

# The Effects of Exercise Training on Abdominal Visceral Fat, Body Composition, and Indicators of the Metabolic Syndrome in Postmenopausal Women With and Without Estrogen Replacement Therapy: The HERITAGE Family Study

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The purpose of this research was to investigate the effects of a priori estrogen replacement therapy (ERT) and endurance exercise training in postmenopausal women on abdominal visceral fat (AVF) and other selected variables related to body composition and the metabolic syndrome (MS). Forty-eight healthy and previously sedentary postmenopausal women (mean age, 54.3 years) who were enrolled in the HERITAGE Family Study (HFS) served as subjects. Of these 48 women, 18 were currently taking ERT and the remaining 30 were taking no supplemental estrogen (NHRT). Computed tomography (CT) scans were used to assess AVF as well as total abdominal fat (TAF) and abdominal subcutaneous fat (ASF). Body mass index (BMI) and waist-to-hip ratios (WHR) were calculated while body fat percentage (%FAT) and total fat mass (FATM) was assessed using underwater weighing. Blood assays for HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), and triglycerides (TG) were conducted at a Centers for Disease Control (CDC) certified laboratory, while blood pressure measurements were assessed using an automated system. All measurements were obtained in duplicate before and after a regimen of endurance exercise training. Analysis of variance (ANOVA) showed AVF to be an average of 31.6 cm<sup>2</sup> less in the women receiving ERT, but lost statistical significance when AVF was adjusted for FATM. Mean values for TAF, ASF, and waist girth were also less in the women receiving ERT, but only waist girth achieved statistical significance. No differences were found in BMI or %FAT, but mean WHR was 5% smaller in the ERT group. Baseline values for HDL-C was higher and LDL-C lower in the ERT group. Prevalence of the MS tended to be greater in the NHRT group, but did not achieve statistical significance. There were no differences in training responses in any of the body composition variables between groups, however, in the ERT group LDL-C decreased with training while TG increased. It was concluded that postmenopausal women taking ERT tended to have lower values of AVF and other indicators of body composition, a more favorable lipid profile, and a slightly reduced risk of the MS when compared with women not taking supplemental hormones. Also exercise training did not improve the overall MS status of either group, as LDL-C status improved in the ERT group while TG decreased in the NHRT group.

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**P**REVIOUS STUDIES have linked an excessive amount of abdominal visceral fat (AVF) with the metabolic syndrome (MS).<sup>1,2</sup> The MS, as defined by the National Cholesterol Education Program, includes the presence of 3 or more of the following risk factors: fasting plasma glucose (GLUC) ( $\geq 110$  mg/dL), serum triglycerides (TG) ( $\geq 150$  mg/dL), serum HDL-cholesterol (HDL-C) ( $< 40$  mg/dL in men and  $< 50$  mg/dL in

women), blood pressure ( $\geq 130$  mm Hg systolic and/or  $\geq 85$  mm Hg diastolic), and waist girth ( $> 40$  inches for men and  $> 35$  inches for women). The presence of the MS has been associated with an increased risk for atherosclerotic disease.<sup>3</sup>

There appears to be an increase in the deposition of AVF with aging. In women, this increase is accentuated with menopause.<sup>4,5</sup> Further, hormone replacement therapy (HRT) appears to attenuate the postmenopausal increase in AVF.<sup>4,6</sup> In a study of obese postmenopausal women, Sites et al<sup>7</sup> reported a lower total fat mass (FATM) and AVF in those on hormones compared with nonusers. However, a recent study by Kanaley et al<sup>8</sup> found no difference in the amount of AVF in women taking hormones compared with nonusers matched for body mass index (BMI). In addition, Ryan et al<sup>9</sup> found that women matched for age, weight, and BMI who were taking either estrogen or estrogen plus progesterone did not differ in AVF when compared with those not on a hormone regimen. Further, studies using surrogate measures for AVF, such as waist circumference and waist-to-hip ratio (WHR), do not support the benefit of hormone replacement.<sup>6</sup> There is a similar discrepancy in results when comparing selected risk factors for the MS in postmenopausal women taking hormones with those not taking hormones with some studies suggesting lower risk and others showing no change in risk.<sup>5,6</sup>

Given the conflicting results from studies in this area coupled with the recent controversial finding that hormone replacement may, in fact, be deleterious to the health of postmenopausal women,<sup>10</sup> it is important to further delineate the potential differences in AVF and risk factors comprising the MS in those taking hormones compared with those not taking hormones.

