

Influence of Weight Management and Exercise on Other Outcomes

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Cancer-Related Outcomes

- Quality of Life
- Physical Function
- Fatigue
- Body composition (weight, %fat, LBM, BMD)
- Lymphedema
- Sleep
- Arthralgia/Joint Pain
- Treatment Adherence
- Comorbidities
- Cardiovascular Disease
- Cognitive Function
- Peripheral Neuropathy

Quality of Life (QOL)

- QOL refers to physical, emotional, mental and social well-being
- Commonly measured via self-report: SF-36 and FACT surveys
- Interventions during treatment seek to influence treatment effectiveness and manage side effects.
- Interventions post-treatment seek to speed recovery, improve QOL.
- Interventions may not improve all dimensions of QOL.
- Concerns with attention effect and ceiling effect

Cancer-Related Fatigue

- Cancer-related fatigue is the most commonly reported symptom by cancer survivors.
- Cancer-related fatigue is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer that is not proportional to recent activity and interferes with usual functioning.
- Exercise may improve fatigue by increasing cardiorespiratory fitness levels and cardiac output.
- Few studies enroll patients with fatigue.

Benefits of Exercise after a Cancer Diagnosis

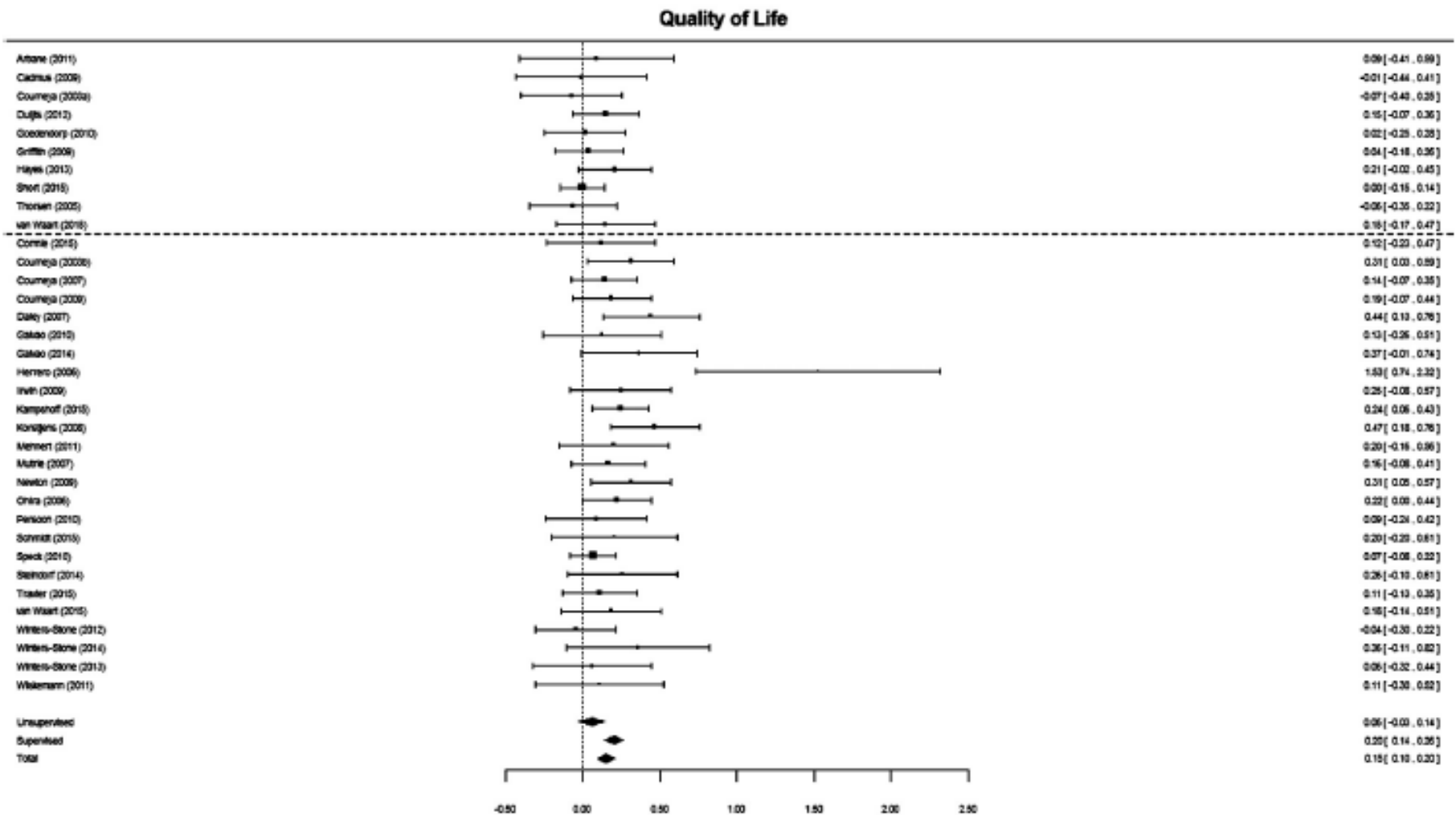
American College of Sports Medicine Roundtable on Exercise Guidelines for Cancer Survivors

