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Stress-related changes in body form – Results from the Whitehall II study

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Abstract

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 don't. Heart-rate-variability (HRV) reflects 'autonomic variability' and is related to stress responses to psychosocial challenges. We hypothesized that the combined effects of 'stress exposure' and 'autonomic variability' predict long-term changes in body form.

Methods—Data of 1369 men and 612 women from the Whitehall II cohort were analyzed. Body-mass-index, hip-to-height-ratio and waist-to-height-ratio were measured at three time points over a ten-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: $F=5.0, P=0.008$). We found statistical trends that women displayed similar patterns of stress-related changes in body form ($P=0.061; P=0.063$).

Conclusion—Assessing 'psychological distress' and 'autonomic variability' predicts changes in body form. Psychological distress was found 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'.

Keywords

psychological distress; autonomic variability; body form; obesity

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

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'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, too (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 was found 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 an one-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; from patients who experienced a myocardial infarction one quarter gained body mass, one quarter lost body mass, while the remaining quarters 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 they develop low stress responses. Repetition-induced stress response attenuation is referred to as 'stress habituation'. Kirschbaum and co-workers showed in their classical human experiment on 'stress habituation' that non-habituators maintain a high cortisol response when repeatedly exposed to a psychosocial challenge, whereas habituators initially respond strongly to stress, but develop attenuated stress responses over time (7).

The stress responses are coordinated by two main neuroendocrine systems: the hypothalamic–pituitary–adrenal (HPA) system and the autonomic nervous system. As a biomarker of HPA activity cortisol concentrations 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'. Heart rate variability (HRV) reflects 'autonomic variability'. Thus, HRV is often used as an indicator of cardiac autonomic modulation (8). HRV can be relatively simply determined, while cortisol measures require standardized conditions for assessment (e.g. exact timing of sampling). Cortisol reactivity to mental challenges 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 psychological stress are related to higher autonomic variability (9).

Autonomic variability (HRV) and cortisol responses to a psychosocial 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-waisted phenotype) (14). High cortisol responses to psychosocial challenges were found associated with the lean phenotype exhibiting a large visceral fat mass (i.e., the lean-but-wide-waisted phenotype). The latter finding became evident in a milestone study by Epel and co-workers. 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 ‘non-habituators’ as they continued to show 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 conclusions 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 atherosclerosis. First, in a subset of Whitehall study participants, chronically 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 greatest atherosclerotic progression of the carotid artery walls (17). And 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 here used the longitudinal data set from the Whitehall II study to investigate how stress exposure (psychological distress measure) and autonomic variability (assessed by HRV) affect body form in the long run.

Methods

Study population

The Whitehall II cohort is a large ongoing study investigating determinants of health in British civil servants. In 1985, a cohort of 10,308 participants was initially recruited. Since this first phase of data collection, questionnaires and clinical data have been assessed every two to five years. HRV was assessed in phase 5 (1997-1999), phase 7 (2002-2004) and phase 9 (2007-2009). In phase 5, a total number of 7829 civil servants participated. Of these, 3365 participants had HRV measures. Furthermore, 1384 participants had missing data on the main factors of our analyses, leaving a final sample of 1369 men and 612 women. There was a slight participation bias, in that men included in our analysis were about 0.5years younger compared to men excluded from our analysis (55.3±0.2 vs. 55.8±0.1years; P=0.009). However, there was no observable difference regarding the BMI of both groups (25.9±0.1 vs. 26.1±0.1kg/m^2; P=0.081). The same applied to women. Women included in our analysis were younger compared to women excluded in our analysis (55.7±0.2 vs. 56.3±0.2years; P=0.037), but there was no observable difference regarding the BMI of both groups (26.4±0.2 vs. 26.5±0.2kg/m^2; 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 by an electronic scale; height was measured using a stadiometer. BMI was calculated as body mass (kg) divided by height (m) 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 [cm]. Elevated values in BMI were set at ≥25kg/m^2; for waist-to-hip-ratio (whr) at ≥0.9 (men) or ≥0.85 (women) as suggested by the WHO (19). Anthropometric variables were combined into phenotypes: 1. lean phenotype (BMI<25kg/m^2 and whr<0.9 (men) or <0.85 (women)); 2. Lean-but-wide-waisted phenotype (BMI<25kg/m^2 and whr≥0.9 (men) or ≥0.85 (women)); 3. Corpulent-but-narrow-waisted phenotype (BMI≥25kg/m^2 and whr<0.9 (men) or <0.85 (women)); 4. Corpulent-and-wide-waisted phenotype (BMI≥25kg/m^2 and whr≥0.9 (men) or ≥0.85 (women)). Noteworthy, the waist circumference measurement protocol used here differs from the measurement protocol suggested by the WHO (midpoint between the lower margin of the least palpable rib and the top of the iliac crest) (19), which might have an impact on our definition of the wide-waisted phenotype. Because the incidences of phenotypes depends on cut-off values, we used the analysis on the wide-waisted phenotype only for the reason of better illustration. Our main results are based on ANOVA analyses, for which these constraints do not apply.