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This inquiry becomes even more important when the link between AVF and the MS with numerous cardiovascular disorders is considered.<sup>1,2,11</sup>

The primary purpose of this investigation, therefore, was to determine if levels of AVF, other indicators of body composition, along with selected risk factors associated with the MS were different in postmenopausal women who were taking a regimen of hormone replacement consisting solely of conjugated estrogen (ERT) versus those not taking any form of hormone replacement therapy (NHRT). A secondary purpose was to determine if the responses to endurance exercise training for these variables differed between the 2 groups (ERT *v* NHRT). Subjects for this study would come from the HERITAGE Family Study (HFS). The HFS is a large multicenter clinical study exploring possible genetic influences on physiologic response variability and the changes in risk factors for coronary disease and diabetes consequent to endurance exercise training.<sup>12</sup>

## MATERIALS AND METHODS

### Subjects

Subject recruitment was undertaken by each of the 4 clinical centers, which at the time of study onset were located at Arizona State University, Laval University, the University of Minnesota, and the University of Texas at Austin. The Washington University School of Medicine served as the coordinating center for all data. All subjects had to pass a comprehensive physical examination by a physician, which included both resting and exercise electrocardiograms. Inclusionary and exclusionary criteria have been described in detail by Bouchard et al.<sup>12</sup> The study protocol was approved by the institutional review board at each of the clinical centers, and written informed consent was obtained from each subject.

The subset of subjects used in these analyses had not had a menstrual cycle in over 2 years, ranged in age from 40 to 65 years, and included both white ( $n = 34$ ) and black ( $n = 14$ ) women. Eighteen of the subjects [age (mean  $\pm$  SD) =  $52.3 \pm 6.3$  years] were taking high-dose conjugated estrogen (ERT) for the treatment of menopausal symptoms, while the other 30 ( $56.4 \pm 5.4$  years) were not on any type of hormonal regimen (NHRT). The women taking hormones had been doing so for a mean of 3.9 years with all subjects having taken them for a minimum of 1 year. Although the specific drug type and dosage of estrogen was not recorded, baseline serum levels of estrogen and progesterone were obtained at the study onset, with estradiol concentrations (mean  $\pm$  SD) of  $241 \pm 258$  and  $90 \pm 298$  pmol  $\cdot$  L<sup>-1</sup> in the ERT and NHRT groups, respectively. Student's *t* test demonstrated a significant difference in estradiol means between groups ( $P < .05$ ). The progesterone concentrations were  $< 1.0$  nmol  $\cdot$  L<sup>-1</sup> in both groups.

### Procedures

All physiologic assessments were taken both before and after a 20-week endurance exercise training regimen. The procedures for the complete battery of tests used in HERITAGE have been presented in a previous publication.<sup>12</sup> Only those procedures used for obtaining the data presented in this report are detailed in this section.

**Body composition.** Computed tomography (CT) scans were used to obtain measures of abdominal total fat (ATF), abdominal subcutaneous fat (ASF), and AVF using the procedures of Sjöström.<sup>13</sup> Scanning was performed at 125 kV and a slice thickness of 8 mm. Scans were taken between the 4th and 5th lumbar vertebrae with the subjects in the supine position and their arms extended above their heads. Waist girth measurements were taken at the level of the umbilicus using a fiberglass anthropometric tape, which was in direct contact with the skin

(Grafcop Fiberglass Tape, model 17-1340-2, Grahams-Fields Inc, Hauppauge, NY). The hip girth was taken at the greatest hip circumference over a bathing suit or gym shorts. All measurements were taken at least twice using the procedures recommended by Lohman et al.<sup>14</sup> WHR was then computed. Height and weight were measured to the nearest centimeter and 0.1 kg using a stadiometer and a balance beam. BMI was calculated as weight (kg) divided by height squared (m<sup>2</sup>). Body density was determined by hydrostatic weighing with measured residual lung volumes as detailed by Wilmore et al.<sup>15</sup> Ten trials were obtained and the heaviest 3 weights were averaged in the computation of body density. Relative body fat percentages (%FAT) were estimated from body density using the equations of Lohman<sup>16</sup> for white women, Siri<sup>17</sup> for white men, Ortiz et al.<sup>18</sup> for black women, and Schutte et al.<sup>19</sup> for black men.

