β2- and β3-Adrenergic receptor polymorphisms and exercise hemodynamics in postmenopausal women

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McCole, Steve D., Alan R. Shuldiner, Michael D. Brown, Geoffrey E. Moore, Robert E. Ferrell, Kenneth R. Wilund, Andrea Huberty, Larry W. Douglass, and James M. Hagberg. β2- and β3-Adrenergic receptor polymorphisms and exercise hemodynamics in postmenopausal women. J Appl Physiol 96: 526–530, 2004; 10.1152/japplphysiol.00498.2003.—We sought to determine whether common genetic variations at the β2 (β2-AR, Gln27Glu) and β3 (β3-AR, Trp64Arg) adrenergic receptor gene loci were associated with cardiovascular (CV) hemodynamics during maximal and submaximal exercise. CV hemodynamics were assessed in 62 healthy postmenopausal women (20 sedentary, 22 physically active, and 20 endurance athletes) during treadmill exercise at 40, 60, 80, and 100% maximal exercise. CV hemodynamics were assessed in 62 healthy postmenopausal women (20 sedentary, 22 physically active, and 20 endurance athletes) during treadmill exercise at 40, 60, 80, and 100% maximal O2 uptake using acetylene rebreathing to quantify cardiac output. The β2-AR genotype and habitual physical activity (PA) levels interacted to significantly associate with arteriovenous O2 difference (a-vDo2) during submaximal exercise (P = 0.05), with the highest submaximal exercise a-vDo2 in sedentary women homozygous for the β2-AR Gln allele and no genotype-dependent differences in submaximal exercise a-vDo2 in physically active and athletic women. The β2-AR genotype also was independently associated with a-vDo2 during submaximal (P = 0.004) and ~100% maximal O2 uptake exercise (P = 0.006), with a 1.2–2 ml/100 ml greater a-vDo2 in the Gln/Gln than in the Gln/Glu genotype women. The β3-AR genotype, independently or interacting with habitual PA levels, was not significantly associated with any CV hemodynamic variables during submaximal or maximal exercise. Thus it appears that the β2-AR genotype, both independently and interacting with habitual PA levels, is significantly associated with a-vDo2 during exercise in postmenopausal women, whereas the β3-AR genotype does not appear to be associated with any maximal or submaximal exercise CV hemodynamic responses in postmenopausal women.

A number of common polymorphic genetic variations, particularly those in the renin-angiotensin system, are related to pathologies within the cardiovascular (CV) system (5, 24). Some recent evidence indicates that common polymorphic genetic variations within the sympathetic nervous system (SNS) may also associate with CV pathologies (10, 15, 25, 26, 28) and with CV physiological function (4, 8). The SNS is critical in regulating the CV hemodynamic responses during stress, especially exercise. However, it is not known whether common genetic variations that may affect SNS activity associate with CV hemodynamics during submaximal or maximal exercise.

We selected the common Gln27Glu β2-adrenergic receptor (β2-AR) variant as one locus of primary interest, because β2-ARs are intimately involved in the regulation of peripheral vascular smooth muscle tone and, therefore, could directly affect total peripheral resistance (TPR) and indirectly affect exercise blood pressure (BP) and stroke volume (SV), cardiac output (Q), heart rate (HR), and arteriovenous O2 difference (a-vDo2). This variant has been found to associate with altered peripheral blood flow regulation (4). We also selected the Trp64Arg β3-adrenergic receptor (β3-AR) variant for study, because although the β3-AR is thought to be primarily involved in the regulation of metabolic processes (11, 16), β3-ARs are found in the heart, and the Trp64Arg variant has been found to associate with hypertension and BP independent of its metabolic effects (26, 28).

Therefore, our working hypothesis was that common genetic variations at the β2-AR and β3-AR gene loci would associate with CV hemodynamics during submaximal and maximal exercise. Specifically, we hypothesized that women homozygous for the Gln27 β2-AR allele would have higher HR, SV, Q, systolic and diastolic BP, and TPR and lower a-vDo2 during submaximal and maximal exercise than women with other Gln27Glu β2-AR genotypes. We also specifically hypothesized that women carrying the Arg64 β3-AR allele would have higher HR, SV, Q, systolic and diastolic BP, and TPR and lower a-vDo2 during submaximal and maximal exercise than women homozygous for the Trp64 β3-AR allele. Because SNS function is markedly affected by endurance exercise training (29, 30), we also hypothesized that these common β2-AR and β3-AR polymorphic variations would interact with habitual physical activity (PA) level to associate with CV hemodynamics during submaximal and maximal exercise. We addressed this hypothesis by studying subjects with markedly different habitual PA levels.