EXPERT PANEL

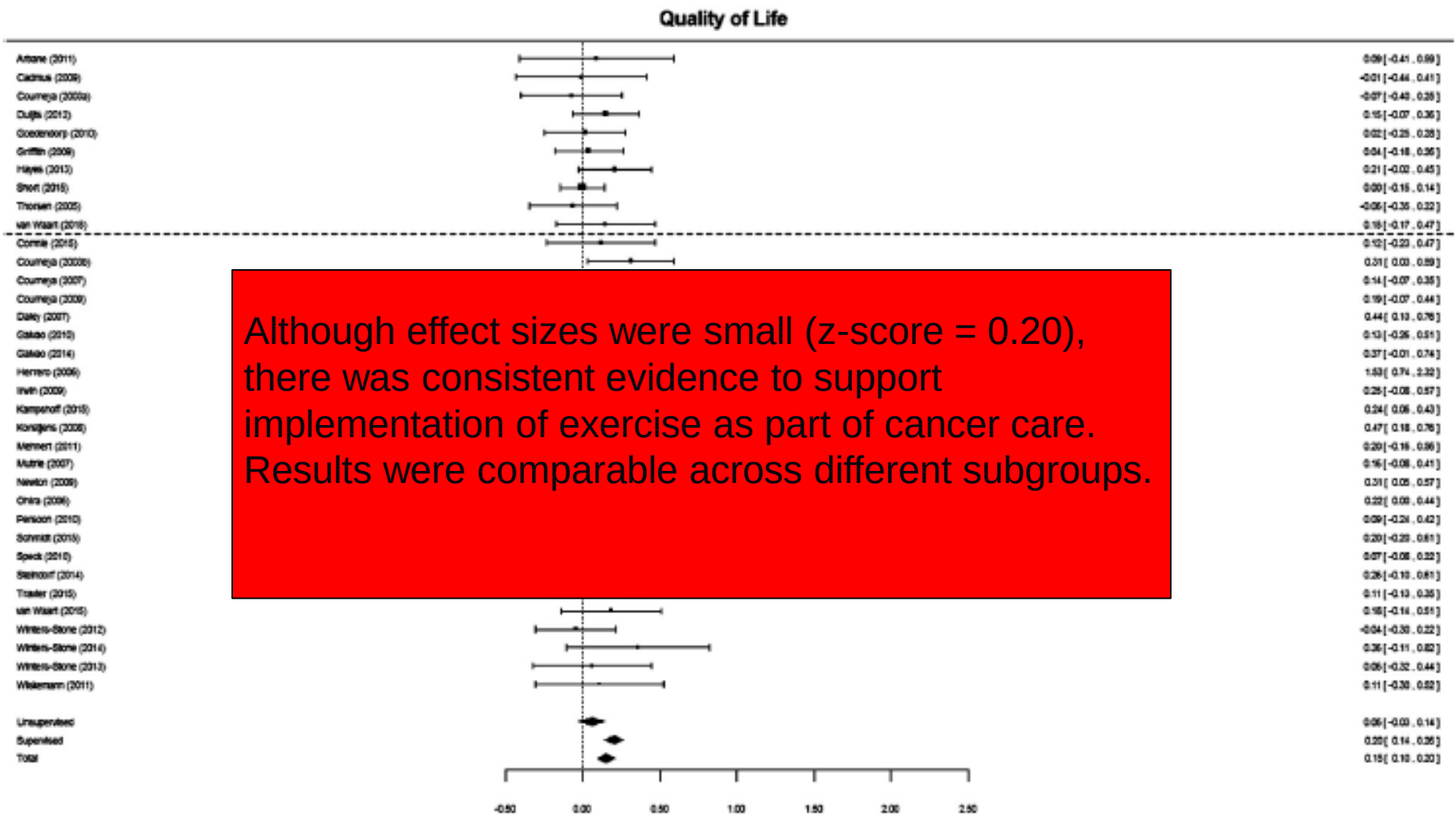
Kathryn H. Schmitz, PhD, MPH, FACSM
Kerry S. Courneya, PhD
Charles Matthews, PhD, FACSM
Wendy Demark-Wahnefried, PhD
Daniel A. Galvão, PhD
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Carole M. Schneider, PhD, FACSM
Vivian E. von Gruenigen, MD
Anna L. Schwartz, PhD, FAAN

