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Genetic Moderators of the Impact of Physical Activity on Depressive Symptoms

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Abstract

Background—Converging evidence suggests that physical activity is an effective intervention for both clinical depression and sub-threshold depressive symptoms; however, findings are not always consistent. These mixed results might reflect heterogeneity in response to physical activity, with some subgroups of individuals responding positively, but not others.

Objectives—1) To examine the impact of genetic variation and sex on changes in depressive symptoms in older adults after a physical activity (PA) intervention, and 2) determine if PA differentially improves particular symptom dimensions of depression.

Design—Randomized controlled trial.

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Setting—Four field centers (Cooper Institute, Stanford University, University of Pittsburgh, and Wake Forest University).

Participants—396 community-dwelling adults aged 70–89 years who participated in the Lifestyle Interventions and Independence for Elders Pilot Study (LIFE-P).

Intervention—12-month PA intervention compared to an education control.

Measurements—Polymorphisms in the serotonin transporter (5-HTT), brain-derived neurotrophic factor (*BDNF*), and apolipoprotein E (*APOE*) genes; 12-month change in the Center for Epidemiologic Studies Depression Scale total score, as well as scores on the depressed affect, somatic symptoms, and lack of positive affect subscales.

Results—Men randomized to the PA arm showed the greatest decreases in somatic symptoms, with a preferential benefit in male carriers of the *BDNF*Met allele. Symptoms of lack of positive affect decreased more in men compared to women, particularly in those possessing the 5-HTT L allele, but the effect did not differ by intervention arm. *APOE* status did not affect change in depressive symptoms.

Conclusions—Results of this study suggest that the impact of PA on depressive symptoms varies by genotype and sex, and that PA may mitigate somatic symptoms of depression more than other symptoms. The results suggest that a targeted approach to recommending PA therapy for treatment of depression is viable.

Keywords

exercise intervention; depression; aging; BDNF; APOE; serotonin transporter

INTRODUCTION

Traditional treatment for late-life depression with pharmacotherapy is efficacious in many patients [1] but often is accompanied by deleterious side effects, including increased falls and hyponatraemia [2]. Consequently, recent efforts have focused on alternative non-pharmacological interventions, particularly for older adults experiencing clinically significant sub-threshold depressive symptoms. Converging evidence suggests that physical activity (PA) is an effective intervention for both clinical depression and sub-threshold depressive symptoms [3]. Clinical trials have found similar efficacy for PA and antidepressant medication in the treatment of depression [4], with PA providing greater protection against relapse compared to medication [5].

Other studies, including previous work in the Lifestyle Interventions and Independence for Elders Pilot Study (LIFE-P) [6], showed no overall impact of physical activity increases on depressive symptoms. These inconsistencies may be due in part to methodological issues, but may also reflect heterogeneity in response to PA, with some subgroups of individuals responding to PA, but not others. Attempts to target traditional antidepressant treatments have examined the impact of genetic variation on treatment efficacy. These studies focus on genes that are putatively related to antidepressant mechanisms, such as the serotonin transporter gene (5-HTT) for selective serotonin reuptake inhibitors, or genes that are related to the risk of depression, including the brain-derived neurotrophic factor (*BDNF*) and

apolipoprotein E (*APOE*) genes. The role of these particular genes in the antidepressant response has been documented by recent meta-analyses [7–9], which showed that the *APOE* ϵ 4 allele, the *BDNF*Met allele, and the 5-HTT long (L) allele are associated with higher likelihood of positive response and remission after antidepressant treatment. It is unclear whether genetic differences also impact the efficacy of PA in treating depression or depressive symptoms, as the evidence is limited and results are mixed. One study reported that young adults with at least one 5-HTT L allele showed greater reductions in depressive symptoms after a 5-week exercise intervention [10]. In contrast, a recent cross-sectional study in middle-aged adults found that the *BDNF*Val66Met polymorphism did not moderate the relationship between self-reported physical activity and depressive symptoms [11]. This question has not been investigated in older adults.

Also unclear is whether PA impacts particular symptom dimensions of depression more than others. Depression is a clinically heterogeneous disorder that comprises a variety of different symptoms (e.g., depressed affect, reduced positive affect, and somatic symptoms). Emerging evidence suggests that specific dimensions of depressive symptoms are related to specific brain changes and domains of cognitive dysfunction [12, 13]. Corroborating the distinction of symptom dimensions of depression, there is evidence of distinct vascular, degenerative and inflammatory contributors to different depressive symptom clusters [14], and genetic work has shown significant positive familial correlations for different symptom dimensions [15]. As such, it is possible that PA would improve certain types of depressive symptoms, but not others.

Moreover, the impact of PA on depressive symptoms may vary by sex. Numerous studies have shown that men and women not only differ in their risk for depression and vulnerability to depression-related negative sequelae, but also in the associations of genotype with depression risk and response to depression treatment [16, 17]. Some studies have reported a sex difference on the relationship between PA and depressive symptoms, with the effect being found exclusively or to a greater extent in either men [e.g., 18] or women [e.g., 11]. A recent meta-analysis of randomized trials showed a stronger effect of exercise in men [19].

