

## SHORT COMMUNICATION

### Effects of Dietary Weight Loss and Exercise on Insulin-Like Growth Factor-1 and Insulin-Like Growth Factor Binding Protein-3 in Postmenopausal Women: A Randomized Controlled Trial

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## ABSTRACT

High levels of insulin-like growth factor (IGF)-1 may increase the risk of common cancers in humans. We hypothesized that weight loss induced by diet and/or exercise would reduce IGF-1 in postmenopausal women. Four hundred and thirty nine overweight or obese ( $\text{BMI} \geq 25\text{kg/m}^2$ ) women (50-75 y) were randomly assigned to: i) exercise (N=117), ii) dietary weight-loss (N=118), iii) diet + exercise (N=117), or iv) control (n=87). The diet intervention was a group-based program with a 10% weight loss goal. The exercise intervention was 45 min/day, 5 days/week of moderate-to-vigorous intensity activity. Fasting serum insulin-like growth factor (IGF)-1 and insulin-like growth factor binding protein (IGFBP)-3 were measured at baseline and 12 months by radioimmunoassay. Higher baseline BMI was associated with lower IGF-1 and IGF-1/IGFBP-3 molar ratio. While no significant changes in either IGF-1 or IGFBP-3 were detected in any intervention arm compared to control, the IGF-1/IGFBP-3 ratio increased significantly in the diet (+5.0%,  $p < 0.01$ ) and diet + exercise (+5.4%,  $p < 0.01$ ) groups compared to control. Greater weight loss was positively associated with change in both IGF-1 ( $p_{\text{trend}} = 0.017$ ) and IGF-1/IGFBP-3 ratio ( $p_{\text{trend}} < 0.001$ ) in the diet group, but inversely with change in IGFBP-3 in the diet + exercise group ( $p_{\text{trend}} = 0.01$ ). No consistent interaction effects with baseline BMI were detected. Modified IGF-1 bioavailability is unlikely to be a mechanism through which caloric restriction reduces cancer risk in postmenopausal women.

**Keywords:** lifestyle, intervention, obesity, energy balance, insulin

## INTRODUCTION

Biological and epidemiological evidence suggests that high levels of insulin-like growth factor (IGF)-1 may increase risk for several common cancers (1, 2). IGF-1 has mitogenic and antiapoptotic properties that are modulated through IGF binding proteins (IGFBP) (1). Most circulating IGF-1 is bound to one of six IGFBPs, the most abundant being IGFBP-3, while a small amount remains unbound and biologically active. Modifications in IGF-1 bioavailability have been proposed as a mechanism linking obesity and cancer risk (3, 4) while animal studies suggest that alterations in IGF-1, as well as other cytokines and inflammatory factors, may mediate the antiproliferative, pro-apoptotic, and anticancer effects of negative energy balance (5).

Calorie restriction in rodents and other animal models decreases serum IGF-1 concentrations up to 40% (6, 7) but the effects in humans are equivocal (8-10). One explanation may be that, unlike insulin, human IGF-1 does not appear elevated in obese individuals, but peaks in persons with BMI values of 24-27 kg/m<sup>2</sup> (11). Alternately, caloric restriction models in animals may not be relevant to humans because they are typically initiated in young ages, thereby preventing obesity, whereas calorie restriction has been tested in humans who are already obese. It is postulated that obesity-related hyperinsulinemia inhibits IGFBP production and results in elevated levels of free IGF-1. In turn, this exerts a negative feedback on growth hormone secretion, thereby lowering IGF-1 (12). Few studies examining the interrelationships between energy balance, IGF-1 and cancer risk factors have considered differential effects according to baseline weight or body composition.

The purpose of this study was to investigate the independent and combined effects of 12 months of dietary weight loss and/or aerobic exercise on IGF-1, IGFBP-3, and the IGF-1/IGFBP-3 molar ratio as a proxy for free IGF-1 (13) in overweight and obese postmenopausal women. A secondary purpose was to examine the degree to which any intervention effects were moderated by

baseline adiposity. We hypothesized that IGF-1 and the IGF-1/IGFBP-3 molar ratio would be significantly decreased in women randomized to diet and diet + exercise, but that this effect would be stronger among women with baseline BMI  $<28 \text{ kg/m}^2$ .

