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## SHORT COMMUNICATION

**Effect of short-term weight loss on mental stress-induced cardiovascular and pro-inflammatory responses in women**Romano Endrighi<sup>1,2</sup>, Mark Hamer<sup>2</sup>, Ruth A. Hackett<sup>2</sup>, Livia A. Carvalho<sup>2</sup>, Sarah E. Jackson<sup>3</sup>, Jane Wardle<sup>3</sup>, and Andrew Steptoe<sup>2</sup><sup>1</sup>Department of Medical and Clinical Psychology, F. Edward Hébert School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD, USA, <sup>2</sup>Department of Epidemiology and Public Health (Psychobiology Group), and <sup>3</sup>Department of Epidemiology and Public Health (Health Behavior Research Center), Institute of Epidemiology and Health Care, University College London, London, UK**Abstract**

Epidemiologic evidence links psychosocial stress with obesity but experimental studies examining the mechanisms that mediates the effect of stress on adiposity are scarce. The aim of this study was to investigate whether changes in adiposity following minimal weight loss affect heightened stress responses in women, and examine the role of the adipokine leptin in driving inflammatory responses. Twenty-three overweight or obese, but otherwise healthy, women (M age = 30.41 ± 8.0 years; BMI = 31.9 ± 4.1 kg/m<sup>2</sup>) completed standardized acute mental stress before and after a 9-week calorie restriction program designed to modify adiposity levels. Cardiovascular (blood pressure and heart rate) and inflammatory cytokines (leptin and interleukin-6; IL-6) responses to mental stress were assessed several times between baseline and a 45-min post-stress recovery period. There were modest changes in adiposity measures while the adipokine leptin was markedly reduced (−27%) after the intervention. Blood pressure reactivity was attenuated (−3.38 ± 1.39 mmHg) and heart rate recovery was improved (2.07 ± 0.96 bpm) after weight loss. Blood pressure responses were inversely associated with changes in waist to hip ratio post intervention. Decreased levels of circulating leptin following weight loss were inversely associated with the IL-6 inflammatory response to stress ( $r = -0.47$ ). We offered preliminary evidence suggesting that modest changes in adiposity following a brief caloric restriction program may yield beneficial effect on cardiovascular stress responses. In addition, reductions in basal leptin activity might be important in blunting pro-inflammatory responses. Large randomized trials of the effect of adiposity on autonomic responses are thus warranted.

**Introduction**

Obesity and excess adiposity are important risk factors for cardiovascular disease (CVD) mortality (Adams et al., 2006), cancers and several metabolic abnormalities (Guh et al., 2009). Epidemiological evidence implicates psychosocial stress as a risk factor in obesity (Wardle et al., 2011) but the mechanisms involved are unclear.

Some evidence suggests that overweight individuals might be hyper-responsive to stress which may then lead to further accumulation of adipose tissue and the development of CVD risk factors including hypertension and type-2 diabetes (Chida & Steptoe, 2010). Impaired stress reactivity may therefore be

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a common feature in obesity and CVD. However, psychophysiological studies that have examined whether overweight or obese individuals are hyper responsive to stress have yielded inconsistent results (Goldbacher et al., 2005; Phillips et al., 2012; Steptoe & Wardle, 2005). One reason for the inconsistent findings may be that previous work has mostly been observational. An alternative method to test this hypothesis is to examine the effect of weight loss on several stress response markers in overweight or obese individuals and whether they relate to changes in adiposity measures. One study reported improvements in blood pressure recovery from acute stress following modest weight loss over 12 weeks (Torres & Nowson, 2007), though this effect was partly accounted for by lower basal blood pressure and antihypertensive use in the weight loss group.

Other mechanisms also seem to be important. The adipokine leptin is relevant in obesity-related CVD risk through central and peripheral mechanisms including sympathetic activation, vascular inflammation and endothelial dysfunction (Hou & Luo, 2011). In obese individuals, circulating leptin is markedly elevated suggesting tissue resistance to the effect of this adipokine (Considine, 2005).