METHODS

Sixty-two healthy postmenopausal Caucasian women were recruited to participate in the study. Women were considered postmenopausal if they had elevated levels of follicle-stimulating and luteiniz-

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ing hormones and reported a lack of menses for >2 yr. Women were
 Grouped into three PA categories (sedentary, physically active, and
 endurance athlete) on the basis of their habitual PA history as defined
 previously (6). Briefly, women were classified as “sedentary” if they
 were not regularly performing aerobic exercise. “Physically active”
 women were accumulating ≥90 min of aerobic exercise during at
 least three exercise sessions per week. Women were classified as
 “athletes” if they were training vigorously for competition in endur-
 ance events. Approximately half of the women in each group were on
 hormone replacement therapy (HRT). The PA and HRT status of all
 subjects had been constant for >2 yr before the study. The Institu-
 tional Review Board of the University of Pittsburgh approved the
 study, and all subjects provided their written informed consent before
 they were subjected to testing.

 Sedentary and physically active subjects underwent a screening
 graded maximal exercise test to exclude those with evidence of CV
disease (19). Sedentary and physically active women with no evidence
 of CV disease performed a second graded maximal treadmill exercise
test to measure maximal $O_2$ uptake ($V_{O2\text{max}}$) (19). Endurance athletes
 completed a single graded maximal treadmill exercise test for screen-
ing and $V_{O2\text{max}}$ measurement, BP, HR, and ECG were monitored
 before, during, and after each test. $O_2$ uptake ($V_{O2}$) was measured
 continuously during all exercise tests using a respiratory mass spec-
trometer (Marquette), mixing chamber (Rayfield), turbine volum-
 meter system (model VMM, Interface Associates), and customized
 validated metabolic software (19). Exercise continued until the subject
 reached exhaustion or showed signs or symptoms of CV decompen-
sation. Subjects not reaching standard criteria to determine that a true
 $V_{O2\text{max}}$ was achieved repeated the test until these criteria were
 exceeded (19). Body composition was determined with dual-energy
 X-ray absorptiometry (model DPX-L, Lunar, Madison, WI).

 $Q$ was measured by acetylene rebreathing after ~6 min of treadmill
 exercise at 40, 60, and 80% $V_{O2\text{max}}$ and during the last minute of an
 exercise bout designed to elicit $V_{O2\text{max}}$ in ~6 min (19). SV was
determined by dividing $Q$ by HR measured via ECG just before the
 rebreathing maneuver. $V_{O2}$ was monitored throughout each exercise
 bout, and $a-V_{O2}$ was calculated by dividing $V_{O2}$ by $Q$. TPR was
 calculated as mean arterial pressure (MAP) divided by $Q$, with MAP
 estimated as diastolic BP + ½ * (systolic BP - diastolic BP) based
 on BP measured by auscultation immediately preceding each Q
determination. The independent associations between exercise hemo-
dynamics, habitual PA levels, and HRT have been published previ-
ously (18, 19). In these previous studies, HRT was not associated with
different CV hemodynamic responses to exercise, and the data from
 the women on HRT and those not on HRT are pooled in this study.

 DNA was isolated from peripheral venous blood samples from all
 subjects using standard procedures (20). DNA from each subject was
 typed for the Gln27Glu β2-AR (14) and Trp64Arg β3-AR (27)
 variants using standard procedures.

