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Post-treatment weight change in oral cavity and oropharyngeal squamous cell carcinoma

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Abstract

Purpose—Incidence of head and neck cancer (HNC) due to HPV infection has been increasing. Treatment regimens have evolved. These changes might result in alterations of assumed treatment related weight changes for HNC patients. We aimed to compare the trajectory of pre- to post-treatment weight changes of oropharyngeal squamous cell carcinoma (OPSCC) versus oral cavity squamous cell carcinoma (OCSCC) patients, and to compare weight changes between patients with primary surgery ± adjuvant therapy to patients with primary radiation and/or chemotherapy.

Methods—This retrospective cohort study examined adult OPSCC and OCSCC patients with initial definitive treatment at the University of Pennsylvania from 1/1/2009 to 12/31/2010. Patient demographics, medical history, treatments, and pre-and post-treatment body weight data were collected from electronic medical records. Mixed effects modeling was performed.

Results—Among 354 patients who met the inclusion criteria, 290 (82%) survivors were available for inclusion by 24-month follow-up. More than 70% OPSCC and OCSCC patients were overweight or obese at all pre-and post-treatment time-points. The average weight among OPSCC patients was 6.63 kg higher than OCSCC patients at all time-points (mean=6.63, 95% CI, 2.46-10.79, $p=0.002$). After adjusting for potential confounders, patients with primary surgery had significantly more weight gain from pre-treatment to 12-18 month post-treatment follow-up as

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compared to patients with primary radiation and/or chemotherapy (adjusted mean=4.01, 95% CI, 0.16-7.87, $p=0.041$).

Conclusion—Overweight and obesity may be a new challenge in OPSCC and OCSCC patient care. Further study is needed to evaluate whether exercise and nutritional interventions can improve their survivorship.

Keywords

Weight; Oral cavity squamous cell carcinoma; Oropharyngeal squamous cell carcinoma; Surgery; Radiation; Chemotherapy

Introduction

Head and neck squamous cell carcinoma (HNSCC) is traditionally thought of as being a disease associated with alcohol and tobacco, and weight loss is common in this population. More than 50% of patients with advanced HNSCC were reported to have significant weight loss and possible cachexia back in the 1990s.[1, 2] However, as smoking becomes less prevalent, the profile of the patients diagnosed with head and neck cancer is shifting. For example, the number of HNSCC related to Human Papillomavirus (HPV) infection has risen dramatically over the past few decades.[3] Molecular and epidemiologic data associate HPV primarily with cancers that arise in the oropharynx, including base of tongue and tonsils.[4] It has been reported that population-level incidence of HPV-positive oropharyngeal SCC increased by 225% from 1988 to 2004, while the incidence for HPV-negative SCC declined by 50%.[5] Chaturvedi et al classified oral cavity SCC (OCSCC) as potentially HPV unrelated SCC and oropharyngeal SCC (OPSCC) as potentially HPV related SCC. This research found that patients with OPSCC were significantly younger, more likely to be male, white, and had significantly better survival as compared to patients with OCSCC.[3] However, it remains unclear whether baseline weight and post-treatment weight change differs between patients with OPSCC and OCSCC. Moreover, treatment options for OPSCC have also evolved over the past few decades. The treatment protocols for OPSCC have changed from traditional open surgery that splits the jaw[6] to concurrent chemoradiation with significant acute and late toxicity,[7, 8] as well as to newly developed minimally invasive Trans-Oral Robotic Surgery (TORS) that reduces the toxic side effects of chemoradiation.[9-11] Although studies have shown that HNSCC patients exhibit a significant weight loss during and then immediately following radiation and/or chemotherapy,[12-17] few studies have evaluated the post-treatment weight change patterns in HNSCC patients who underwent surgery. With the increase of HPV-related HNSCC patient population and the evolution of treatment regimens, it is important to understand whether the baseline weight distribution and post-treatment weight change in this new OPSCC population are different from the potentially HPV unrelated OCSCC population, so that appropriate survivorship programs can be designed to improve patient outcomes and quality of life. Thus, our goal was to compare the baseline weight and post-treatment weight change patterns of OPSCC patients to OCSCC patients, as well as to compare post-treatment weight change between patients with primary surgery with or without adjuvant therapy to patients with primary radiation and/or chemotherapy.

