7, and 9 as dependent variable; age, HRV at phase 5, and psychological distress (GHQ-30) as independent variables.

The inner-subject effect "time × psychological distress" remained significant after separate adjustment for the following covariates: age, life satisfaction (F = 4.3; P = 0.015), relatives with schizophrenia (F = 3.5; P = 0.033), marital status (F = 5.6; P = 0.005), employment summary (F = 4.3; P = 0.015), MET mild exercise (F = 3.9; P = 0.023), cigarette smoking categorical (F = 4.1; P = 0.020), antihypertensive drugs (F = 3.8; P = 0.024), CVD medication (F = 3.6; P = 0.029), ACE inhibitors (F = 4.0; P = 0.021), anxiolytics (F = 4.1; P = 0.018), diuretics (F = 4.2; P = 0.017), nitrate medicine (F = 3.9; P = 0.023), rheumatic arthritis drugs (F = 4.0; P = 0.022), any long-standing illness (F = 3.5; P = 0.034), hypertension (F = 3.7; P = 0.027).

The inner-subject effect "time × HRV" remained significant after separate adjustment for the following covariates: relatives with alcoholism (F = 4.9; P = 0.009), relatives with schizophrenia (F = 5.1; P = 0.007), marital status (F = 4.9; P = 0.008), income (F = 3.9; P = 0.023), employment summary (F = 4.8; P = 0.010), MET mild exercise (F = 4.4; P = 0.014), cigarette smoking categorical (F = 4.5; P = 0.012), antihypertensive drugs (F = 4.1; P = 0.019), CVD medication (F = 3.9; P = 0.022), ACE inhibitors (F = 4.1; P = 0.014), anxiolytics (F = 4.6; P = 0.012), diuretics (F = 4.4; P = 0.014), nitrate medicine (F = 4.6; P = 0.011), rheumatic arthritis drugs (F = 4.6; P = 0.011), general health index (F = 4.7; P = 0.011), any long-standing illness (F = 5.0; P = 0.008), hypertension (F = 4.2; P = 0.017).

The inner-subject effect "time × psychological distress" remained significant after separate adjustment for the following covariates: parents unemployed (F = 4.0; P = 0.020), cigarette smoking (F = 3.3; P = 0.040), incident diabetes (F = 3.7; P = 0.027).

Some clinical implications may arise from the available data on stress habituation (35). According to this framework, habituators adapt when living in uncertainty and display attenuated autonomic, endocrine, and metabolic reactions, when being repeatedly exposed to the same inhospitable environment. In this way, habituators may succeed in reducing their allostatic load. However—and here the questionnaire either because they were not exposed to an inhospitable environment or because they have already become habituated to it. In this way, habituation may mask the exposure to a stressful environment by its buffering effect on psychological distress. Moreover, we could not investigate the changes in stress responses as they occur after repeated psychosocial challenges, as was done in the experimental studies by Kirschbaum and Epel (7,15). Instead, we made use of biomarkers for autonomic variability. However, we analyzed a larger study sample with a long follow-up. Moreover, as suggested by the data of Kunz-Ebrecht and colleagues, high cortisol responses to psychological stress are related to higher autonomic variability (9).
data in this paper is in line with previous predictions (3)—habitua-
tors are at risk of developing a corpulent phenotype. In contrast, nonhabitui-
tors, who are prone to develop a lean-but-wide-waisted phenotype (15), are fully exposed to high allostatic load and exhibit a high cardiovascular mortality risk (35). Encouragingly, stress relief programs have been shown to reduce cortisol responses, allostatic load, and cardiovascular mortality (36-39).

Conclusion
Our analysis supports the notion that the combination of psychological distress and autonomic variability predicts stress-induced phenotypic plasticity; high psychological distress was found to be associated with an increased risk of developing the wide-waisted phenotype. In con-
trast, high psychological distress combined with low autonomic vari-
ability was found to be associated with an increased risk of developing the corpulent phenotype. Given that habituation is one of the most fre-
cquent causes for acquired states with low autonomic variability, our
data suggest that nonhabituiators are prone to develop visceral fat accum-
ulation, while habituators are prone to develop subcutaneous fat accumu-
lation.