 For each dependent variable (systolic and diastolic BP, HR, $Q$,
 TPR, and $a-V_{O2}$), we conducted a mixed-model repeated-measures
 factorial ANOVA (SAS online version 8.1, 1999). The three levels of
 PA and the genotypes at the β2-AR and β3-AR loci form the
 factorials, and each subject was measured for each dependent variable
 at 40, 60, 80, and ~100% $V_{O2\text{max}}$, resulting in four repeated mea-
sures. Random effects included variation among subjects, covariance
 among repeated measures, and the residual variation within subjects.
 Different covariance structures were used to fit the correlation be-
tween repeated measures (exercise intensity) within subject, and the
 best-fitting variance-covariance structure was chosen using the Bayes-
 ian information criterion. If the ANOVA model was significant for a
 genotype or genotype-by-habitual PA level interaction effect, con-
 trasts were conducted for appropriate means comparisons among
 genotypes using t probabilities to identify significant differences. The
 Kenward-Roger degrees-of-freedom method was used. Each model
 and dependent variable also adequately met the assumptions of
 variance homogeneity and normality. Because not all trials yielded
 technically valid results, the sample sizes for the different CV hemo-
dynamic variables during exercise vary somewhat; these sample sizes
 are included in Tables 3 and 4, where these results are presented. $P <$
 0.05 was considered statistically significant. Least squares means ±
 SE are reported correcting for any unequal replication; the least
 squares means for submaximal exercise are those averaged across
 the 40, 60, and 80% $V_{O2\text{max}}$ exercise intensities.

 RESULTS

 β2-AR genotype distribution. As we previously reported
 (21), β2-AR allele and genotype distributions in this group
 were similar to previously reported distributions in larger
 populations (9) (Table 1). However, as we reported previously
 (21), when stratified by the level of PA, frequency of the
 β2-AR Glu/Glu genotype was lower than expected in the
 athletic group. The sedentary and physically active women
 exhibited genotype distributions similar to those reported pre-
 viously.

 β2-AR genotype and subject characteristics. There were no
 significant differences in age, weight, height, or maximum HR
 among β2-AR genotype groups (Table 2). There were signif-
 icant differences in $V_{O2\text{max}}$ and percent body fat among the
 β2-AR genotype groups. However, when the lower-than-ex-
 pected frequency of the β2-AR Glu/Glu genotype in the
 athletes was considered in the statistical analysis, the differences
 for $V_{O2\text{max}}$ and percent body fat among the β2-AR genotype
 groups were no longer significant.

 β2-AR genotype and ~100% $V_{O2\text{max}}$ hemodynamics. Tests of
 the interaction between β2-AR genotype and PA levels were
 not significant for any of the measured CV hemodynamic
 variables during ~100% $V_{O2\text{max}}$ exercise (Table 3). However,

<p>| Table 1. β2-AR and β3-AR allele and genotype distributions in study population and general population |
|-------------------------------------------------------------|--------------|-------------|</p>
<table>
<thead>
<tr>
<th>Allele</th>
<th>Genotype</th>
<th>Allele</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gln</td>
<td>Glu</td>
<td>Gln</td>
<td>Glu/Gln</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>-------</td>
<td>-----------</td>
</tr>
<tr>
<td>Total</td>
<td>0.63</td>
<td>0.37</td>
<td>0.36</td>
</tr>
<tr>
<td>Sedentary</td>
<td>0.61</td>
<td>0.39</td>
<td>0.41</td>
</tr>
<tr>
<td>Physically active</td>
<td>0.60</td>
<td>0.40</td>
<td>0.37</td>
</tr>
<tr>
<td>Athletes</td>
<td>0.61</td>
<td>0.39</td>
<td>0.26</td>
</tr>
<tr>
<td>General population</td>
<td>0.58</td>
<td>0.42</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Data from the general population for the β2-adrenergic receptor (β2-AR) allele and genotype frequencies are from Kortner et al. (9), and β3-adrenergic receptor (β3-AR) allele and genotype frequencies are from Widen et al. (28) and Walston et al. (27).
the interaction between β2-AR genotype and PA levels approached statistical significance for diastolic BP \( (P = 0.07) \). The β2-AR genotype was independently and significantly associated with a-vD\(\text{O}_2\) during \( \sim 100\% \) \( \text{VO}_{2\text{max}} \) exercise, with the Gln/Gln genotype women having a 2 ml/100 ml higher a-vD\(\text{O}_2\) than the Glu/Glu genotype women. β2-AR was not independently and significantly associated with any other CV hemodynamic variable during maximal exercise.