The goal of the present investigation was to expand upon previous work in the LIFE-P cohort [6] by examining the role of variants in the *BDNF*, 5-HTT, and *APOE* genes in the antidepressant response to a physical activity intervention, and by separately examining different symptom dimensions of depression. Based on previous studies documenting a better treatment response in depressed carriers of the *APOE* ϵ 4 allele, the *BDNF*Met allele, and the 5-HTT L allele, we expected LIFE-P participants possessing these genetic markers to show the greatest reduction in depressive symptoms after a 12-month PA intervention compared to an educational control intervention.

METHODS

Participants

Data for the present investigation came from the Lifestyle Intervention and Independence for Elders Pilot (LIFE-P) Study, a randomized controlled trial evaluating the effect of physical activity on physical performance measures linked with mobility disability. Details of the

study design for LIFE-P have been described elsewhere [20]. Briefly, community-dwelling adults aged 70–89 years were recruited from four field centers (Cooper Institute, Stanford University, University of Pittsburgh, and Wake Forest University). Participants were required to have a sedentary lifestyle (<20 minutes of structured physical activity per week during the previous month) and a score of <10 on the Short Physical Performance Battery [21], but be able to complete a 400-m walk unaided in less than 15 minutes. Major exclusion criteria included presence of severe heart failure, uncontrolled angina, and other severe illnesses that might interfere with physical activity. The National Institutes of Health and by the Institutional Review Boards of all participating institutions approved the study procedures. All participants provided written informed consent. A total of 424 participants were enrolled between May 2004 and February 2005. Participants were randomly assigned to either a physical activity or health education control arm, described briefly below and in more detail elsewhere [20]. At baseline and at 6 and 12 months, comprehensive standardized assessments were conducted by trained research staff masked to intervention assignment. Of the 424 participants in LIFE-P, 396 consented to DNA testing, of which 365 had available baseline and follow-up data for the variables used in the present investigation. Sample characteristics for the present investigation are provided in Table 1.

Physical Activity (PA) Intervention

Participants randomly assigned to the PA arm performed aerobic, strength, flexibility, and balance training in both center- and home-based settings. Walking was the primary mode of aerobic activity, given its widespread popularity and ease of administration across a broad segment of the older adult population. Other forms of endurance activity (e.g., stationary cycling) were utilized when regular walking was contraindicated. Each center-based session began with a brief warm-up, followed by 40 minutes of moderate-intensity walking, and concluding with 15 minutes of flexibility and balance training exercises.

PA intensity was gradually increased over the first 2–3 weeks, with a target of reaching moderate intensity as assessed by the Borg scale [22], a numerical scale indicating a rating of perceived exertion from minimal to maximal. Participants were asked to walk at a target intensity of 13 (somewhat hard) and perform strength training at an intensity of 15–16 (hard). The proportion of center-based to home-based sessions changed during the course of treatment: The number of center-based sessions was reduced to two times per week and home-based activities were increased during weeks 9–24. In the maintenance phase (week 25 to the end of the study), participants were encouraged to perform home-based physical activity a minimum of 5 days per week, and one weekly center-based session was offered.

Control Intervention

A successful aging health education intervention served as an attention control arm. Half of participants were randomly assigned to the control arm and attended education workshops on health topics of relevance to older adults, such as nutrition, medication use, foot care, and preventive medicine. Each class was concluded with gentle seated upper extremity stretching. These classes lasted approximately 60 minutes and were given weekly for the first 26 weeks, and then monthly until the end of the study. This amount of contact time is

similar to the contact time for control arms employed in other successful randomized trials of physical activity in older adults [6].

Depressive Symptom Measurement

The Center for Epidemiologic Studies Depression Scale [CES-D; 23] was administered at baseline and at 12-months. The CES-D has shown a consistent factor structure across numerous patient populations and ethnic groups, which has been confirmed by meta-analysis [24]. The four-factor structure of the CES-D includes depressed affect (e.g., sadness and fearfulness), somatic symptoms (e.g., loss of appetite, concentration difficulties), lack of positive affect (e.g., diminished capacity to experience pleasure), and interpersonal difficulties (i.e., perceived problems in social relationships) subscales. Baseline and 12-month scores were used in analyses for the current investigation.