## **METHODS**

The Nutrition and Exercise in Women (NEW) study was a 12-month randomized controlled trial testing caloric restriction and exercise on circulating hormones and other outcomes. Study procedures were reviewed and approved by the Fred Hutchinson Cancer Research Center Institutional Review Board in Seattle, WA. All participants provided informed written consent.

### ***Participants & Interventions***

The study methods have been previously described (14). Briefly, participants were postmenopausal women (50-75 y) with a BMI  $\geq 25.0$  ( $\geq 23.0 \text{ kg/m}^2$  if Asian-American), recruited through media and mass mailings. Exclusion criteria included:  $>100$  min/week of moderate physical activity; diagnosed diabetes or fasting blood glucose  $\geq 126 \text{ mg/dL}$ ; serious medical condition(s); postmenopausal hormone use;  $>2$  alcoholic drinks/day; current smoking; participation in another structured weight loss program; contraindication to participation (e.g. abnormal exercise tolerance test).

Eligible women were randomized to one of: i) reduced-calorie dietary modification (N=118); ii) moderate-to-vigorous intensity aerobic exercise (N=117); iii) combined diet and exercise (N=117); or iv) control (no intervention) (N=87). Computerized random assignment, using permuted blocks randomization to achieve a proportionally smaller control group, was stratified according to BMI ( $\geq$  or  $<30 \text{ kg/m}^2$ ) and race/ethnicity.

The dietary intervention was a modification of the Diabetes Prevention Program (DPP)(15) and Look AHEAD (Action for Health in Diabetes)(16) lifestyle behavior change programs with goals of:

1200-2000 kcal/day, <30% daily calories from fat, and 10% weight loss. The exercise intervention goal was 45 minutes of moderate-to-vigorous ( $\geq 4$  metabolic equivalents [METs]) intensity exercise at a target heart rate of 70-85% observed maximum, 5 days/week. Participants attended three facility-based supervised sessions/week, and exercised 2 days/week at home.

### **Measures**

All study measures were obtained and analyzed by trained personnel who were blinded to participants' randomization status.

At baseline (pre-randomization) and 12 months, demographic information, height, weight, medical history, dietary intake, supplement use and physical activity data were collected (14). Body composition was measured by DXA whole-body scanner (GE Lunar, Madison, WI, USA).

Twelve-hour fasting venous blood (50 mL) was collected during clinic visits (no exercise within 24 hours, no alcohol within 48 hours). Blood was processed within 1 hour and samples were stored at  $-70^{\circ}\text{C}$ . Blood samples were analyzed in batches such that each participant's samples were assayed simultaneously, the number of samples from each group were approximately equal, participant randomization dates were similar, and sample order was random.

IGF-1 and IGFBP-3 assays were performed at the Jewish General Hospital (Montreal, Canada) using reagents from the Diagnostic Systems Laboratory, Beckman Coulter (Webster, TX, USA). The intra-assay coefficients of variation (CV) were 4.2% and 3.8% for IGF-1 and IGFBP-3, respectively; inter-assay CVs were 5.4% and 4.9% for IGF-1 and IGFBP-3, respectively. The molar ratio of IGF-1/IGFBP-3 was calculated as a proxy for free IGF-1:  $[\text{IGF-1 (ng/mL)} \times 0.130] / [\text{IGFBP-3 (ng/mL)} \times 0.036]$  (13).

### **Statistical Analysis**

For the primary analysis, no change from baseline was assumed in cases of missing data. Age-adjusted partial correlation coefficients were performed between baseline measures. The mean 12-month change in IGF-1, IGFBP-3, and the IGF-1/IGFBP-3 ratio in each intervention group was compared to controls using the generalized estimating equations (GEE) modification of linear regression to account for intra-individual correlation over time. Assuming 80% power to make three primary pairwise comparisons (diet+exercise vs. exercise; diet+exercise vs. diet; and diet vs. exercise), the minimum detectable differences in IGF-1, IGFBP-3, and the IGF-1/IGFBP-3 ratio were estimated at 14.36, 305, and 0.009, respectively (type I error=0.05). Bonferroni adjustment for multiple comparisons was made (two-sided  $\alpha=0.05/3=0.016$ ). Intervention effects were examined based on assigned treatment at randomization, regardless of adherence or study retention (i.e. intent-to-treat).

