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In Vivo β-Adrenergic Receptor Responsiveness: Ethnic Differences in the Relationship with Symptoms of Depression and Fatigue

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Abstract

Background—Depressive symptoms and fatigue frequently overlap in clinical samples and the general population. The link of depressive symptoms and fatigue with increased risk of cardiovascular disease has been partly explained by shared biological mechanisms including sympathetic overactivity. Prolonged sympathetic overactivity downregulates the responsiveness of the β-adrenergic receptor (β-AR), a receptor that mediates several end-organ sympathetic responses.

Purpose—The authors studied whether depression and fatigue are related to reduced β-AR responsiveness within the human body (in vivo) in an ethnically diverse sample of African and Caucasian Americans.

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Methods—The chronotropic$_{25}$ dose (CD_{25}) was used to determine in vivo β-AR responsiveness in 93 healthy participants. Psychometric measures included the Center of Epidemiological Studies-Depression Scale and the Multidimensional Fatigue Symptom Inventory.

Results—Hierarchical regression analyses (adjusted for age, gender, body mass index, blood pressure, smoking, and ethnicity) revealed that mental fatigue was significantly related to reduced β-AR responsiveness (i.e., higher CD_{25} values) in the whole sample. Moderation analyses indicated significant ethnicity × depression/fatigue interactions. Depressive symptoms, total fatigue, emotional fatigue, mental fatigue, and physical fatigue were related to reduced β-AR responsiveness in Caucasian American but not in African Americans.

Conclusions—Our findings suggest that symptoms of depression and fatigue are related to decreased in vivo β-AR responsiveness in Caucasian Americans. The lack of this association in African Americans highlights the importance for considering ethnicity as a potential moderator in research focusing on associations between psychological variables and cardiovascular function.

Keywords

β-adrenergic receptor; African Americans; Caucasian Americans; Depression; Fatigue

Introduction

Depressive symptoms and fatigue frequently overlap in clinical samples, primary care patients, and the general population [1-5]. Although severe manifestations of these symptoms lead to clinical diagnoses (e.g., major depression and chronic fatigue syndrome), they are everyday phenomena and continuously distributed within the population [6-8]. The substantial overlap in these symptoms has been partly explained by common precipitants (e.g., prolonged psychological distress or illness). In addition, shared interacting biological mechanisms have been suggested to underlie depressive symptoms and fatigue, such as the cytokine-induced sickness response, neuroendocrine alterations, and autonomic nervous system dysregulation characterized by sympathetic overactivity and decreased parasympathetic tone [3,9-14].

Symptoms of depression and fatigue may have predictive value for cardiovascular disease (CVD) morbidity and mortality. On the other side, these symptoms increase in patients with cardiovascular events [15-23]. This relationship may be partly based on sympathetic nervous system (SNS) overactivity. SNS overactivity is considered a risk factor for CVD [24-26] and both depression and fatigue have been related to indices of sympathetic predominance, such as increased heart rate, reduced heart rate variability, or higher levels of norepinephrine in both clinical and nonclinical samples [13,27-33]. Curiously, a wide range of research indicates ethnic differences in depression/fatigue, cardiovascular functioning, and relationships between these variables [34-40].

Several studies on the associations between psychological features and SNS functioning have used more global or indirect indicators of SNS functioning inferred from hemodynamic/electrophysiological assessment or analyzed catecholamines in blood or urine samples. A promising approach to study SNS functioning involves measuring

responsiveness of the β-adrenergic receptor (β-AR) because this receptor mediates a wide range of catecholamine-induced end-organ sympathetic responses, such as vasodilatation, heart rate increase, and immune functions [41]. As sympathetic stimulation downregulates β-AR responsiveness, reduced β-AR responsiveness is considered an indicator of prolonged SNS overactivity and a physiological reflection of chronic stress [41,42].