**Blood analysis.** Blood samples were obtained in the morning after a 12-hour fast and collected into vacutainer tubes containing EDTA. Plasma samples from the HERITAGE clinical centers were packed in ice and sent to the Lipid Research Center at the Laval University Medical Center, a CDC-certified laboratory. Serum TG concentrations were determined by enzymatic methods using a Technicon RA-500 analyzer (Bayer, Tarrytown, NY) while HDL-C levels were assessed after precipitation of LDL-cholesterol (LDL-C) in the infranantant by the heparin-manganese chloride method.<sup>20</sup> Plasma GLUC was measured using an enzymatic technique,<sup>21</sup> while plasma insulin was assessed using a radioimmunoassay method with polyethylene glycol separation.<sup>22</sup> Estradiol and progesterone concentrations were determined by standard radioimmunoassay techniques. Posttraining assessments for all lipid variables and hemodynamic variables were obtained approximately 72 hours after the last bout of exercise.<sup>12</sup>

**Blood pressure.** Subjects were asked to report to the testing lab before 11 AM and were instructed to refrain from using tobacco and caffeine products at least 2 hours prior to arrival. They were also not to have done any physical exercise within the last 12 hours. Blood pressure measurements were taken on 2 consecutive days using the Colin STBP-780 automated blood pressure unit (San Antonio, TX). The subject was seated in a reclining chair in a semirecumbent position with the arms relaxed and supported. After a rest period of at least 5 minutes, the subject was fitted with the proper cuff size and at least 4 blood pressure assessments were taken at 2-minute intervals. The mean of the blood pressures for the 2 consecutive days was recorded as the pretraining resting blood pressure. See the report by Wilmore et al.<sup>23</sup> for further details.

**Training program.** The 20-week training regimen was conducted on cycle ergometers (Universal Aerobicycle, Cedar Rapids, IA). The ergometers were interfaced with a computer system (Universal Gym Mednet, Cedar Rapids, IA) that controlled ergometer power output, thereby allowing for the maintenance of a constant training heart rate (HR). Training intensity was initially set at a HR equivalent to 55% of each subject's maximal oxygen consumption ( $\dot{V}O_{2max}$ ) for 30 min  $\cdot$  day<sup>-1</sup> with a frequency of 3 days  $\cdot$  wk<sup>-1</sup>. By the end of the 14th week of training, the intensity and duration of the exercise bouts progressed to 75% of  $\dot{V}O_{2max}$  for 50 min  $\cdot$  day<sup>-1</sup>, 3 days  $\cdot$  wk<sup>-1</sup>, which was maintained throughout the remaining 6 weeks of the regimen.

To calculate training intensity for the regimen,  $\dot{V}O_{2max}$  was obtained for each subject using a SensorMedics 2900 metabolic measurement cart in conjunction with a SensorMedics Ergo-Metrics 800S cycle ergometer (Yorba Linda, CA).  $\dot{V}O_{2max}$  was reported as the highest  $\dot{V}O_2$  obtained during the test. Criteria for the attainment of  $\dot{V}O_{2max}$  required the subjects to achieve one of the following: respiratory exchange ratio (RER)  $> 1.1$ , a plateau in  $\dot{V}O_2$  despite an increasing power output, or the attainment of a maximum HR that was within  $\pm 10$  beats of an age-predicted maximum. This is described in further detail by Skinner et al.<sup>24</sup>

**Table 1. Means and Standard Deviations of Pretraining Dependent Study Variables for Subjects Taking ERT and Subjects Not Taking Hormones**