Genotyping

DNA was isolated from whole blood using a commercially available DNA isolation kit, and the concentration and purity (260/280) were determined by a UV spectrophotometer. The 5-HTT gene short (484 bp) and long (528 bp) variant alleles (insertion/deletion polymorphism) were genotyped by PCR amplified fragment length polymorphism. The following forward 5'-GCGTTGCCGCTCTGAATGC-3' and reverse 5'-GAGGGACTGAGCTGGACAACCAC-3' PCR primers were used to amplify the short (484 bp) and long (528 bp) variant alleles. The amplified PCR products from DNA samples along with positive and negative controls were run on 1% agarose gel and the results were interpreted by two different trained personnel. The *BDNF* Val66Met rs6265 and *APOE* rs4412 polymorphisms were genotyped by Taqman[®] genotyping method on ABI 7900 HT platform using the following genotyping probes (IDs C__11592758_10 and C__2230322_20) respectively. The assays were performed and analyzed according to the manufacture's recommendations (Life Technologies, CA, USA). The *APOE* rs420358 polymorphism was genotyped by Pyrosequencing genotyping method [25], using the following PCR and sequencing primers; forward biotinylated PCR primer 5'-GCGGACATGGAGGACGTG-3', reverse PCR primer 5'-TACTGCGCAGGCGCTTCT-3', and reverse sequencing primer 5'-ACTGCACCAGGCGGC-3'. The Pyrosequencing reactions were carried out using the Pyrosequencing HS 96 platform according to the manufacturer's recommendations and the genotypes were automatically called by PSQ HS 96 SNP software (Qiagen, Valencia, CA, USA).

Statistical Analyses

Analyses of variance compared baseline continuous demographic characteristics and CES-D scores for the full sample, as well as CES-D scores by sex and genotype. Chi-square tests compared genotype frequency and categorical demographic characteristics across sex.

Our primary hypotheses were tested with analyses of covariance. Dominant models rather than additive models were used for analysis of 5-HTT (presence vs. absence of the L allele) and *APOE* (presence vs. absence of the ϵ 4 allele) due to small sample sizes for the interaction terms of genotype by sex in the additive models. The 12-month changes in total

CES-D score and its subscales were treated as dependent variables in separate models. The interpersonal problems subscale was not included in the analyses due to the restricted range of scores on the subscale, which comprises only 2 items. Intervention arm, genotype, and sex were included as predictors. The 3-way interaction among intervention arm, genotype, and sex and their pairwise two-way interactions were also tested. Stratified analyses were explored for interactions with $p < .10$. Non-significant interaction terms were removed in stages until a final, parsimonious model was reached. All models included age, race/ethnicity, testing site, and baseline outcome as covariates. A significance threshold of $p < .05$ was used.

RESULTS

Demographic characteristics, genotype distribution and baseline CES-D scores are summarized for the total sample and for women and men separately in Table 1. No significant sex differences were observed in demographic characteristics or baseline CES-D scores ($ps > .085$). The percentage of participants who possessed the *BDNF* Met allele, 5-HTT L allele, and *APOE* $\epsilon 4$ allele was 29.6%, 77.5%, and 25.9%, respectively. All frequencies were in Hardy-Weinberg equilibrium. Genotype distribution was similar for men and women ($ps > .41$). Baseline scores on the CES-D, including the depressed affect, somatic symptoms, and lack of positive affect subscales are presented by sex and genotype in Table 2. The mean CES-D total score at baseline was 7.29 ± 6.75 ; scores were similar across genotype and sex \times genotype ($ps > .15$).

The main effect of intervention arm was not significant in any of the models ($ps > .11$). ANCOVAs examining the impact of PA, *BDNF* status and sex on 12-month change in depressive symptoms revealed an intervention arm \times sex effect, $F_{1, 347} = 4.13$, $p = .043$, for somatic symptoms (Figure 1; Table 3). Men in the PA arm showed the greatest decrease in somatic symptoms over 12 months, with minimal change in the control arm. Symptoms decreased to a lesser extent in women, and were similar for the PA and control arms. Based on a marginal 3-way interaction between intervention, *BDNF* status, and sex, $F_{1, 347} = 3.09$, $p = .079$, we performed analyses stratified by intervention arm. In the PA arm, men who possessed the Met allele showed greater decreases in somatic symptoms compared to Met negative men and to women, $F_{1, 172} = 4.54$, $p = .043$ (Figure 2). No significant effects were observed in the control arm.

In the analysis of 5-HTT status, significant sex, $F_{1, 335} = 4.99$, $p = .026$, and genotype \times sex, $F_{1, 335} = 4.27$, $p = .035$, effects were observed for the lack of positive affect subscale, such that those depressive symptoms decreased most after 12 months in men compared to women, and more so in 5-HTT L-negative compared L-positive men (Figure 3). Results did not differ by intervention arm.

No significant effects were found in the *APOE* analyses ($ps > .20$).

DISCUSSION

Converging evidence suggests that PA improves mood, leads to depression remission, and protects against recurrence of depressive symptoms, and previous work has identified

genetic variations that predict treatment response to antidepressant medication [3–5, 7–9]. It is less clear whether or not factors such as genetic variation and sex moderate the antidepressant effect of PA, or if PA differentially affects distinct symptom dimensions of depression in a nonclinical older population. The current study addressed these questions. We found a three-way relationship between intervention, *BDNF* genotype and sex for somatic symptoms of depression, suggesting that the impact of PA on depressive symptoms indeed varies by genotype, sex, and symptom dimension.

