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Initial Body Fat Gain is related to Brain Volume Changes in Adolescents: a Repeated-Measures Voxel Based Morphometry Study

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Abstract

Objective—Individuals with obesity versus those within a healthy weight range show brain volume differences, but it is unclear whether these differences reflect initial vulnerability factors or are secondary to weight gain. We tested whether brain volumes predict increases in body fat and investigated volumetric changes associated with initial body fat gain in adolescents.

Methods—162 healthy weight adolescents (M age = 15.3±1.1; 81 females) were scanned at baseline. Sixty subjects (M baseline age: 15.2±1.1; M follow-up age: 17.7±1.2; 34 females) completed a second scan at 2- or 3-year follow-up. Voxel-based morphometry assessed global and regional gray matter (GM) and white matter (WM) volumes. Body fat percentage was assessed yearly over follow-up.

Results—Baseline global/regional GM/WM volume did not predict body fat gain over follow-up. Adolescents who gained body fat showed greater decreases in GM volume in the putamen compared to those who showed loss of body fat. Adolescents who gained body fat showed greater increases in WM volume in the anterior cingulate cortex compared to those who showed stability of or loss of body fat.

Conclusions—Body fat gain versus stability and loss produce GM and WM volume changes, rather than baseline volumetric differences predicting body fat gain.

Keywords

obesity; body fat; voxel-based morphometry; brain volume; reward

Introduction

Obesity impacts 25% of adolescents in the United States¹ and adolescents with obesity are more likely to experience lifelong difficulties with weight.² However, widely implemented treatments rarely result in lasting weight loss.³ An improved understanding of neural

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vulnerability factors that increase risk for future weight gain may inform the design of more effective behavioral and pharmacological treatments.

Prospective studies have examined functional neural vulnerability factors that predict future weight gain. Elevated reward region (e.g., striatum) responsivity to energy-dense food cues predicted future weight gain in several studies.⁴⁻⁶ Yet, there has been less attention to structural neural vulnerability factors that may predict weight gain, which include gray matter (GM) and white matter (WM) volume. GM consists of neuronal cell bodies, neuropil, glial cells and capillaries that relay incoming sensory signaling and outgoing motor signaling. WM consists of myelin sheathing that insulates the axons of neural cells, which increases the speed of neural transmission. Cross-sectional studies have found differences in GM and WM volume in reward (e.g., striatum) and inhibitory control regions (e.g., inferior frontal gyrus) between adolescents^{7, 8} and adults⁹⁻¹¹ with obesity versus those within a healthy weight range but these studies cannot determine whether these structural differences are a precursor for future weight gain or the result of elevated adipose tissue or overeating.

Abnormalities in GM and WM volume in reward- and inhibitory regions may increase subjective reward from food and risk that individuals will consume palatable foods when exposed to food cues, prompting increased intake of energy-dense food. Alternatively, an increase in adiposity may prompt volumetric changes in the brain. Inflammatory cytokines/adiopokines such as fibrinogen, IL-1 β , IL-6, and C-reactive protein are associated with excess adipose tissue.^{12, 13} IL-6 levels correlate negatively with global brain volume and regional GM volume in the hippocampus and medial PFC¹⁴ and correlate with both body fat and hippocampal gray matter volume.¹⁵ Further, monkeys on a long-term, calorie-restricted diet show reduced levels of IL-6 and decreased IL-6-related global GM and WM atrophy, as well as GM atrophy in parietal and temporal regions.¹⁶ Inflammatory markers may be the mechanism by which obesity is related to low GM volume. Moreover, Haltia et al.¹⁷ hypothesized that an increase in body fat may enhance the density of myelin, which increases WM volume, consistent with evidence that individuals with obesity versus those within a healthy weight range show significantly higher concentrations of serum free acids and that serum free fatty acid concentration and regional WM volume in subjects with obesity were positively associated. Haltia et al.¹⁷ also found that global WM as well as regional WM volumes in the temporal lobe were partially reduced by a controlled very low-calorie diet for 6 weeks in subjects with obesity. Relatedly, healthy dietary intake is positively associated with total brain volume and global GM volume.^{18, 19}

Only one study tested the relation of GM and WM volume to future weight gain; lower GM volume in prefrontal inhibitory regions (i.e., superior frontal gyrus and middle frontal gyrus) showed a marginal relation to future weight gain over 1-year follow-up in adolescents varying in weight from lean to obese.²⁰ Thus, the first aim of this report is to test whether individual differences in total GM and WM volume, and differences in GM and WM volume in regions implicated in reward and inhibitory control, predict future weight gain in a larger sample of adolescents followed over a longer follow-up. To rule out the possibility that a history of overweight or obesity contributed to any baseline volumetric differences, we recruited a healthy weight sample, allowing the prediction of initial excessive weight gain.