	NHRT (n = 30, 22 white, 8 black)	ERT (n = 18, 11 white, 7 black)
With MS (%)	26	11
With 2 or more MS criteria (%)	70	39
Body weight (kg)	76.8 ± 15.5	69.6 ± 11.4
Body mass index	29.3 ± 4.9	26.6 ± 4.1
Waist-to-hip ratio	0.90 ± 0.08	0.85 ± 0.06*
Waist girth (cm)	99.7 ± 15.0	91.0 ± 8.3*
Height (cm)	161.6 ± 7.2	161.7 ± 6.9
Fat mass (kg)	31.2 ± 15.9	25.7 ± 13.01
Body fat (%)	40.8 ± 6.5	37.4 ± 5.0
AVF (cm <sup>2</sup> )	121.6 ± 57.7	90.0 ± 26.5†
ASF (cm <sup>2</sup> )	396.4 ± 102.1	353.2 ± 112.5
ATF (cm <sup>2</sup> )	517.9 ± 139.7	443.2 ± 122.3
$\dot{V}O_{2max}$ (mL O <sub>2</sub> /kg/min)	21.3 ± 4.0	22.1 ± 4.8
Systolic BP (mm Hg)	124.9 ± 14.5	123.9 ± 17.7
Diastolic BP (mm Hg)	70.7 ± 8.4	71.5 ± 9.9
HDL-C (mg/dL)	46.1 ± 10.2	55.7 ± 13.5*
LDL-C (mg/dL)	141.7 ± 22.7	119.3 ± 30.6*
Triglycerides (mg/dL)	109.6 ± 35.6	136.0 ± 69.1
Insulin (pmol/L)	57.7 ± 37.3	57.0 ± 46.6
Glucose (pmol/L)	5.5 ± 1.3	5.1 ± 0.7

\*Significantly different from those not taking estrogen ( $P < .05$ )

†Significantly different from those not taking estrogen ( $P < .05$ ), but not different when adjusted for total fat mass.

**Data analysis.** All data were analyzed using the SAS statistical package (version 6.12; SAS Institute, Cary, NC). An initial analysis of the total data set using a  $2 \times 2$  analysis of variance (ANOVA) with interaction indicated that racial difference in AVF was not a significant factor in interpreting differences between the ERT and NHRT groups. Therefore, differences between ERT and NHRT groups were tested by 1-way analysis of covariance with FATM as the covariate. Testing for training change differences between groups was included in the initial  $2 \times 2$  ANOVA using posttraining-pretraining values ( $\Delta$  or change variables) as dependent variables. Training changes within each group were tested with dependent  $t$  tests. Chi-square analysis was used to determine if the incidence of the MS was different between the ERT and NHRT groups. Comparison-wise type 1 error rate was set at 0.05.

## RESULTS

ANOVA revealed that AVF levels were 26.0% less in the ERT group ( $P < .05$ ). While there were substantial racial differences in AVF levels, this did not affect the difference between the ERT and NHRT groups, as both blacks and whites in the ERT group had lower AVF levels compared with the NHRT group (ie, 70.4 v 101.4 cm<sup>2</sup> in blacks; 102.6 v 128.0 cm<sup>2</sup> in whites). It should be noted, however, that the ERT-related differences in AVF disappeared when adjusted for FATM. Waist girth and WHR were significantly lower in the ERT group, but body weight, BMI, %FAT, ATF, ASF, and  $\dot{V}O_{2max}$  were not different between ERT groups. While both systolic and diastolic blood pressures were significantly higher in blacks ( $P < .05$ ), they did not differ by ERT group. HDL-C was 20.9% higher and LDL-C was 15.8% lower in the ERT group. Clearly, taking estrogen was associated with a more favorable lipid profile in our subjects. Neither insulin nor

glucose values differed by hormone status. All values are presented in Table 1.

Using the National Cholesterol Education Program standards for the MS, 26% of those in the NHRT group were classified as having the MS versus only 11% of those in the ERT group (Table 1). However, this percentage difference was not statistically significant ( $\chi^2 = 1.65$ ,  $P > .05$ ). On further analysis, the percentage of subjects meeting 2 or more of the MS criteria was 70% for those in the NHRT group versus 39% in ERT group ( $\chi^2 + 4.5$ ,  $P < .05$ ), possibly suggesting that those taking estrogen were at slightly lower risk for developing the MS in the future.

As would be expected,  $\dot{V}O_{2max}$  improved in both the ERT and NHRT groups as a result of the endurance exercise training regimen. As can be seen in Table 2, LDL-C increased in the NHRT group and decreased in the ERT group; however, only the increase in the NHRT group achieved statistical significance. TG declined slightly in the NHRT group, while showing a modest increase in the ERT group, but neither change achieved statistical significance. Group responses to training differed for both LDL-C and TG.

