DHEA, DHEA-S and cortisol responses to acute exercise in older adults in relation to exercise training status and sex

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Running title: Exercise and hormones in older adults

Tables: 3

Figures: 2

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Abstract

The aim of the present study was to investigate resting measures of dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulphate (DHEA-S) and cortisol, and the response and recovery of these hormones to acute exercise, in male and female older adults of different exercise training status. Participants were 49 community dwelling older adults (23 females) aged between 60 - 77 years who were either: sedentary (n = 14), moderately active (n= 14), or endurance trained (n = 21). Participants undertook an acute bout of exercise in the form of an incremental submaximal treadmill test. The exercise lasted on average 23min 49sec (SD = 2min 8sec) and participants reached 76.5% (SD = 5.44) of predicted maximal HR. Blood samples were collected prior to exercise, immediately, and 1h post exercise. DHEA levels significantly increased immediately post exercise, however, DHEA-S levels only significantly increased in females. Cortisol significantly decreased immediately post exercise, and 1 h post exercise compared to pre. There were no significant differences in resting hormone levels, nor hormonal responses to exercise between training status groups. The findings suggest that exercise can stimulate DHEA production in older adults, and that hormonal responses to exercise differ between male and female older adults.

Introduction

Dehydroepiandrosterone (DHEA) and its sulphated metabolite, dehydroepiandrosterone sulphate (DHEA-S) are androgens produced by the adrenal cortex. DHEA/S has been proposed to affect various systems of the body and be anti-ageing (Chahal and Drake, 2007). It has been established that DHEA/S is immune enhancing, where cortisol, also produced by the adrenal cortex, is immunosuppressive if chronically elevated (Buford and Willoughby, 2005). DHEA and DHEA-S production peaks at age 20-30 and then declines progressively with age (Belanger et al., 1994; Labrie et al., 1997; Orentreich et al., 1992). In contrast, cortisol has been reported to increase with age (Deuschle et al., 1997; VanCauter et al., 1996), although counter evidence exists (Orentreich et al., 1992). Reductions in DHEA/S have been implicated in the disturbance of other physiological systems, such as the musculoskeletal system (Walston et al., 2006). Further, over-representation of cortisol compared to DHEA, and the consequent increase in the cortisol:DHEA ratio with ageing (Phillips et al., 2007), is associated with immune impairments and infection risk in older adults (Butcher et al., 2005). Exercise has been proposed as an intervention to protect against changes in the neuroendocrine system with ageing and improve immunity in older adults (Phillips et al., 2007).

DHEA-S has been found to be significantly higher in older men who are endurance trained (Tissandier et al., 2001) and who regularly cycled at moderate intensity (Ravaglia et al., 2001). In contrast, DHEA-S levels have been found to be similar between older male runners and sedentary controls (Arai et al., 2006). These studies did not include women; however,

other studies investigating VO_{2max} and energy expenditure rather than exercise training status have. DHEA-S correlated positively with VO_{2max} (Bonnefoy et al., 1998; Bonnefoy et al., 2002) and estimated energy expenditure in older women, but not men (Bonnefoy et al., 1998; Kostka et al., 2002). In contrast, Abbasi et al (1998) reported an association between VO_{2max} and DHEA-S in men but not women, although this finding did not withstand adjustment for age. However, in these studies participants were of average fitness levels and not endurance trained. In addition, those who take part in moderate activities have not been compared to those who are endurance trained within the same study, nor has DHEA-S been examined in parallel with DHEA. Thus it seems important to examine whether or not higher levels of habitual physical activity might have a greater effect on DHEA and DHEA-S levels in both men and women.

DHEA (Aldred et al., 2009; Cumming et al., 1986) and DHEA-S (Tremblay et al., 2004) have been shown to increase in response to acute exercise in younger adults. Endurance trained young males showed attenuated increases in hormone concentrations in response to exercise compared to resistance trained individuals (Tremblay et al., 2004). One study has compared hormonal responses to resistance exercise in middle aged strength trained and untrained men (Cadore et al., 2008). There were no differences in hormones between trained and untrained men at rest; however, untrained men demonstrated a significant increase in DHEA and cortisol in response to acute resistance exercise, where trained men did not. This study suggests trained and untrained middle aged individuals may elicit different hormonal responses to exercise, however, less is known regarding responses in elderly individuals. As older adults of different training status and fitness may vary in hormone levels at rest, they may also display different hormonal responses to acute exercise.