Further, only one repeated-measures brain imaging study has tested whether weight gain is associated with change in total or regional GM or WM volume, which is critical for determining whether weight gain alters brain volume. A greater increase in BMI over a 5-year period was associated with smaller declines in hippocampal volume, but no other changes in GM or WM volume.²¹ The fact that the sample in this study was largely overweight or obese at baseline might have made it difficult to detect changes in brain volume resulting from weight gain, as any structural changes in response to elevated adiposity might have been already present at baseline. Further, that study involved adults, which might not be ideal because the established age-related declines in brain volume²² might have made it difficult to separate changes resulting from ageing versus gaining weight. Accordingly, the second aim was to test whether adolescents who were in a healthy weight range at baseline and gained weight over a 2-3 year follow-up showed differential change in GM and WM volume than adolescents who showed weight stability or weight loss over follow-up.

Methods

Participants

We recruited 162 healthy weight adolescents (82 female, 80 male; M age = 15.3 ± 1.1 ; M body fat percentage = 18.4 ± 7.7 ; M body mass index [BMI] = 20.8 ± 1.9 ; M zBMI = 0.06 ± 0.6 ; 4% Hispanic, 1% Native American, 1% Asian/Pacific Islanders, 76% European Americans, and 18% mixed racial heritage) in a US city via advertisements for a 3-year prospective study. Exclusion criteria were a baseline BMI (kg/m^2) <18 or >25 , current use of psychoactive medications or drugs more than weekly, pregnancy, head injury with a loss of consciousness, significant cognitive impairment, major medical problems, or current Axis I psychiatric disorder. Parents provided written informed consent and adolescents provided written assent. Oregon Research Institute's Institutional Review Board approved all methods.

All participants completed the baseline scan, but 7 did not provide any follow-up data and thus were excluded from the prospective analyses testing the associations between GM and WM volumes and future body fat gain. Due to high cost of MRI scanning, we were unable to re-scan all participants at follow-up. Therefore, only those who showed either a 3% increase in body fat, a 3% decrease in body fat, or showed less than a 2% change in body fat over 2- or 3-year follow-up were invited to repeat the scan a second time at 2- or 3-year follow-up. We operationalized body fat gain, loss, and stability in this fashion because, based on the body fat change observed in the first year of follow-up, it seemed like these definitions would yield large enough cell sizes for adequate power. To maximize group differences, we did not re-scan subjects with a body fat change between 2-3%. We scanned participants who satisfied the change in body fat criteria at 2-year follow-up to maximize the sizes of the gain and loss groups, as we were concerned that they might not still satisfy the change criteria at 3-year follow-up. However, if a participant showed further gain or loss in body fat, we invited them to repeat the scan at 3-year follow-up and used the data from that latter scan. Exclusion criteria for the follow-up scan were similar to those for the baseline scan.

A participant flow chart is shown in Fig. 1. Sixty-five participants (37%) completed a second scan at 2- or 3-year follow-up. Data from five participants were excluded from analyses due to: excessive movement ($n = 1$), incomplete scans ($n = 2$) and acquisition errors ($n = 2$), resulting in $n = 60$ (adolescents who gained body fat $n = 34$; adolescents who showed stable body fat $n = 12$; adolescents who showed loss of body fat $n = 14$). Ten of the subjects (29%) who gained body fat transitioned from healthy weight at baseline to either overweight ($n = 8$) or obese ($n = 2$) at follow-up according to BMI percentile norms (M BMI percentile at follow-up = 90.5 ± 4.3).