Our primary finding was a preferential benefit of PA on somatic depressive symptoms in male *BDNFMet* allele carriers. The impact of *BDNF* genotype on change in depressive symptoms after PA is consistent with our hypothesis and parallels the antidepressant literature. Although there are reports of no effect of *BDNF* on antidepressant response [26], recent meta-analyses have concluded that Met carriers have a more positive response to pharmacotherapy for depression [7]. Additionally, a recent study reported that Met-positive individuals had a more positive acute mood response to a bout of moderate intensity exercise relative to those without a Met allele [27]. Our finding is in contrast to a recent study that reported no moderating effect of *BDNF* on the relationship between physical activity and depressive symptoms [11]; however, the former study was based on self-report of PA in middle aged participants, unlike our randomized PA trial in older adults.

Taken together, it appears that for some individuals, PA, similar to antidepressant medication, may impact depressive symptoms through its effect on BDNF. This is not surprising given the functions of the BDNF protein in the nervous system. BDNF is a member of the neurotrophin family that has a critical role in central nervous system functions including cell survival and differentiation, axonal growth, and the function and plasticity of synapses [28]. BDNF is a neurotransmitter modulator that is highly expressed in the central nervous system, particularly in the hippocampus and other brain regions related to mood, such as the frontal lobes and striatum [29]. In depression, BDNF expression is reduced in areas such as the hippocampus and prefrontal cortex and increased in the nucleus accumbens and amygdala, but antidepressant treatment normalizes BDNF levels [30]. PA has also been shown to increase levels of BDNF [31], which may explain the antidepressant effect of PA. In light of the association between the *BDNFMet* allele and reduced BDNF secretion [32], it is plausible that Met carriers preferentially benefit from PA due to their inherent physiological disadvantage.

In the present study, the benefits of PA on depressive symptoms were specific to somatic symptoms; there was no impact of PA on total symptoms or on symptoms of depressed affect or lack of positive affect. A growing body of evidence supports the importance of examining symptom dimensions of depression separately rather than treating symptoms as homogeneous. Different symptom dimensions of depression appear to have distinct cognitive and neural correlates, etiological contributors, and genetic associations [12–15], and at least one study found that the impact of genotype on antidepressant treatment response is specific to particular symptom dimensions [33]. Given the physical nature of PA interventions, the specificity of our finding to somatic symptoms could be seen as an indication that PA simply improves physical functioning. However, the somatic subscale of the CES-D includes items such as “I had trouble keeping my mind on what I was doing” and

“...everything I did was an effort,” which do not directly reflect physical functioning. Thus, the nature of the items comprising the subscale suggests that the improvements are not solely due to changes in physical functioning. Future work relating changes in depressive symptoms after PA to depression biomarkers may clarify the mechanism underlying the effect. For example, depressive symptoms, particularly in older adults, are associated with white matter changes in the brain. We recently showed that this may be driven by somatic symptoms and depressed affect, as only these factors were associated with greater white matter lesion volume in older men, and with increases in white matter lesion volume over time in both men and women [12]. PA improves white matter integrity [34], thus, it is plausible that PA -related changes in white matter results in reduced somatic symptoms of depression after PA.

We found that men, but not women, showed improvements in somatic symptoms with increases in PA. This is in line with previous findings of sex differences in depression risk and correlates, as well as response to depression treatment [12, 16, 17]. For example, there is evidence that *BDNF* genotype is associated with higher depression risk only in men or to a greater extent in men [11]. Previous work has also shown sex effects on the association of *BDNF* with antidepressant treatment response, but these studies found an effect only in women [35]. The reasons for our sex difference effect are unclear. The result is not explained by greater regression to the mean in men, since men and women did not differ in somatic symptom scores at baseline. A recent meta-analysis [36] concluded that the *BDNF* Val66Met polymorphism may play a larger role in the neurobiological underpinnings of depression in men than in women. This conclusion was based on evidence of sexual dimorphisms in brain structures involved in the neurobiology of depression, particularly the hippocampus [37]. The possibility that the biological underpinnings of depressive symptoms differ in men and women is supported by studies showing stronger and more consistent neural correlates of depression in men compared to women [e.g., 38]. Thus, men may benefit more from PA interventions if PA leads to change in underlying neurobiological mechanisms that are affected more in depressed men than in depressed women. Future work with larger samples will be important for replicating our finding, particularly given the fairly small number of men in our pilot study.