- Reviewed 85 exercise intervention trials in patients during and after cancer treatment
- Most studies showed favorable effects on:
 - QOL
 - Physical Function
 - Fatigue
 - Muscular strength
 - Most studies in breast cancer
 - First trial published in 1989 (Winningham ML)

Effect of Exercise on QOL: Meta-analysis of 34 trials



Effect of Exercise on QOL: Meta-analysis of 34 trials



Exercise on cancer-related fatigue during and after breast cancer treatment

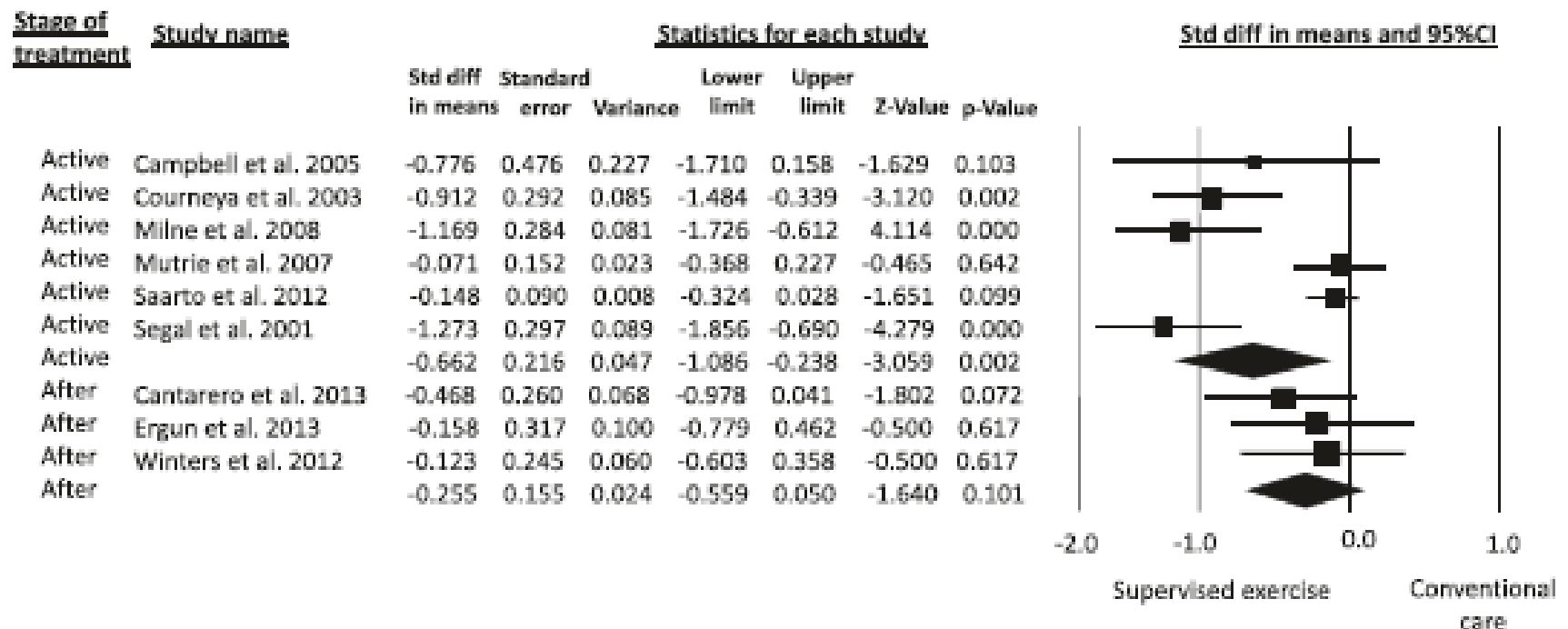
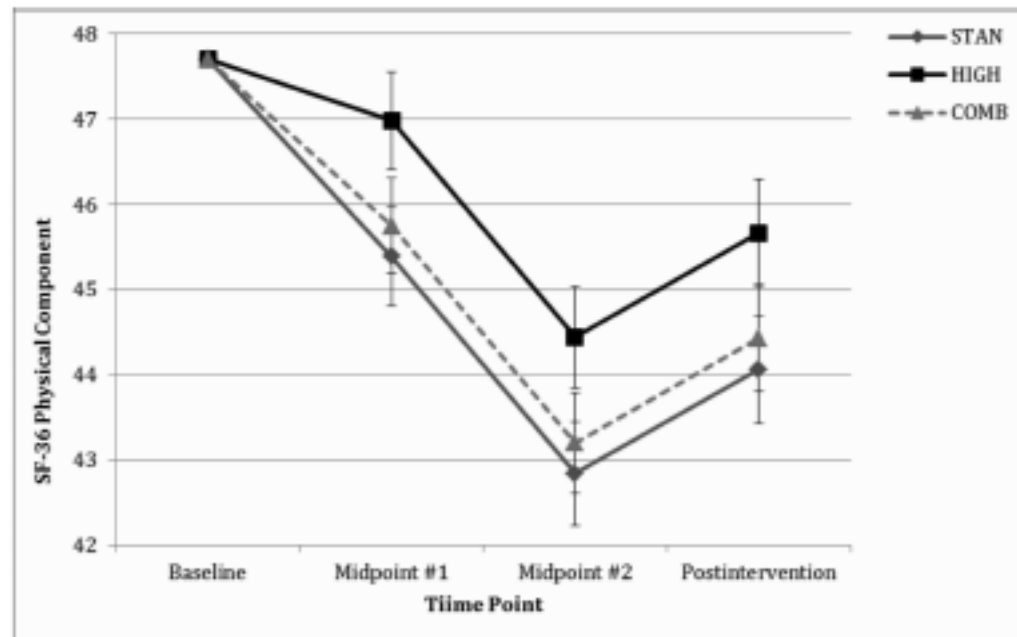
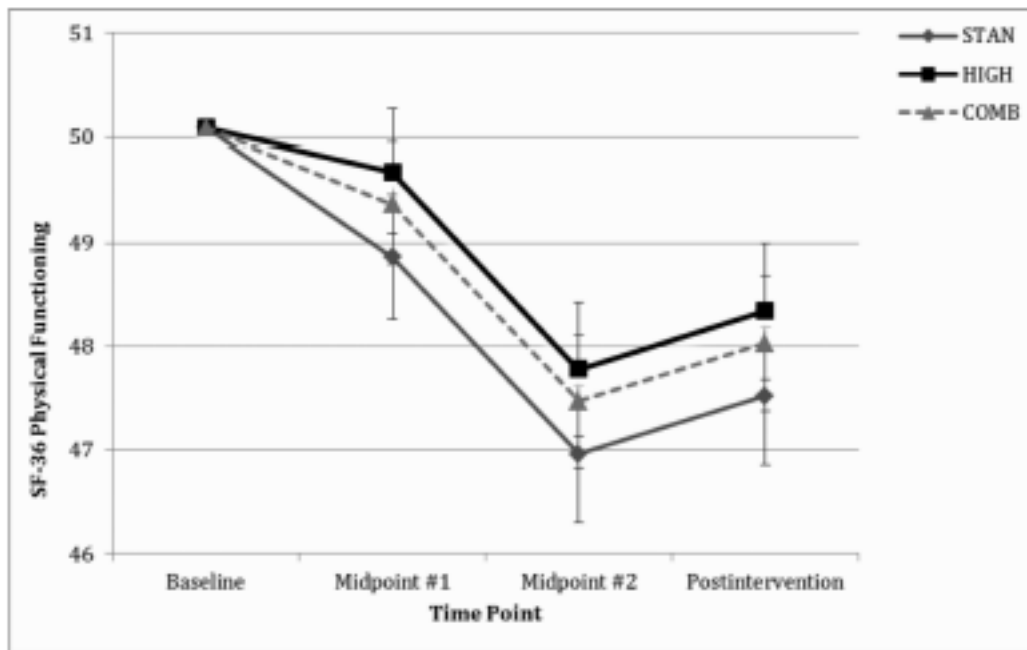


Figure 5 Metaanalysis for the effect estimate of supervised resistance training on CRF in Breast cancer survivors according to the anti-cancer treatment stage. Standardized mean difference was (SMD) calculated for the Random effects model of metaanalysis. IV, inverse of variance; CI, confidence interval.