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Previously, we demonstrated that resting leptin level is associated with greater interleukin-6 (IL-6) responses to acute stress in healthy women (Brydon et al., 2008), suggesting that this adipokine may be a mechanism partially mediating the negative effects of stress and obesity on CVD risk. Based on this finding (Brydon et al., 2008), we reasoned that changes in circulating leptin achieved through loss of adiposity should also be associated with attenuated IL-6 responses to stress.

In this study, we therefore hypothesized that weight loss would induce a reduction in CV stress reactivity, and further predicted that changes in circulating leptin achieved through weight loss would partly drive lower pro-inflammatory IL-6 responses to stress.

## Methods

### Design and participants

We conducted a 9-week calorie restriction program in 38 overweight or obese, but otherwise healthy women (18–45 years; BMI 27.5–42.5 kg/m<sup>2</sup>). Exclusion criteria included smoking, current medication use including beta-blockers and statins, diagnosed hypertension or chronic physical illness, partaking in regular exercise or structured diet regime and unable to attend weekly meeting with the dietitian's research team. Based on an expected difference in blood pressure response pre–post weight loss of small to moderate size, a sample size of  $n = 41$  was anticipated. Of the 38 participants enrolled, one became pregnant and withdrew, two withdrew due to diet issues, three withdrew citing personal reasons and nine were lost at follow-up leaving a final sample of 23. Age, adiposity measures, baseline leptin, IL-6 and blood pressure did not differ between completers and non-completers ( $ps > 0.21$ ). Ethical approval was granted by UCLH Human Ethics Committee and informed consent was obtained. Standardized stress testing was administered at baseline (pre-weight loss) and at 9-week follow-up (post-weight loss).

### Materials

#### *Weight loss*

The program consisted of a calorie restriction plan (600 calorie deficit partial meal replacement plus a personal, daily calorie allowance) with a researcher led, weekly meeting component. Researchers calculated the participant's estimated daily energy requirement (Schofield, 1985) and designed a daily non-meal replacement meal plus low calorie snacks. Weekly meetings were based on a cognitive-behavioral approach to weight loss that included taught skills such as controlling portion size, managing triggers for overeating, self-monitoring and stimulus control and response substitution. In case of non-attendance, a telephone call was scheduled to ensure adherence to the program.

#### *Anthropometrics*

Participants' height was measured to the nearest 0.1 cm using a stadiometer. Body fat and body mass were assessed using a body composition analyzer (Tanita BC-418 segmental body composition analyzer, Tanita Corporation of America, Inc.,

Arlington Heights, IL) scale with participants standing in light clothing. BMI was computed as body mass in kilograms divided by the square of the height in meters [kg/m<sup>2</sup>]. Waist circumference was measured using a metal anthropometric tape midway between the lowest rib and iliac crest whereas hip circumference was measured at the level of the great trochanters, and the waist-to-hip ratio (WHR) was computed. Measures were obtained by a research nurse at a consistent time of the day for each participant across the repeated assessments.

#### *Acute stress*

Mental stress was elicited with two 5-minute, standardized psychosocial stress tasks (mirror tracing and public speaking) administered under time pressure as previously described (Brydon et al., 2005). These tasks reliably perturb the CV and immune system and effects are reproducible over time (Hamer et al., 2006). However, activation of the HPA axis (as indexed by salivary cortisol increases) in response to this stress protocol is generally of modest magnitude. In the mirror-tracing task, participants were instructed to trace around a marked contour of a star with an electronic stylus while looking at the star's own reflection in a mirror. To sustain demand, participants were told that most people complete the drawing five times within the 5 min allowed with few errors.

In the public speaking task, participants were presented with two scenarios in which they were required to either defend themselves in order to avoid redundancy or argue for the safety of an ill elderly relative in a nursing home. Participants were told that the performance would be video recorded and rated by experts. Written instructions were provided prior to each task.

Subjective ratings of engagement were also obtained after each task using a 7-point Likert scale anchored at 1 (not at all involved) and 7 (very much involved) to index participant's involvement in executing the tasks. Stress testing was administered at the same time during the baseline (pre-weight loss) and follow up (post-weight loss) sessions.

