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The Effect of a 6-Month Exercise Intervention Trial on Allostatic Load in Black Women at Increased Risk for Breast Cancer: The FIERCE Study

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Abstract

Background: Allostatic load comprises cardiovascular, metabolic, and inflammatory markers, which is characterized by abdominal obesity, high blood glucose levels, impaired glucose tolerance, dyslipidemia, and hypertension, and associated with an increased risk in breast cancer.

Methods: The study was a 6-month, 3-arm randomized controlled trial of two moderate-intensity exercise interventions (compared with a control group) among obese, physically inactive, postmenopausal black women aged 45 to 65 years, who were at increased risk for breast cancer based on the CARE model. 213 participants were randomly assigned to: 1) supervised, facility-based aerobic exercise intervention (n= 73); 2) home-based exercise intervention (n = 69); or 3) a wait-listed control group (n =71). The intervention effects of exercise on allostatic load were examined with intent-to-treat analyses using generalized linear models.

Results: It was revealed that statistically significant decreases in allostatic load over the 6-month period for both exercise intervention groups, (i.e., home-based and supervised arms) compared to the controls, were observed among the total population, $p_{c\text{-}h}$ =0.023 and $p_{c\text{-}s}$ = 0.035 as well as among women with a family history of breast cancer, $p_{c\text{-}h}$ =0.006 and $p_{c\text{-}s}$ =

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Availability of data and material (data transparency): All data and materials as well as coding used in our statistical software support the findings of the study.

Ethics approval: The procedures used in this study adhere to the tenets of the Declaration of Helsinki. Approval was obtained from the Georgetown University IRB2012–012: An Exercise RCT Targeting African-American Women with Metabolic Syndrome and High Risk for Breast Cancer. Clinical trial registration number NCT02103140.

Conflicts of interest/Competing interests: The authors have no relevant financial or nonfinancial interests to disclose.

Conclusions: Short-term aerobic activity improved allostatic load scores in metabolically unhealthy postmenopausal black women at increased risk for cancer. Clinical trial registration number NCT02103140.

Keywords

allostatic load; exercise intervention; breast cancer; postmenopausal women; blacks

Introduction

Allostatic load is described as the physiological wear and tear on one's body caused by long-term exposure to environmental and social stressors [1]. During the post-menopausal years, women tend to experience a multitude of physiological changes as well as social transitions [2,3] causing the body to respond physiologically to a myriad of stressors through a process called allostasis[4]. For women of certain racial and ethnic groups, allostatic load tends to take more of a toll. In a qualitative examination of midlife sources of stress in African-American women, it was found that women reported stress resulting from finances, caring for family members, relationships, personal health and aging, race, and raising children [5]. Allostatic load comprises cardiovascular, metabolic, and inflammatory markers (similar to those represented in metabolic syndrome) [6]. Metabolic syndrome (MetS), which, is characterized by abdominal obesity, high blood glucose levels, impaired glucose tolerance, dyslipidemia, and hypertension, has been associated with a 17% increase in breast cancer [7].

Data show that Black women have a higher prevalence of allostatic load, [8] metabolic syndrome [9–11] and breast cancer mortality [12]. For example, in the National Health and Nutrition Examination Survey, Geronimus [8] examined allostatic load scores in Black and White adults (aged 18–64) and found Blacks had higher alloststic scores than did Whites and had a greater probability of high scores at all ages. Data also show that Black women are 20% more likely to have MetS than White women and have a higher prevalence of certain MetS components [9–11]. Also, based on American Cancer Society statistics during 2008–20012, breast cancer death rates were 42% higher in black women compared to white women, despite similar incidence rates [12].

Understanding lifestyle factors that reduce allostatic load (and ultimately MetS and breast cancer risk) in this vulnerable population is a necessary research pursuit. While there is data that support physical activity is associated with individual components of allostatic load, a limited number of studies have focused on physical activity and composite allostatic load. For example, in a national examination of allostatic load for Black and White adults aged 18–64 years mean allostatic scores for Blacks were significantly higher than mean scores for Whites [8]. Moreover, Black women had higher allostatic scores than Black men.