β-AR responsiveness can be measured in vitro by assessing isoproterenol-induced cyclic adenosine monophosphate production in human peripheral blood mononuclear cells (PBMC) or in vivo by assessing the chronotropic$_{25}$ dose (CD_{25}). CD_{25} refers to the dose of isoproterenol that is necessary to increase heart rate by 25 beats per minute (bpm). High CD_{25} values indicate low receptor responsiveness [41,42]. Although both measures are interrelated [43], CD_{25} may be more valid than in vitro assessment because the neurohormonal environment of a PBMC cell receptor may differ from a postsynaptic cell receptor within an organ like the heart [41]. Studies using the CD_{25} method have found relationships of β-AR function with several stress-related states, such as type A behavior pattern, subjective social status, anxiety, and hostility [36,44-49]. Moreover, CD_{25} values have been reported to be higher in African Americans than in Caucasian Americans [36].

Although associations of depression and fatigue with sympathetic functioning have frequently been studied, less research has been done on the relationship of these symptoms with β-AR function. We examined whether symptoms of depression and fatigue are related to in vivo β-AR responsiveness in African Americans and Caucasian Americans. Considering the relevance of ethnicity to depressive symptoms, fatigue and cardiovascular functioning, we also focused on potential differences in depression/fatigue-CD_{25} relationships between African Americans and Caucasian Americans. It was hypothesized that symptoms of depression and fatigue may be related to reduced β-AR responsiveness (i.e., higher CD_{25} values).

Methods

Participants

Participants were unmedicated volunteers recruited from the local San Diego, California area. Recruitment occurred through local papers, online advertisements, community flyers, and word of mouth. As part of a larger study on the health of African Americans and Caucasian Americans, the study group for isoproterenol testing was roughly evenly divided between Caucasian Americans (20 women and 30 men) and African Americans (19 women and 24 men). Age ranged between 19 and 51 years (see Table 1 for sample characteristics). The study was approved by the University of California, San Diego Institutional Review Board, and all subjects gave both written and verbal consent. Exclusionary criteria were: current diagnoses of a clinical illness other than hypertension, history of psychosis or sleep disorder, current alcohol or drug abuse, moderate or heavy smoking (>10 cigarettes/day), increased caffeine intake (>600 mg/day), hormonal medication (including the contraceptive pill or hormone replacement therapy), blood pressure≥170/105 mmHg, severe obesity (class II obesity, body mass index (BMI)≥35), and any medication use. Two subjects with antihypertensive medication were accepted for participation and enrolled after a 3-week drug washout period supervised by the study physician.

In Vivo Testing of β-Adrenergic Receptor Responsiveness

The CD_{25} isoproterenol stimulation test was used to assess *in vivo* β-AR function. Low CD_{25} values indicate high β-AR sensitivity [41,42]. Heart rates were assessed by electrocardiogram. After a 30-min rest and assessment of basal blood pressure and heart rate, an intravenous low-dose bolus (0.1 μg) of isoproterenol was administered to ensure that no adverse reactions to the drug occurred. Following the 0.1-μg bolus, participants were infused with incremental bolus doses (0.25, 0.5, 1.0, 2.0, and 4.0 μg) until an increase of heart rate by 25 bpm above basal heart rate was observed or until the 4.0-μg bolus was completed. The maximum heart rate after each bolus was calculated as the mean of the three shortest *R–R* intervals [42]. There was a 5-min time interval between bolus injections. Standardized calculation of CD_{25} values was performed as described previously [42].

Depression, Fatigue, and Covariate Measures

Participants completed psychological questionnaires the following day. The severity of depressive symptoms was assessed with the 20-item Center of Epidemiological Studies—Depression (CES-D) scale [50]. The CES-D primarily addresses cognitive/affective features of depression. The range of scores is 0–60 with higher scores indicating more severe depressive symptoms. The mean score for patients with a diagnosis of clinical depression is 39, whereas scores higher than 15 suggested an increased risk of depression. High internal consistency as measured by Cronbach's alpha has been reported for the general population, clinical samples and across several ethnicities [50,51].

