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Better postdiagnosis diet quality is associated with less cancer-related fatigue in breast cancer survivors

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Abstract

Purpose—A comprehensive understanding of the role of modifiable health behaviors in effective management of cancer-related fatigue is needed. Among breast cancer survivors, we examined how postdiagnosis diet quality, independently and jointly with physical activity, is related to fatigue, and the potential mediating role of inflammation.

Methods—770 women diagnosed with stage 0-IIIa breast cancer in the Health, Eating, Activity, and Lifestyle study completed food frequency and physical activity questionnaires 30-months postdiagnosis. We scored diet quality using the Healthy Eating Index-2010 (HEI-2010). Serum concentrations of C-reactive protein (CRP) were measured in fasting 30-ml blood samples. Multidimensional fatigue was measured 41-months postdiagnosis using the 22-item revised Piper Fatigue Scale. In multivariate linear models, we determined whether fatigue was associated HEI-2010 quartiles (Q1-Q4), and a variable jointly reflecting HEI quartiles and physical activity levels.

Results—Survivors with better quality diets (Q4 vs. Q1) had lower total fatigue (4.1 vs. 4.8, p-contrast=0.003) and subscale scores (behavioral severity: 3.4 vs. 4.2, p-contrast=0.003; affective meaning: 3.9 vs. 4.8, p-contrast=0.007; sensory: 4.4 vs. 5.2, p-contrast=0.003; cognitive: 4.6 vs. 5.0, p-contrast=0.046). Least squares estimates of fatigue were similar in models including CRP. Compared to survivors with poor quality diets and no physical activity, survivors with better

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Conflicts of interest

The authors have no conflicts of interest to report.

quality diets and meeting physical activity recommendations had significantly lower behavioral severity (3.2 vs. 4.7, p -contrast=0.002) and sensory (3.8 vs. 4.8, p -contrast=0.006) fatigue scores.

Conclusion—In this large breast cancer survivor cohort, postdiagnosis diet quality was inversely and independently associated with fatigue.

Implications—Future interventions designed to improve multiple energy balance behaviors can provide insight into their associations with fatigue.

Keywords

diet; fatigue; breast cancer survivor; health behavior; inflammation

Introduction

In the United States (US), over 2.5 million women are living with a personal history of breast cancer, and this population is growing [1, 2]. It is estimated that an additional 232,670 US women will be newly diagnosed with invasive breast cancer in 2014 [3]. The most frequent, distressing, and undertreated cancer symptom reported by cancer survivors is fatigue [4]. Fatigue has a complex, subjective, multi-etiological, and multidimensional nature [5], and even five years after diagnosis, it continues to burden many breast cancer survivors [6]. Persistent fatigue following cancer treatment has been associated with depression, pain, sleep disturbance, and poor quality of life [7, 8] especially diminished ability to participate in daily life roles and social activities [9]. In order to develop better interventions for breast cancer survivors, it is important to understand the role of modifiable lifestyle factors that may impact fatigue and the mechanisms by which they may do so.

Inflammation has been identified as a potential driver of fatigue in post-treatment breast cancer survivors [10], and lower levels of chronic inflammation have been associated with better postdiagnosis diet quality [11] and higher postdiagnosis physical activity [12]. In our past research in the Health Eating Activity and Lifestyle (HEAL) study of breast cancer prognosis, two key postdiagnosis health behaviors, having higher physical activity [12] and better diet quality [11] were associated with lower chronic inflammation. Whereas postdiagnosis physical activity can decrease fatigue and its impact [13–16], and this association has been observed in the HEAL study [17, 9], few studies have examined the association of diet and fatigue, and only one has explored inflammation as a potential mechanism [18].

In HEAL participants, higher intake of ω -6 relative to ω -3 polyunsaturated fatty acids was associated with greater chronic inflammation and greater odds of fatigue [18]. In small cross-sectional studies of ~40 cancer survivors, individual components of the diet such as a lower intake of calories from fat [19] and a higher intake of fiber [19], whole grains [20], and vegetables [20] have been related to less fatigue. Given that foods are not consumed in isolation and because individual dietary components may have potentially synergistic or antagonistic effects [21] on both inflammation and fatigue, studies on overall diet quality, inflammation, and fatigue are needed to advance dietary recommendations for cancer survivors.