#### *Cardiovascular outcomes*

Blood pressure and heart rate responses were obtained with a Finometer Pro (Wesseling, 1996). Data were collected continuously and then averaged over specified 5 min trials to yield rest (last 5 of a 30-min resting period), stress reactivity (mean of each 5-min task) and stress recovery (last 5 of a 45-min post-stress period) values. Reactivity to the tasks was highly correlated and was averaged to yield a single stress value as previously recommended (Kamarck & Lovallo, 2003).

#### *Adipokine and cytokine assays*

Whole blood (10 ml) was drawn using a 21-gauge needle into vacutainer tubes containing EDTA and serum separator gel. Samples were centrifuged at  $1246 \times g$  for 10 min at room temperature. IL-6 was measured at rest and 45-min post-stress using a high sensitivity, two-site assay (ELISA; R&D Systems, UK) with a limit of detection 0.016 pg/ml and

intra and inter assay coefficient of variation (Cv) of 7 and 7.2%, respectively. Leptin was measured at rest only using an ELISA assay with a limit of detection of less than 0.007 ng/mL (intra-inter assay Cv 3.1 and 4.3%). Samples were assayed in duplicate according to respective protocols. Concentrations of each analyte was determined with a microplate reader (Molecular Devices, UK) using the SoftMax Pro 5 software (Molecular Devices, Sunnyvale, CA) with a four-parameter logistic curve data reduction fit.

## Procedure

Instructions requiring participants to abstain from caffeine and to choose a low fat breakfast on the scheduled appointment day were mailed in advance. Sessions were scheduled to begin between 10.00 AM and 12.00 PM. On the appointment day, anthropometric measures were obtained according to protocol and participants were escorted to a stress laboratory where they rested for 30 min before mental stress was carried out. Participants were instructed to rest quietly for 45 min after stress induction and were subsequently taken to a research room to meet the dietician research team.

Nine weeks later participants were recalled into the stress laboratory for repeated assessment of anthropometric measures and psychophysiological testing following the same procedure outlined above.

## Statistical analyses

Interleukin-6 values were logarithmically transformed to normalize the distribution; natural values are presented to aid interpretation. Changes in adiposity measures, cytokine and adipokine markers following weight loss were examined using related *t*-tests and are summarized in Table 1.

Mixed ANOVAs were used to examine group differences in CV and IL-6 responses to stress during the pre-weight loss testing session only between participants completing ( $n = 23$ ) and non-completing ( $n = 15$ ) the study.

Differences in stress-induced CV and inflammatory responses before and after weight loss were examined using repeated measures ANOVAs. Interaction effects were examined by comparing acute reactivity (mean stress–rest value) and recovery scores (45 min post-stress–rest values) using *t*-tests; partial correlations was used to examine associations between the acute stress responses and changes in the adiposity measures (adjusting for pre-weight loss stress

responses) and are summarized in Table 2. Associations between changes in leptin and inflammatory IL-6 reactivity were examined using partial correlation analyses (adjusting for pre-weight loss reactivity).

## Results

There were significant reductions in adiposity measures and resting blood pressure following weight loss (Table 1); circulating serum leptin decreased by 27% ( $-9.33 \pm 11.48$  ng/mL) and, as expected, was highly correlated with changes in body mass ( $r = 0.53$ ).

There were no group differences in SBP [ $F_{2,72} = 2.40$ ,  $p = 0.1$ ] or IL-6 [ $F_{1,35} = 0.21$ ,  $p = 0.65$ ] responses to stress at the pre-weight loss session only between participants completing and those not completing the study. Mean heart rate (HR) during stress was generally lower in participants not completing the study ( $M = 76.96$ ,  $SE = 3.31$  versus  $M = 80.33$ ,  $SE = 2.67$ ,  $p = 0.03$ ).

## Cardiovascular stress responses

Participants engagement during the stress tasks did not differ across the pre- and post-weight loss testing sessions ( $p = 0.53$ ), suggesting equal level of involvement during acute stress.