We did not find the expected effect of 5-HTT or *APOE* on the antidepressant effect of PA. Our hypothesis was based on evidence linking the 5-HTT L allele and *APOE* ϵ 4 genotype with better response to treatment with antidepressant medication [7–9]. Additionally, 5-HTT has recently been shown to impact reductions in depressive symptoms after a 5-week exercise intervention in young adults [10]. However, the relationship between these genotypes and response to PA is not fully established, as the literature is limited and some studies failed to find these associations [39, 40]. Our ability to detect possible relations may have been affected by insufficient power or the low severity of depressive symptoms. There is also evidence that gene-gene interactions should be considered, particularly the interaction between 5-HTT and *BDNF* polymorphisms [41, 42]. We were unable to test possible gene-gene interactions in this pilot study due to the sample size. Future extensions of the present work in the full LIFE trial (n = 1635) will allow us to address this issue in a larger sample.

Our results should be considered in the context of the characteristics of the study sample. Participants in LIFE-P were sedentary older adults at risk for disability who ranged in age from 70–89 years and who were not recruited based on a depression diagnosis. The impact of genetic variation on changes in depressive symptoms after PA may differ in clinical samples of individuals diagnosed with major depression or in a different age cohort. Given the variety of genes that have been linked to depression risk and antidepressant treatment response, future studies should also examine the association of additional genotypes on changes in depressive symptoms after PA in subthreshold depression as well as major depression. Nonetheless, this pilot study provides initial evidence that the type of comprehensive PA intervention used in the LIFE-P trial may potentially impact the somatic domain of depressive symptoms in older men, even without a diagnosis of clinical depression. In addition, the results suggest that PA may be particularly impactful in mitigating somatic depressive symptomatology in those men with specific genetic markers, paving the way for future research aimed at targeting such subgroups of older adults for further investigation. This line of work will be important for establishing the clinical significance of changes in depressive symptoms after PA. Based on evidence that the presence of even one depressive symptom increases the risk for negative functional outcomes [43, 44], the 1- to 2-point changes in depressive symptoms in the current study are likely to be clinically meaningful. Thus, this work has the potential to inform targeted non-pharmacological interventions for subthreshold depression in older adults.

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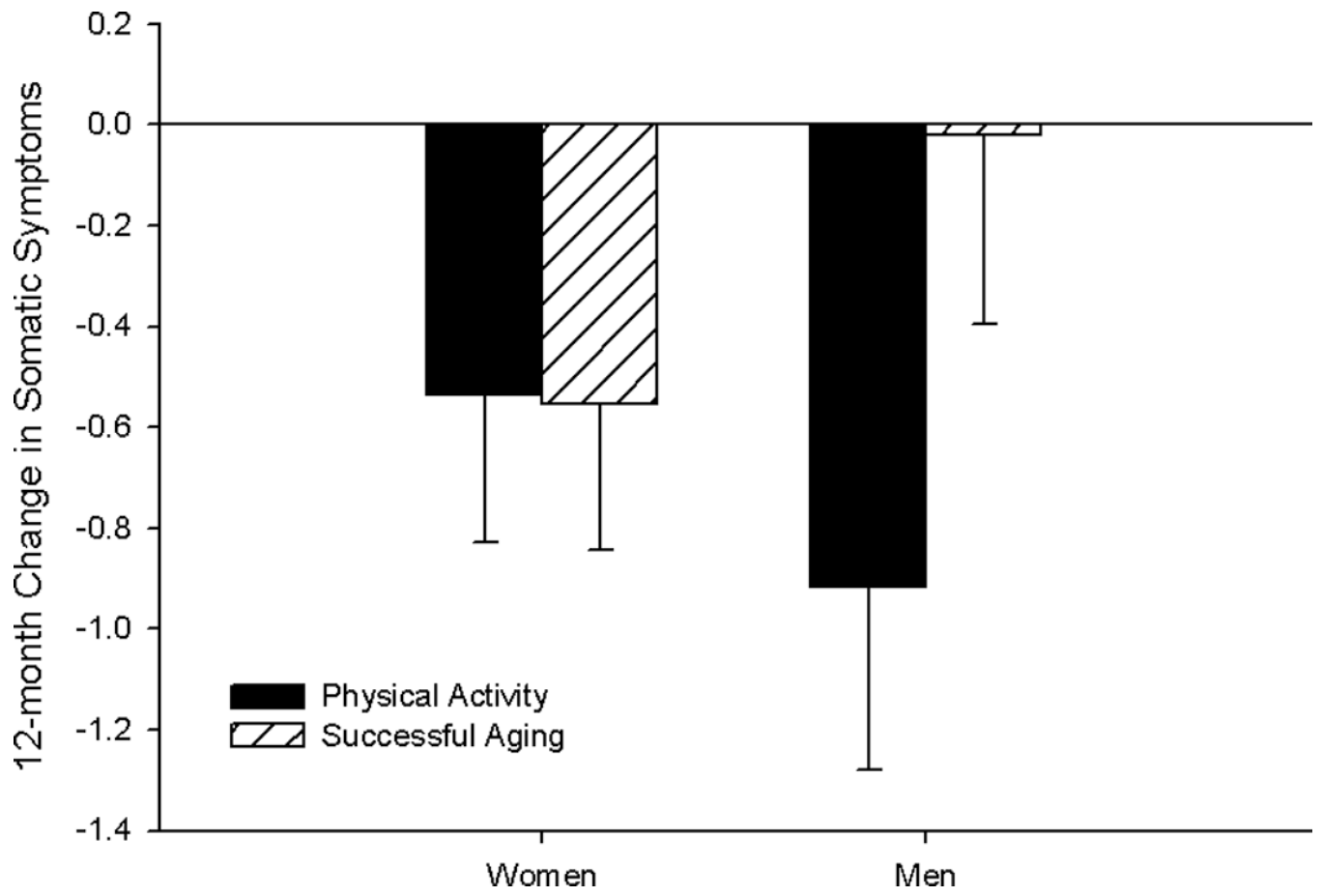