Assessment of psychological distress

Psychological distress was assessed using the General-Health-Questionnaire (GHQ-30). The GHQ-30 is widely used in many studies of well-being to detect those 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 of 0 to a response of ‘same as usual/no more than usual’. GHQ-30 caseness was defined as a score of ≥5 (21).

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 over 5min (GE Medical Systems, Milwaukee, Wisconsin). Individual 10-second electrocardiograms were captured. Five minutes of beat-to-beat HR data at a frequency of 500Hz were re-sampled 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 set at ≥ 50 percentile (34.7SDNN for men and 34.0SDNN for women) to split the sample into halves.

Covariates

We considered a wide range of covariates (supplemental table 1), 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,
- socio-economic position,
- exercise,
- nutrition,
- sleep duration,
- alcohol and nicotine abuse,
- use of medication,
- known diseases and general health.

Statistical analysis

Data analysis was performed using SPSS software (SPSS 23.0, Inc., Chicago, USA). 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. Chi-squared 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.

Results

Subjects' characteristics and their changes in body form

Participant characteristics are presented in table 1. When analysing the study population as a whole, both men and women showed on average an increase in body mass, 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 analysing 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, 2.6% displayed the ‘lean-but-wide-waisted’ phenotype, and 34.6% the ‘corpulent-but-narrow-waisted’ phenotype.

We next analysed 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. 21% of initially lean men developed a 'lean-but-wide-waisted' phenotype, and 7% the 'corpulent-but-narrow-waisted' phenotype. For women we found that 71%, who were initially lean in phase 5, stayed lean about 10 years later. 8% of initially lean women developed a 'lean-but-wide-waisted' phenotype, and 15% the 'corpulent-but-narrow-waisted' phenotype. The remaining participants developed a mixed phenotype with traits of the latter two phenotypes.

The changes of body form depend on psychological distress and autonomic variability

For better illustrating reason, 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 *and* low autonomic variability showed greatest increases in body mass (figure 2, **panel A**). The same group also showed greatest increases in hip-to-height-ratio (figure 2, **panel B**). Those participants who reported high levels of psychological distress showed the highest increases in waist-to-height-ratio (figure 2, **panel C**). It looks like the women showed the same pattern (figure 3 **panels A-C**). We found statistical trends that women who displayed elevated levels of psychological distress *and* low autonomic variability showed greatest increases in body mass (P=0.061; figure 3, **panel A**) and hip-to-height-ratio (P=0.063; figure 3, **panel B**). Those women who reported high levels of psychological distress showed the highest increases in waist-to-height-ratio (P=0.053; figure 3, **panel C**).

In the ANOVA for repeated measures approach, we could 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 (supplemental table 2), hip-to-height-ratio (supplemental table 3) and waist-to-height-ratio over time (supplemental table 4). 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 (supplemental table 5), while we could not detect an impact of psychological distress and autonomic variability on waist- or hip-to-height-ratios in women (supplemental tables 6 and 7).