Methods

We conducted a retrospective cohort study. This study was approved by the institutional review board of the University of Pennsylvania. Because this was a retrospective review of patient medical records, the Institutional Review Board (IRB) approved a waiver of the consent process. No patients were re-contacted for this study.

Study population

Adult OCSCC and OPSCC patients who were at least 18 years old at the time of cancer diagnosis and who underwent initial head and neck cancer treatment at the University of Pennsylvania Health System from January 1, 2009 to December 31, 2010 were identified via the Penn Cancer Registry. Patients included in the analysis had complete pre-treatment information, weight at 0-6 month post-treatment follow-up, 1 post-treatment follow-up with body weight recorded and were at least 18-24 months post-treatment by the time of data collection. The patients were followed up until January 16, 2013. We collected patient age, sex, race, cancer sites, histology, American Joint Committee on Cancer (AJCC) stage, and cancer treatment from the Penn Cancer Registry, and patient smoking history, height, weight and comorbidities from the Penn Data Store. The Penn Cancer Registry is an information system that contains a systematic collection of demographics, diagnostic findings, medical history, cancer information, cancer therapy, follow-up and patient outcome data for all persons that are diagnosed and/or treated for a diagnosis of a malignant or neoplastic disease (cancer) within the Hospital of the University of Pennsylvania, the Pennsylvania Hospital, and the Penn Presbyterian Medical Center. The Penn Data Store is Penn Medicine's Clinical Data Warehouse, which integrates clinical data elements to support medical research and patient care initiatives through the health system. The data are integrated from the outpatient electronic medical record and a number of inpatient databases throughout the Hospital of the University of Pennsylvania, the Pennsylvania Hospital, and the Penn Presbyterian Medical Center.

Exposures

The primary exposures of interests of the study were: 1) treatment types and 2) cancer site based on HPV-relatedness. First, we grouped the OCSCC and OPSCC patients into those with primary surgery with or without adjuvant therapy and those with primary radiation and/or chemotherapy. Second, it has been proven that HPV related HNSCC primarily arises in the oropharynx, including the lingual and palatine tonsils and base of tongue.[3, 4] Thus, based on the literature,[3] OPSCC was defined as including the base of tongue, tonsil, oropharynx, pharynx, soft palate, vallecula and Waldeyer's ring; and OCSCC was defined as including cancers of the tongue, gum, floor of mouth, hard and junction palate, alveolar and other/unspecified parts of the mouth. We excluded all other HNSCC. All these anatomic sites were well classified and listed in the Penn Cancer Registry.

Covariates

Patient's demographics, height, weight, smoking status, cancer site, AJCC stage, treatment types and co-morbidities were collected from the medical record at baseline. Baseline body mass index (BMI) was calculated as (weight in kg)/(height in meters squared). Being

underweight was defined as BMI<18.5, normal was BMI 18.5-24.9, overweight was BMI 25.0-29.9, and obesity was BMI ≥30. The Charlson comorbidity index was calculated based on the baseline co-morbidities.[18]

Outcomes

The primary outcome was defined as the average body weight change from pre-treatment to post-treatment follow-up for all the body weights collected from each individual. Pre- and post-treatment was defined by the beginning of the first treatment, (e.g., surgery, radiation or chemotherapy). Body weight was collected during routine clinical visits, and patients with different treatments had different follow up frequencies. Thus, we calculated the average body weight for all the body weights collected during each of the following time period: 1) from diagnosis to the beginning of the first treatment, which can be surgery, radiation or chemotherapy, i.e. pre-treatment; 2) from the beginning of the first treatment to 6 month after the beginning of the first treatment, i.e. 0-6 month post-treatment; 3) from 6 months after the beginning of the first treatment to 12 months after the beginning of the first treatment, i.e. 6-12 month post-treatment; 4) from 12 months after the beginning of the first treatment to 18 months after the beginning of the first treatment, i.e. 12-18 month post-treatment; and 5) from 18 months after the beginning of the first treatment to 24 months after the beginning of the first treatment, i.e. 18-24 month post-treatment.