Unfortunately, fewer Black women meet regular physical activity recommended levels [13]. Given that Black women have high rates of allostatic load, metabolic syndrome and breast cancer mortality, and lower physical activity rates, examining the effect of exercise on allostatic load within Black women with MetS and at risk for breast cancer would make a significant contribution to the scientific literature. Therefore, the current study investigated

the effects of a 6-month supervised and home-based aerobic exercise intervention on changes in allostatic load among Black women with MetS at risk for breast cancer. To our knowledge, this is the first study to investigate the effect of an exercise intervention on allostatic load in this population.

Methods

Study Population

The FIERCE study was a 6-month, 3-arm randomized controlled trial of two moderate-intensity exercise interventions (compared with a control group) among obese, physically inactive, postmenopausal black women aged 45 to 65 years, who are at increased risk for breast cancer based on the CARE model. The methods for the FIERCE study have been previously published [14]. In brief, 213 participants were randomly assigned to 1 of 3 clinical trial arms: 1) a supervised, facility-based aerobic exercise intervention (n= 73); 2) a home-based exercise intervention (n = 69); and 3) a wait-listed control group whose participants were asked to maintain their baseline daily activities for the duration of the study (n =71). Blood sample collection and processing fasting baseline venous blood samples were drawn in the morning. During follow-up visits, fasting morning blood samples were drawn 16 to 24 hours after the most recent exercise session for participants in the intervention arms to minimize the measurement of acute effects of exercise. The family history of breast cancer in a first-degree relative (ie, mothers, daughters, and sisters) was assessed through self-report. Information on demographic and lifestyle factors, including smoking, was collected through self-reported questionnaires.

Outcomes

The components used to assess Allostatic Load (AL) are shown in Table 1 with corresponding cutoff values. Based on the cutoff value, each AL component was categorized as a dichotomous variable (1, if the condition was present, 0, otherwise); and the AL score was calculated as the sum of the indicators of the components. We also created Al score as a standardized continuous variable, labelled as z-score of AL(zAL), which was derived by summing the standardized AL components. AL components were standardized by subtracting the cutoff value from observed component value, and then dividing this by the sample standard deviation of the AL component.

Covariates

Information on demographic and lifestyle factors was collected through self-reported questionnaires. Exercise behavior was assessed using the International Physical Activity Questionnaire (IPAQ), a structured interview that measures a person’s time spent engaging in exercise over a 7-day period. Covariates of interest for AL analyses included age. Education level, marital status, smoking, physical activity, family history of breast cancer, five-year individual invasive breast cancer risk was assessed using the “CARE” model, history of mammographic screening, self-reported menopausal symptoms, and history of hypertension and hypercholesterolemia.

Statistical Analysis

Baseline characteristics are presented as frequency and percentages by study intervention arms. Cochran-Mantel-Haenszel (CMH) tests were used to examine associations between baseline characteristics and study arms. Values of AL and zAL at baseline (means and standard deviations) are presented for each study arm. Their associations with baseline covariates were evaluated using the two sample t-test or one-way ANOVA. The main outcome analysis of the effect of exercise intervention groups (versus control) on zAL at 6 months was performed on an intention-to-treat basis. We calculated the 6-month change by subtracting the baseline AL component / zAL from the 6-month follow-up value, followed by modeling on intervention arms using generalized linear models that adjusted for the baseline AL component / zAL. The models were fit individually for each AL component and zAL, and no other covariate was considered in the model except for baseline value of the corresponding AL component or zAL. Pairwise comparisons between the three arms are also reported. In addition, subgroup analyses of the effect of interventions on zAL stratified by family history of breast cancer in first degree relatives, were also conducted adjusting for baseline zAL values. All statistical tests were two-sided, with a significance level of 0.05. Statistical analyses were performed using SAS software (Version 9.4; SAS Institute, Cary, NC).