A small number of studies have investigated these hormones in older adults, but have mainly been restricted to postmenopausal females; less is known about males and older individuals. For example, DHEA significantly increased to exercise in females aged up to 69. This was restricted to resistance exercise and was not observed with endurance exercise (Copeland et al., 2002). Early postmenopausal females demonstrated an increase in DHEA-S immediately and 2 h post a combined endurance and strength training session (Kemmler et al., 2003). Another study in postmenopausal females found an increase in DHEA, but not DHEA-S, in response to submaximal exercise (Giannopoulou et al., 2003). A more recent study of older men and women reported that neither DHEA or DHEA-S increased immediately after acute submaximal exercise (Aldred et al., 2009), although this study only tested seven participants and no samples were taken during the recovery period. The lack of clear consensus may be due to the different exercise protocols employed and participants studied. With regard to cortisol, one study examined older fit and unfit females' baseline levels of cortisol, response and recovery to acute submaximal exercise, and failed to observe any significant differences between groups (Traustadottir et al., 2004), although DHEA/S were not measured in this study. To our knowledge, responses of DHEA, DHEA-S and cortisol to acute exercise in older males and females in relation to different levels of training status, has yet to be examined.

If exercise is to be used as a possible intervention to buffer against age induced changes in the neuroendocrine system, such as the reduction in DHEA/DHEA-S, then it is important to establish: first, whether exercise training influences levels of these hormones in older age; and second, whether training or sex affect hormonal responses to exercise. Therefore, the

aim of the present study was to investigate resting measures of DHEA, DHEA-S and cortisol, and their response to and recovery from acute exercise, in male and female older adults of different exercise training status. It was hypothesised first, that older adults who were exercise trained would present with a more favourable hormonal profile: higher levels of DHEA/S and a lower cortisol:DHEA ratio. Second, it was hypothesised that sedentary individuals would have a greater hormonal response to acute exercise.

Methods

Participants

Participants were 49 community dwelling older adults (23 females) recruited from the West Midlands area aged between 60 - 77 years. Inclusion criteria were: no endocrine or immune disorder, no psychiatric illness, no eating disorder, and not taking glucocorticoid medication. Twenty percent of participants reported suffering from a chronic illness; hypertension and asthma, and 43% reported taking medication; antihypertensives, non-corticosteroid inhalers, statins, and gastrointestinal medications. All participants described themselves as "white" ethnicity, and in terms of socio-economic status, 86% of participants classified themselves as non-manual based on their previous or current occupation using the Registrar General's Classification of Occupations (Classification of Occupations, 1980). Participants were either sedentary (n = 14), moderately active (n= 14), or endurance trained (n = 21). The sedentary participants were recruited from the local community and were not currently involved in any regular exercise nor had they been for 5 years prior to the study. Moderately active participants were recruited from local rambling groups, keep fit classes, aqua-fit classes, and gymnasia. Endurance trained older athletes were recruited from local running clubs and at races. Details of the exercise behaviour of participants are described in relation to the

exercise diary below. There was no significant difference in socio-economic status, chronic illness, or medication use between the exercise groups.

Study design

This study was a cross sectional investigation of the DHEA, DHEA-S and cortisol response and recovery to acute exercise in untrained, moderately trained, and untrained older adults. It comprised an acute exercise bout and the completion of a 14 day exercise diary. All participants gave written informed consent prior to the study, which was approved by the University Research Ethics Committee.

Exercise diary

To confirm the allocation at recruitment to sedentary, moderately active and endurance trained groups, participants completed a consecutive 14 day exercise diary where they recorded: what activity they did, the duration of the activity, and the intensity of the exercise. The intensity of the exercise was determined using a 0-10 RPE scale (Borg, 1998) where 0 was rest and 10 was maximal effort; participants were briefed on the use of the RPE scale and instructions and examples were also provided in the diary. The diary was analysed to determine how long was spent in moderate and vigorous activity based on MET values for a given activity (Ainsworth et al., 2000) and RPE (Nelson et al., 2007). The activities of the moderate group were mainly rambling, golf, yoga, badminton, swimming, and keep fit classes. The endurance trained group were runners, and cycling, circuit training and karate were also reported among this group. Minutes spent in moderate and vigorous exercise over the 14 day period were averaged per week. From this, an exercise score was created using

the criteria from the Whitehall study (Marmot et al., 1991). This uses a 0-5 categorical scoring system e.g. if they spent 1-2 h performing an activity they were awarded a score of 1, 3-5 h a score of 2 and so on. A combined exercise score was calculated by multiplying the category score by a weighting of 2 for moderate, and 3 for vigorous activity. As shown in Table 1, the exercise groups had significantly different exercise scores and significantly varied in moderate and vigorous exercise.