Discussion

Using the Whitehall data set of 1369 men and 612 women, we investigated how the factors ‘psychological distress’ and ‘autonomic variability’ interact and how their interaction relates to changes in body form during a ten-year period. We could 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 also reported that ‘autonomic variability’ was strongly linked to body form. Low HRV was found in people displaying high body mass (10-13), whereas high HRV was found in people displaying large visceral fat (14). Moreover, epidemiological evidence demonstrated that individuals with low HR responses to psychosocial stress and low blood pressure responses to psychosocial stress were at risk of gaining body mass over the next decades (23, 24). Experimental studies suggested that ‘low stress responses’ might be a key feature in participants with high body mass, since they 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’ associated with an increased risk of developing visceral fat (increased waist-to-height-ratio). As mentioned in the introduction, Epel and coworkers have shown that those subjects who maintained ‘high stress responses’ when repeatedly challenged with a psychosocial stressor (i.e., the non-habituators) exhibited more central fat (15). Given Epel's findings, our data suggest that high stress exposure causes increases in visceral fat in non-habituators.

The 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 attenuating the amygdala 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 SNS 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 the homotypic stressors at home, did not habituate to heterotypic stressors at work, since these stressors did 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 non-homogeneous study population, consisting of habituators and non-habituators. Complex environments acting on non-homogeneous 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 questionnaire either because they were not exposed to an inhospitable environment or because they have already 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 – what has been 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).

The neuroendocrine and metabolic mechanisms underlying our observations are supposed to be complex and cannot be inferred from the data analysed here. However, the fundamental biological mechanisms of cerebral and peripheral energy metabolism, which operate differently in ‘habituators’ and ‘non-habituators’, have been proposed by a theoretic framework that brought together the concepts of the ‘Selfish Brain theory’ and ‘allostatic load’ (3). As early as 2015, the authors of that theoretic framework have forecasted changes in phenotype in habituators and non-habituators as they are reported now in the current paper.

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 are the data in current paper in line with the previous predictions (3) — habituators are at risk of developing a corpulent phenotype. In contrast, non-habituators, 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).

In 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 associated with an increased risk of developing the ‘wide-waisted phenotype’. In contrast, ‘high psychological distress’ combined with ‘low autonomic variability’ was found associated with an increased risk of developing the ‘corpulent phenotype’. Given that habituation is one of the most frequent causes for acquired states with low autonomic variability, our data suggest that non-habituators are prone to develop visceral fat accumulation, while habituators are prone to develop subcutaneous fat accumulation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Acronyms

ANOVA	analysis of variance
BMI	body mass index
GHQ	general health questionnaire
HRV	heart rate variability
MET	metabolic equivalent of task
SEM	standard error of the mean

What is already known about this subject?

- Chronic distress is known to be associated with both, body mass gain and body mass loss. Research regarding these findings is insufficient yet.
- The combination of ‘high stress exposure’ and ‘high stress responses’ has been shown by other researchers to predict morbidity risk.

What does our study add?

- The combination of stress exposure and autonomic variability determines the risk of long-term changes in body form.
- Psychological distress was found 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’.