To address this gap in the literature, we investigated relationships between diet quality, independently and combined with recreational moderate-vigorous physical activity (MVPA), and cancer-related fatigue among a large cohort of women with early-stage breast cancer. We also explored the role of inflammation as a potential mediator of the diet quality-fatigue relationship.

Methods

The HEAL study is a multi-ethnic prospective cohort study that has enrolled 1,183 women with first primary breast cancer drawn from Surveillance, Epidemiology, and End Results (SEER) population-based cancer registries in New Mexico, Los Angeles County, and Western Washington. The study was designed to determine whether lifestyle, hormones, or other exposures affect breast cancer prognosis. Details of the study have been published [22–24]. Written informed consent was obtained from all study participants at each assessment, and the study was approved by the institutional review board at each participating center, in accord with assurances filed with and approved by the US Department of Health and Human Services.

Data for the current study derive from three self-report assessments of the HEAL cohort, at 6 months, 30-months, and 41-months postdiagnosis. Of the 1,183 women in the HEAL Study who completed the baseline assessment approximately 6 months after diagnosis, 808 women completed both the 41-month assessment of fatigue and the 30-month assessment of diet. We excluded women with recurrences or new primary diagnosis between baseline and the 41-month assessment ($n=34$), because active treatment may affect measurement of diet and fatigue. We further excluded women missing data on physical activity ($n=3$) or comorbidities ($n=1$). The final sample included 770 women.

Data Collection

Diet—To measure diet at the 30-month assessment, we used a 122-item self-administered food-frequency questionnaire developed and validated for the Women's Health Initiative (WHI) [25], adapted from the Health Habits and Lifestyle Questionnaire [26]. The WHI-FFQ was designed to capture foods relevant for multi-ethnic and geographically diverse population groups; it has been shown to produce reliable ($r_{\text{all nutrients}}=0.76$) and comparable estimates to 8 days of dietary intake from 24-hour dietary recalls and 4-day food records ($r=0.37, 0.62, 0.41, 0.36$, with energy, percent energy from fat, carbohydrate and protein) [25]. New Mexico participants reported their usual dietary intake for the previous year, whereas participants at the other two centers reported usual intake for the previous month. The nutrient database used to analyze the WHI-FFQ is derived from the Nutrition Data Systems for Research (NDS-R®, version 2005, University of Minnesota, Minneapolis, MN) [27, 28]. NDS-R® provides nutrient information for >140 nutrients and compounds including energy, saturated fat, and sodium.

To measure diet quality, we used the Healthy Eating Index-2010 (HEI-2010) [29] which was created by the U.S. Department of Agriculture and the National Cancer Institute and aligns with the 2010 U.S. Dietary Guidelines for Americans [30]. We calculated HEI-2010 scores

using diet data in units of MyPyramid equivalents by establishing a customized link [31] between NDS-R and the MyPyramid Equivalents Database version 2 (MPED) [32].

The HEI-2010 has been previously described [29] and scores 12 dietary components, using an energy-adjusted density approach to set standards (e.g., per 1000 calories or as a percent of calories). Six components—total fruit; whole fruit; total vegetables; greens and beans; total proteins; and seafood and plant proteins are worth 0–5 points. Five components—whole grains; dairy; fatty acids; refined grains, and sodium—are worth 0–10 points; and one component—empty calories (calories from solid fats and added sugars that add no nutrients)—is worth 0–20 points. The latter three components are reverse-scored. For each participant, we scored each component and calculated a total score (100 possible points). We classified HEI-2010 scores into quartiles to best separate those with “better quality” diets (Q4) and “poor quality” diets (Q1).

Fatigue—At approximately 41-months postdiagnosis, fatigue was measured using the Piper Fatigue Scale [33] which has been shown to be a reliable and valid measure of subjective fatigue.²² The 22 items were coded into four scales, each with a range of 1–10): 1) *behavioral severity*: the observable behavioral changes in activities of daily living resulting from fatigue; 2) *affective meaning*: the emotional meaning attributed to fatigue; 3) *sensory*: the physical symptoms of fatigue; and 4) *cognitive/mood*: the mental and emotional symptoms related to fatigue. We also calculated the average of four dimension scores as an estimate of overall fatigue. In HEAL the response time frame was changed from the original Piper Fatigue Scale from “past week” to “past month” to minimize the effect of acute situational events and to enhance our assessment of each survivor’s general state of fatigue. The scale’s four factor structure was confirmed for the HEAL cohort (Cronbach’s alphas for the subscales ranged from 0.92–0.97).