Measures

Body Fat—Air displacement plethysmography (ADP) assessed body fat percentage of participants at baseline and at all follow-ups with the Bod Pod S/T using recommended procedures and age/sex appropriate equations.²³ We focused on body fat rather than BMI because the former is a more precise measure of adipose tissue volume and is not influenced by variation in lean muscle mass. Body density was calculated as body mass divided by body volume. Height was measured to the nearest millimeter and weight was assessed to the nearest 0.1 kg after removal of shoes and coats. Two measures of each were obtained and averaged. Body fat percentage estimates show test-retest reliability ($r = .92-.99$) and correlate with DEXA and hydrostatic weighing estimates of body fat ($r = .98-.99$).²⁴

Substance use—To more fully characterize the sample, substance use was measured with 8 items measuring the frequency of use of beer/wine/wine coolers, hard liquor, cigarettes, marijuana, stimulants, downers, inhalants, and hallucinogens in the past year (i.e., 0 = *never*, 1 = *a few times*, 2 = *less than monthly*, 3 = *1–3 times a month*, 4 = *1–2 times a week*, 5 = *3–4 times a week*, 6 = *5–7 times a week*). This scale has shown internal consistency (mean $\alpha = .86$) and test-retest reliability (mean $r = .86$).²⁵

MRI data acquisition—At baseline, scanning was performed in a Siemens Allegra 3-Tesla, head-only MRI scanner (Allegra Siemens Medical System, Malvern, PA, USA). High-resolution structure MRI sequences (FOV = 256×256 mm², 256×256 matrix, thickness = 1.0 mm) were acquired. Follow-up scans were primarily performed on the Allegra (93%), but 4 of the 60 participants were scanned with a Siemens Skyra 3T scanner (MP-RAGE with a TR/TE of 2100ms/ 2.4ms, flip angle of 15°, TI of 1100ms, matrix size of 256x256, FOV of 22cm, slice thickness of 1mm).

Imaging and statistical analysis—Baseline T1 images were preprocessed with Statistical Parametric Mapping 8 software (SPM8; <http://www.Fil.ion.ucl.ac.uk/spm>) and the VBM8-toolbox (<http://dbm.neuro.uni-jena.de/vbm8>) with default settings. For the repeated-measures, T1 images were preprocessed using the longitudinal processing pipeline as offered in the VBM8-toolbox. Images were normalized to MNI space with the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL)²⁶ using the DARTEL template. A nonlinear deformation was applied to the normalized segmented images to correct for individual differences in brain volume. Images were smoothed to an 8-mm full width at half maximum Gaussian kernel.

To test the hypothesis that baseline regional GM and WM volumes predict future body fat gain, we performed multiple regression analyses in SPSS with body fat slopes reflecting body fat change over 3-year follow-up. Body fat data from baseline, and 1-, 2-, and 3-year follow-ups were used in random intercept, mixed effects growth curve analyses (SAS Inc. ver. 9.3, Cary, NC) to model body fat change, which offers a sensitive technique for modeling change in continuous variables and uses maximum likelihood estimation to accommodate missing data.²⁷ Body fat intercept, coded to reflect baseline body fat, was included as a covariate. Total intracranial volume (TICV; the cumulative volume of gray matter, white matter, and cerebrospinal fluid) at baseline was also added as a covariate to control for individual differences in overall head size. For the repeated scan analyses ($n = 60$), we used a flexible factorial design with three factors (subject, group, and time). TICV significantly increased from baseline to follow-up (M_{60} baseline TICV = 1104.9 ± 123.9 ; M_{60} follow-up TICV = 1171.6 ± 132.8 ; $t(59) = 10.9$, $p < 0.001$). Thus, TICV at both assessments was added as a covariate in the flexible factorial design analyses. Age at both scans was also included as a covariate of no interest. Alcohol use, cigarette use, drug use, and scanner type did not have a significant effect on our outcome variables and were therefore not included as covariates in our analyses. In all analyses, an absolute threshold mask was set at 0.1 for all comparisons to avoid possible edge effects around the border between GM and WM. For both the prospective and the repeated-scan analyses, the statistical threshold was set at a voxel-level threshold of $p < 0.001$ and a cluster-level threshold of p family-wise error (FWE) < 0.05 . However, because this is the first MRI study in adolescents examining volumetric changes as a result of body fat gain, we also report peaks that survived the slightly more liberal statistical threshold of $P < 0.001$, p false discovery rate (FDR) < 0.05 in the repeated scan analyses.