Fatigue was assessed with the 30-item short form of the Multidimensional Fatigue Symptom Inventory (MFSI), which was designed to assess multidimensional aspects of fatigue. The scale has six subscales (total fatigue, general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor). Although originally designed for cancer patients, the MFSI has also been shown to be valid and highly reliable in both clinical samples and the general population [52,53]. The range of scores is 0–24 for each subscale and −24 to 96 for the total fatigue score, which is calculated by subtracting the vigor score from the sum of the four fatigue scales. In a population-based sample of African Americans, mean scores (standard deviations) were 4.02 (4.44) for physical fatigue, 4.02 (4.44) for physical fatigue, 4.23 (4.12) for mental fatigue, 4.02 (4.58) for emotional fatigue, 7.28 (5.90) for general fatigue, and 13.75 (5.55) for vigor [53]. Higher scores indicate more fatigue.

Demographic and health-related variables, such as age, gender, BMI, smoking status (smoker/nonsmoker), and blood pressure may be related to β-AR function [36,41,44] and may also be confounded with symptoms of depression and fatigue [5,54-56]. Thus, these variables were considered as control variables in adjusted regression models.

Statistical Analyses

Statistical analyses were conducted with SPSS version 17.0 for Windows (Chicago, SPSS, Inc.). CD_{25} values above 3 standard deviations were considered to be outliers and treated as missing values. Screening for multivariate outliers was performed by calculating studentized deleted residuals and centered leverage values [57]. The rate of missing values for CD_{25} was 3 %. With respect to psychosocial measures and covariates, the rate of missing values was

<7 % for each variable. Correlational analyses were conducted for the total sample and separately for African and Caucasian Americans to examine associations between study variables. Hierarchical regression analyses were conducted to examine if symptoms of depression and fatigue explained variance in CD_{25} (after taking into account aforementioned covariates) and whether ethnicity moderated this relationship between depression/fatigue and CD_{25}. Hierarchical regression analyses were separately conducted for each psychometric scale. Covariates were entered on step 1, ethnicity on step 2, centered depression/fatigue scores on step 3, and centered depression/fatigue score by ethnicity interaction terms on step 4. Interactive effects were further examined by a subsequent series of ethnicity stratified regressions. These separate regressions consisted of the covariates entered on step 1 and depression/fatigue scores entered on the final step. To increase robustness of results and because not all psychological measures were normally distributed (tested by Kolmogorov–Smirnov tests), *t* tests, correlational analyses, and regression analyses were performed by bootstrapping with 1,000 bootstrap samples and bias-corrected and accelerated (BCa) confidence intervals.

Results

Table 1 shows sample characteristics as well as differences between African and Caucasian Americans. Independent-sample *t* tests indicated that in vivo β-AR sensitivity (CD_{25}), depressive symptoms, and fatigue did not differ by ethnic groups. However, African Americans were significantly older (p <0.001), had higher BMI values (p <0.001) and were more likely to smoke (p <0.05).

Table 2 shows bivariate correlations of study variables with CD_{25} for the whole sample and for each ethnic group. Correlation analyses indicated that individuals with more physical and mental fatigue exhibited higher CD_{25} values (i.e., reduced β-AR sensitivity; p <0.05). Ethnicity stratified analyses indicated differences in depression/fatigue-CD_{25} relationships between African and Caucasian Americans. While β-AR sensitivity was significantly related to depression (p <0.05), total fatigue (p <0.01), physical fatigue (p <0.001), emotional fatigue (p <0.01), and mental fatigue (p <0.01) in Caucasian Americans, no significant relationship between psychometric measures and CD_{25} was observed for African Americans (p>0.1). Between-group comparison of correlation coefficients, which were calculated with Cohen and Cohen's formula 2.8.5 [58] after Fisher's *r*-to-*z* transformation, indicated that correlation coefficients for CD_{25} and all psychopathological measures differed between ethnic groups (p >0.5).

Table 3 illustrates results of adjusted hierarchical regression analyses for the whole sample. After adjusting for covariates (step 1) and ethnicity (step 2), a significant main effect was shown for mental fatigue (p <0.05). Table 3 shows that depression, total fatigue, physical fatigue and emotional fatigue interacted with ethnicity (step 4) to predict CD_{25} (p <0.05). Figure 1 displays these moderating effects.