The effect of weight loss on IGF-1, IGFBP-3, and the IGF-1/IGFBP-3 ratio was examined using a stratified analysis (<5%, 5-10%, and >10% weight loss) performed within each arm, without imputation for missing values. These analyses were repeated after stratification by baseline BMI (<28 vs.  $\geq 28$  kg/m<sup>2</sup>) using the cut-point around which IGF-1 peaks in humans (11). The potential moderating effect by baseline BMI was tested by including an appropriate interaction term in each model.

All statistical analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC, USA).

## **RESULTS**

At 12 months, 399 participants completed a physical exam, a DXA scan, and provided a blood sample; 40 did not complete the study. Participant characteristics, intervention adherence, 12-month weight and body composition changes have been previously published (14). Mean age and BMI were

58.0 years and 30.9 kg/m<sup>2</sup>. Most women (65%) were college graduates and 85% were non-Hispanic white. Mean weight changes were -2.4% (p=0.03) in the exercise group, -8.5% (p<0.001) in the diet group, and -10.8% (p<0.001) in the diet + exercise group, compared to -0.8% among controls.

Exercise groups participated in moderate-to-vigorous activity for a mean (SD) 163.3 (70.6) mins/wk (exercise), and 171.5 (62.9) mins/wk (diet + exercise). Both groups significantly increased average pedometer steps/day (+2416 and +3471 steps/d, respectively) compared to baseline. In both diet groups, women attended an average of 27 diet counseling sessions (86%).

### *Baseline Associations*

The age-adjusted partial correlations between BMI and IGF-1, IGFBP-3, and the IGF-1/IGFBP-3 ratio at baseline are shown in **Figure 1**. Both IGF-1 and the IGF-1/IGFBP-3 molar ratio were inversely associated with BMI, while IGFBP-3 showed no association. In addition to age (-0.13, p=0.008), baseline IGF-1 concentrations were also significantly inversely associated with , waist circumference (-0.25, p<0.0001), and % body fat mass (-0.20, p<0.0001). IGFBP-3 was significantly inversely associated with % body fat (-0.11, p=0.02). The IGF-1/IGFBP-3 molar ratio was significantly inversely associated with age (-0.10, p=0.04), waist circumference (-0.33, p<0.0001), and % body fat (-0.17, p<0.001).

### *Intervention Effects*

Compared to controls, neither IGF-1 nor IGFBP-3 changed significantly in either group receiving dietary intervention (**Table 1**). The IGF-1/IGFBP-3 molar ratio increased significantly in the diet group (p=0.008) and in the diet + exercise group (p=0.004). No significant change in IGF-1, IGFBP-3 or their molar ratio was detected among exercisers compared to controls.

Greater weight loss was associated with an increase in IGF-1 and the IGF-1/IGFBP-3 molar ratio among women randomized to diet alone (**Table 2**), while we observed an inverse trend greater between weight loss and IGFBP-3 in the diet + exercise group.

In the stratified analysis (BMI  $\geq 28$  vs.  $< 28$ ) the IGF-1/IGFBP-3 ratio was significantly increased among women with BMIs  $\geq 28$  kg/m<sup>2</sup> randomized to diet + exercise compared to controls. No significant differences were detected in women with BMIs  $< 28$  kg/m<sup>2</sup>. A greater decrease in IGFBP-3 was observed among women with BMI  $\geq 28$  vs.  $< 28$  in the diet + exercise group ( $p_{\text{interaction}} = 0.005$ ) (supplementary table).

## DISCUSSION

No significant changes in IGF-1 or its main binding protein, IGFBP-3, were detected in any intervention arm compared to control; however, the IGF-1/IGFBP-3 molar ratio increased significantly in the diet and diet + exercise groups. This suggests that lifestyle-based weight loss of 8-10% may increase IGF-1 bioavailability in overweight and obese postmenopausal women - an effect that is counter-intuitive to the anticipated effect of weight loss on cancer risk, and opposite to the effects consistently observed in animal models (5). However, as noted above, the majority of published animal studies have not tested caloric restriction weight loss in already obese animals, and therefore do not serve as true models for overweight/obese persons undergoing weight loss. Furthermore, by comparison to animal models in which caloric restriction does alter IGF-1 and impede tumor growth, the degree of change in energy balance was relatively modest in this study (17, 18). Equivalently severe exercise and/or caloric restriction may not be practical in most human populations.