As expected, systolic and diastolic blood pressure (SBP and DBP) robustly increased in response to stress (time effect  $p < 0.001$ ). We found a SBP [ $F_{(2,44)} = 5.24$ ,  $p = 0.009$ ] and DBP [ $F_{(2,44)} = 3.43$ ,  $p = 0.004$ ] session by time interaction which indicated attenuated reactivity to acute stress post-compared to pre-weight loss [SBP =  $-3.38 \pm 1.39$  mmHg,  $t_{(22)} = -2.42$ ,  $p = 0.002$ ; DBP =  $-2.18 \pm 0.94$  mmHg,  $t_{(22)} = -2.31$ ,  $p = 0.03$ ]. Attenuated SBP reactivity was also associated with changes in adiposity, indexed by the WHR ( $r = -0.46$ ,  $p = 0.03$ ; Figure 1) but it was not significantly associated with the other adiposity measures (Table 2). Attenuated DBP reactivity instead was only marginally associated with changes in WHR ( $r = -0.39$ ,  $p = 0.06$ ). No pre–post weight loss differences in either SBP or DBP were observed during stress recovery ( $p \geq 0.26$ ).

HR also increased in response to acute stress (time effect  $p < 0.001$ ) but with no significant session by time interaction [ $F_{(2,44)} = 1.92$ ,  $p = 0.16$ ]. Nonetheless, HR stress recovery improved post-weight loss [ $2.07 \pm 0.96$  bpm,  $t_{(22)} = 2.14$ ,  $p = 0.04$ ]. Improved HR recovery was also associated with changes in fat mass ( $r = 0.53$ ,  $p = 0.01$ ), body mass ( $r = 0.65$ ,

Table 1. Changes in adiposity measures, blood pressure and adipokines after weight loss ( $n = 23$ ).

Variable	Baseline	Follow-up	Change	<i>t</i> (Df)	<i>p</i>
Body mass (kg)	84.30 $\pm$ 14.24	81.48 $\pm$ 15.31	2.80 $\pm$ 3.14	4.28 (22)	<0.001
WC (cm)	90.49 $\pm$ 9.79	87.96 $\pm$ 10.70	2.53 $\pm$ 4.36	2.77 (22)	0.01
WHR	0.81 $\pm$ 0.07	0.80 $\pm$ 0.07	0.004 $\pm$ 0.03	0.62 (22)	0.54
BMI (kg/m <sup>2</sup> )	32.00 $\pm$ 3.98	30.92 $\pm$ 4.54	1.07 $\pm$ 1.18	4.34 (22)	<0.0001
Fat mass (kg)	34.41 $\pm$ 10.38	31.24 $\pm$ 10.28	3.16 $\pm$ 2.48	6.11 (22)	<0.001
SBP (mmHg)	116.15 $\pm$ 10.15	111.83 $\pm$ 7.90	4.31 $\pm$ 6.71	3.07 (22)	0.005
IL-6 (rest) (pg/ml)*	1.71 $\pm$ 2.31	1.16 $\pm$ 0.66	0.55 $\pm$ 2.22	1.19 (22)	0.24
Leptin (ng/ml)	36.27 $\pm$ 18.77	26.94 $\pm$ 17.80	9.33 $\pm$ 11.47	3.89 (22)	0.001

\*Log transformed values used in analyses.

Values are means  $\pm$  SD. BMI = body mass index; WC = waist circumference; WHR = waist-hip ratio; SBP = Systolic blood pressure; IL-6 = Interleukin-6.

Table 2. Partial correlations between changes in adiposity measures and leptin post-weight loss, and cardiovascular and interleukin-6 acute stress responses ( $n=23$ ).