Follow-up ethnicity stratified regression analyses, adjusted for aforementioned covariates, indicated that CD_{25} was significantly predicted by total fatigue (ΔR^2=0.15, ΔF =7.4, b = 0.03, BCa 95 % CI (0.01, 0.04), β=0.43, p <0.05), physical fatigue (ΔR^2=0.17, ΔF =8.75, b

=0.12, BCa 95 % CI (0.01, 0.22), β =0.43, p <0.01), emotional fatigue (ΔR^2=0.10, ΔF =4.68, b =0.08, BCa 95 % CI (0.001, 0.16), β =0.33, p <0.05), mental fatigue (ΔR^2=0.16, ΔF =8.06, b =0.09, BCa 95 % CI (0.03, 0.15), β =0.43, p <0.01), and tended to be predicted by depression in Caucasian Americans (ΔR^2= 0.07, ΔF =3.52, b =0.03, BCa 95 % CI (−0.002, 0.05), β = 0.28, p <0.1). No significant relationship was observed in African Americans (p >0.1). The results of adjusted ethnicity stratified regressions have to be interpreted with caution given the reduced statistical power.

Discussion

Depressive symptoms, total fatigue, emotional fatigue and physical fatigue were associated with reduced in vivo β-AR responsiveness (i.e., higher CD_{25} values) in Caucasian Americans but not in African Americans. The observed association in Caucasian Americans is consistent with previous studies reporting associations of depression and fatigue with hemodynamic and electrophysiological indicators of sympathetic overactivity or autonomic imbalance in clinical samples and in the general population [13,27-32]. Moreover, reduced in vitro β-AR responsiveness on lymphocytes was found in clinically depressed patients [59]. As both depression and fatigue have been linked to higher levels of norepinephrine [27,32], downregulation of β-AR function may result from chronically increased norepinephrine levels.

The relationship between symptoms of depression/fatigue and reduced β-AR responsiveness may be bi-directional. On one hand, a higher number of depressive symptoms and fatigue may reduce the individuals' ability to cope with stressors, resulting in exaggerated stress responses, prolonged sympathetic overactivity, and thus reduced β-AR responsiveness [41,60,61]. On the other hand, altered β-AR function may contribute to symptoms of fatigue and depression by causing several maladaptive β-AR-mediated sympathetic responses which affect a wide range of neuroendocrinological and immunological pathways [12,13,41,62].

With respect to the observed ethnicity and depression/fatigue interactions, similar findings have been previously reported in other samples and studies. For example, it was shown that depression scores are significantly related to β-AR-mediated responses to mental stress (i.e., increases in heart rate and stroke volume) among Caucasian Americans but not among African Americans [63,64]. Anger suppression and hostility and psychological constructs that are linked to depressive symptoms [65,66], were more strongly related to systolic blood pressure [37] and higher CD_{25} values [36] in Caucasian than in African Americans.

Biopsychosocial and genetic ethnic differences may contribute to different association patterns. For example, several genetic and biochemical aspects of β-AR receptors and of pathways that interact with β-AR functioning differ between both ethnic groups [67-69] and there are large ethnic differences in the hypotensive response to β-AR blocking drugs [70]. Moreover, a number of symptom and disease-related ethnic differences have been reported such as higher risk of hypertension and CVD in African Americans [71,72], increased lifetime prevalence for major depression in Caucasian Americans [73] and ethnic differences in attitudes and beliefs toward psychological problems (e.g., higher stigmatization in African Americans) [74].

Given the small number of studies that have used the CD_{25} method, it is noteworthy that we did not observe a significant difference in β-receptor sensitivity between African and Caucasian Americans. This finding is inconsistent with a previous study that reported increased CD_{25} values in African Americans [36] but consistent with another study showing no significant effect of race on CD_{25} [75].

Limitations should be considered when interpreting our results. Given the cross-sectional design, causality in the relation between symptoms of depression/fatigue and CD_{25} cannot be determined. Moreover, although the observed ethnic differences in smoking status, BMI and age may reflect in part "real-world" differences in the USA, these differences may bias our results although we did control for them in adjusted regression models. Our findings are also limited because we only have observed a population-based sample. Clinical groups (e.g., patients with major depression or cancer) and non-clinical groups may differ in terms of how symptoms of depression and fatigue relate to the β-AR functioning.