Figure 1. Least squares means for 12-month change in somatic symptoms by sex and intervention group.

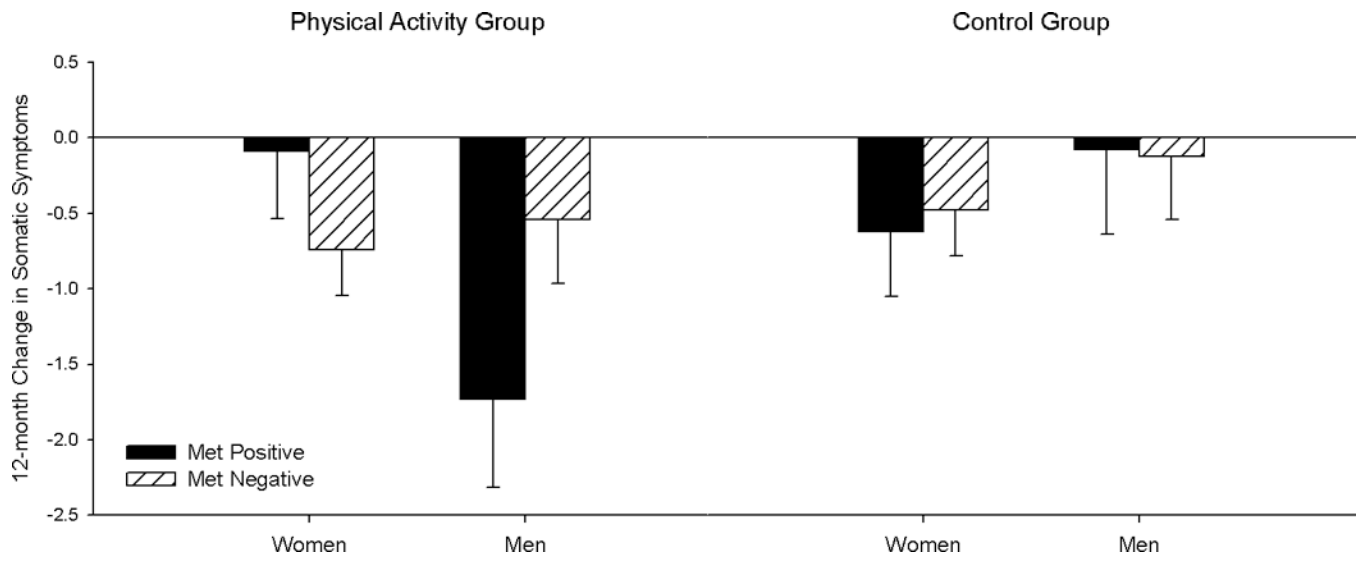


Figure 2. Least squares means for 12-month change in somatic symptoms by BDNF genotype, sex and intervention group.