Results

The mean age of the participants was 58.3 years, with more than 90% having a high school or higher education. Participants had low mean exercise levels at the baseline (4 MET-h/wk) and had a high daily caloric intake (2000 kcal). A family history of breast cancer in a first-degree relative was reported by 40% of the participants, and the average projected 5-year absolute risk of breast cancer based on the CARE model in this group was 1.85.

Mean allostatic load scores are shown in Table 2 by selected baseline characteristics. There were statistically significant differences observed for smoking and family history of breast cancer for both AL and zAL scores. Current smokers had higher AL scores compared to never smokers, AL scores of 3.83 and 3.55, $p<0.05$, respectively. Also women with a family history of breast cancer had a higher AL score compared to women with no family history of breast cancer, 3.98 and 3.55, $p<0.001$, respectively. Women with a history of hypertension had higher AL scores compared to women with no history of hypertension, 3.96 and 3.34, $p<0.001$, respectively. Finally, women with no history of menopausal symptoms had higher AL scores compared to women with a history of menopausal symptoms, 4.35 and 3.60, $p<0.001$, respectively. Similar findings were observed for zAL (Table 2).

Changes in allostatic load over a 6-month time period by exercise intervention and family history of breast cancer are shown in Table 3. It was revealed that statistically significant decreases in allostatic load over the 6-month period for both exercise intervention groups, (i.e., home-based and supervised arms) compared to the controls, were observed among the total population, $p_{c\text{-}h} =0.023$ and $p_{c\text{-}s} = 0.035$ as well as among women with a family history of breast cancer, $p_{c\text{-}h} =0.006$ and $p_{c\text{-}s} = 0.012$.

Discussion

In the present study we assessed changes in allostatic load, in an exercise intervention of black women with MetS at risk for breast cancer over a 6-month time period. It was revealed that smoking, family history of breast cancer, history of hypertension and no history of menopausal symptoms were associated with significantly higher levels of allostatic load compared to those without these characteristics. We also found that decreases in allostatic load occurred as a result of participating in both supervised and home-based exercise in the total sample as well as among a sub-sample of women with a family history of breast cancer.

We examined how certain lifestyle (e.g. smoking) and medical factors (e.g. family history of breast cancer, history of hypertension, history of menopausal symptoms) were associated with allostatic load. Our findings revealed that being a current smoker was related to higher levels of allostatic load compared to non-smokers. As previously mentioned, allostatic load is a biological indicator of chronic stress. African-American women in midlife tend to experience high levels of environmental and social stress [5] that can cause certain individuals to resort to maladaptive coping strategies, such as smoking. For example, in a study of 198 African-American women (smokers vs. non-smokers) it was reported that smokers reported significantly more general stress than non-smokers [15] Therefore, our findings of allostatic load (a biological indicator of stress) being related to smoking status were consistent with our expectations.

Our study also found that at baseline, women with a history of hypertension had greater allostatic load compared to women without a history of hypertension. This finding is in agreement with other studies such as Mattei et al [16] who reported that adults in the Boston Puerto Rican Health Study (ages 45–75) showed significant relationships between increasing categories of allostatic load and various chronic diseases, including hypertension. A likely biological explanation for this finding could be that after stressors are triggered, the first reaction of the allostatic physiological response are parameters in the hypothalamic-pituitary dadrenal (HPA) axis and the sympathetic nervous system (SNS) [17], both linked to hypertension.

Additionally, we found that at baseline, women with a family history of breast cancer also had higher levels of allostatic load compared with women without a family history of breast cancer. As indicated, allostatic load is a physiological indicator of stress. Having an immediate family member with cancer can be a life stressor to relatives, mainly because it triggers thoughts they will suffer from cancer in the future. A study by Kash et al [18] found that among 270 women with a family history of breast cancer (one or more first-degree relatives with breast cancer), 27% of the women were defined as having a level of psychological distress consistent with the need for counseling. Again, since allostatic load is a physiological indicator of stress, it makes sense that women at risk for breast cancer (who likely experience distress resulting from this high-risk status), also exhibit high allostatic load levels.