Statistical analysis

First, we summarized the characteristics of the adult OCSCC and OPSCC patients enrolled. Second, we graphed mean body weights to detect the trajectory of weight change from pre-treatment to post-treatment 0-6, 6-12, 12-18 and 18-24 month follow-up. Linear mixed-effects regression model was developed with: 1) time as a fixed effect categorical variable, 2) treatment types and cancer site as the exposure of interests, and 3) the interaction between time and treatment in order to allow the effects of treatment types and cancer site to vary over time. We then conducted likelihood ratio tests to test whether the effects of treatment types and cancer site on post-treatment weight change were time-varying. If the likelihood ratio tests was >0.05 , it means the effects of treatment types or cancer site on post-treatment weight change were not time-varying, and thus the non-significant interaction between time and treatment types, or time and cancer site would be dropped from the final model. Other covariates were evaluated as potential confounders in the final model, and those with $p<0.05$ were retained in the final model. The model also included random effects for patient to account for the correlation between repeated measures per patient. Mixed effects models can provide an unbiased estimate when follow-up data was missing at random. If a weight was missing at a certain time point, the rest of the weights from the same patient can still be included in the model. Adjusted β coefficients and 95% confidence intervals (CIs) were calculated for each variable in the final model. The adjusted β coefficient can be interpreted as the adjusted mean weight loss (negative β coefficient) or weight gain (positive β coefficient) between patients with and without the condition while holding the other variables in the model constant. A value of $p < 0.05$ was considered statistically significant. Statistical analyses were conducted using STATA 12 (Stata Corp, College Station, Texas).

Results

Among the 2096 patients with cancer in the head and neck region identified using the Penn Cancer Registry from 2009 and 2010, we identified 354 OCSCC and OPSCC patients who met our inclusion criteria. Of these, 64 patients (18%) did not survive the designated 24-month follow-up period. Figure 1 depicts the weight change over time by survival. For patients who did not survive to 24 month follow up, their mean weights at all time points prior to death were included in the dash line. We can see from the graph that the mean weight gain in survivors (solid line) started after 6 months post-treatment, while for patients who did not survive by 24 months follow up, the mean weight gain started after 12 months post-treatment in patients who survived at least that long. Characteristics of the 290 survivors included in our study are summarized in Table 1, and only these survivors were included in the rest of the analyses. The mean age was 60.0 ± 12.0 years old; 214 patients (74%) were male; 249 (86%) were white; 74 (25%) were obese; 185 (64%) had OPSCC; 149 (57%) had AJCC stage IV disease; 212 (73%) had surgery, 180 (62%) had radiation and 141 (49%) had chemotherapy.

Table 2 shows the mean weight and BMI change over time. The mean weight loss from pre-treatment to 0-6 month post-treatment was 5 kg (6% of baseline mean body weight), and the mean weight gain from the 0-6 month follow-up period to the 18-24 month follow-up period was 2 kg (2% of baseline mean body weight). However, when we looked at the mean BMI change over time, the mean BMIs at pre- and post-treatment follow up time intervals were all in the overweight range. We further compared the mean weight and BMI change over time by cancer site as shown on Table 2. OPSCC patients had heavier weights than OCSCC patients at all pre- and post-treatment time points, and OPSCC patients had higher BMI than OCSCC patients at pre-treatment and 18-24 month post-treatment time-points.

Figure 2 shows the percentage of patients in each BMI category at pre- and post-treatment follow up. More than 70% of the patients were overweight or obese at both the pre-treatment and all the post-treatment follow up, despite of the weight loss immediately following treatment. Because the data was collected from routine clinical practice, not all patients had follow-up or follow-up weights measured. The follow up rate was 87% at 6-12 month (n=253), 79% at 12-18 month (n=229), and 64% at 18-24 month follow-up (n=185). Comparison of patient baseline characteristics between those with and without weights measured at 18-24 month follow-up, revealed no significant differences for variables included in table 1.

In order to explore the factors associated with patients weight change, we graphed the patients long-term weight change by treatment types (Figure 3A), and cancer site (Figure 3B). It appears from the graphs that patients with primary surgery $\pm$ adjuvant therapy and patients with OPSCC had more post-treatment weight gain during follow up than patients with primary radiation and/or chemotherapy and patients with OCSCC, respectively.