Physical activity—At the 30-month assessment, data were collected on aerobic recreational MVPA in the last year using the Modifiable Activity Questionnaire developed by Kriska [34]. We classified each activity according to its corresponding metabolic equivalent of task (MET) value in the “Compendium of Physical Activities.”[35] For all activities with MET values ≥ 3 , we summed the products of activity MET values and hours spent in each activity to arrive at MET-hrs/week spent in MVPA for each participant

C-reactive protein—A 30 mL fasting blood sample was collected from participants at the 30-month assessment. Blood was processed within 3 hours of collection and serum was stored in 1.8 mL tubes at -70° to -80° C until analysis. CRP was measured by latex-enhanced nephelometry using a high-sensitivity assay [36] on the Behring Nephelometer II analyzer (Dade Behring Diagnostics, Deerfield, IL) at the University of Washington Medical Center (Seattle, WA). The lowest detection limits for CRP was 0.2 mg/L, and the inter-assay coefficients of variation were 5%–9% [12]

Additional risk factors—Height was measured 6-months postdiagnosis and weight at 30-months postdiagnosis. BMI was calculated as weight (kg)/ height (m^2) and was categorized into the World Health Organization’s (WHO) BMI categories (underweight <18.5 ; normal: 18.5 to <25 ; overweight: 25 to <30 ; obese: 30 to <40 ; very obese: 40 kg/ m^2). For

participants' breast cancer diagnoses, detailed information on treatment and surgical procedures was obtained from cancer registry, physician, and hospital records. Co-morbid conditions were abstracted from the medical record at the hospital location of the most definitive therapy, and we calculated the Charlson Comorbidity Score [37]. Calculation of the Charlson Comorbidity Score has been previously described [38]; the condition of any cancer was excluded because all HEAL women had breast cancer. At baseline (6-months postdiagnosis), information on age, race, and education was collected. At 30-months postdiagnosis, participants reported current use of anti-depressants.

Statistical Analysis

We calculated means, standard deviations, and frequencies of demographic, clinical, and health behavior characteristics of our study population by quartiles of HEI-2010 scores.

In multivariate linear regression models, we regressed fatigue on HEI-2010 quartiles and a combined variable jointly reflecting HEI-2010 quartiles and MET-h/week MVPA (0; >0 and <9; 9). We calculated adjusted least square means for all fatigue scores. We controlled for confounders that changed the magnitude of the beta coefficients by at least 10% or were important to include for comparison with relevant published literature. To test whether any one component was responsible for the overall association of diet quality with fatigue, we ran models for each of the 12 HEI-2010 component scores, adjusting for the residual HEI-2010 score (HEI-2010 total score-HEI-2010 component score). Because diet quality may affect fatigue via its effects on chronic inflammation, we also investigated how controlling for CRP in the model affected estimates.

All statistical analyses were planned a-priori and conducted using SAS (version 9.3, Cary, NC), and used a two-sided $\alpha=0.05$. When examining the association of two health behaviors (diet and physical activity) with fatigue and its dimensions, we used a significance level of $0.05/4=0.013$, because we made four comparisons of fatigue levels among survivors with different diet and physical activity levels.

Results

As shown in Table 1, compared to survivors with lower HEI-2010 scores, survivors with higher HEI-2010 score were older, engaged in more MVPA, consumed fewer calories, had lower BMIs, and were more likely to be non-Hispanic White.

Survivors with better vs. poor quality diets (Q4 vs. Q1) had lower total fatigue (4.1 vs. 4.8, $p\text{-contrast}=0.003$) and subscale scores (behavioral severity: 3.4 vs. 4.2, $p\text{-contrast}=0.003$; affective meaning: 3.9 vs. 4.8, $p\text{-contrast}=0.007$; sensory: 4.4 vs. 5.2, $p\text{-contrast}=0.003$; cognitive: 4.6 vs. 5.0, $p\text{-contrast}=0.022$), after adjustment for age, caloric intake, alcohol, physical activity, BMI, treatment, race/ethnicity, antidepressant use and comorbidities (Table 2).