To conclude, our findings suggest that symptoms of depression and fatigue are related to decreased in vivo β-AR responsiveness in Caucasian Americans. As decreased in vivo β-AR responsiveness results from prolonged sympathetic overactivity, our findings replicate previous research showing that depressive symptoms and fatigue may be related to increased sympathetic activity. Our findings also extend previous research by showing a direct link between these symptoms and β-AR function within the human body. Considering that altered β-AR sensitivity has been implicated in the pathophysiology of CVD [26] our findings may have clinical implications for understanding the interaction between depression/fatigue and CVD. The lack of this association in African Americans highlights the importance for considering ethnicity as a potential moderator in research focusing on associations between psychological variables and cardiovascular function.

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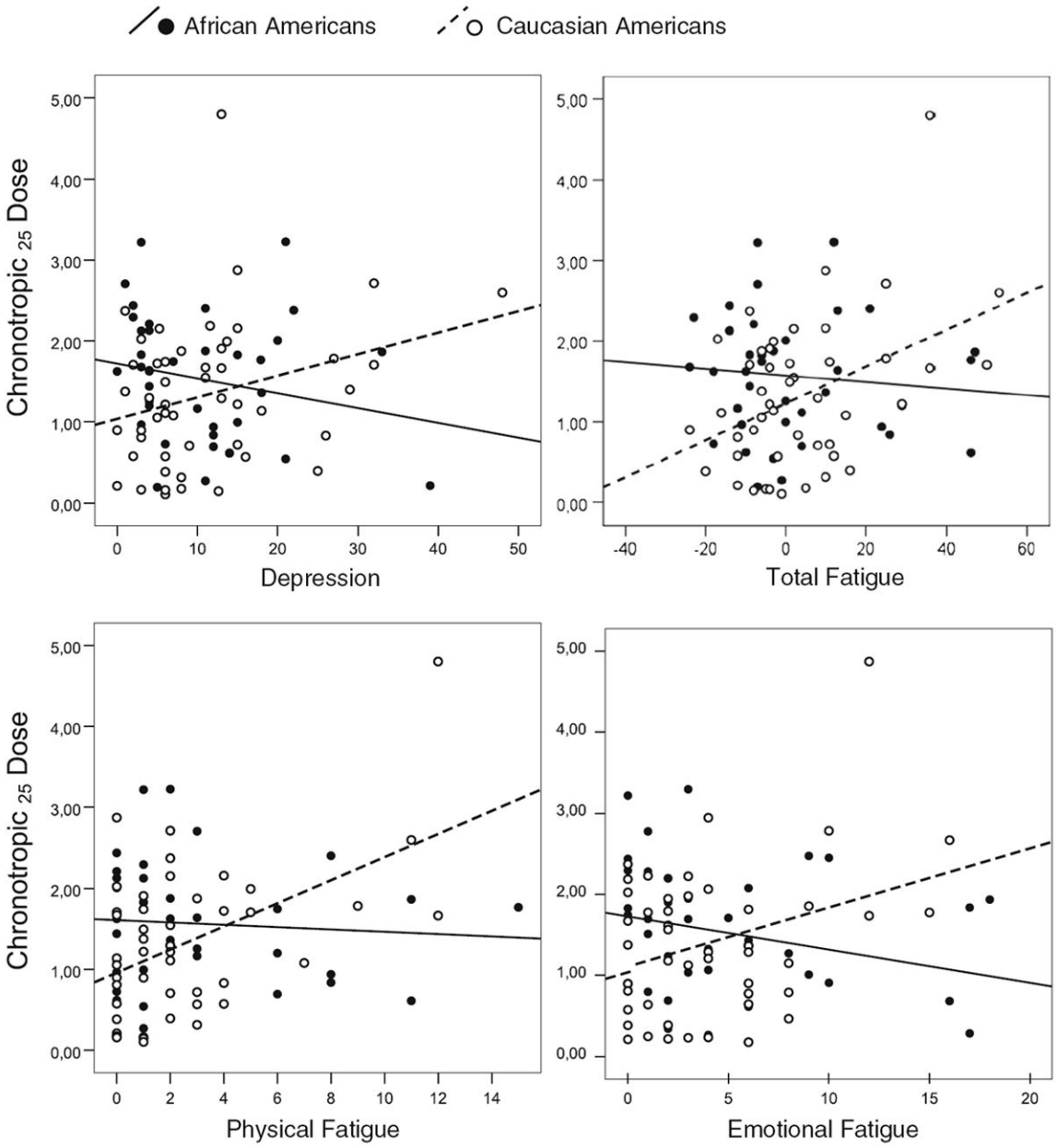