In order to quantify these differences, we performed linear mixed effect models. The mean weights of OPSCC patients were 6.63 kg significantly higher than OCSCC patients at all time-points (mean=6.63, 95% CI, 2.46-10.79, $p=0.002$). The likelihood ratio tests for

interactions with time were significant for treatment types, but not for cancer site, suggesting the effect of cancer site on post-treatment weight change did not vary over time, so we adjusted it as a potential confounder in the final statistical model. Table 3 shows the results from the linear mixed effects model. We calculated both the unadjusted and adjusted β coefficients with 95% CIs to compare how much the β coefficients changed after adjustment. After adjusting for potential confounders in the final model, compared to patients with primary radiation and/or chemotherapy, patients with primary surgery $\pm$ adjuvant therapy had 1.82 kg significantly more weight gain from baseline to 12-18 month follow up (adjusted β coefficient=1.82, 95%CI, 0.07, 3.57, $p=0.041$), and marginally significant 1.84 kg more weight gain from baseline to 18-24 month follow up (adjusted mean=1.84, 95%CI, -0.05, 3.73, $p=0.057$); and both effects were significant in the unadjusted analysis.

Discussion

Describing the long-term weight change in all AJCC stages of OCSCC and OPSCC patients who underwent different treatment regimen is an important step to understand the long-term post-treatment recovery challenges. This understanding may allow for the design of pertinent energy balance programs with appropriate physical activity and nutritional interventions to improve the survivorship in this understudied and growing HNSCC population. The complexity of nutritional issues among head and neck survival has been reported, but warrants further investigation. Contrary to what might be concluded based on the well-recognized treatment related weight loss in the HNSCC patients,[15, 19, 20] we found that more than 70% of OCSCC and OPSCC patients were overweight or obese across all pre-treatment and post-treatment time points. To our knowledge, this has not been reported in the literature. Our study also showed that the OPSCC had higher mean weights at all pre-treatment and post-treatment time points as compared to OCSCC. With the increasing of HPV positive OPSCC,[5] overweight and obesity may become a new challenge in improving HNSCC survivorship. Overweight and obesity affect the majority of adults in the United States, and it has been reported that the prevalence of obesity was 35.5% among adult men and 35.8% among adult women in 2009-2010.[21] Our study showed that the prevalence of overweight and obese in OCSCC and OPSCC patients is similar as the general American population, and underweight is not a common problem in this new OPSCC and OCSCC population. The high prevalence of baseline obesity in our OPSCC and OCSCC patients suggests that future nutrition interventions should help these patients maintain a healthy post-treatment BMI, instead of gaining weight back alone.

Although OPSCC patients were more likely to have post-treatment weight gain during the 2-year follow-up as compared to the OCSCC patients, the mean weight changes from baseline to 18-24 month follow up were not statistically different between the 2 groups in our mixed effects model. This may be because OPSCC patients had significant higher baseline mean weights than OCSCC patients, and thus, when we calculated the weight changes from baseline, the effects became non-significant. However, given the post-treatment mean weight gain from 0-6 to 18-24 month follow-up after initial rapid post-treatment weight loss in OPSCC patients, further studies are needed to evaluate whether 6 months after the beginning of treatment is a good time to implement exercise and nutrition programs to improve cancer

survivorship, and whether OPSCC patients are more likely to benefit from these survivorship programs, because OPSCC is often diagnosed at younger ages and has improved survival outcome as compared to OCSCC.[3]

Our study also found that there was a 1.82 kg higher weight gain from baseline to 12-18 month follow-up in OCSCC and OPSCC patients with primary surgery with or without adjuvant therapy as compared to those with primary radiation and/or chemotherapy after adjusting for potential confounders. At our medical center, both OCSCC and OPSCC patients are evaluated for surgery including TORS. Surgery is recommended to all patients who are surgical candidates, along with the options of radiation with or without chemotherapy based on the clinical practice guidelines.[22] Although we cannot rule out the possibility that the difference in post-treatment weight gain between treatment types was due to confounding by indication, patients in both treatment groups had similar mean pre-treatment weights, and we adjusted for potential confounders in our final mixed effects model to identify the independent effect of treatment on post-treatment weight change. In addition, the slight post-radiation and/or chemotherapy weight gain in our study is consistent with other studies in the literature.[13, 23, 24] Most of the published studies only recorded weight change during radiation and/or chemotherapy or 6 months post-treatment.[12, 14, 25] A few studies have suggested that advanced head and neck patients with significant weight loss after radiation and/or chemotherapy are able to maintain their weight after 6-month follow-up,[13, 23, 24] but the data about post-treatment weight change in surgical HNSCC patients was scant. Our study filled this knowledge gap and showed that OCSCC and OPSCC patients with primary surgery with or without adjuvant therapy had steady post-treatment weight gain during 2-year follow up after the initial weight loss following treatment.