Our results also indicate that women in the exercise arms, i.e. supervised or home-based, had significant improvements in allostatic load. This occurred for the total sample as well

as among those with a family history of breast cancer. As previously mentioned, it is well known that physical activity has many benefits associated with single biomarkers of allostatic load (cardiovascular, metabolic, and immune) but only a few studies have focused on physical activity and composite allostatic load scores [19] Our results coincide with the study by Upchurch [19] who investigated the association between leisure-time physical activity and allostatic load level among a large sample of White, Black and Mexican-American midlife women (40–59 years of age). A negative relationship was found between leisure-time activity and level of allostatic load across all racial, ethnic and age categories. Also, as mentioned by Upchurch [19], while it is beneficial to know that leisure-time activity as well as moderate activity (prescribed in our study) produces clinically meaningful reductions in allostatic load, a review by Brown et al [20] concluded that even modest gains in women's physical activity lowers health risks.

Lastly, our finding that exercise produced reductions in allostatic load in women with a family history of breast cancer could be due to the awareness in this sub-sample of women of risk reduction benefits that exercise has on breast cancer risk. A qualitative research study of 32 White and Black women (aged 35–74) with a family history of breast cancer substantiate this assertion [21]. In this study, thirteen women reported that they engaged in recommended exercise levels. Most of these women were White, with elevated risk perception. An additional twelve women exercised regularly, but not enough to meet recommended guidelines. The remaining 7 did not exercise but three of them attributed lack of exercise to breast cancer risk. Results from this study indicate that although not all women met recommended physical activity guidelines, most recognized the importance of exercise on reducing breast cancer risk.

There is one limitation to the study of importance, i.e., the calculation of Allostatic Load. This variable can be calculated based on over twenty different ways. Therefore, there are inconsistent ways of defining allostatic load in the comparison studies. However, we did use z-scores to attempt a standardization for future comparisons.

There have been very few studies focused on the effect of physical activity on allostatic load and our study is the only exercise intervention focused on allostatic load in a Black population. Understanding the physiological toll that environmental and social stress has on Black women, and how exercise can help alleviate allostatic load in this population makes a great contribution to the scientific literature and builds the foundation for future research in this area.

Acknowledgments

Declarations

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Table 1.

Allostatic Load Variables and Metabolic Syndrome Cutpoints

Cardiovascular
Systolic Blood pressure. (≥ 130mmHg)
Diastolic Blood pressure (≥ 85mmHg)
Triglycerides (≥ 150mg/dL)
HDL (<50mg/dL)
Metabolic
Fasting glucose (≥100mg/dL)
Body Mass Index (30kg/m^2)
Waist circumference (>88cm)
Immune
C-reactive protein. (> 10 mg/L)

Table 2a.