Fig. 1.

Scatter plots illustrating associations between psychometric measures and in vivo β-adrenergic receptor responsiveness (CD_{25}) in terms of significant depression/fatigue × ethnicity interactions (see Table 3 for regression analyses). Higher values of CD_{25} indicate reduced sensitivity of β-adrenergic receptors

Table 1

Descriptive statistics of sample and study variables

	Total (*n* =93)	African Americans (*n* =43)	Caucasian Americans (*n* =50)
Age (years)***	35.1 (9.7)	39.0 (7.8)	31.8 (10.0)
Females (*N* (%))	39 (41.9)	19 (20.4)	20 (21.5)
Body mass index (kg/m^2)***	26.3 (3.6)	27.9 (2.8)	24.9 (3.6)
Mean arterial blood pressure (mmHg)	91.7 (12.4)	94.1 (11.8)	89.5 (12.7)
Current smoker (*N*, (%))*	10 (10.8)	8 (8.6)	2 (2.2)
β-adrenergic receptor responsiveness (CD_{25})	1.4 (0.8)	1.5 (0.8)	1.3 (0.9)
Depression (CES-D)	10.7 (9.3)	10.3 (8.7)	11.0 (9.9)
Total fatigue (MFSI total score)	2.5 (17.6)	1.2 (18.2)	3.6 (17.1)
MFSI general fatigue	5.6 (5.4)	5.1 (5.9)	6.0 (4.9)
MFSI physical fatigue	2.6 (3.4)	2.7 (3.7)	2.5 (3.1)
MFSI emotional fatigue	4.2 (4.5)	4.5 (5.1)	4.0 (4.1)
MFSI mental fatigue	4.6 (4.7)	3.9 (3.9)	5.2 (5.2)
MFSI vigor	14.3 (4.7)	14.4 (5.3)	14.3 (4.3)

Values shown as mean (SD) unless otherwise noted. Differences between ethnic groups were calculated using *t* tests with 1,000 bootstrap samples and Chi-square tests

CES-D Center for Epidemiologic Studies Depression Scale, *CD_{25}* chronotropic$_{25}$ dose, *MFSI* Multidimensional Fatigue Inventory

* p <0.05 (two tailed);

** p <0.01;

*** p <0.001

Table 2

Pearson correlations (metric variables) and point-biserial correlations (dichotomous variables) of study variables with in vivo β-adrenergic receptor sensitivity (chronotropic$_{25}$ dose)

Study variables	Chronotropic$_{25}$ dose			
	Total	African Americans	Caucasian Americans	Significance (*r*) *z*
Depression (CES-D)	.13 (−.11, .32)	−.23 (−.54, .05)	.32 (.01, .59)*	−2.63**
Total fatigue (MFSI total score)	.18 (−.08, .38)	−.18 (−.43, .07)	.47 (.13, .66)**	−3.22**
MFSI general fatigue	.04 (−.18, .25)	−.18 (−.44, .09)	.25 (−.10, .49)	−2.03*
MFSI physical fatigue	.24 (.01, .45)*	−.11 (−.40, .14)	.51 (.13, .76)***	−3.13***
MFSI emotional fatigue	.14 (−.11, .35)	−.19 (−.47, .09)	.42 (.06, .62)**	−2.98**
MFSI mental fatigue	.25 (.003, .44)*	−.02 (−.31, .22)	.42 (.14, .63)**	−2.17*
MFSI vigor	−.06 (−.26, .17)	.19 (−.12, .53)	*−.26 (−.49, .04)*	2.13*
Age	.25 (.02, .43)*	−.13 (−.43, .19)	.34 (−.003, .58)*	−2.25*
Gender	−.26 (−.45, −.01)*	−.22 (−.61, −.05)	−.21 (−.47, .11)	−0.05
Ethnicity	−.15 (−.38, .05)	–	–	–
Body mass index (kg/m^2)	.17 (−.08, .37)	−.10 (−.43, .25)	.25 (−.15, .52)	*−1.65*
Smoking status	−.06 (−.22, .08)	*−.29 (−.53, −.06)*	.11 (−.01, .35)	*−1.90*
Mean arterial blood pressure (mmHg)	−.07 (−.28, .12)	−.18 (−.49, .15)	−.06 (−.39, .16)	−0.57