The equivocal effect of dietary weight loss on IGF-1 in our trial is consistent with a limited number of other studies in women and men (19-23). In the only other study of exclusively postmenopausal women (n=99, mean BMI 26.9 kg/m<sup>2</sup>), 5 months of dietary intervention yielding a



mean BMI decrease of  $1.62 \text{ kg/m}^2$  did not significantly alter serum IGF-1 compared to weight-stable controls, although IGFBP-1 and -2 were increased (22); IGFBP-3 was not measured. In another 6 month trial comparing intermittent vs. continuous caloric restriction in premenopausal women (mean BMI  $30.6 \pm 5.1 \text{ kg/m}^2$ ), negligible changes in total and free IGF-1 were observed in response to mean weight changes of -6.4 and -5.6 kg in each group, respectively (23). However, both groups experienced similar significant increases in IGFBP-1 and -2.

In contrast, IGF-1 increased significantly after a mean  $9.7 \pm 4.3\%$  weight loss in obese women with a mean BMI of  $37.2 \text{ kg/m}^2$  (19). Likewise, IGF-1 increased significantly in a sample of obese men and women (mean BMI  $32.6 \text{ kg/m}^2$ ) during a 6-month weight loss period, and levels continued to increase despite partial weight regain during the subsequent 6 months (20). In another sample of premenopausal women (mean BMI of  $29.2 \pm 6.2 \text{ kg/m}^2$ ), intentional weight loss  $\geq 5\%$  body weight (vs. weight stable/gain) was associated with a significant increase in serum total IGF-1, while free IGF-1 and IGFBP-3 remained unchanged (21).

Strengths of our study include its large sample and adequate power to examine changes in IGF-1 and IGFBP-3 in three separate lifestyle interventions compared to controls. However, the IGF-1 axis is complex and circulating levels may not reflect local tissue levels, which we were unable to assess. Furthermore, we relied on the IGF-1/IGFBP-3 molar ratio as a surrogate of bioactive IGF-1. Although this ratio is a reasonable approximation of free IGF-1 under normal physiological conditions (13), free IGF-1 is also influenced by levels of other IGFBPs (24). Finally, IGF-1 and IGFBP-3 levels are affected by multiple factors, including gender and race/ethnicity (25); therefore, these results may not be generalizable to men or to populations that are not predominantly Caucasian.

The findings of the current study, plus those of previous studies, suggest that animal models of caloric restriction on IGF-1 and IGFBP-3 are not confirmed with caloric restriction and weight loss in

overweight/obese women. They also suggest that modified IGF-1 bioavailability is unlikely to represent a major mechanistic link through which caloric restriction impacts obesity-associated cancer risk in humans.

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**Figure Legend.** Associations between IGF-1, IGFBP-3 and the IGF-1/IGFBP-3 molar ratio with body mass index (BMI) at baseline among overweight or obese postmenopausal women.



**Table 1.** Baseline, 12-mo (mean, SD), and change in serum IGF-1, IGFBP-3 and IGF-1/IGFBP-3 molar ratio, stratified by intervention arm.

	Mean (SD)		Change	Change %	<i>p</i>
	Baseline	12 month			
<b>CONTROL</b>					
IGF-1 (ng/mL)	178.7 (53.4)	174.0 (53.1)	-4.7	-2.6	<i>ref</i>
IGFBP-3 (ng/mL)	5214 (1102)	5110 (1240)	-104	-2.0	<i>ref</i>
Molar Ratio <sup>†</sup>	0.124 (0.028)	0.123 (0.027)	-0.001	-0.4	<i>ref</i>
<b>EXERCISE</b>					
IGF-1 (ng/mL)	172.8 (47.3)	169.0 (46.2)	-3.8	-2.2	0.81
IGFBP-3 (ng/mL)	5137 (943)	4991 (958)	-146	-2.8	0.63
Molar Ratio <sup>†</sup>	0.121 (0.025)	0.122 (0.024)	0.001	0.8	0.53
<b>DIET</b>					
IGF-1 (ng/mL)	167.9 (46.0)	170.3 (45.5)	2.4	1.4	0.06
IGFBP-3 (ng/mL)	5081 (951)	4921 (1022)	-160	-3.2	0.56
Molar Ratio <sup>†</sup>	0.119 (0.024)	0.125 (0.024)	0.006	5.0	<b>0.008</b>
<b>DIET + EXERCISE</b>					
IGF-1 (ng/mL)	177.1 (57.3)	179.6 (58.5)	2.6	1.4	0.06
IGFBP-3 (ng/mL)	5165 (1051)	4969 (929)	-197	-3.8	0.31
Molar Ratio <sup>†</sup>	0.123 (0.026)	0.130 (0.028)	0.007	5.4	<b>0.004</b>

Results from GEE model, comparing change from baseline to 12-months between each intervention group and controls.