[Insert Table 1 about here]

Blood samples and hormone analysis

Three blood samples were collected: prior to exercise, immediately post exercise, and 1h post exercise. The first blood sample was taken between 8.30-9.30 am, this was on average 3h after participants had woken up. For each blood sample, a 6 ml venous blood was collected from an ante-cubital vein into plain tubes (BD Vacutainer, Plymouth, UK). Blood was allowed to clot at room temperature for 1h, and then centrifuged at 4000 rpm for 5 min, and the separated serum was stored at -20°C until analysis. DHEA, DHEA-S and cortisol were analysed in duplicate using ELISAs based on the principle of competitive binding (IBL International, Hamburg, Germany). The microtiter wells are coated with a polyclonal antibody directed towards DHEA/DHEA-S or cortisol. The hormone in the sample competes with horseradish peroxidase conjugate for binding to the coated antibody. After 60 min incubation the unbound conjugate is washed off. After addition of a substrate solution and further 15 min incubation, the enzymatic reaction is stopped and the concentration of these hormones is inversely proportional to the optical density measured at 450 nm. Intra assay coefficients were < 10%.

196
197 Procedure

198
199 *Pre study screening*

200 Prior to entry to the study, participants completed pre study questionnaires. Participants
201 were asked: if they suffered from any chronic illness, any acute illness, and if they were
202 taking any medication. Participants completed: a physical activity readiness questionnaire
203 (PAR-Q) (Tharrett and Peterson, 1997) the Hospital Anxiety and Depression Scale (HADS)
204 (Zigmond and Snaith, 1983), and the Life Events Survey from the West of Scotland Twenty-
205 07 study (Ford et al., 1994) to assess stressful life events exposure over the past year. No
206 participants met the criteria for high probability of anxiety or depression, and there was no
207 significant difference in stressful life events exposure between exercise groups. Participants
208 were given a 14 day exercise diary and instructions on how to complete it. They were then
209 given an appointment for the acute exercise trial.

210

211 *Acute exercise bout*

212 Participants were asked to refrain from exercise and alcohol 24h prior, and food and caffeine
213 12 h prior to arriving at the laboratory. Participants arrived between 8-9am and, on arrival,
214 had the timeline for the visit described and asked if they had any questions. Their height and
215 weight was measured. They were then were fitted with a heart rate (HR) monitor (Polar,
216 Electro Kempele, Finland). The procedure for Douglas bag gas analysis was explained and
217 they watched a researcher demonstrate how to position the nose clips and insert the
218 mouthpiece. For familiarisation, participants practiced using the nose clip and mouthpiece

and breathed for 1 min in a seated position for familiarisation. They then sat quietly and rested for 15 min before the 1st blood sample was taken, on average this was taken 2 h 45 min after waking (SD = 33 min), and timing of this sample did not differ significantly between groups.

Participants then undertook an acute bout of exercise in the form of an incremental submaximal treadmill test. A researcher demonstrated how to walk on the treadmill for those who had not used one before. Participants then began walking on the treadmill and speed was gradually increased until the participant reached a pace they considered "brisk walking". Once this pace was reached the test commenced comprising 4 min stages. Every 4 min the gradient increased between 2 - 3.5%, depending on the participants HR. During the final minute of each 4 min stage expired air samples were collected into Douglas bags (Cranlea, Birmingham, UK) for the determination of oxygen consumption. HR was monitored continuously throughout exercise and recorded every 15 sec during the final min of each stage, and RPE was obtained at the end of each stage and prior to the termination of the exercise. The test was terminated once the participant had reached 75% of their predicted maximum HR, as determined by the formula 208 – (age × 0.7) (Tanka et al., 2001). In a few cases, participant's HR did not increase proportionally with the exercise, in which case the exercise was terminated once they reached 'hard' on the RPE scale. Once the exercise was finished, participants were seated immediately for another blood sample, and a final blood sample was taken 1 h post exercise.