Results

Sample characteristics and behavioral data

The groups showing differential change in body fat did not differ on sex, parental overweight/obesity, parental education, global GM/WM volume, age, body fat, BMI and zBMI at baseline, time of follow-up scan, alcohol use, cigarette use, and drug use (Table 1). At follow-up, there were significant differences among the three groups in body fat percentage, BMI, and zBMI (Table 1). Pairwise contrasts showed that adolescents who gained body fat had a higher body fat percentage compared to adolescents who showed stable body fat (effect size Cohen's $d^{28} = 0.92$) or loss of body fat ($d = 1.01$).

Relations between global GM and WM volume and body fat gain

Regression models tested the associations between global GM and WM at baseline and body fat gain over 3-year follow-up ($n = 155$). Global GM (partial $r = -0.05$, $p = .56$) and global WM (partial $r = 0.06$, $p = 0.48$) did not predict future body fat gain. Further, the groups showing differential change in body fat percentage did not differ on global GM and WM at follow-up.

Relations between regional GM and WM volume at baseline and body fat gain over 3-year follow-up

Whole-brain analyses examined correlations between regional GM/WM at baseline and change in percent body fat over 3-year follow-up. No effects survived the threshold of $p_{FWE} < 0.05$.

Changes in regional GM between adolescents who gained body fat versus those who showed stable body fat or loss of body fat

Whole brain analyses comparing adolescents who gained body fat and those who showed stable body fat on change in regional GM did not result in significant group $\times$ time interactions.

Analyses comparing adolescents who gained body fat versus those who lost body fat on change in regional GM showed a significant group $\times$ time interaction in the right putamen (MNI coordinates: $x = 36$, $y = -16$, $z = -9$, $p_{FWE} = 0.003$) with adolescents who gained body fat showing a decrease in putamen GM versus those who lost body fat (Fig 2A; Table 2). There were no additional group $\times$ time interactions at the more liberal threshold of $p_{FDR} < 0.05$.

Changes in regional WM between body fat gain versus body fat stable and body fat loss groups

Whole brain analyses comparing adolescents who gained body fat and those who showed stable body fat on change in regional WM did not result in significant group $\times$ time interactions at $p < 0.001$, $p_{FWE} < 0.05$. However, at the more liberal statistical threshold of $p_{FDR} < 0.05$, we found an interaction in the right subgenual anterior cingulate cortex (ACC; MNI coordinates: $x = 5$, $y = 30$, $z = -6$; $p_{FDR} = 0.04$; Table 2): adolescents who gained body fat showed an increase in WM versus those who showed stable body fat.

Analyses comparing adolescents who gained body fat versus those who lost body fat on change in regional WM showed a significant group $\times$ time interaction in the right dorsal and subgenual ACC ($p_{FWE} = 0.002$) with adolescents who gained body fat showing an increase in WM relative to those who showed body fat loss (Fig 2B; Table 2).

Discussion

Adolescents who gained body fat showed a significant decrease in putamen GM volume compared to those who showed body fat loss over follow-up. The putamen responds to a variety of rewarding stimuli, including palatable energy-dense food.²⁹ The observed reduction in putamen GM volume extends the findings of previous cross-sectional VBM data^{10, 30, 31} and appears to dovetail with evidence that individuals with obesity versus those within a healthy weight range show reduced striatal activation in response to palatable energy-dense food receipt.³² The associations between body fat gain and decreases in putamen GM volume may be mediated by inflammatory markers^{14, 15} and increases in fasting plasma leptin, a hormone that is produced in proportion to the amount of body fat.³³ However, this effect did not occur when comparing adolescents who gained body fat with those that

showed body fat stability, suggesting that this effect could have been driven by a combination of both body fat gain and body fat loss.