When we investigated how each HEI-2010 component was related to total fatigue, adjusting for residual HEI-2010 score, only one component- empty calories- was statistically significantly related ($\beta_{Q4:Q1}=-0.59$, $p=0.025$), but the magnitude of this association was not

as strong as that of HEI-2010 score ($\beta_{Q4:Q1}=-1.36$, $p=0.002$) (data not shown). When we controlled for CRP among the 677 women with biomarker data, CRP acted as a confounder, but least squares estimates of fatigue scores were of similar magnitude, and all except cognitive fatigue were still statistically significantly different (data not shown).

As shown in Table 3, compared with survivors with poor quality diets and no physical activity, survivors with better quality diets and recommended amount of physical activity had lower behavioral severity (3.2 vs. 4.7, $p\text{-contrast}=0.002$) and sensory (3.8 vs. 4.8, $p\text{-contrast}=0.006$) scores. The patterns of differences in total, affective meaning, and cognitive fatigue did not differ statistically. Further, the association of diet quality with fatigue appeared to be most prominent among women who were engaging in some postdiagnosis MVPA but who were still not meeting guidelines ($n=325$). In this group of women engaging in “some” activity, higher HEI-2010 scores were associated with lower total fatigue (4.1 vs. 4.8, $p\text{-contrast}=0.003$), behavioral severity (3.6 vs. 4.6, $p\text{-contrast}=0.006$), affective meaning (4.1 vs. 5.1, $p\text{-contrast}=0.008$) and sensory (4.8 vs. 5.7, $p\text{-contrast}=0.006$) subscale scores (Table 3).

Discussion

To our knowledge, this is the first study to examine the association of overall diet quality and fatigue among breast cancer survivors. Across dimensions of fatigue, having a better vs. poor quality diet was associated with 8–20% lower fatigue scores. Furthermore, only one component, empty calories, was significantly associated with fatigue, when the residual HEI-2010 score was taken into account. However, this association was weaker in magnitude than that of the overall HEI-2010 score and fatigue, indicating that no one component was responsible for the overall diet quality and fatigue association and suggesting that dietary components can have synergistic effects.

Given that least squares estimates of fatigue were of similar magnitude when we controlled for CRP as a confounder, our results suggest that inflammation may only be a partial mediator of the diet quality-fatigue relationship. It is biologically plausible that diet quality may affect fatigue through multiple biological mechanisms in addition to inflammation, including other metabolic pathways as well as direct effects on fatigue. More work is needed to fully understand the biologic basis of the association between diet quality and fatigue

This study provides support that the combination of having a diet consistent with the US Dietary Guidelines and engaging in the recommended amount of physical activity may be beneficial for fatigued breast cancer survivors, especially in relation to the behavioral severity and sensory aspects of fatigue. Of particular interest, the impact of having a better vs. poor quality diet seemed strongest among survivors engaging in some postdiagnosis physical activity (0.1–8.9 MET-h/wk) but who were not meeting guidelines, but this association was not significant among survivors meeting guidelines or those who were inactive. A few explanations are possible.

Among those who are already meeting physical activity guidelines, upon visual comparison, the levels of fatigue appeared lower and the range of fatigue scores between those with

better and poor quality diets was smaller than the range among those engaging in some MVPA; thus, the independent effect of diet in this group might be smaller because there is less room to make a difference. However, a better diet quality combined with no activity did not have a significant association with fatigue scores, so it is possible that although diet quality may be independently related to fatigue, the impact of a better diet quality on fatigue is stronger in the presence of some physical activity. Our results suggest that for breast cancer survivors affected by cancer-related fatigue, the adoption of a better quality diet might have the most impact in the presence of some recreational physical activity. Future studies with multiple measurements of diet, physical activity, and fatigue in post-treatment breast cancer survivors will be valuable in advancing the science in this area, which will ultimately inform guidelines for patient care.

This study builds on our previous work demonstrating that 1) a higher intake of omega6/omega-3 PUFAs was linked to greater inflammation and fatigue [18]; 2) a better diet quality was linked to better mental and physical functioning [24], and higher physical activity was linked with less fatigue [17, 9]. Further, our work adds to the evidence base on benefits of a diet consistent with US national dietary guidance, such as improved survival [39, 31] and lower levels of chronic inflammation [11].