## DISCUSSION

The major finding of this study was the substantially lower risk for cardiovascular and metabolic diseases associated with ERT compared with NHRT on the basis of unadjusted AVF, HDL-C, and LDL-C values and secondarily on the basis of waist girth and WHR. Furthermore, it can be inferred that there was a slightly lower risk for developing the MS in those using ERT compared with nonusers. These results are in contrast to the results of the estrogen plus progestin component of the Women's Health Initiative clinical trial, which was stopped prematurely by the Data and Safety Monitoring Board on the basis of the finding that hormone replacement increased risk for

**Table 2. Means and Standard Deviations of the Training-Induced Change Values in the Dependent Variables for Subjects Taking ERT and not taking hormones (posttraining-pretraining)**

	NHRT (n = 30, 22 whites, 8 blacks)	ERT (n = 18, 11 whites, 7 blacks)
Body weight (kg)	0.1 ± 2.5	0.5 ± 2.9
Body mass index	0.1 ± 1.0	0.1 ± 1.1
Waist-to-hip ratio	0.00 ± 0.03	0.00 ± 0.02
Waist girth (cm)	-0.9 ± 3.1	-0.1 ± 3.4
Fat mass (kg)	-0.4 ± 2.5	0.1 ± 2.7
Body fat (%)	-0.6 ± 2.1	-0.2 ± 2.1
AVF (cm <sup>2</sup> )	-3.8 ± 20.4	-6.0 ± 13.5
ASF (cm <sup>2</sup> )	-4.8 ± 31.1	5.5 ± 32.7
ATF (cm <sup>2</sup> )	-8.6 ± 41.4	-0.5 ± 41.4
$\dot{V}O_{2max}$ (mL O <sub>2</sub> /kg/min)	4.3 ± 1.8†	4.8 ± 1.5†
Systolic BP (mm Hg)	-1.2 ± 9.2	-1.2 ± 9.6
Diastolic BP (mm Hg)	0.2 ± 5.0	-0.1 ± 5.5
HDL-C (mg/dL)	1.8 ± 4.8	2.5 ± 5.4
LDL-C (mg/dL)	7.0 ± 15.6†	-5.5 ± 11.8*
Triglycerides (mg/dL)	-3.6 ± 16.7	16.4 ± 34.6*
Insulin (pmol/L)	-0.7 ± 17.8	-2.5 ± 30.8
Glucose (pmol/L)	0.0 ± 0.6	0.1 ± 0.5

\*Significantly different from those not taking estrogen ( $P < .05$ )

†Significant change from pretraining value ( $P < .05$ )

both cardiovascular disease and breast cancer.<sup>10</sup> The reason for this disparity is not immediately obvious, but may be related to the fact that our subjects took estrogen alone without progesterone. This discussion will attempt to focus on several issues that should be considered when interpreting the results from the present study.

In reviewing studies on hormone replacement and its relationship to AVF, most have been cross-sectional in nature. Few have used a longitudinal design. Further, many studies have used surrogate measures of AVF, such as waist circumference and WHR. Few have actually attempted to estimate AVF using more direct measures, such as CT or magnetic resonance imaging (MRI) technology. Several studies have used dual photon absorptiometry (DPA) or dual energy x-ray absorptiometry (DXA), yet neither DPA nor DXA are capable of differentiating AVF from ASF. The ideal study would use either CT or MRI technology to estimate AVF and use a randomized intervention longitudinal study design. Unfortunately, there are no such studies in the existing literature, so this discussion will focus on both longitudinal studies using indirect estimates of AVF and cross-sectional studies using CT or MRI technology.

Espeland et al<sup>25</sup> reported that women in the placebo-controlled, randomized clinical trial (Postmenopausal Estrogen/Progestin Intervention [PEPI]) taking hormones averaged 1.2 cm less increase in waist girth and 1.0 kg less weight gain when compared with the placebo group at the end of a 3-year intervention period. Similarly, Reubinoff et al<sup>26</sup> found WHR unchanged following 12 months of hormone replacement, while WHR increased in the control group over the same time period. However, Kritz-Silverstein and Barrett-Connor<sup>27</sup> found no differences in the change in WHR between estrogen users and nonusers over a 15-year follow-up period. Four other longitudinal studies, ranging in duration from 1 to 3 years used either DPA or DXA to assess changes in central body fat distribution.<sup>28-31</sup> In 3 of these studies, hormone replacement was not associated with an increase in AVF when compared with NHRT groups,<sup>29-31</sup> but was associated with a decrease in waist area in 1 of these studies.<sup>31</sup> In the fourth study,<sup>28</sup> after a 2.9-year treatment period, the group taking hormones experienced a relatively greater increase in trunk fat mass compared with the placebo group.