There are several limitations in our study. First, not every patient had all post-treatment follow-up visits with body weight recorded. We compared patient characteristics and there were no differences between patients with and without weights at 18-24 month follow-up. The mixed-effects regression model we used can provide an unbiased estimate when the patients with missing follow-up data had similar characteristics as patients without missing follow-up data. Second, we did not have test results for HPV status, such as immunohistochemistry for p16, to further evaluate whether the baseline weight and post-treatment weight change were different between p16 positive OPSCC and p16 negative OPSCC. Third, we could not establish a standard eligibility criterion for the insertion of gastrostomy feeding tubes via retrospective chart review to determine their effects on long-term weight change in patients who need them. Newman et al analyzed patients with advanced head and neck cancer treated with a targeted chemoradiation protocol, and showed that patients with normal or nearly normal swallowing function without tube feeding were more likely to regain weight at the 12-18 month follow-up compared to patients with tube feeding.[23] Since we examined patients with all stages of head and neck cancer, if we simply compare patients with and without gastrostomy feeding tubes, the benefit of gastrostomy feeding tubes in advanced cancer may be biased towards the null. Fourth, we did not have high quality alcohol use data from the medical records to adjust it in the analysis. Fifth, BMI is not sensitive to change, and thus it was not used for the longitudinal analysis. Sixth, patients with advanced T stage cancers may have more treatment related

weight loss, and these patients were more likely to have chemoradiation than surgery. However, we did not have the complete TNM stage to rule out the possibility that the significantly larger weight gain in the primary surgery group was due to less advanced T stage cancers in the group as compared to the chemoradiation group. Seventh, although there was a statistically significant difference in weight gain between patients with surgery and those with chemoradiation, the clinical significance of this less than 2kg difference is unclear. Eighth, due to the retrospective nature of the study, we did not have body composition data to further evaluate whether post-treatment weight gain is associated with fat gain or lean mass gain. Finally, there may be other factors associated with long-term weight gain that were not collected or adjusted in the model.

In conclusion, despite weight loss immediately after treatment, OCSCC and OPSCC survivors generally gain weight during 2-year follow-up, and over 70% of these patients were overweight or obese at all pre-treatment and post-treatment time points. OPSCC patients seem to have higher mean weights at all pre-treatment and post-treatment time points as compared to OCSCC patients, although this difference was not statistically significant in the adjusted model. In addition, patients with primary surgery with or without adjuvant therapy had significantly more weight gain from baseline to 12-18 month follow up as compared to patients with primary radiation and/or chemotherapy, but due to lack of complete TNM stages in our study and the fact that chemoradiation is often used for advanced T stage cancer, we cannot rule out the possibility that the difference in weight loss was confounded by tumor size. The high prevalence of baseline obesity in OPSCC and OCSCC patients found in our study provides evidence to guide future nutrition interventions in this new HNSCC population to maintain a healthy BMI, instead of gaining weight back alone. Future studies are needed to evaluate the body composition of these patients, as well as to determine whether changes of body fat and lean mass are associated with different HNSCC treatment outcomes and qualities of survivorship. In addition, pilot randomized clinical trials are needed to determine whether the delivery of energy balance programs, such as physical activity and nutritional interventions, can increase lean body mass and decrease fat and improve survivorship, especially in OPSCC patients and patients with primary surgery. At many cancer centers, there are already programs in place to address the complex nutritional issues in this population. Those interventions may need to expand focus to include obesity prevention and treatment, given shifts in the HNC survivorship population.

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Figure 1.
Weight change over time stratified by survival (N=354)

Figure 2.

Percentage of patients in each BMI category at pre and post treatment follow-up

Figure 3.