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References
1. Agrawal AA. Phenotypic plasticity in the interactions and evolution of species. Science 2001;294:321-326.
2. Via S, Lande R. Genotype-environment interaction and the evolution of phenotypic plasticity. Evolution 1985;39:505-522.
3. Peters A, McEwen BS. Stress habituation, body shape and cardiovascular mortality. Neurosci Biobehav Rev 2015;56:139-150.
4. Serlachius A, Hamer M, Wardle J. Stress and weight change in university students in the United Kingdom. Physiol Behav 2007;92:548-553.
5. Kivimaki M, Head J, Ferrie JE, et al. Work stress, weight gain and weight loss: evidence for bidirectional effects of job strain on body mass index in the Whitehall II study. Int J Obes (Lond) 2006;30:982-987.
6. Lopez-Jimenez F, Wu CO, Tian X, et al. Weight change after myocardial infarction—the Enhancing Recovery in Coronary Heart Disease patients (ENRICHD) experience. Am Heart J 2008;155:478-484.
7. Kirschbaum C, Prussner JC, Stone AA, et al. Persistent high cortisol responses to repeated psychological stress in a subpopulation of healthy men. Psychosom Med 1995;57:468-474.
8. Lombardi F, Stein PK. Origin of heart rate variability and turbulence: an appraisal of autonomic modulation of cardiovascular function. Front Physiol 2011;2:95. doi: 10.3389/fphys.2011.00095
9. Kunz-Ebrecht SR, Mohamed-Ali V, Feldman PJ, Kirschbaum C, Steptoe A. Cortisol responses to mild psychological stress are inversely associated with proinflammatory cytokines. Brain Behav Immun 2003;17:373-383.
10. Zahorska-Markiewicz B, Kugawa E, Kucio C, Klim M. Heart rate variability in obesity. Int J Obes Relat Metab Disord 1993;17:21-23.
11. Rodriguez-Colon SM, Bixler EO, Li X, Vgontzas AN, Liao D. Obesity is associated with impaired cardiac autonomic modulation in children. Int J Pediatr Obes 2011;6s:128-134.
12. Felber Dietrich D, Schindler C, Schwartz J, et al. Heart rate variability in an ageing population and its association with lifestyle and cardiovascular risk factors: results of the SAPALDIA study. Europace 2006;8:521-529.
13. Felber Dietrich D, Ackermann-Liebrich U, Schindler C, et al. Effect of physical activity on heart rate variability in normal weight, overweight and obese subjects: results from the SAPALDIA study. Eur J Appl Physiol 2008;104:557-565.
14. Gao YY, Lovejoy JC, Sparti A, Bray GA, Keys HK, Parthington C. Autonomic activity assessed by heart rate spectral analysis varies with fat distribution in obese women. Obes Res 1996;4:55-63.
15. Epel ES, McEwen B, Seeman T, et al. Stress and body shape: stress-induced cortisol secretion is consistently greater among women with central fat. Psychosom Med 2000;62:623-632.
16. Seldenerjak A, Hamer M, Lahiri A, Penninns BW, Steptoe A. Psychological distress, cortisol stress response and subclinical coronary calcification. Psychoneuroendocrinology 2012;37:48-55.
17. Lynch JW, Everson SA, Kaplan GA, Salonen R, Salonen JT. Does low socioeconomic status potentiate the effects of heightened cardiovascular responses to stress on the progression of carotid atherosclerosis? Am J Public Health 1998;88:389-394.
18. Everson SA, Lynch JW, Kaplan GA, Lakka TA, Sivenius J, Salonen JT. Stress-induced blood pressure reactivity and incident stroke in middle-aged men. Stroke 2001;32:1263-1270.
19. World Health Organization. Waist Circumference and Waist-Hip Ratio: Report of a WHO Expert Consultation. Geneva: WHO; 2011.
20. Jackson C. The General Health Questionnaire. Occup Med (Lond) 2006;57:79. doi: 10.1093/occmed/kql169
21. Brunner EJ, Shipley MJ, Britton AR, et al. Depressive disorder, coronary heart disease, and stroke: dose-response and reverse causation effects in the Whitehall II cohort study. Eur J Prev Cardiol 2014;21:340-346.