Three cross-sectional studies examined the influence of hormone replacement on AVF using either CT scans<sup>7,9</sup> or MRI<sup>8</sup> to quantify AVF. In 2 of these studies,<sup>8,9</sup> AVF was not different between hormone groups, although the groups were matched for BMI and total body fat mass in 1 study<sup>8</sup> and for BMI, age, and weight in the other.<sup>9</sup> Sites et al<sup>7</sup> reported lower values for weight, BMI, total body fat mass, and AVF in hormone users compared with nonusers. After adjusting AVF values for total body fat mass, there was only a trend for a lower AVF in hormone users ( $P = .09$ ).

With respect to blood lipids, the ERT group in the present study had higher HDL-C levels and lower LDL-C levels, thus a more favorable lipid profile. However, there was a trend for TG values to be higher in the ERT group ( $P = .09$ ). Kanaley et al<sup>8</sup> reported trends for HDL-C, LDL-C, and TG similar to those in the present study, but the differences between groups were not significant for any of the three. Haarbo et al<sup>30</sup> reported decreases in total cholesterol and LDL-C, but no change in

HDL-C, in their hormone replacement groups over a 2-year intervention period.

From a statistical standpoint, the exercise training regimen did not improve any of the 6 factors related to the MS, regardless of estrogen replacement status (4.6% increase in HDL-C, 2.4% increase in TG, 0.3% reduction in GLUC, 0.5% reduction in waist girth, 0.5% reduction in systolic blood pressure, and a 0.4% increase in diastolic blood pressure). In fact, the only statistically significant improvement seen related to cardiac risk was the 4.9% reduction in LDL-C in the NHRT group. These percentages are not unlike those seen in the rest of the HERITAGE cohort (3.1% increase in HDL-C, 0.6% reduction in TG, 0.2% increase in systolic blood pressure, and a 0.8% increase in diastolic blood pressure).<sup>23,32</sup> In the complete data set, however, the increase in HDL-C, although smaller than the one we found, was statistically significant, suggesting a lack of statistical power in the analysis of the subset of the data we used in the present study.

Our results regarding the lack of significant exercise-induced improvement in such MS risk markers as HDL-C and TG in postmenopausal women are not unique. Grandjean et al<sup>33</sup> found a 6% reduction in HDL-C and a 7% increase in TG after a 12-week exercise program consisting of 3 to 4 bouts per week and 75% to 85%  $\dot{V}O_{2max}$ . Almost identical results were obtained by Klebanoff et al.<sup>34</sup> Some studies, however, have shown improvements in these variables. For example, Lindheim et al<sup>35</sup> found exercise training to induce a 2% reduction in TG, a 14.8% increase in HDL-C in women taking estrogen, and a 17.2% increase in HDL-C in women not taking estrogen. Although the reason for the discrepancies in the results of these studies remains unclear, it may be related to whether or not the estrogen was administered by the investigators, the specific dosages of estrogen given to the subjects, and the length of time the subject remained on the estrogen therapy. All of these factors were different among the studies cited above, while the frequency, intensity, and duration of the exercise training regimens were similar and were of sufficient volume to elicit favorable adaptations seen in other studies using other populations.

In summary, the present study found that postmenopausal women on ERT had lower values for AVF, waist circumference and WHR, a more favorable lipid profile, and a slightly reduced risk of the MS when compared with women not on ERT. Although it is possible that the reason our results differ from others in the literature may be related to the fact that our subjects took only estrogen with no progesterone, further study in this area is needed before such determination can be made. Further, exercise training did not improve the overall MS status of either group, although LDL-C increased in the NHRT group. The existing research literature, using both cross-sectional and longitudinal intervention designs, generally supports the findings of this study, with several notable exceptions as presented above.

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