Adolescents who gained body fat also showed greater increases in WM volume in the dorsal and subgenual ACC compared to those who lost body fat and in the subgenual ACC compared to those who showed stable body fat. Although the latter finding was only significant with the slightly more liberal threshold of $pFDR < 0.05$, the fact that the increase in ACC WM volume occurred when comparing adolescents who gained body fat with both control groups suggests that these findings are robust. The dorsal ACC has been implicated in a diversity of functions, including cognitive control.³⁴ The subgenual ACC has been implicated in emotional processing.³⁵ The significant increase in ACC WM volume is seemingly inconsistent with the findings that elderly with obesity versus those within a healthy weight range show less ACC WM volume.³⁶ However, a possible explanation for these mixed findings is that participants in the current study were younger and all in a healthy weight range at baseline while the sample in the previous study consisted of elderly adults varying in weight from healthy weight to obese. Age-related declines²² might have contributed to the associations between adiposity and lower ACC WM volume in the previous study. Further, increases in WM are often the result of a healthy expansion of myelin. Given that most of the adolescents who gained body fat remained in a healthy weight range, it is possible that the increases in regional ACC WM reflect increased myelination. Alternatively, increases in regional WM volume have been associated with the accumulation of fat in the central myelin resulting in denser myelination and with lower WM integrity.³⁷ Therefore, another possible explanation is that the observed increases in WM reflect accumulation of excess white matter. Finally, WM volume is dependent on the contrast in signal intensity between GM and WM.^{38, 39} Given that adiposity has an effect on signal contrast,⁴⁰ the inconsistencies in findings of our study and the previous study might be due to the differences in effect of adiposity on signal intensity in WM. Future studies are needed to understand the observed associations between body fat gain and WM volume changes. For example, future work should include Diffusion Tensor Imaging (DTI) to examine causes of increases in regional WM volume as a consequence of body fat gain as this technique makes it possible to test whether increases in white matter volume reflects increased myelination or accumulation of excess white matter.

We did not find support for the hypothesis that global and regional GM and WM volume abnormalities increase risk for future body fat gain. In a previous study,²⁰ we found that trend-level reduced GM volumes in inhibitory control regions predicted weight gain over 1-year follow-up in individuals varying in weight from healthy weight to obese. Given that in the current study we observed several significant changes in GM and WM density that were associated with body fat gain, but had greater sensitivity to detecting a relation between baseline GM and WM volumes and future body fat gain, this pattern of findings suggests that differences in GM and WM volume between humans with obesity versus those within a healthy weight range are more likely to be a result of obesity or habitual intake of energy-dense foods, than an initial vulnerability factor.

This study has several limitations. First, although the repeated-measures design increases sensitivity because each subject serves as their own control, the moderately overall small

sample size and the small cell sizes of the body fat stable and loss groups may have limited sensitivity. However, the fact that we did observe significant volumetric changes confirmed that we had sufficient power to detect effects. Nonetheless, future studies with larger samples are needed to replicate the present findings. Second, only 5% of the subjects who gained body fat transitioned from healthy weight to obesity at follow-up. Therefore, we did not have power to detect the effects of obesity onset on changes in GM and WM volume. Future studies should examine obesity-onset related brain changes. Third, future studies are needed to study the effects of obesity duration and weight fluctuation on brain volume changes in adolescents. Fourth, although we found associations between body fat gain and changes in brain volume, our study was not designed to investigate the pathophysiological mechanisms underlying these changes. Further work is needed to understand the underlying cellular changes (e.g., changes in synaptic interconnections) that might occur.

In sum, results suggest that initial body fat gain in healthy weight adolescents is associated with changes in regional GM and WM volume over long-term follow-up but that baseline GM/WM volumes do not predict future body fat gain. To our knowledge, this is the first prospective study to test these associations over a long-term follow-up in adolescents. Our findings represent a novel contribution in that our sample consisted of adolescents who had a healthy weight at baseline, which reduces the possibility that age-related declines and previous obesity contributed to GM/WM abnormalities.

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Study importance

- Individuals with obesity versus those within a healthy weight range show differences in brain volume
- It is unclear whether these differences reflect risk factors or are secondary to weight gain
- This is the first prospective study to tests whether structural differences in adolescents are a precursor for future body fat gain or the result of an increase in adipose tissue over a long-term follow-up

Figure 1.
Participant flow chart.

Figure 2.

A) Decreases in regional GM volume in right putamen (MNI coordinates: = 36, -16, -9, $Z = 4.04$, $p_{FWE} = 0.003$, $k = 930$) and **B)** increases in regional WM volume in right ACC (MNI coordinates: 11, 33, 7, $Z = 4.01$, $p_{FWE} = 0.001$, $k = 817$) in the body fat gain versus body fat loss group ($n = 14$) over follow-up.