REHAB and START Exercise Trials

- REHAB Trial:
 - 53 Postmenopausal breast cancer survivors; **post-treatment**
 - Stationary bicycling, 3 x/wk, 15 wks ~30 min/session
 - QOL increased by 8% in exercise group vs. no change in control group, $p = .001$
 - VO₂max increased by 17% in exercise group, with change in VO₂max correlated with change in QOL ($r = .45$, $p < .05$).
 - Significant improvements in fatigue.
- START Trial:
 - 242 breast cancer survivors; **during chemotherapy**
 - 3-arm RCT: usual care, aerobic exercise, resistance training
 - Neither exercise group improved QOL nor fitness, but did improve self-esteem, fitness, body composition and chemotherapy completion rate.
 - RDI was 84.1% in usual care vs. 89.8% (RT) and 87.4 (AE); % receiving 85% of RDI was 65.9% (UC), 78.0% (RT) and 74.4% (AE).
- CARE Trial:
 - 301 breast cancer survivors; **during chemotherapy**
 - 3-arm RCT: 30 min aer, 60 min aer, 60 min aer+RT



- No between-group differences for primary endpoint of physical functioning
- Higher dose of exercise may manage declines during treatment better than recommended amount of exercise.
- No usual care group; effects may be significantly better if compared to UC.

Exercise and Chemotherapy Completion Rate

Table 6. Rates of and Reasons for Chemotherapy Dose Reduction

Characteristic	Total (N = 230)	OnTrack (n = 76)	Onco-Move (n = 77)	Usual Care (n = 77)
Patients requiring dose adjustments, No. (%)	61 (26)	9 (12)	26 (34)	26 (34)
Mean prescribed length of chemotherapy, days	118.6	119.2	119.9	116.7
Reasons for chemotherapy adjustment, No. (%)				
Neuropathy	19 (31)	3	10	6
Myelosuppression	7 (11)	2	2	3
Febrile neutropenia	7 (11)	0	1	6
Nausea and vomiting	7 (11)	2	2	3
Pain	6 (10)	1	2	3
Infection	4 (7)	0	1	3
Dyspnea	4 (7)	0	2	2
Edema	3 (5)	0	3	0
Cardiac signs or symptoms	2 (3)	0	2	0
Obstipation/diarrhea	2 (3)	1	1	0
Average % dose reduction*		9.8	9.7	25.2

*Average dose reductions per group among participants needing a dose adjustment.

Statistically significant attenuated increases in fatigue with supervised exercise.

Effect of Diet and Exercise on Physical Functioning: The RENEW Trial

Outcomes	Mean (SE)				Mean Group Difference (95% CI)	P Value of Group Effect	
	Intervention (n = 319)		Control (n = 322)			Unadjusted	Adjusted ^b
	Baseline	Change at 12 mo	Baseline	Change at 12 mo			
Primary outcome SF-36 physical function (range, 0-100)	75.9 (1.1)	-2.15 (0.9)	75.6 (1.1)	-4.84 (0.9)	2.69 (0.17 to 5.21)	.03	.03
Health-related quality of life on SF-36 General health (range, 15-100)	71.8 (0.9)	0.77 (0.72)	72.6 (0.9)	-1.94 (0.80)	2.71 (0.58 to 4.84)	.02	.03

- **Maintaining functional independence as we age is a priority.**
- **1-year intervention in 641 older breast, prostate and colorectal cancer survivors**
- **Telephone and mail-based intervention**