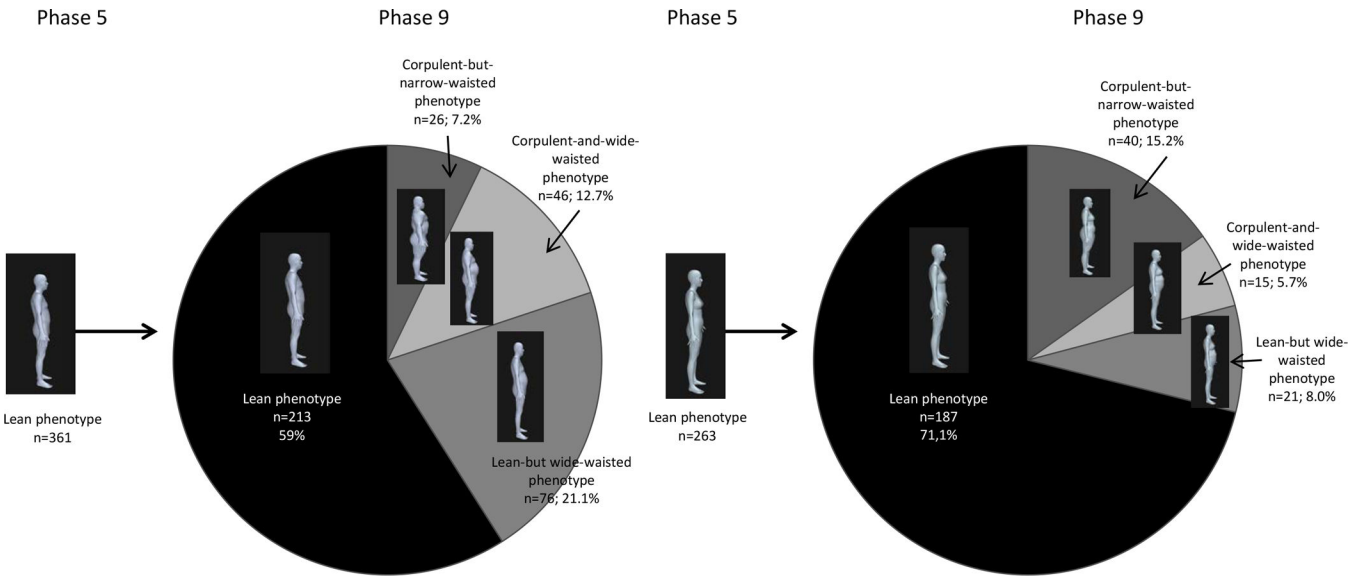

Figure 1. Phenotypic plasticity of body form in men (left panel) and women (right panel)

In the current paper we used the term 'lean phenotype' for people with a BMI <25 kg/m^2 and a waist-to-hip ratio (whr) <0.9 (men) or <0.85 (women), the term 'corpulent phenotype' for people with a BMI ≥25 kg/m^2, the term 'narrow-waisted phenotype' for people with a whr <0.9(men) or <0.85 (women) and the term 'wide-waisted phenotype' for people with a whr ≥0.9 (men) or ≥0.85 (women). Illustrations are created by a 'body visualizer' program available at http://bodyvisualizer.com/male.html. (MPI IS Perceiving Systems Department; Max Planck Gesellschaft)