Table 1

Characterization of Body Fat Gain (n = 34), Body Fat Stable (n = 12), and Body Fat Loss (n = 14) Groups

	Body fat gain (n = 34)	Body fat stable (n = 12)	Body fat loss (n = 14)		
	<i>Percentage (n)</i>	<i>Percentage (n)</i>	<i>Percentage (n)</i>	<i>F(2,57)</i>	<i>p</i>
Males	44.1% (14)	58.3% (7)	35.7% (5)	1.16	.32
Parental overweight/ Parental obesity	76.5% (26)	58.3% (7)	92.9% (13)	2.20	.12
2-year follow-up scan	64.7% (22)	75% (9)	64.3% (9)	0.25	.80
3-year follow-up scan	35.3% (12)	25% (3)	35.7% (5)		
Baseline	<i>Mean ± SD</i>	<i>Mean ± SD</i>	<i>Mean ± SD</i>		
Global GM volume	517.5 ± 62.0	554.7 ± 39.1	498.2 ± 79.3	2.69	.08
Global WM volume	462.0 ± 62.2	499.8 ± 48.1	462.2 ± 64.9	1.88	.16
Age	15.3 ± 1.1	15.4 ± 1.2	14.9 ± 0.5	1.15	.32
Parental education	4.4 ± 1.0	4.3 ± 1.0	3.8 ± 1.3	1.78	.18
Body fat percentage	19.8 ± 6.8	17.4 ± 9.2	22.8 ± 5.4	1.88	.16
BMI	21.5 ± 2.0	20.6 ± 1.9	20.3 ± 1.4	2.74	.07
zBMI	0.3 ± 0.5	-0.1 ± 0.9	0.1 ± 0.5	2.00	.14
Alcohol use	0.3 ± 0.5	0.1 ± 0.3	0.3 ± 0.6	0.84	.44
Cigarette use	0.3 ± 0.2	0.0 ± 0.0	0.1 ± 0.3	0.51	.60
Drug use	0.0 ± 0.1	0.0 ± 0.1	0.1 ± 0.3	0.77	.47
Follow-up	<i>Mean ± SD</i>	<i>Mean ± SD</i>	<i>Mean ± SD</i>		
Global GM volume	538.9 ± 95.8	551.3 ± 40.8	517.3 ± 69.2	0.59	.56
Global WM volume	471.7 ± 73.0	506.2 ± 59.6	489.1 ± 73.2	1.13	.33
Age	17.8 ± 1.4	17.7 ± 1.3	17.1 ± 0.7	1.80	.18
Body fat percentage	26.6 ± 9.8	17.6 ± 9.5	17.5 ± 6.7	7.23	.00
BMI	24.6 ± 4.0	21.5 ± 2.1	20.5 ± 1.5	9.23	.00
zBMI	0.6 ± 0.8	-0.2 ± 1.1	0.0 ± 0.7	5.15	.01
Alcohol use	1.0 ± 1.4	0.8 ± 1.2	0.8 ± 0.8	0.20	.82
Cigarette use	0.3 ± 0.9	0.2 ± 0.4	0.8 ± 1.8	1.20	.31
Drug use	0.2 ± 0.3	0.2 ± 0.5	0.3 ± 0.4	0.65	.53

Table 2

Group-by-Time Interactions in regional GM and WM volumes between Body Fat Gain (n = 34) versus Body Fat Stable (n = 12) Groups and between Body Fat Gain versus Body Fat loss (n = 14) Groups

	<i>k</i>	Z-value	MNI coordinates	pFWE corrected p-value	pFDR corrected p-value
GM volumes					
<i>Body fat gain > body fat loss</i>					
<u>Baseline > Follow-up:</u>					
Putamen	930	4.04	36, -16, -9	0.003	0.004
Putamen		3.92	30, -9, -12		
Putamen		3.88	24, 2, -5		
WM volumes					
<i>Body fat gain > body fat stable</i>					
<u>Follow-up>baseline:</u>					
ACC	206	3.53	5, 30, -6	0.20	0.04
ACC		3.45	0, 32, 1		
<i>Body fat gain > body fat loss</i>					
<u>Follow-up>baseline:</u>					
ACC	817	4.01	11, 33, 7	0.001	0.002
ACC		3.98	5, 24, 18		
ACC		3.67	9, 29, -8		