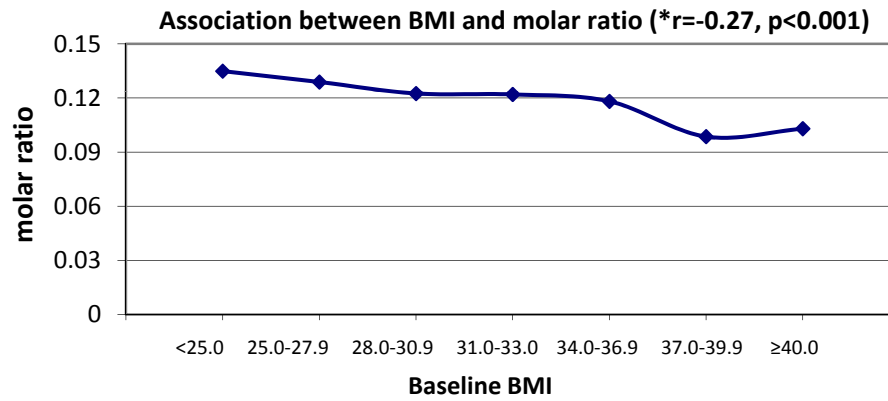
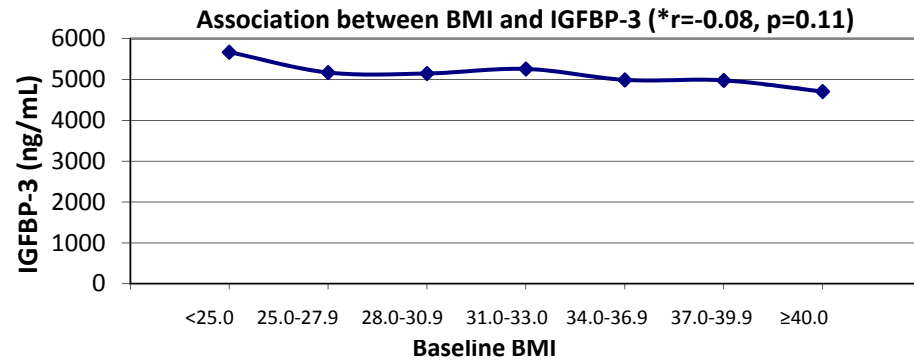
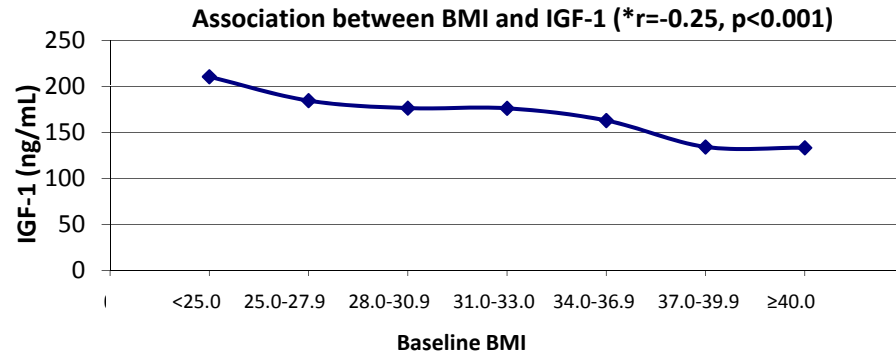
<sup>†</sup>Molar ratio = [IGF-1 (ng/mL) x 0.130] / [IGFBP-3 (ng/mL) x 0.036]

**Table 2.** Baseline and 12 mo (Mean, SD), and % change in IGF-1, IGFBP-3 and the IGF-1/IGFBP-3 molar ratio, stratified by weight loss.