Outcome predictor	SBP (mmHg)	DBP (mmHg)	HR (bpm)	HR rec. (bpm)	IL-6 (pg/mL)
$\Delta$ Body mass (kg)	-0.01	0.11	0.30	0.65	-0.26
	$p=0.98$	$p=0.61$	$p=0.18$	$p<0.01$	$p=0.23$
$\Delta$ Body mass index ( $\text{kg}/\text{m}^2$ )	-0.01	0.09	0.31	0.61	-0.28
	$p=0.97$	$p=0.67$	$p=0.15$	$p<0.01$	$p=0.20$
$\Delta$ Waist-to-hip ratio	-0.46	-0.39	-0.25	-0.03	0.09
	$p=0.03$	$p=0.06$	$p=0.26$	$p=0.91$	$p=0.69$
$\Delta$ Waist circumference (cm)	-0.33	-0.30	-0.09	0.20	-0.1
	$p=0.14$	$p=0.17$	$p=0.66$	$p=0.36$	$p=0.66$
$\Delta$ Fat mass (kg)	0.06	0.19	0.38	0.53	-0.18
	$p=0.78$	$p=0.40$	$p=0.08$	$p=0.01$	$p=0.41$
$\Delta$ Leptin (ng/mL)	-0.12	-0.08	0.06	0.22	-0.47
	$p=0.58$	$p=0.73$	$p=0.79$	$p=0.33$	$p=0.03$

Outcomes are SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate reactivity to stress (difference scores between rest and mean acute stress values); HR rec = heart rate recovery from stress (difference score between 45-min post-stress and rest values); IL-6 = interleukin-6 (difference score between rest and 45-min post-stress values). Predictors are computed as change scores ( $\Delta$ ) between pre- and post-weight loss values (greater scores indicate greater reductions). All correlations are adjusted for the corresponding stress response value at baseline (pre-weight loss) testing. Values are partial correlation coefficient “ $r$ ” and  $p$  values.

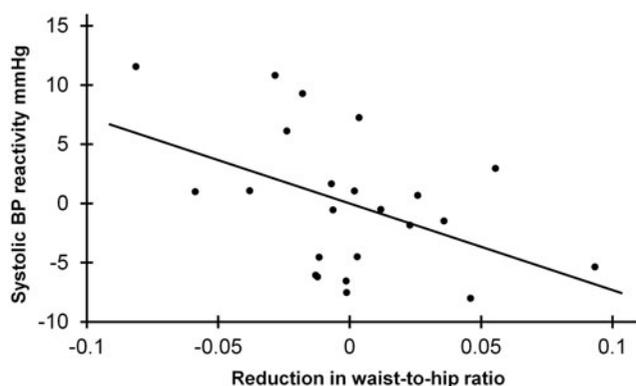


Figure 1. Systolic blood pressure stress reactivity and changes in adiposity. Lower stress-induced blood pressure responses are associated with greater reductions in adiposity after weight loss independent of pre-weight loss blood pressure responses.

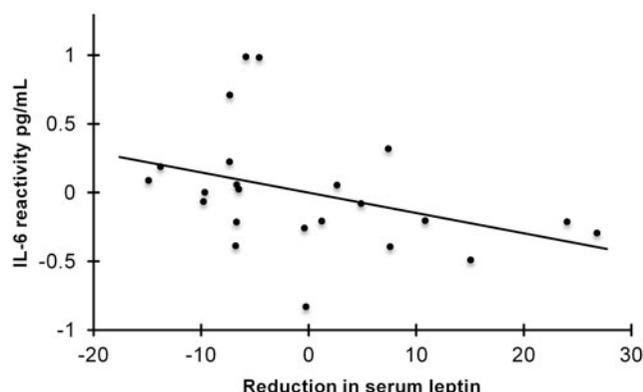


Figure 2. Associations between changes in leptin and pro-inflammatory IL-6 responses to acute mental stress. Greater weight loss-induced changes in leptin are associated with an attenuated IL-6 response to acute stress.

$p=0.001$ ) and BMI ( $r=0.61$ ,  $p=0.02$ ), but not with WHR ( $r=-0.03$ ,  $p=0.91$ ) or WC ( $r=0.20$ ,  $p=0.36$ ; Table 2).