Carbon dioxide production and oxygen consumption were determined from Douglas bag samples using an infrared carbon dioxide analyser and a paramagnetic oxygen analyser (Analyser Series 1440, Servomex, Crowborough, East Sussex, UK). Expired air volumes

were measured using a dry gas meter (Harvard Apparatus, Edenbridge, Kent, UK) and corrected to standard temperature and pressure. Maximal oxygen consumption ($V0_{2max}$) was predicted using a regression equation created from plotting the relationship between HR and oxygen consumption during the final 3 stages of exercise.

Statistical analyses

Univariate ANOVA was used to examine differences between exercise groups for: age, BMI, VO_2max, and HR, RPE and exercise duration. Repeated measures ANOVA was used to examine the DHEA, DHEA-S and cortisol response to exercise, test any main effects of group, and finally to examine any group × time interactions. Repeated measures ANOVA was also used to investigate any sex differences in hormone responses. Where significant effects emerged, subsequent ANCOVA was performed to adjust for any potential confounding variables, such as age. Greenhouse-Geisser corrections were applied with the repeated measures analyses and partial η^2, a measure of effect size, is reported throughout.

Results

Group characteristics

Table 2 displays age, BMI and predicted VO_{2max} for the exercise groups. Age, $F(2,46) = 5.06$, $p = .01$, $\eta^2 = .180$, and BMI, $F(2,46) = 8.94$, $p < .001$, $\eta^2 = .280$, differed significantly between exercise groups. VO_{2max} also differed significantly between groups, $F(2,39) = 22.14$, $p < .001$, $\eta^2 = .532$, and this group effect withstood adjustment for age. In comparison to VO_{2max} criteria for sex and age group (McArdle et al., 2001) males in the untrained, moderate, and trained groups were classified as having average, good and

excellent aerobic fitness for their age group, respectively. Females in the untrained and moderate groups were classed as average, and trained females were classed as excellent for their age group.

[Insert Table 2 about here]

Acute exercise

The mean duration of the incremental exercise test was 23min 49sec (SD = 2min 8sec) and the mean final RPE obtained at the end of exercise was 5.1 (SD = 1.08), which was equivalent to 'hard'. The final HR achieved at the end of the exercise was 132.7 (SD = 9.91) bpm, this was equivalent to 76.5% (SD = 5.44) of predicted maximal HR. There were no significant differences between exercise training status groups or sex for: exercise duration; final RPE, final HR, or percentage HR.

DHEA, DHEA-S and cortisol

Training status

There were no significant group differences in any of the hormone parameters, at any of the time points. Accordingly, all subsequent results are reported for participants as a whole. VO_{2max} was positively associated with DHEA-S levels in women, although this was not statistically significant, $r(18) = .42$, $p = .07$. There were no other trends for VO_{2max} and hormone levels.

DHEA

There was a significant main effect of time for DHEA where DHEA levels increased immediately post exercise, $F(2,92) = 6.62$, $p = .004$, $\eta^2 = .126$. This effect is displayed in Figure 1a.

DHEA-S

There was a trend for DHEA-S to increase immediately post exercise, but this failed to reach statistical significance ($p = .07$). However, the effect was significant for females, $F(2,42) = 4.37$, $p = .02$, $\eta^2 = .172$. Compared to pre, females had a significant increase in DHEA-S immediately post exercise. Although they did not exhibit a response to exercise, males had significantly higher overall DHEA-S levels than woman, $F(1,43) = 4.48$, $p = .04$, $\eta^2 = .094$. Descriptive statistics of hormone levels for males and females are displayed in Table 3.

[Insert Table 3 about here]

Cortisol

As shown in Figure 1b, there was a significant main effect of time for cortisol which decreased immediately post exercise, and 1 h post exercise compared to pre, $F(2,92) = 19.58$, $p < .001$, $\eta^2 = .299$. Males had significantly higher cortisol levels than women, $F(1,47) = 4.06$, $p = .05$, $\eta^2 = .079$, (Table 3).