	N	IGF-1				IGFBP-3				Molar Ratio†			
		Baseline	12-mo	% Change	<i>p</i>	Baseline	12-mo	% Change	<i>p</i>	Baseline	12-mo	% Change	<i>p</i>
<b>CONTROL</b>													
weight loss		181.0	172.5			5262	5126			0.124	0.122		
<5%	67	(52.5)	(50.9)	-4.7	<i>ref</i>	(1064)	(1159)	-2.6	<i>ref</i>	(0.027)	(0.026)	-2.0	<i>ref</i>
		174.1	187.0			5029	4855			0.125	0.137		
5-10%	9	(57.6)	(69.7)	7.4	0.008	(1205)	(1164)	-3.5	0.84	(0.036)	(0.037)	9.6	0.0003
		173.7	183.8			5628	6026			0.110	0.114		
>10%	4	(66.3)	(52.9)	5.8	0.45	(1180)	(2340)	7.1	0.55	(0.024)	(0.16)	3.4	0.36
					<i>p</i> <sub>trend</sub> =0.13				<i>p</i> <sub>trend</sub> =0.59				<i>p</i> <sub>trend</sub> =0.03
<b>EXERCISE</b>													
weight loss		172.9	167.0			5242	5055			0.119	0.119		
<5%	75	(48.8)	(46.6)	-3.4	<i>ref</i>	(983)	(1007)	-3.6	<i>ref</i>	(0.024)	(0.022)	0.2	<i>ref</i>
		181.0	182.8			5086	5041			0.129	0.131		
5-10%	26	(45.7)	(49.2)	1.0	0.33	(837)	(850)	-0.9	0.23	(0.027)	(0.029)	2.0	0.63
		189.8	167.3			5166	4665			0.132	0.130		
>10%	4	(57.4)	(46.7)	-11.8	0.03	(918)	(1103)	-9.7	0.13	(0.027)	(0.022)	-1.1	0.81
					<i>p</i> <sub>trend</sub> =0.88				<i>p</i> <sub>trend</sub> =0.89				<i>p</i> <sub>trend</sub> =0.77
<b>DIET</b>													
weight loss		167.2	163.3			5065	5044			0.119	0.118		
<5%	28	(48.9)	(50.6)	-2.3	<i>ref</i>	(955)	(1286)	-0.4	<i>ref</i>	(0.026)	(0.029)	-0.9	<i>ref</i>
		175.9	172.2			5190	4997			0.122	0.125		
5-10%	27	(49.1)	(39.5)	-2.1	0.97	(962)	(761)	-3.7	0.4	(0.026)	(0.023)	1.9	0.43
		161.0	171.8			5030	4767			0.116	0.130		
>10%	49	(41.8)	(45.1)	6.7	0.03	(837)	(871)	-5.2	0.22	(0.023)	(0.022)	12.3	<0.001
					<i>p</i> <sub>trend</sub> =0.017				<i>p</i> <sub>trend</sub> =0.22				<i>p</i> <sub>trend</sub> <0.001
<b>DIET + EXERCISE</b>													
weight loss		158.2	163.2			4962	4983			0.115	0.118		
<5%	18	(47.9)	(50.1)	3.2	<i>ref</i>	(973)	(979)	0.4	<i>ref</i>	(0.027)	(0.027)	2.8	<i>ref</i>
		167.7	173.7			4702	4708			0.129	0.134		
5-10%	21	(53.8)	(46.2)	3.6	0.93	(985)	(890)	0.1	0.95	(0.028)	(0.025)	3.9	0.75
		188.6	189.8			5342	5004			0.127	0.136		
>10%	69	(60.1)	(64.2)	0.7	0.68	(1072)	(938)	-6.3	0.04	(0.025)	(0.027)	7.1	0.19
					<i>p</i> <sub>trend</sub> =0.59				<i>p</i> <sub>trend</sub> =0.01				<i>p</i> <sub>trend</sub> =0.16

†Molar ratio = [IGF-1 (ng/mL) x 0.130] / [IGFBP-3 (ng/mL) x 0.036]





\*r denotes the age-adjusted partial correlation coefficient

# Cancer Epidemiology, Biomarkers & Prevention

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## Effects of Dietary Weight Loss and Exercise on Insulin-Like Growth Factor-1 and Insulin-Like Growth Factor Binding Protein-3 in Postmenopausal Women

Caitlin Mason, Liren Xiao, Catherine Duggan, et al.

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