### β2-AR genotype and submaximal exercise hemodynamics.

The interaction between β2-AR genotype and PA levels was significant for a-vD\(\text{O}_2\) during submaximal exercise, with β2-AR Gln homozygotes having the highest submaximal exercise a-vD\(\text{O}_2\) among sedentary women (11.9 ± 0.3, 10.3 ± 0.4, and 9.9 ± 0.6 ml/100 ml for β2-AR Gln/Gln, Gln/Glu, and Glu/Glu, respectively) and there being no genotype-dependent differences in submaximal exercise a-vD\(\text{O}_2\) among physically active (12.5 ± 0.4, 11.9 ± 0.4, and 11.4 ± 0.9 ml/100 ml for β2-AR Gln/Gln, Gln/Glu, and Glu/Glu, respectively) and athletic (11.9 ± 0.4 and 12.1 ± 0.3 ml/100 ml for β2-AR Gln/Gln and Gln/Glu, respectively) women. The β2-AR genotype was also independently and significantly associated with submaximal exercise a-vD\(\text{O}_2\), with a 1.2 ml/100 ml higher submaximal exercise a-vD\(\text{O}_2\) in the β2-AR Gln than in the Glu homozygotic women (Table 3).

### β2-AR genotype, subject characteristics, and exercise hemodynamics.

No women in the present study were homozygous for the variant Arg64 β3-AR allele; thus comparisons could only be made between heterozygotes and those homozygous for the common Trp64 β3-AR allele (Table 1). The distributions of β3-AR alleles and genotypes in the total population and in each of the three PA groups in the present study are similar to those reported in larger population studies (27, 28). The overall distribution also is in Hardy-Weinberg equilibrium.

Age, body weight, height, percent body fat, and maximum HR did not differ between the two β2-AR genotypes (Table 2). \( \text{VO}_{2\text{max}} \), whether expressed in liters per minute or milliliters per kilogram per minute, was significantly higher in the β3-AR Gln/Glu/Glu genotype women. However, because of the lack of Arg alleles in the sedentary women, when habitual PA level was included in the analyses, these genotype-dependent differences in \( \text{VO}_{2\text{max}} \) were no longer significant.

### β3-AR genotype and exercise hemodynamics.

The interactions between β3-AR genotype and PA levels were not significant for any of the measured CV hemodynamic variables during \( \sim 100\% \) \( \text{VO}_{2\text{max}} \) exercise. However, the interaction between β3-AR genotype and PA levels approached the level of statistical significance for a-vD\(\text{O}_2\) during 100% \( \text{VO}_{2\text{max}} \) exercise \( (P = 0.06) \). The β3-AR genotype was not independently associated with any of the maximal exercise CV hemodynamic variables measured in the present study (data not shown). No significant interactions between β3-AR genotype and PA levels affected CV hemodynamics during submaximal exercise. Furthermore, β3-AR genotype did not independently associate with any of the CV hemodynamic measures during submaximal exercise (data not shown).

### Table 2. Subject characteristics, \( \dot{\text{V}}\text{O}_{2\text{max}} \), and maximal HR as a function of β2-AR and β3-AR genotype

<table>
<thead>
<tr>
<th>β2-AR Genotype</th>
<th>( \text{β3-AR Genotype} )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glu/Glu (n = 23)</strong></td>
<td><strong>Glu/Glu (n = 30)</strong></td>
</tr>
<tr>
<td><strong>Age, yr</strong></td>
<td>63±2</td>
</tr>
<tr>
<td><strong>Body wt, kg</strong></td>
<td>62±3</td>
</tr>
<tr>
<td><strong>Height, cm</strong></td>
<td>158±2</td>
</tr>
<tr>
<td><strong>Body fat, %</strong></td>
<td>38±3</td>
</tr>
<tr>
<td><strong>( \text{V}_{\text{O2max}} )</strong> l/min</td>
<td>1.72±0.08</td>
</tr>
<tr>
<td><strong>ml/kg (-1) min (-1)</strong></td>
<td>29.1±1.6</td>
</tr>
<tr>
<td><strong>HR(_\text{max} ), beats/min</strong></td>
<td>165±5</td>
</tr>
</tbody>
</table>

Values are means ± SE. \( \text{VO}_{2\text{max}} \), maximal \( \text{O}_2 \) uptake; HR\(_\text{max} \), maximal heart rate. *Significantly different \( (P < 0.05) \) from β2-AR Gln/Glu; ‡significantly different \( (P < 0.05) \) from β3-AR Trp/Trp.