Baseline characteristics by study arms

Characteristic	Control (N=70)	Home-based	Supervised (N=73)	p-value
Age, (n)				0.87
<=59 (102)	34 (47.89)	34 (49.28)	34 (46.58)	
>59 (111)	37 (52.11)	35 (50.72)	39 (53.42)	
Education level (n)				0.78
≤ High school (17)	6 (8.57)	4 (5.80)	7 (9.59)	
High school/some college (109)	35 (50.00)	41 (59.42)	33 (45.21)	
≥ College (86)	29 (41.43)	24 (34.78)	33 (45.21)	
Marital status (n)				0.97
Single/Never married (64)	23 (32.39)	17 (24.64)	24 (32.88)	
Married/Living with partner (56)	18 (25.35)	20 (28.99)	18 (24.66)	
Divorced/Separated/Widowed	30 (42.25)	32 (46.38)	31 (42.47)	
*Smoking (n) **				0.71
Current smoker (30)	11 (15.49)	14 (20.29)	5 (6.85)	
Former smoker (71)	20 (28.17)	21 (30.43)	30 (41.10)	
Never smoker (112)	40 (56.34)	34 (49.28)	38 (52.05)	
Time spent-walking (min/week), (n)				0.88
<=20.0 (121)	38 (53.52)	43 (62.32)	40 (54.79)	
>20.0 (92)	33 (46.48)	26 (37.68)	33 (45.21)	
*Family history of breast cancer (n)**				0.47
Yes (85)	24 (33.80)	32 (46.38)	29 (39.73)	
No (128)	47 (66.20)	37 (53.62)	44 (60.27)	
Absolute 5-year risk of breast cancer (n)				0.19
<=1.586 (101)	39 (54.93)	30 (43.48)	32 (43.84)	
>1.586 (112)	32 (45.07)	39 (56.52)	41 (56.16)	
Mammography screening (ever) (n)				0.73
Yes (194)	64 (90.14)	63 (91.30)	67 (91.78)	
No (19)	7 (9.86)	6 (8.70)	6 (8.22)	
*History of hypertension, (n) ***				0.01
Yes (130)	47 (66.20)	50 (72.46)	33 (45.21)	
No (83)	24 (33.80)	19 (27.54)	40 (54.79)	
History of hypercholesterolemia (n)				0.63
Yes (69)	20 (28.17)	26 (37.14)	23 (31.94)	
No (144)	51 (71.83)	44 (62.86)	49 (68.06)	
History of menopausal symptoms (n)				0.33
Yes (179)	56 (78.87)	61 (88.41)	62 (84.93)	
No (34)	15 (21.13)	8 (11.59)	11 (15.07)	

P-value based on Cochran-Mantel-Haenszel test

Table 2b.

Mean Allostatic Load z-score (zAL) by Selected Baseline Characteristics

Characteristic	zAL, x (S.D.)	*p*-value
Age, (n)		0.160
<=59 (102)	1.46 (3.93)	
>59 (111)	0.93 (3.85)	
Education level (n)		0.731
≤ High school (17)	1.01 (2.88)	
High school/some college (109)	1.55 (3.92)	
≥ College (86)	0.72 (4.02)	
Marital status (n)		0.494
Single/Never married (64)	2.03 (4.07)	
Married/Living with partner (56)	0.97 (4.16)	
Divorced/Separated/Widowed (93)	0.74 (3.55)	
***Smoking** (n) *		**0.024**
Current smoker (30)	1.91 (3.70)	
Former smoker (71)	1.69 (4.08)	
Never smoker (112)	0.66 (3.77)	
Time spent-walking (min/week), (n)		0.443
<=20.0 **(121)**	1.34 (3.89)	
>20.0 **(92)**	0.98 (3.89)	
***Family history of breast cancer** (n)**		**0.049**
Yes (85)	1.76 (4.05)	
No (128)	0.80 (3.74)	
Absolute 5-year risk of breast cancer (n)		0.699
<=1.586 **(101)**	1.26 (3.85)	
>1.586 **(112)**	1.11 (3.94)	
Mammography screening (ever) (n)		0.821
Yes **(194)**	1.17 (3.84)	
No **(19)**	1.26 (4.45)	
***History of hypertension**, (n) **		**<0.001**
Yes (130)	1.89 (3.83)	
No (83)	–0.01 (3.70)	
History of hypercholesterolemia (n)		0.988
Yes **(69)**	0.92 (3.10)	
No **(144)**	1.30 (4.21)	
***History of menopausal symptoms** (n)*		**<0.001**
Yes (179)	0.73 (3.62)	
No (34)	3.56 (4.44)	

* P < .05

** P<.001

P-values based on two-sample t-test or one-way ANOVA.

Table 3.