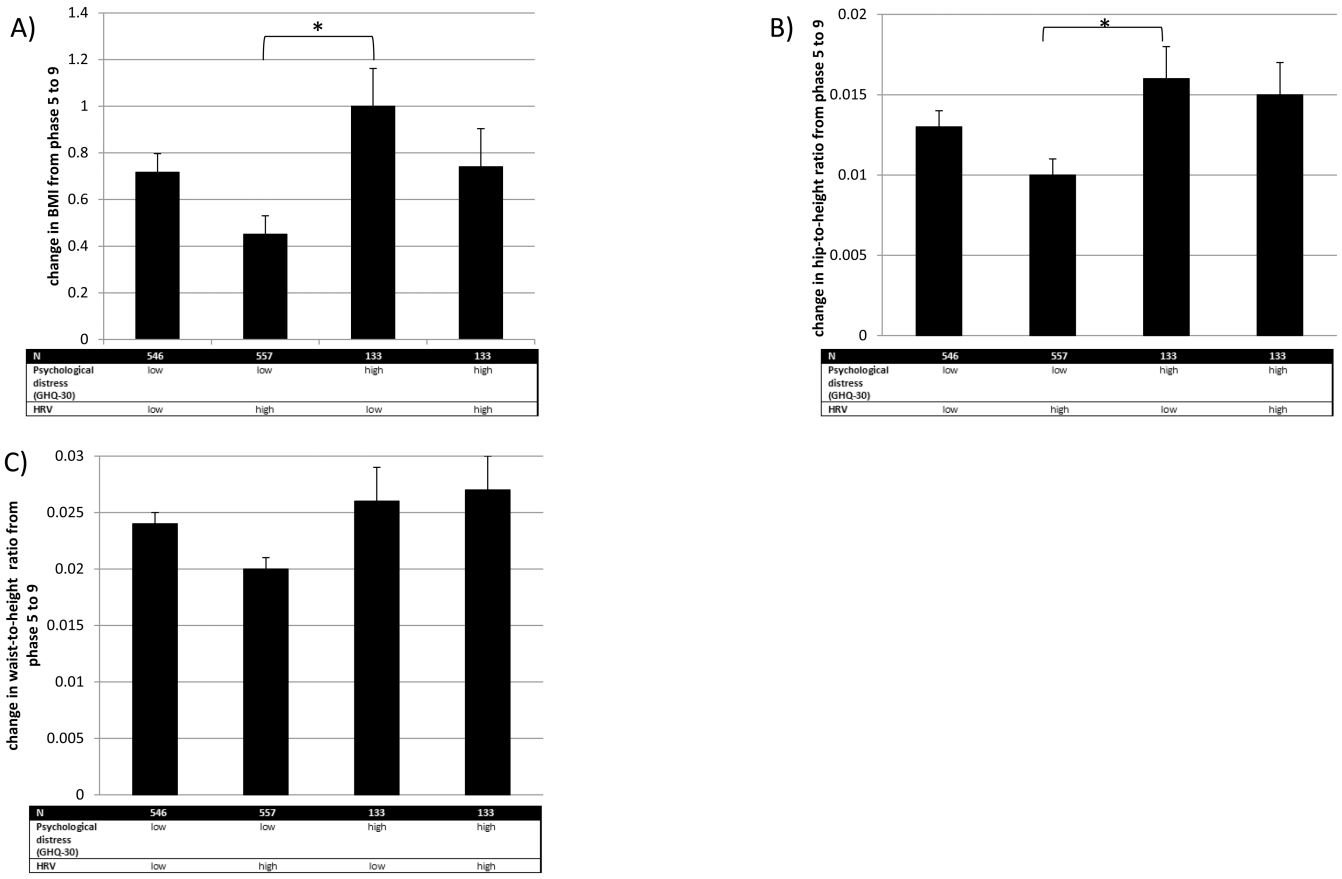

Figure 2.

Panel A: High psychological distress and low HRV were associated with increases in body mass in men (n= 1369). General linear model with age as a covariate; test of intra-subject effects: F=4.0; P=0.007; *significant differences were found for group 2 vs. 3 P=0.014

Panel B: High psychological distress and low HRV were associated with increases in hip-to-height ratio in men (n=1369). General linear model with age as a covariate; test of intra-subject effects: F=4.4; P=0.004; *significant differences were found for group 2 vs. 3 with P=0.021

Panel C: Changes in waist-to-height ratio over time in dependence of autonomic variability and psychological distress in men (n=1369). General linear model with age as a covariate; test of intra-subject effects: F=2.7; P=0.046.