### Table 3. Exercise CV hemodynamics as a function of β2-AR genotype

<table>
<thead>
<tr>
<th>Maximal Exercise</th>
<th>Submaximal Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gln/Gln (n = 21–25)</td>
<td>Gln/Glu (n = 20–27)</td>
</tr>
<tr>
<td><strong>BP, mmHg</strong></td>
<td><strong>BP, mmHg</strong></td>
</tr>
<tr>
<td><strong>Systolic</strong></td>
<td>182±3</td>
</tr>
<tr>
<td><strong>Diastolic</strong></td>
<td>83±2</td>
</tr>
<tr>
<td><strong>HR, beats/min</strong></td>
<td>161±3</td>
</tr>
<tr>
<td><strong>Q, l/min</strong></td>
<td>10.8±0.3</td>
</tr>
<tr>
<td><strong>SV, ml</strong></td>
<td>67±3</td>
</tr>
<tr>
<td><strong>TPR, dyn·cm(^{-5})</strong></td>
<td>908±37</td>
</tr>
<tr>
<td><strong>a-vD(\text{O}_2), ml/100 ml</strong></td>
<td>15.7±0.3</td>
</tr>
</tbody>
</table>

Values are means ± SE. BP, blood pressure; HR, heart rate; Q, cardiac output; SV, stroke volume; TPR, total peripheral resistance; a-vD\(\text{O}_2\), arteriovenous \( \text{O}_2 \) difference. *Significantly different \( (P < 0.05) \) from β2-AR Gln/Glu. Submaximal exercise values are those evaluated for a relative exercise intensity of 60% \( \text{VO}_{2\text{max}} \) as a covariate.

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DISCUSSION

The present results indicate that a common variant at the β2-AR locus is independently associated with a-VD\(\text{O}_2\) during maximal and submaximal exercise in postmenopausal women. Furthermore, this variant also interacts with habitual PA levels to significantly associate with a-VD\(\text{O}_2\) during submaximal exercise. However, a common variant at the β3-AR locus does not appear to associate independently or interactively with habitual PA levels with CV hemodynamic responses to maximal or submaximal exercise in postmenopausal women. We had initially hypothesized that both of these variants would be associated with alterations in a number of CV hemodynamic responses to submaximal and maximal exercise intensities. However, only a-VD\(\text{O}_2\) was independently and interactively associated with β2-AR genotype. Adding strength to this relation is the fact that a-VD\(\text{O}_2\) was related to β2-AR genotype in two separate analyses at submaximal and maximal exercise, making it more likely that this is a true positive finding.

A 1997 review by Bouchard et al. (3) indicated that genetic factors play a significant and substantial role in determining CV hemodynamics at rest and during submaximal exercise. Others reported 24–47% heritabilities of a variety of exercise hemodynamic parameters (2). Recently, the HERITAGE study found 40–45% heritabilities of submaximal exercise SV and Q in ~100 Caucasian two-generation families (1). Landry et al. (13) reported that exercise hemodynamic adaptations with exercise training were more similar in monozygotic than in dizygotic twins. The HERITAGE study also recently found 24–38% heritabilities of submaximal exercise SV and Q adaptations with endurance exercise training (1).

More recent investigations have assessed the impact of specific common allelic variants within the renin-angiotensin-aldosterone system, most notably the angiotensin-converting enzyme (ACE) insertion/deletion and the M235T angiotensinogen (AGT) variants, on a limited number of CV hemodynamic variables during exercise (12, 22, 23). These previous studies generally assessed genotype-dependent associations with CV hemodynamic responses to the same absolute submaximal exercise work rates among individuals. Such a design does not account for the known and substantial effect of relative exercise intensity on CV hemodynamic responses and may obscure genotype-dependent differences in CV hemodynamic responses to exercise. We previously reported that common variants of ACE and AGT were associated with the responses of several CV variables, in particular HR, during submaximal exercise at the same relative work rate and during maximal exercise in postmenopausal women (7, 17). The design of the present study was similar, inasmuch as we assessed the association between two variants at loci within the SNS and CV hemodynamic responses to exercise at a number of work rates matched for relative exercise intensity across subjects.