Effect of Weight Loss on QOL: The ENERGY Trial

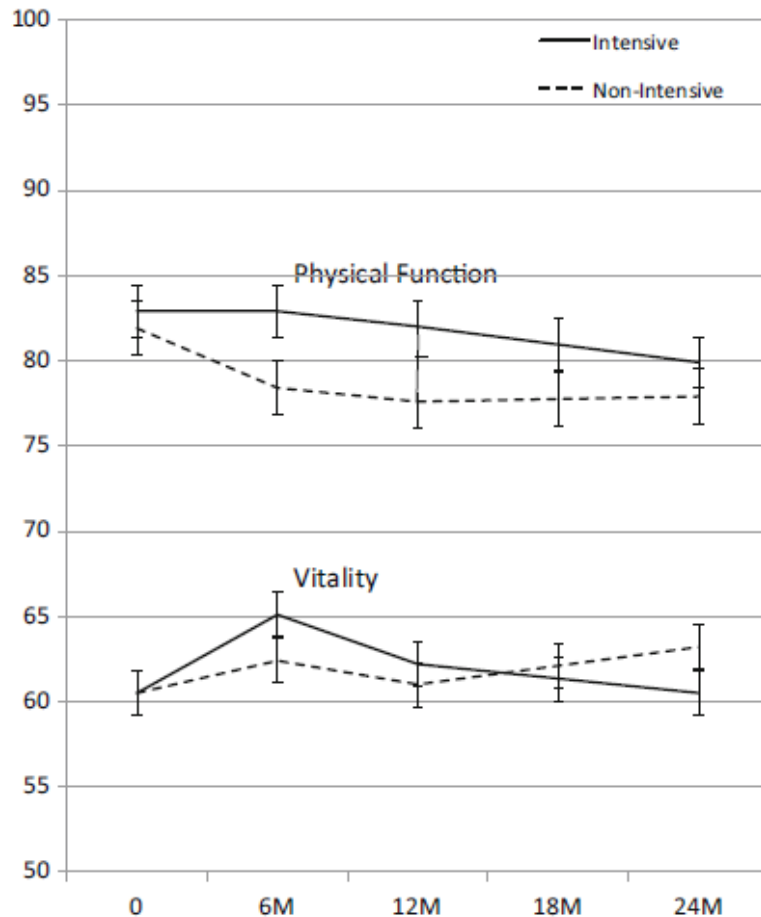
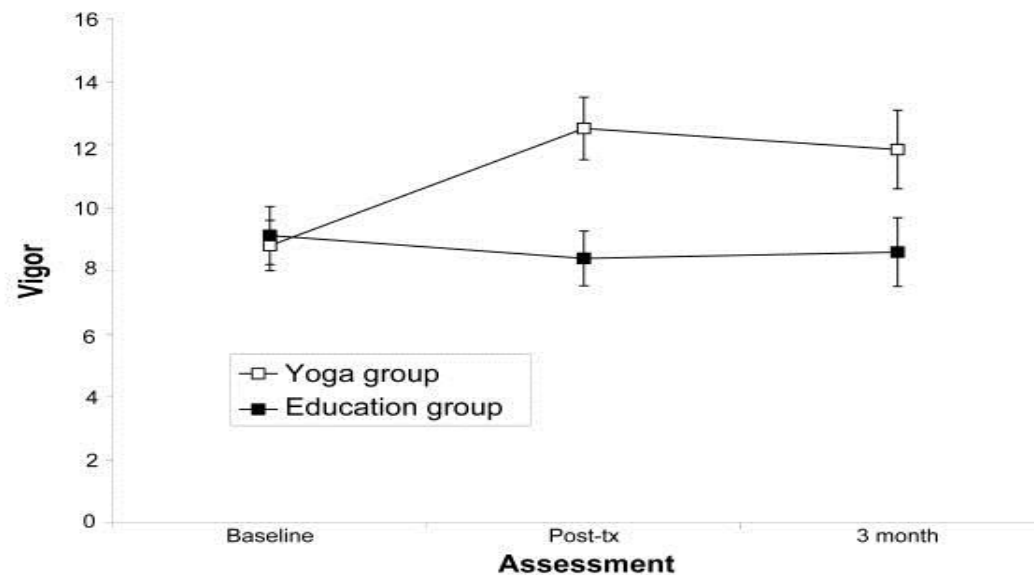
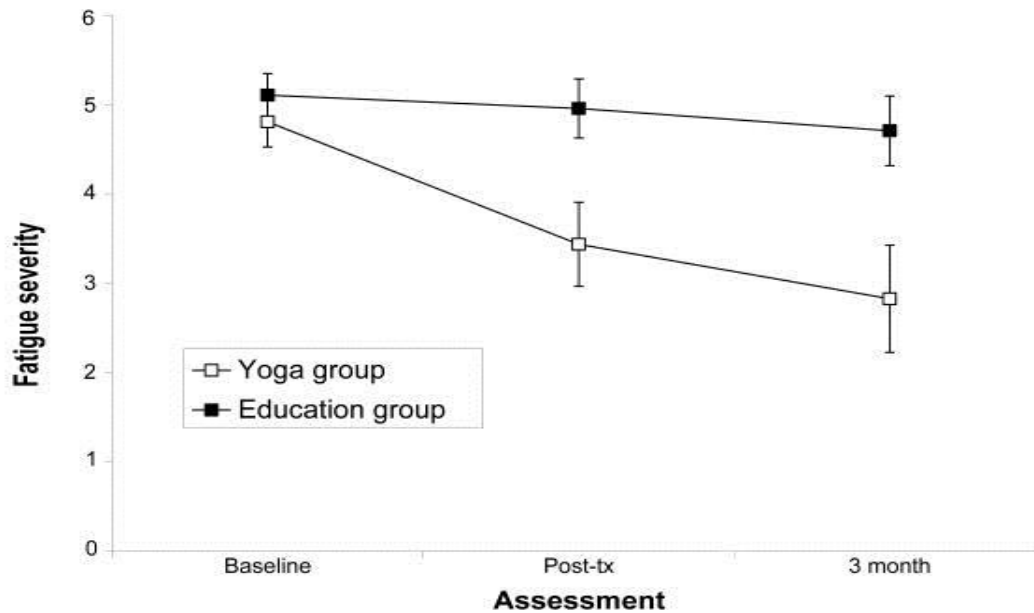