Cortisol:DHEA/DHEA-S ratio

There was a significant main effect of time for the cortisol:DHEA ratio, $F(2,90) = 20.04$, $p < .001$, $\eta^2 = .308$, where the ratio decreased immediately post and 1 h post exercise compared to pre (Figure 2a). The cortisol:DHEA-S ratio also decreased significantly immediately post and 1 h post exercise compared to pre, $F(2,78) = 19.08$, $p < .001$, $\eta^2 = .329$ (Figure 2b).

[Insert Figures 1 and 2 about here]

Discussion

Older adults demonstrated a significant increase in DHEA immediately post exercise. DHEA has been previously shown to increase in response to submaximal aerobic (Giannopoulou et al., 2003) and resistance exercise (Copeland et al., 2002) in postmenopausal women, and this study extends previous findings to older males. Despite a similar exercise protocol, the present findings contrast with those from a recent study which failed to find an increase in DHEA with exercise in individuals aged between 65 - 75 years (Aldred et al., 2009). However, this could reflect the small sample size employed in this previous investigation.

Cortisol decreased immediately post and 1 hour post exercise compared to pre exercise. Independent activation of the zona fasciculata and zona reticularis has been noted previously (Velardo et al., 1991). A decrease in cortisol post exercise has also been noted in postmenopausal females, (Kemmler et al., 2003), this decrease continued throughout the 2 h recovery period. As with the present study, Kremmler et al (2003) exercised their participants in the morning, however, the authors suggested that their observed decreases were above that of normal diurnal decline. It is difficult to separate the effects of exercise from the effects of diurnal variation. However, the first blood sample taken in the present study was nearly 3 h after waking; therefore, participants would have already experienced the large decrease in cortisol that occurs following the cortisol awakening response. This is suggested by cortisol diurnal rhythm data collected on average a week before acute exercise testing in the present participants (unpublished data available on request). Further, the present finding is in contrast to Traustadottir et al. (2004), who reported an increase in

cortisol in older females after 15 minutes of cycling, this exercise bout also took place in the morning period, suggesting time of day is not responsible for this difference.

As a result of the decrease in cortisol, which was not apparent with DHEA/S, the cortisol:DHEA/S ratio significantly decreased immediately and 1 h post exercise. This represents more favourable endocrine profile, although it may be that this only occurs if exercise takes place in the morning period. Identical exercise in the afternoon would be required to determine whether this is the case. If the effect is limited to morning exercise, it could be that this is because it is the optimal time to alter the balance between cortisol and DHEA/S and thus promote greater protection against decrements in immunity linked to higher cortisol levels. However, this is highly speculative, and exercise of a longer duration or a higher intensity in the morning may still produce an increase in cortisol. It is known that only high intensity or exhaustive exercise results in increases in cortisol, with a threshold of 60% VO_{2max} required for its release (Bishop, 2006; Pedersen and Hoffman-Goetz, 2000). Therefore, although participants were exercised to 75% of their predicted maximum capacity, as the exercise was graded, and not at a predetermined intensity, it is possible that they did not exercise for a sufficient period at 60% VO_{2max} or above to elicit an increase in cortisol.

To our knowledge, this is the first study to examine the responses of DHEA/S alongside cortisol to acute exercise in relation to exercise training status in elderly participants. The present findings suggest that sedentary, moderately trained and endurance trained older adults do not vary in their hormonal responses to exercise. This implies that older adults, regardless of training status, are able to produce a DHEA response to exercise. This finding is in contrast to those of Cadore et al (2008) who found that trained middle-aged men required a greater exercise stimulus to produce a hormonal response. However, this study used strength

trained individuals and investigated acute resistance exercise in middle aged, not elderly individuals. Although no effects of training status were found, the response of DHEA-S to exercise did differ between sexes. Females showed a significant increase in DHEA-S immediately post exercise whereas males did not. This increase in DHEA-S is consistent with prior research in early postmenopausal females (Kemmler et al., 2003) although males were not tested in this previous study.