### IL-6 acute stress reactivity and changes in leptin

Interleukin-6 averaged 1.71 pg/mL (SD = 2.31) at rest increasing to 1.76 pg/mL (SD = 2.40) 45 min post-stress at baseline. At follow-up testing, IL-6 averaged 1.16 pg/mL (SD = 0.66) at rest increasing to 1.35 pg/mL (SD = 0.78) 45 min post-stress.

There was a significant main effect of time for the IL-6 response [ $F_{(1,22)}=6.35$ ,  $p=0.02$ ], however, there was no session by time interaction [ $F_{(1,22)}=1.55$ ,  $p=0.23$ ] indicating no significant changes in the IL-6 responses pre- to post-weight loss.

Interleukin-6 reactivity post-weight loss was significantly associated with changes in leptin ( $r=-0.47$ ,  $p=0.03$ ) independent of pre-weight loss reactivity suggesting that individuals with greater reductions in basal leptin following weight loss had lower inflammatory stress responses (Figure 2).

### Discussion

Nine weeks of caloric restriction resulted in modest but significant reductions in adiposity measures, blood pressure and circulating basal leptin. Blood pressure responses to acute stress were lower after weight loss and were associated with changes in adiposity (Figure 1). In addition, there was an improvement in heart rate recovery from acute stress which was also associated with changes in adiposity.

These novel findings tentatively suggest a link between reduction in adiposity and more favorable CV responses to acute mental stress. The effect of adiposity on CVD risk factors is thought to be stronger in women (Li et al., 2006), and since women have generally more adipose tissue than men the finding presented herein may be of particular relevance to this population. Given the association between exaggerated CV responses to stress and future CVD risk factors (Chida & Steptoe, 2010), the fact that modest changes in adiposity may impact stress responses might be clinically important.

We observed smaller pro-inflammatory IL-6 responses in participants with greater reduction in circulating leptin following weight loss. It is known that leptin stimulates pro-inflammatory cytokines activity in macrophage cells and promotes a pro-atherogenic environment, but less is known about the role of leptin in stimulating pro-inflammatory activity in response to psychosocial stress. This finding is in agreement with our previous study that found associations between circulating leptin and IL-6 reactivity (Brydon et al., 2008), and adds preliminary evidence, in humans, indicating that leptin is implicated in the inflammatory response to stress.

Given that higher circulating leptin is predictive of CVD risk (Patel et al., 2008), and that pro-inflammatory stress responses are also associated with some CVD risk factors (Brydon & Steptoe, 2005), leptin may be an important adipokine mediating the negative effect of stress in overweight women.

This study has several limitations; chiefly among them is the lack of a non-weight loss control group. There were, however, significant correlations between reactivity and changes in some of the adiposity measures, and the acute stress paradigm used in this study has shown robust reproducibility over repeated administrations (Hamer et al., 2006). Evidence also shows that inflammatory responses do not seem to habituate to repeated exposure to stress (McInnis et al., 2014). Nevertheless, without a control group, we cannot be certain that the findings observed were indeed attributable solely to changes in adiposity measures.

There was a relatively high dropout rate from this study. However, with a sample of  $n = 23$ , we had 0.87 power ( $1 - \beta$ ) to detect the achieved large ( $R^2 = 0.20$ ) blood pressure effect. Furthermore, pre-weight loss adiposity and physiological variables, blood pressure and IL-6 stress responses, did not differ between completers and non-completers. Nevertheless, the characteristics of participants that did not complete the study may have differed in other respects and future work in this area should consider this issue. The average weight loss achieved in the study was modest and the duration of the intervention relatively brief. It is unclear whether more drastic weight loss or longer intervention may result in greater attenuation in CV or inflammatory responses. Finally, we only collected a post-stress blood sample 45 min after stress which might have prevented us from examining a more robust inflammatory response given that IL-6 is known to continually increase up the 2 h post-stress exposure.

Modest changes in adiposity following a brief weight loss program had favorable effects on CV stress responses and changes in circulating leptin predicted a blunting in IL-6 reactivity. Randomized trials on the effect of weight loss on stress responses are warranted.

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### Declaration of interest

The authors report no conflicts of interest. This research was funded by the British Heart Foundation.

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