Key strengths of this study include our large, diverse group of survivors recruited through population-based cancer registries, as well as the use of the multidimensional HEI-2010, which is able to capture the potentially synergistic nature of multiple important dietary components [29] and allowed us to distinguish survivors with better- versus poor-quality diets (Q4 vs. Q1) and the multidimensional, validated Piper Fatigue Scale. Our detailed assessment of physical activity also allowed us to categorize women by their postdiagnosis recreational physical activity level [40]. For covariate purposes, we had high-quality data on treatment and comorbidities abstracted from physician and hospital records and objectively measured weight and height of participants. The women in our study were representative of American women seen in routine clinical practice versus tertiary cancer hospitals. Last, we were able to explore the influence of CRP (one of the major biomarkers associated with fatigue) on this association.

Study limitations include measurement error inherent to the FFQ [41]. Additionally, although we had detailed data allowing for careful control of the major confounders and to show that associations were unlikely to be artifacts of reverse causation, given the observational nature of this study, it remains possible that those who chose a better quality diet had less fatigue for reasons that we did not examine. Although, on average, the diet assessment preceded the fatigue assessment by 11 months, we are not able to determine causality or rule out reverse causality, examine how change in diet quality is associated with fatigue, or determine how associations might vary by season, due to the lack of multiple measurements and observational nature of our study. Lastly, of the 192 of 770 survivors in our study with better quality diets, only 18 were inactive after diagnosis, so we did not have sufficient statistical power to test whether the addition of MVPA to a better quality diet was associated with less fatigue than just having a better quality diet.

In this large breast cancer survivor cohort, postdiagnosis diet quality was inversely and independently associated with all dimensions of fatigue. The Dietary Guidelines for Americans aim to provide a dietary pattern that, if followed, could reduce the risk of major chronic disease. This study provides new evidence on how adherence to both US diet and physical activity guidelines is associated with lower behavioral severity and sensory aspects of cancer-related fatigue. Future interventions designed to improve several energy balance behaviors, that include multiple, longitudinal measurements of these behaviors and of fatigue, can provide insight into their effects on fatigue and inform patient care guidelines.

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Table 1:

Demographic, Clinical, and Lifestyle Characteristics of Women in the Health, Eating, Activity, and Lifestyle Study By Quartiles of HEI-2010 scores

	Poor Quality Diets			Mixed Quality Diets			Better Quality Diets			<i>p</i> -value
	Healthy Eating Index-2010 Score Quartile 1	No.	%	Healthy Eating Index-2010 Score Quartile 2	No.	%	Healthy Eating Index-2010 Score Quartile 3	No.	%	
Number of participants		192			193			192		
Age										
Mean (SE)	55.3 (0.7)			57.8 (0.7)			57.7 (0.7)		59.3 (0.7)	0.0001
Race/Ethnicity										<0.0001
White, non-Hispanic	42	81		55	107		68	134	70	
Hispanic	17	32		16	31		8	10	5	
Black, non-Hispanic	38	73		25	49		20	43	6	
American Indian, Asian, Other	3	6		3	7		3	5	1	
Menopausal Status										0.076
Premenopausal	40	76		34	66		35	55	29	
Postmenopausal	53	102		59	114		61	131	68	
Unknown	7	14		7	13		4	6	3	
Treatment										0.068
Surgery only	32	62		30	58		31	59	31	
+ radiation	38	74		38	73		37	68	35	
+ chemotherapy	11	21		12	24		4	23	12	
+ radiation and Chemotherapy	18	35		20	38		29	42	22	
Antidepressant use										0.531
Yes	18	35		14	27		18	27	14	
No	82	157		86	166		82	165	86	
Charlston comorbidity score										0.479
Mean (SE)	0.1 (0.03)			0.2 (0.03)			0.2 (0.03)		0.1 (0.03)	
HEI-2010 score (100 points possible)										
Mean (SE)	49 (0.4)			62 (0.2)			69 (0.2)		78 (0.3)	<0.0001
Energy/day (kcal)										
Mean (SE)	1739 (85)			1435 (46)			1378 (40)		1247 (35)	<0.0001

	Poor Quality Diets			Mixed Quality Diets			Better Quality Diets			<i>I</i> <i>p</i> -value
	Healthy Eating Index-2010 Score Quartile 1	No.	%	Healthy Eating Index-2010 Score Quartile 2	No.	%	Healthy Eating Index-2010 Score Quartile 3	No.	%	
Alcohol (g)										
Mean (SE)			3.6 (0.7)			4.4 (0.7)			3.9 (0.5)	0.561
MET-hours/week of postdiagnosis recreational physical activity										
0			28			17			9	
0.1–8.9			46			45			38	
9+			26			38			53	
BMI										
Mean (SE)			29.5 (0.5)			29.0 (0.5)			27.2 (0.4)	<0.0001

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p-value for chi-square test for categorical variables or trend test for continuous variables

Table 2.