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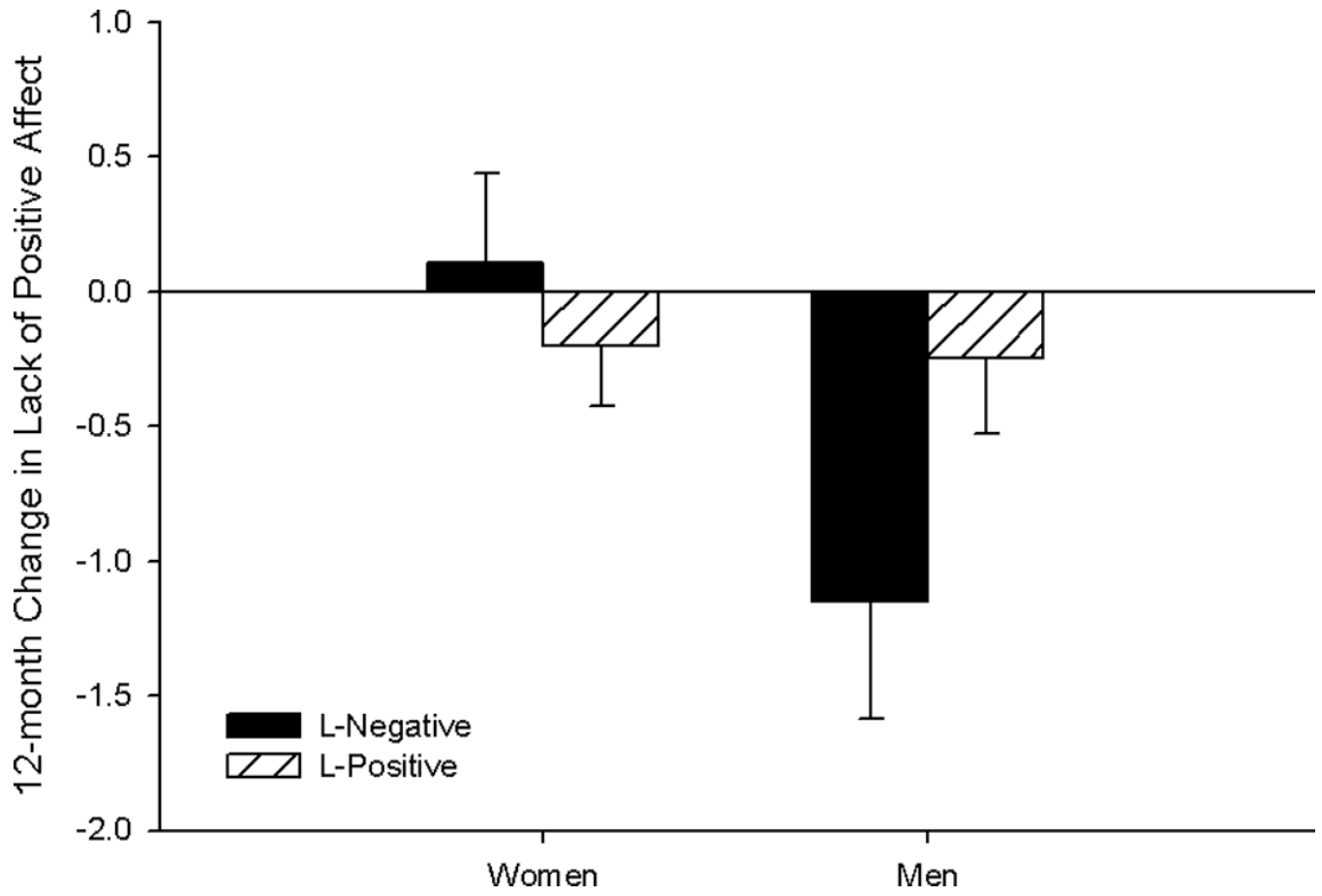


Figure 3. Least squares means for 12-month change in symptoms of lack of positive affect by 5-HTT genotype and sex.

Table 1

Demographic characteristics, genotype and baseline CES-D scores.

	Total Sample	Women	Men
<i>N</i>	365 ^a	249	116
Age (yrs)	76.79 (4.26)	76.71 (4.12)	76.94 (4.56)
<i>Race (Caucasian/AA/Other)</i>	283/63/19	190/49/10	93/14/9
<i>BDNF Status (Met+/Met-)</i>	107/255	70/178	37/77
5-HTT Status (L+/L-)	269/78	185/52	84/26
<i>APOE Status (ε4+/ε4-)</i>	93/266	66/177	27/89
Baseline CES-D Scores			
Total Score	7.29 (6.75)	7.25 (6.38)	7.40 (7.52)
Depressed Affect	1.54 (2.43)	1.66 (2.49)	1.28 (2.28)
Somatic Symptoms	3.38 (2.93)	3.31 (2.69)	3.53 (3.40)
Lack of Positive Affect	2.19 (2.53)	2.10 (2.40)	2.38 (2.78)
% with CES-D 16	11.2%	10.4%	12.9%

^aTotal sample varied across gene: *BDNF* = 362, 5-HTT = 347, *APOE* = 359

CES-D = Center for Epidemiologic Studies Depression Scale; AA = African-American; *BDNF* = brain-derived neurotrophic factor; *APOE* = apolipoprotein E

Table 2

Baseline CES-D scores by sex and genotype.