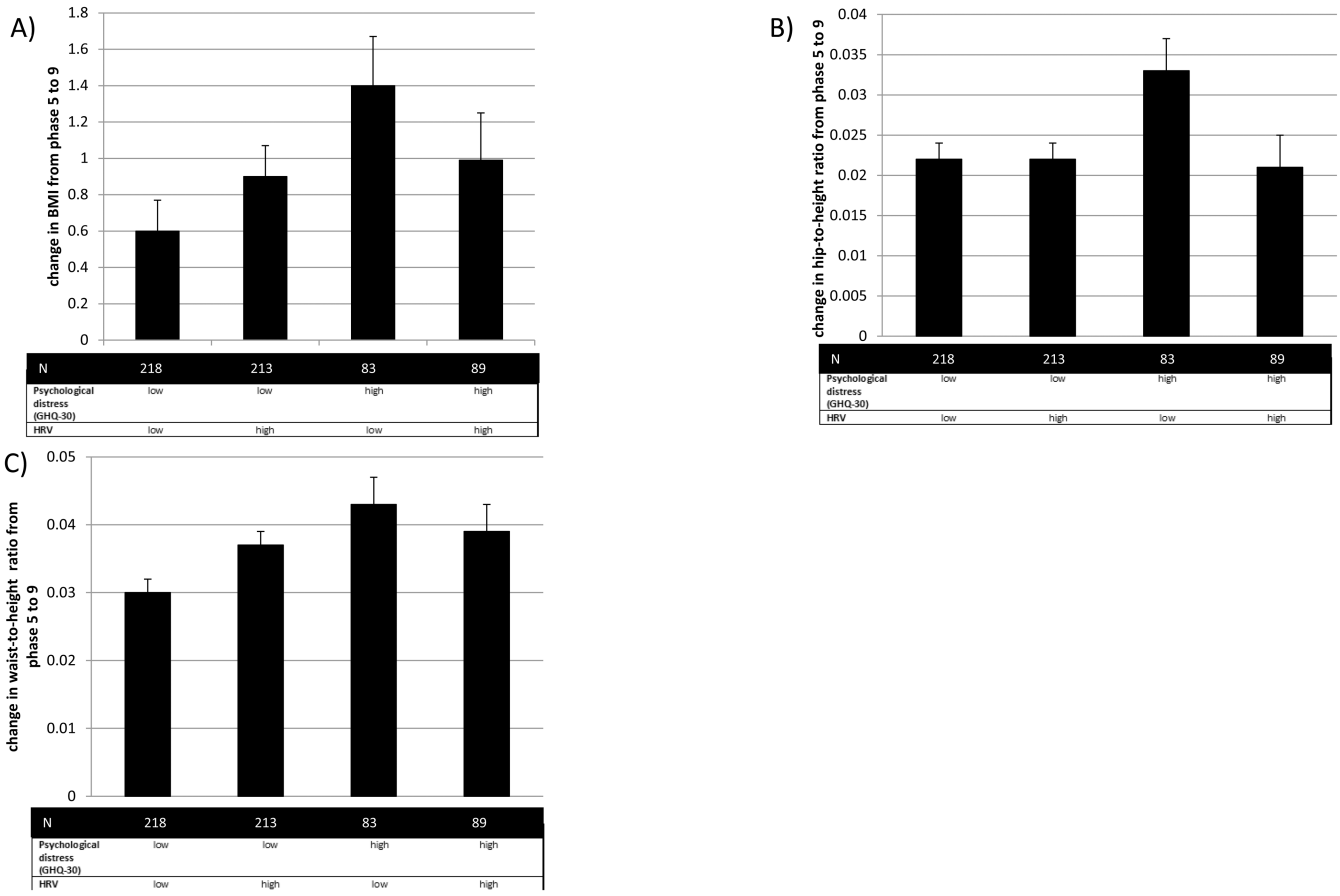

Figure 3.

Panel A: Changes in body mass over time in dependence of autonomic variability and psychological distress in women (n= 603). General linear model with age and having periods as covariates; test of intra-subject effects: F=2.3; P=0.073; trend for differences between group 1 vs. 3 P=0.061

Panel B: Changes in hip-to-height ratio over time in dependence of autonomic variability and psychological distress in women (n=603). General linear model with age and having periods as covariates; test of intra-subject effects: F=2.4; P=0.063; trend for differences between group 1 vs. 3 P=0.089

Panel C: Changes in waist-to-height ratio over time in dependence of autonomic variability and psychological distress in women (n=603). General linear model with age and having periods as covariates; test of intra-subject effects: F=2.6; P=0.053; trend for differences between group 1 vs. 3 P=0.063

Note a reduced number of cases due to missing values for the covariate “having periods”