22. Britton A, Shipley M, Malik M, Haukova K, Hemingway H, Marmot M. Changes in heart rate and heart rate variability over time in middle-aged men and women in the general population (from the Whitehall II Cohort Study). Am J Cardiol 2007;100:524-527.
23. Phillips AC, Roseboom TJ, Carroll D, de Rooij, SR. Cardiovascular and cortisol reactions to acute psychological stress and adiposity: cross-sectional and prospective associations in the Dutch Famine Birth Cohort Study. Psychosom Med 2012;74:699-710.
24. Carroll D, Ginty AT, Der G, Hunt K, Benzeval M, Phillips AC. Increased blood pressure reactions to acute mental stress are associated with 16-year cardiovascular disease mortality. Psychophysiology 2012;49:1444-1448.
25. Kabera B, Hubold C, Zug S, et al. The brain’s supply and demand in obesity. Front Neuroenergetics. 2012:4:4. doi: 10.3389/fnene.2012.00004
26. Jones A, McMillan MR, Jones RW, et al. Adiposity is associated with blunted cardiovascular, neuroendocrine and cognitive responses to acute mental stress. PLoS One 2012;7:e39143. doi:10.1371/journal.pone.0039143
27. Hill MN, McLaughlin RJ, Bingham B, et al. Endogenous cannabinoid signaling is essential for stress adaptation. Proc Natl Acad Sci U S A 2010;107:9406-9411.
28. Freund TF, Katona I, Piomelli D. Role of endogenous cannabinoids in synaptic signaling. Physiol Rev 2003;83:1017-1066.
29. Hill MN, Tasker JK. Endocannabinoid signaling, glucocorticoid-mediated negative feedback, and regulation of the hypothalamic-pituitary-adrenal axis. Neuroscience 2012:204.5-16.
30. Carlson G, Wang Y, Alger BE. Endocannabinoids facilitate the induction of LTP in the hippocampus. Nat Neurosci 2002;5:723-724.
31. Maggio N, Segal M. Striking variations in corticosterone modulation of long-term potentiation along the septotemporal axis of the hippocampus. J Neuroscience 2007;27:5757-5765.
32. Maggio N, Segal M. Differential modulation of long-term depression by acute stress in the rat dorsal and ventral hippocampus. J Neurosci 2009;29:8633-8638.
33. Bhattacharjee S, Viss N, Chu A, Soriano L, Meijer OC, Dallman MF. A corticotropin-releasing hormone-mediated pathway to the paraventricular thalamus is recruited in chronically stressed rats and regulates hypothalamic-pituitary-adrenal function. J Neuroscience 2002;20:5564-5573.
34. Müller MJ, Braun W, Pourhassan M, Geisler C, Bosy-Westphal A. Application of standards and models in body composition analysis. Proc Nutr Soc 2016;75:181-187.
35. Peters A, McEwen BS, Friston K. Uncertainty and stress: why it causes diseases and how it is mastered by the brain [published online May 30, 2017]. Prog Neurobiol. doi:10.1016/j.pneurobiol.2017.05.004
36. Storch M, Gaab J, Kettel Y, Stussi AC, Fend H. Psychoneuroendocrine effects of resource-activating stress management training. Health Psychol 2007;26:456-463.
37. Gaab J, Blattler N, Menzi T, Pabst B, Stoyer S, Ehler U. Randomized controlled evaluation of the effects of cognitive-behavioral stress management on cortisol responses to acute stress in healthy subjects. Psychoneuroendocrinology 2003;28:767-779.
38. Orth-Gomer K, Schneiderman N, Wang HX, Wallin C, Blom M, Jernberg T. Stress reduction prolongs life in women with coronary disease: the Stockholm Women’s Intervention Trial for Coronary Heart Disease (SWITCHD). Circ Cardiovasc Qual Outcomes 2009;2:25-32.
39. Gullickson M, Burell G, Vessby B, Lundin L, Toss H, Svarisvind K. Randomized controlled trial of cognitive behavioral therapy vs standard treatment to prevent recurrent cardiovascular events in patients with coronary heart disease: Secondary Prevention in Uppsala Primary Health Care project (SUPRIM). Arch Intern Med 2011;171:134-140.