Baseline Allostatic Load Components by Exercise Intervention Arm

Variables	Supervised		Home Based		Control		*p*-value
	Baseline, mean (SD)	**6month change, mean (%)****	**Baseline, mean (SD)**	**6month change, mean (%)**	**Baseline, mean (SD)**	**6month change, mean (%)**	
Cardiovascular markers							
*Systolic blood pressure** *(mm Hg)*	126.33 (14.65)	−1.07 (−0.85)	134.81 (16.19)	−1.15 (−0.86)	134.83 (19.62)	3.24 (2.40)	P_{C-H}=0.150 P_{C-S}=0.005 P_{H-S}=0.148
Diastolic blood pressure (mm Hg)	79.60 (8.67)	−0.72 (−0.90)	84 (11.84)	−1.58 (−1.89)	83.28 (11.57)	0.27 (0.33)	P_{C-H}=0.494 P_{C-S}=0.089 P_{H-S}=0.304
HDL (mg/dl)	59.64 (17.48)	4.80 (8.05)	59.86 (18.91)	4.01 (6.70)	61.04 (18.67)	0.46 (0.75)	P_{C-H}=0.451 P_{C-S}=0.190 P_{H-S}=0.572
CRP (mg/l)	8.38 (12.11)	−1.47 (−17.58)	9.03 (15.65)	−3.38 (−37.37)	7.56 (10.44)	−1.00 (−13.27)	P_{C-H}=0.374 P_{C-S}=0.731 P_{H-S}=0.221
Metabolic Markers							
Body Mass Index	35.23 (6.09)	0.29 (0.83)	36.02 (7.22)	−1.45 (−4.02)	36.29 (8.02)	0.61 (1.68)	P_{C-H}=0.231 P_{C-S}=0.991 P_{H-S}=0.235
Waist circumference (cm)	107.99 (14.31)	−1.37 (−1.26)	109.61 (13.15)	−1.46 (−1.33)	110.70 (14.58)	−0.28 (−0.25)	P_{C-H}=0.911 P_{C-S}=0.471 P_{H-S}=0.546
High plasma glucose (mg/dl)	103.44 (13.68)	−0.24 (−0.24)	102.83 (13.37)	−1.21 (−1.17)	102.32 (12.93)	0.77 (0.75)	P_{C-H}=0.544 P_{C-S}=0.875 P_{H-S}=0.665
Triglycerides (mg/dl)	109.00 (67.84)	5.81 (5.33)	114.20 (54.88)	−2.26 (−1.98)	116.71 (65.38)	0.81 (0.69)	P_{C-H}=0.634 P_{C-S}=0.824 P_{H-S}=0.807

* P_{C-S}=0.005, P values for comparing the changes adjusting for baseline values of the outcomes; P_{C-H}: home-based vs. control group; P_{C-S}: supervised vs. control group; P_{H-S}: home-based vs. supervised group

** 6-month percent change is calculated by subtracting the baseline value from the 6-month follow-up value divided by the baseline value; and expressed as a %

Table 4.

Change in Allostatic Load by Exercise Intervention Arm and Family History of Breast Cancer

	Supervised	Home Based	Control	P Values*
Total Population				
Baseline zAL, mean(SD)	0.44 (3.76)	1.65 (3.55)	1.47 (4.27)	
*6 month zAL change,** mean (SE)*	−0.42 (2.84)	−0.71 (2.83)	0.40 (2.61)	P_{C-H} = 0.023 P_{C-S} = 0.035
No Fam Hx BrCa				
Baseline zAL, mean(SD)	0.5 (3.6)	1.22 (3.2)	0.73 (4.29)	
*6 month zAL change,** mean (SE)*	−0.11 (3.05)	−0.27 (2.81)	0.21 (2.77)	P_{C-H} = 0.447 P_{C-S} = 0.395
Fam Hx BrCa				
Baseline zAL, mean(SD)	0.35 (4.04)	2.15 (3.9)	3.02 (3.88)	
*6 month zAL change,** mean (SE)*	−0.94 (2.46)	−1.26 (2.82)	0.87 (2.21)	P_{C-H} = 0.006 P_{C-S} = 0.012

*P values for comparing the changes adjusting for baseline values of the outcomes; P_{C-H}: home-based vs. control group; P_{C-S}: supervised vs. control group

**6-month change is calculated by subtracting the baseline value from the 6-month follow-up value