(A) Weight change over time among survivors stratified by treatment type. (B) Weight change over time among survivors stratified by cancer site (N=290)

Table 1

Characteristics of the oral cavity and oropharyngeal squamous cell carcinoma survivors (N=290)

Characteristics	Mean $\pm$ SD or N (%)
Age (mean $\pm$ SD)	60.0 $\pm$ 12.0
Sex	
Male	214 (74%)
Female	76 (26%)
Race	
Caucasian	249 (86%)
African American	27 (9%)
Other	14 (5%)
Smoking History	
Never	56 (19%)
Former	211 (73%)
Current	23 (8%)
BMI Category	
<18.5	7 (2%)
18.5-24.9	106 (36%)
25.0-29.9	103 (36%)
30.0	74 (25%)
Cancer Site	
Oral cavity	105 (36%)
Oropharynx	185 (64%)
AJCC Stage	
I	48 (18%)
II	21 (8%)
III	43 (16%)
IV	149 (57%)
Treatment	
Surgery	212 (73%)
Chemotherapy	141 (49%)
Radiation	180 (62%)
Charleston comorbidity index	
0	162 (59%)
1	64 (23%)
2	52 (18%)

Table 2

Weight and BMI by cancer site at pre-treatment and follow-up visits

	Pre-Treatment	0-6 Month	6-12 Month	12-18 Month	18-24 Month
(mean $\pm$ SD)	(n=290)	(n=290)	(n=253)	(n=229)	(n=185)
Weight (kg)					
Overall	84 $\pm$ 21	79 $\pm$ 19	79 $\pm$ 18	80 $\pm$ 19	81 $\pm$ 20
OCSCC	77 $\pm$ 20	74 $\pm$ 19	75 $\pm$ 18	76 $\pm$ 19	75 $\pm$ 17
OPSCC	86 $\pm$ 22	80 $\pm$ 19	80 $\pm$ 19	83 $\pm$ 19	86 $\pm$ 21
BMI (kg/m²)					
Overall	28.0 $\pm$ 6.7	26.3 $\pm$ 5.9	26.6 $\pm$ 5.8	27.0 $\pm$ 6.4	28.7 $\pm$ 7.7
OCSCC	27.1 $\pm$ 6.4	26.2 $\pm$ 6.0	26.9 $\pm$ 6.1	26.9 $\pm$ 7.0	27.8 $\pm$ 6.2
OPSCC	28.5 $\pm$ 6.8	26.3 $\pm$ 5.8	26.4 $\pm$ 5.6	27.0 $\pm$ 6.0	29.3 $\pm$ 8.5

OCSCC: Oral cavity squamous cell carcinoma; OPSCC: oropharyngeal squamous cell carcinoma

Table 3

Unadjusted and adjusted coefficients and 95% CIs from linear mixed effects regression models (N=290)

Difference of weight change	Unadjusted			Adjusted		
	Coef.	95% CI	p-value	Coef.	95% CI	p-value
Treatment types (allow the effects to vary over time)						
<i>Radiation and/or chemotherapy</i>		Reference			Reference	
<i>Surgery± adjuvant therapy</i>						
Baseline to 0-6 month follow-up	1.93	0.38, 3.49	0.740	1.14	-0.39, 2.67	0.146
Baseline to 6-12 month follow-up	1.94	0.27, 3.62	0.023	0.75	-0.91, 2.40	0.376
Baseline to 12-18 month follow-up	2.47	0.71, 4.24	0.006	1.82	0.07, 3.57	0.041
Baseline to 18-24 month follow-up	2.79	0.89, 4.68	0.004	1.84	-0.05, 3.73	0.057
Other covariates (the effects were averaged across follow-up time)						
Sex						
<i>Female</i>		Reference			Reference	
<i>Male</i>	13.02	8.85, 17.20	<0.001	12.10	8.25, 15.95	<0.001
Cancer site						
<i>Oral cavity</i>		Reference			Reference	
<i>Oropharynx</i>	6.63	2.46, 10.79	0.002	3.28	-0.86, 7.43	0.120
Stage						
<i>I</i>		Reference			Reference	
<i>II</i>	-7.32	-15.63, 0.99	0.084	-7.86	-14.42, -1.29	0.019
<i>III</i>	-1.62	-8.88, 5.63	0.661	-3.88	-10.21, 2.45	0.230
<i>IV</i>	3.63	-1.82, 5.63	0.192	-0.76	-5.88, 4.37	0.772
Baseline BMI						
<i>Normal</i>		Reference			Reference	
<i>Overweight</i>	5.92	-1.83, 9.09	<0.001	5.69	4.56, 6.83	<0.001
<i>Obese</i>	13.00	4.83, 17.01	<0.001	12.87	11.25, 14.49	<0.001
<i>Underweight</i>	-7.58	-11.44, -14.57	<0.001	-7.80	-10.99, -4.61	<0.001