Fig. 2 Change in vitality and physical function over the 24-month study period. For vitality, differences between arms reach borderline significance ($p = 0.0508$) at 6 months but are non-significant at all other time points. For physical function, differences between arms are significant at 6 months ($p = 0.0109$), of borderline significance at 12 months ($p = 0.0512$), and non-significant at all other time points

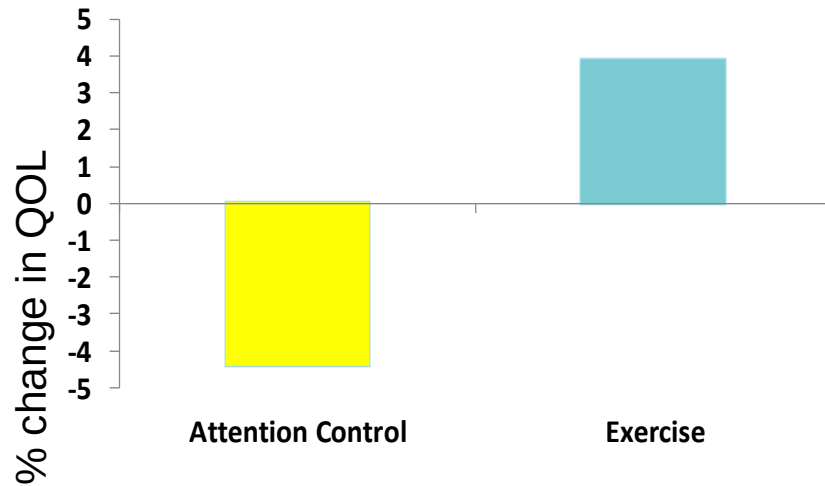
- **Largest weight loss trial in cancer survivors (N = 692)**
- **2-year group and telephone-based intervention**
- **Transitory improvements in physical functioning**
- **Borderline increases in vitality**
- **Need for future research that triages patients to programs that address their needs.**

Yoga and Cancer-Related Fatigue

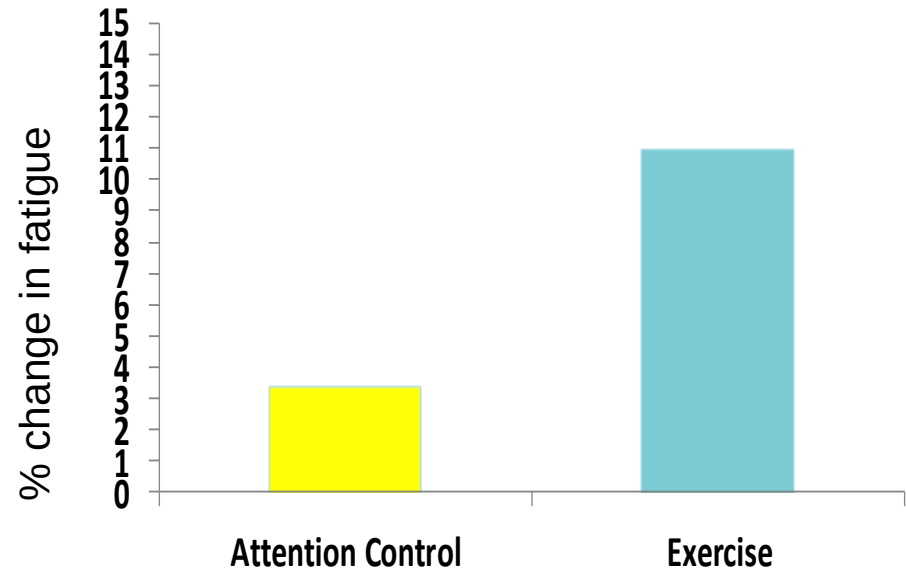


RCT of Exercise in Women with Ovarian Cancer (N = 144)