Table 1

Characterisation of the study population

	Men (n=1369)			Women (n=612)		
	Phase 5	**Phase 7**	**Phase 9**	**Phase 5**	**Phase 7**	**Phase 9**
Age [ys]	55.2±0.2	60.8±0.2	65.8±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±0.3	161.4±0.3***
BMI [kg/m^2]	25.9±0.1	26.5±0.1	26.5±0.1***	26.4±0.2	27.0±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 distress[1]	2.7±0.1	-	-	4.0±0.3	-	-
HRV [SDNN][2]	38.2±0.5	-	-	36.3±0.6	-	-

Values are expressed as mean±SEM

[1] assessed by GHQ-30

[2] Heart rate variability [SD of all intervals between R waves with normal-to-normal conduction].

*** P<0.001; main effect time, ANOVA for repeated measures

Table 2

Body mass index over time in 1369 men

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.

Dependent variable BMI at phases 5, 7, 9	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=0.003 [A, 1]
time × HRV at phase 5	F= 4.8; P=0.011 [A, 2]

[A] All covariates (n=59) were tested regarding their impact on BMI over time (supplemental table 2). The following covariates showed a significant impact on BMI over time (supplemental table 2): age, life satisfaction, MET mild exercise, sleep duration, alcohol dependence, cigarette smoking, rheumatic arthritis drugs, general health index, any longstanding illness, incident diabetes, hypertension. These covariates were considered in the analyses [1-2].

[1] The inner-subject effect ‘time × psychological distress’ remained significant after separate adjustment for the following covariates: age (see table 2), life satisfaction (F=3.8; P=0.029), MET mild exercise (F=5.8; P=0.004), sleep duration (F=5.0; P=0.005), alcohol dependence (F=5.6; P=0.005), cigarette 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), any longstanding illness (F=5.2; P=0.008), incident diabetes (F=6.7; P=0.002), hypertension (F=5.4; P=0.007)

[2] The inner-subject effect ‘time × HRV’ remained significant after separate adjustment for the following covariates: age (see table 2), 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 longstanding 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 1369 men

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.

Dependent variable hip-to-height at phases 5, 7, 9	**Inner-subject effects**	**Dependent variable waist-to-height at phases 5, 7, 9**	**Inner-subject effects**
time	F=1.0; P=0.367	time	F=7.3; P=0.001
time × age	F=5.6; P=0.004	time × age	F=0.5; P=0.608
time × psychological distress at phase 5	F=4.3; P=0.016 [A, 1]	time × psychological distress at phase 5	F=3.4; P=0.038 [B, 3]
time × HRV at phase 5	F=5.0; P=0.008 [A, 2]	time × HRV at phase 5	F=1.8; P=0.174

[A] All covariates (n=59) were tested regarding their impact on hip-to-height ratio over time (supplemental table 3). The following covariates showed a significant impact on hip-to-height ratio over time (supplemental table 3): relatives with alcoholism, relatives with schizophrenia, marital status, income, employment summary, MET mild exercise, cigarette smoking categorical, anti-hypertensive drugs, CVD medication, ACE inhibitors, anxiolytics, diuretics, nitrate medicine, rheumatic arthritis drugs, general health index, any longstanding illness, hypertension. These covariates were considered in the analyses [1-2].

[1] The inner-subject effect ‘time × psychological distress’ remained significant after separate adjustment for the following covariates: relatives with alcoholism (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), anti-hypertensive 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 longstanding illness (F=3.5; P=0.034), hypertension (F=3.7; P=0.027).

[2] 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), anti-hypertensive drugs (F=4.1; P=0.019), CVD medication (F=3.9; P=0.022), ACE inhibitors (F=4.4; 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 longstanding illness (F=5.0; P=0.008), hypertension (F=4.2; P=0.017).

[B] All covariates (n=59) were tested regarding their impact on waist-to-height ratio over time (supplemental table 4). The following covariates showed a significant impact on waist-to-height ratio over time (supplemental table 4): parents unemployed, MET mild exercise, cigarette smoking, ACE inhibitors, incident diabetes, and hypertension. These covariates were considered in analysis [3].

[3] 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).