Correlation analyses based on 1,000 bootstrap samples; 95 % bias corrected and accelerated confidence intervals for correlational coefficients are reported in parentheses. The right column illustrates significant differences between ethnic groups in correlation coefficients calculated with formula 2.8.5 from Cohen and Cohen [58] after Fisher's *r*-to-*z* transformation

CES-D Center for Epidemiologic Studies Depression Scale, MFSI Multidimensional Fatigue Inventory

* $p<0.05$ (two tailed);

** $p<0.01$;

*** $p<0.001$; $p<0.1$ (values set in italics)

Table 3

Summary of adjusted hierarchical regression analyses predicting in vivo β-adrenergic receptor sensitivity (chronotropic$_{25}$ dose) for the whole sample

Model	Step	Predictor	Δ R^2	Δ F	b	β
Initial	1.	Age	0.20	3.96**	0.2 (0.002, 0.04)	0.25*
		Gender			−0.57 (−0.89, −0.25)	−0.34**
		Body mass index			0.03 (−0.03, 0.10)	0.14
		Mean arterial blood pressure			−0.11 (−0.03, 0.002)	−0.16
		Smoking status			−0.34 (−0.80, 0.13)	0.21
	2.	Ethnicity	<0.01	0.07	−0.05 (−0.55, 0.41)	−0.03
Depression (CES-D)	3.	Depression	0.01	1.06	0.10 (−0.01, 0.03)	0.11
	4.	Ethnicity × depression	0.05	4.41*	0.04 (0.01, 0.08)	0.36*
Total fatigue (MFSI total score)	3.	Total fatigue	0.01	*2.89*	0.01 (−0.01, 0.02)	*0.19*
	4.	Ethnicity × total fatigue	0.06	5.54*	0.03 (0.01, 0.05)	0.36*
MFSI general fatigue	3.	General fatigue	0.04	0.32	0.01 (−0.02, 0.05)	0.07
	4.	Ethnicity × general fatigue	0.02	1.68	0.26 (0.02, 0.12)	0.20
MFSI physical fatigue	3.	Physical fatigue	0.04	*3.22*	0.05 (−0.02, 0.11)	*0.17*
	4.	Ethnicity × physical fatigue	0.07	6.29*	0.13 (0.01, 0.22)	0.36*
MFSI emotional fatigue	3.	Emotional fatigue	0.01	0.78	0.02 (−0.03, 0.06)	0.10
	4.	Ethnicity × emotional fatigue	0.05	4.71*	0.09 (0.003, 0.19)	0.31*
MFSI mental fatigue	3.	Mental fatigue	0.05	4.29*	0.04 (0.004, 0.09)	0.22*
	4.	Ethnicity × mental fatigue	0.03	3.07	0.08 (0.001, 0.17)	*0.30*
MFSI vigor	3.	Vigor	<0.01	0.59	−0.02 (−0.06, 0.03)	-0.09
	4.	Ethnicity × vigor	0.01	0.65	−0.02 (−0.12, 0.06)	-0.13

Ninety-five percent bias corrected and accelerated confidence intervals for unstandardized beta (b) are reported in parentheses. Confidence intervals based on 1,000 bootstrap samples

Note.

* p <0.05 (two tailed);

** p <0.01;

*** p <0.001; p <0.1 (values set in italics)