Possible mechanisms for exercise-induced increases in DHEA/S have been outlined previously, with increased secretion rate by the adrenal cortex as a result of ACTH stimulation (Johnson et al., 1997; Keizer et al., 1989; Keizer et al., 1987) and decreased metabolic clearance due to a reduction in hepatic blood flow during exercise (Ponjee et al., 1994) being the most commonly cited. The mechanism responsible for the observed increase in DHEA-S in females but not in males is not clear. DHEA-S is found in higher and more stable concentrations due to its longer half life, it has been suggested that larger increases in DHEA-S are required to observe significant changes (Johnson et al., 1997). Therefore, as women have significantly lower levels of DHEA-S at baseline, they may have greater potential exhibit a significant increase in response to exercise. Resting DHEA-S levels have been shown to be associated with physical activity in females but not males within the same study (Bonnefoy et al., 1998; Kostka et al., 2002); consequently, it could be speculated that females may be more sensitive to exercise induced changes. The ability of an acute exercise bout to increase DHEA/S in older adults may afford a non-pharmacological method for increasing anabolic hormones. However, as levels returned back to baseline within an hour, it is debatable how beneficial such a short term increase. Exercise of a longer duration and higher intensity may be required in order to elevate and maintain DHEA/S levels for a

significant period post exercise, although this needs to be balanced against what exercise protocols older adults can realistically perform.

Acute exercise performed on a regular basis over a period of years does not appear to influence resting hormone levels, as interestingly, there were no differences among older adults in relation to their exercise training status. This is consistent with Arai et al (2006) who found no significant difference in DHEA-S between older male runners and those who were sedentary, and Traustadottir et al (2004) who reported no differences in cortisol levels between fit older women and those who were of average fitness. Although this present finding is in contrast to other studies which suggest DHEA/S is higher in endurance trained (de Gonzalo-Calvo et al., 2011; Tissandier et al., 2001) and moderately trained (Ravaglia et al., 2001) older men. In these previous and current investigations, blood samples were collected at similar times under the same conditions (fasted, rested etc). However, differences could be due to variation in the participants studied, in terms of fitness, training load and how long they have been exercising for.

Our current findings suggest that long term exercise training, be it at a vigorous or moderate intensity, does not lead to a more favourable hormonal profile among older adults compared to those who do not exercise. All participants in the present study were healthy older adults with no endocrine or immune disorders; it is possible that the sedentary group were healthier and fitter than the average older adult and this is why no differences emerged between exercisers and non exercisers. They were of relatively high socio-economic status, as is characteristic of study volunteers and is associated with better health (Anderson and Armstead, 1995). It may be that long term exercise training does not impact upon hormone levels of healthy older adults, but it could have the potential to have a positive effect on more

401 vulnerable older adults, for example, those who are frail, suffer from an illness, depression, or
402 who are experiencing chronic stress (Phillips et al., 2007).

403 In healthy older adults, 6 months of resistance (Häkkinen et al., 2000) or endurance training
404 (Hersey et al., 1994) did not elicit an increase in DHEA/S. However, exercise intervention
405 studies in this area are currently lacking, especially long duration studies and studies of
406 unhealthy populations. Even if long term exercise turns out not to be beneficial from a
407 hormonal perspective, it should still be encouraged as evidence suggests that it has the
408 potential to decelerate immunosenescence (Arai et al., 2006; Nieman et al., 1993; Shinkai et
409 al., 1995), as well as to maintain aerobic capacity and muscular strength thereby preserve
410 physical function with ageing.

411
412 The present study suffers from several limitations. Firstly, as a $VO_{2\ max}$ test was not
413 performed, and aerobic fitness was estimated from a submaximal test. However, maximal
414 exercise testing in older adults raises a number of issues (Hugget et al., 2005) not least the
415 ethics of such testing. As a result of not obtaining a $VO_{2\ max}$, exercise was graded in intensity
416 and was not steady state, which may have produced a different response. Investigating
417 hormonal responses to exercise of different durations and intensities in this population would
418 be valuable; although the feasibility of multiple trials and what demands can be placed on
419 participants may be a limiting factor.

420 In conclusion, older adults demonstrated a significant increase in DHEA in response to acute
421 submaximal aerobic exercise, whereas only older females showed a significant increase in
422 DHEA-S. Further, neither resting hormone levels, nor the response to exercise was
423 influenced by exercise training status. Although these findings suggest that long term

exercise may not affect the hormonal status of older adults, future research involving longitudinal studies and exercise interventions are required to definitively determine whether exercise can be used to maintain or improve the ageing endocrine system.

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554