β2-AR variants have previously been found by others to relate to BP and the prevalence of hypertension (10, 25). We did not find a similar relation with BP during submaximal or maximal exercise in the postmenopausal women in the present study. SNS function at rest and during submaximal and maximal exercise is markedly affected by endurance exercise training (29, 30). Thus it might be expected that the β2-AR genotype would interact with substantially different habitual PA levels to affect CV hemodynamics during exercise. However, there were no significant interactions during maximal exercise in the present study. The only statistically significant interaction during submaximal exercise affected a-VD\(\text{O}_2\) (\(P = 0.05\)) such that genotype-dependent differences only occurred in the sedentary postmenopausal women, with a higher a-VD\(\text{O}_2\) in the Gln than the Glu homozygotes.

We had anticipated that the effects of the β2-ARs on vascular smooth muscle would directly affect TPR and, thereby, potentially affect a-VD\(\text{O}_2\) indirectly. However, we found that the β2-AR genotype was associated with different a-VD\(\text{O}_2\) responses during submaximal and maximal exercise without significantly affecting TPR. The a-VD\(\text{O}_2\) was significantly greater in postmenopausal women who were homozygous for the Gln genotype than in those homozygous for the Glu genotype during maximal and submaximal exercise. Our ANOVA analyses assessed the independent effect of β2-AR genotypes while also accounting for the independent effect of different habitual PA levels. Thus the smaller frequency of Glu homozygotes in the women athletes was accounted for when the independent effect of the β2-AR genotype on these exercise hemodynamic responses was assessed. It is possible that the Gln27Glu β2-AR variant may not directly underlie the genotype-dependent differences in exercise hemodynamic responses we observed in these women, inasmuch as some other marker in linkage disequilibrium with the Gln27Glu β2-AR variant may actually be the allelic variant responsible for these different exercise hemodynamic responses.

β3-ARs are primarily involved in adipocyte lipolysis and skeletal muscle thermogenesis (11, 16). However, Tonolo and coworkers (26) recently reported that this allelic variant was associated with hypertension, and we previously found a significant Trp64Arg β3-AR genotype-dependent effect on BP in nondiabetic subjects (28). However, in the present study, we found no evidence that β3-AR allelic variants, either independently or interactively with habitual PA levels, were associated with any of the CV hemodynamic responses during submaximal or maximal exercise.

Our previous studies with a number of statistically significant results have shown that the sample size used in the present study is sufficiently powerful to identify genetic markers with significant associations with CV hemodynamics during submaximal and maximal exercise (6, 7, 17). A number of previous analyses have been performed on these outcome phenotypes as a function of genotype, and it is possible that some of our findings may have been false-positive statistical relations. Also this study was not initially designed to address these genotype-dependent relations, and these analyses were performed in a retrospective fashion. One previous study in this population determined that women with the ACE II genotype had a 6.3 ml·kg\(^{-1}\)·min\(^{-1}\) higher V\(\text{O}_2\)max than women with the ACE DD genotype and that this difference was associated with genotype-dependent differences in a-VD\(\text{O}_2\) at maximal exercise (6). We also reported that these ACE variants are associated with many CV hemodynamic responses to submaximal exercise (7). In addition, we reported a number of significant associations between CV hemodynamic responses during submaximal and maximal exercise and the AGT polymorphism (17). Therefore, the relative lack of significant associations found with the β2-AR genotype, except for a-VD\(\text{O}_2\), and the β3-AR genotype in the present study suggests that they may
not be strong candidates for future investigations attempting to identify the genetic markers underlying CV hemodynamic responses during exercise.

In conclusion, the a-VO₂ response to submaximal and maximal exercise in postmenopausal women was associated with the β₂-AR genotype, such that a-VO₂ was greater in women with the Gln/Gln genotype than in those homozygous for the Glu allele variant. Variants at the β₂-AR locus, however, are not associated with changes in the CV hemodynamic response to exercise in these women.

GRANTS

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