5-HTT	Total Sample				Women		Men	
	L+	L-	L+	L-	L+	L-	L+	L-
Total CES-D	6.97 (6.36)	8.14 (6.54)	6.88 (6.40)	8.71 (6.70)	7.15 (6.32)	7.00 (6.16)	7.15 (6.32)	7.00 (6.16)
Depressed Affect	1.38 (2.27)	1.90 (2.47)	1.48 (2.46)	2.31 (2.70)	1.15 (1.76)	1.08 (1.69)	1.15 (1.76)	1.08 (1.69)
Somatic Symptoms	3.26 (2.86)	3.58 (2.67)	3.19 (2.82)	3.62 (2.39)	3.40 (2.95)	3.50 (3.20)	3.40 (2.95)	3.50 (3.20)
Lack of Positive Affect	2.14 (2.50)	2.47 (2.66)	2.02 (2.32)	2.58 (2.75)	2.43 (2.83)	2.27 (2.52)	2.43 (2.83)	2.27 (2.52)
BDNF	Met+	Met-	Met+	Met-	Met+	Met-	Met+	Met-
Total CES-D	7.68 (6.64)	7.07 (6.77)	7.53 (6.33)	7.16 (6.43)	7.97 (7.28)	6.86 (7.56)	7.97 (7.28)	6.86 (7.56)
Depressed Affect	1.57 (2.10)	1.51 (2.57)	1.71 (2.18)	1.63 (2.62)	1.30 (1.92)	1.21 (2.43)	1.30 (1.92)	1.21 (2.43)
Somatic Symptoms	3.59 (2.94)	3.28 (2.94)	3.33 (2.56)	3.31 (2.75)	4.08 (3.54)	3.23 (3.34)	4.08 (3.54)	3.23 (3.34)
Lack of Positive Affect	2.33 (2.71)	2.08 (2.38)	2.27 (2.62)	2.04 (2.32)	2.43 (2.92)	2.18 (2.54)	2.43 (2.92)	2.18 (2.54)
APOE	e4+	e4-	e4+	e4-	e4+	e4-	e4+	e4-
Total CES-D	7.90 (7.66)	7.09 (6.46)	7.94 (8.28)	7.00 (5.59)	7.82 (6.03)	7.27 (7.95)	7.82 (6.03)	7.27 (7.95)
Depressed Affect	1.89 (2.84)	1.42 (2.29)	2.15 (3.17)	1.48 (2.21)	1.26 (1.70)	1.28 (2.44)	1.26 (1.70)	1.28 (2.44)
Somatic Symptoms	3.68 (3.10)	3.29 (2.89)	3.50 (3.12)	3.25 (2.54)	4.11 (3.04)	3.36 (3.50)	4.11 (3.04)	3.36 (3.50)
Lack of Positive Affect	2.14 (2.71)	2.19 (2.46)	2.09 (2.81)	2.08 (2.22)	2.26 (2.50)	2.42 (2.87)	2.26 (2.50)	2.42 (2.87)

CES-D = Center for Epidemiologic Studies Depression Scale; *BDNF* = brain-derived neurotrophic factor; *APOE* = apolipoprotein E

Table 3

Least squares means for change in CES-D scores after adjusting for intervention by sex, intervention group, and genotype.

	Women						Men					
	PA		SA		PA		SA		PA		SA	
	L+	L-	L+	L-	L+	L-	L+	L-	L+	L-	L+	L-
5-HTT												
Total CES-D	-0.56	-1.11	-1.02	-1.33	-1.93	-1.45	-0.17	-1.91	-1.45	-0.17	-1.91	-1.91
Depressed Affect	0.17	-0.48	-0.16	-0.53	-0.26	-0.49	0.14	0.02	-0.49	0.14	0.02	0.02
Somatic Symptoms	-0.65	-0.38	-0.49	-0.96	-1.25	-0.19	-0.09	-0.05	-0.19	-0.09	-0.05	-0.05
Lack of Positive Affect	-0.11	0.15	-0.29	0.05	-0.30	-0.67	-0.19	-1.77	-0.67	-0.19	-1.77	-1.77
BDNF												
Total CES-D	Met+	Met-	Met+	Met-	Met+	Met-	Met+	Met-	Met+	Met-	Met+	Met-
Depressed Affect	-0.34	-0.84	-1.02	-0.93	-2.61	-1.24	-0.30	-0.91	-1.24	-0.30	-0.91	-0.91
Somatic Symptoms	-0.05	0.02	-0.51	-0.08	-0.58	-0.22	0.13	0.11	-0.22	0.13	0.11	0.11
Lack of Positive Affect	-0.09	-0.74	-0.62	-0.48	-1.73	-0.54	-0.08	-0.12	-0.54	-0.08	-0.12	-0.12
APOE												
Total CES-D	ε4+	ε4-	ε4+	ε4-	ε4+	ε4-	ε4+	ε4-	ε4+	ε4-	ε4+	ε4-
Depressed Affect	-0.58	-0.77	-0.49	-1.15	-0.98	-2.01	-0.66	-0.74	-2.01	-0.66	-0.74	-0.74
Somatic Symptoms	-0.13	0.04	-0.19	-0.27	-0.27	-0.33	0.08	0.12	-0.33	0.08	0.12	0.12
Lack of Positive Affect	-0.37	-0.69	-0.24	-0.65	-0.28	-1.19	-0.68	-0.02	-1.19	-0.68	-0.02	-0.02
	0.00	-0.07	-0.07	-0.21	-0.35	-0.37	-0.07	-0.57	-0.37	-0.07	-0.57	-0.57

PA = physical activity intervention group; SA = successful aging education control group; CES-D = Center for Epidemiologic Studies Depression Scale; *BDNF* = brain-derived neurotrophic factor; *APOE* = apolipoprotein E