Multivariate adjusted least square means (SE) of fatigue scores by HEI-2010 quartiles in the HEAL Cohort[/]

	Fatigue	Fatigue-Behavioral Severity	Fatigue-Affective Meaning	Fatigue-Sensory	Fatigue-Cognitive
HEI-2010 Q1	4.8 (0.3)	4.2 (0.3)	4.8 (0.4)	5.2 (0.3)	5.0 (0.3)
HEI-2010 Q2	4.4 (0.3)	3.8 (0.3)	4.4 (0.4)	4.9 (0.3)	4.6 (0.3)
HEI-2010 Q3	4.3 (0.3)	3.6 (0.3)	4.2 (0.4)	4.6 (0.3)	4.7 (0.3)
HEI-2010 Q4	4.1 (0.3)	3.4 (0.3)	3.9(0.4)	4.4 (0.3)	4.6 (0.3)
<i>p</i> -contrast Q4:Q1	0.003	0.003	0.007	0.003	0.046

[/] Adjusted for age, calories, moderate-vigorous physical activity, body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30–34.9, 35+, missing), treatment, race/ethnicity (non-Hispanic white, Hispanic, black, other), antidepressant use, Charlson comorbidity score, alcohol

Table 3.

Multivariate adjusted [/] least square means (SE) of fatigue scores by HEL-2010 quartiles in the HEAL cohort

		Better quality diet (q4)	Mixed Quality diet (q2 and 3)	Poor quality diet (q1)	p-contrast better vs. poor diet quality	p-contrast better quality diet + MVPA meeting guidelines vs. neither
Fatigue	MVPA meets or exceeds guidelines	3.8 (0.3)	4.4 (0.3)	4.5 (0.4)	0.908	
	Some MVPA	4.3 (0.4)	4.4 (0.3)	5.2 (0.4)	0.003 *	
	No MVPA	4.6 (0.6)	4.5 (0.4)	5.0 (0.4)	0.348	0.014
Behavioral severity	MVPA meets or exceeds guidelines	3.2 (0.4)	3.7 (0.4)	3.8 (0.5)	0.440	
	Some MVPA	3.6 (0.4)	3.8 (0.4)	4.6 (0.4)	0.006 *	
	No MVPA	3.7 (0.7)	4.0 (0.4)	4.7 (0.5)	0.607	0.002 *
Affective meaning	MVPA meets or exceeds guidelines	3.8 (0.5)	4.4 (0.4)	4.6 (0.5)	0.720	
	Some MVPA	4.1 (0.5)	4.3 (0.4)	5.1 (0.5)	0.008 *	
	No MVPA	4.3 (0.8)	4.4 (0.5)	4.8 (0.5)	0.308	0.084
Sensory	MVPA meets or exceeds guidelines	4.0 (0.4)	4.6 (0.3)	4.7 (0.5)	0.719	
	Some MVPA	4.8 (0.4)	4.8 (0.3)	5.7 (0.4)	0.006 *	
	No MVPA	5.0 (0.6)	4.9 (0.4)	5.3 (0.5)	0.375	0.006 *
Cognitive	MVPA meets or exceeds guidelines	4.4 (0.3)	4.8 (0.3)	5.0 (0.4)	0.151	
	Some MVPA	4.6 (0.3)	4.5 (0.3)	5.2 (0.3)	0.019	
	No MVPA	5.3 (0.5)	4.8 (0.4)	5.0 (0.4)	0.357	0.316

[/] Adjusted for age, calories, body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30–34.9, 35+ kg/m², missing), treatment, race/ethnicity (non-Hispanic white, Hispanic, black, other), antidepressant use, Charlston comorbidity score, alcohol

* Significant at P<0.013