Change in QOL and Fatigue



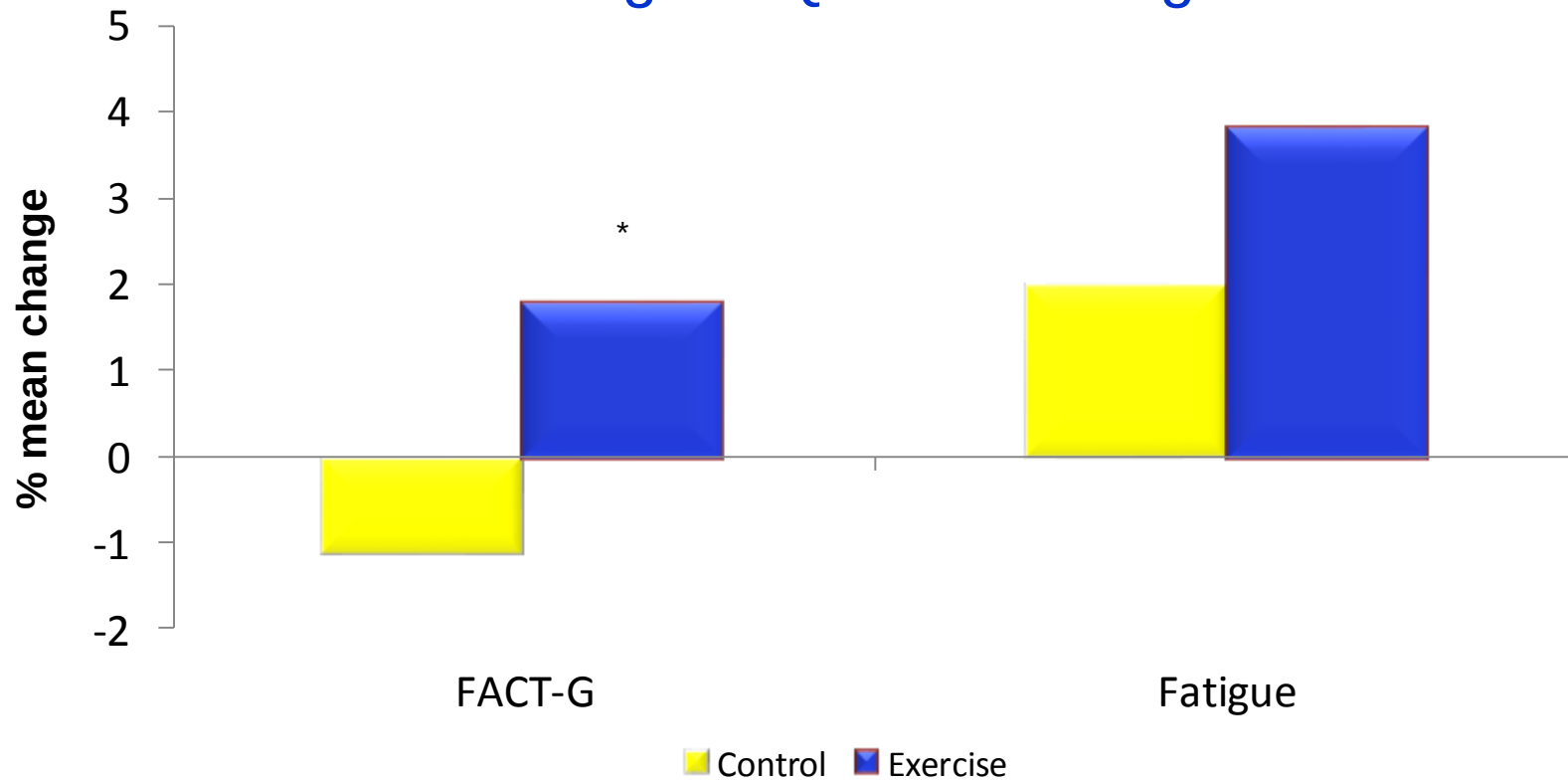
$P=0.016$



$P=0.0652$

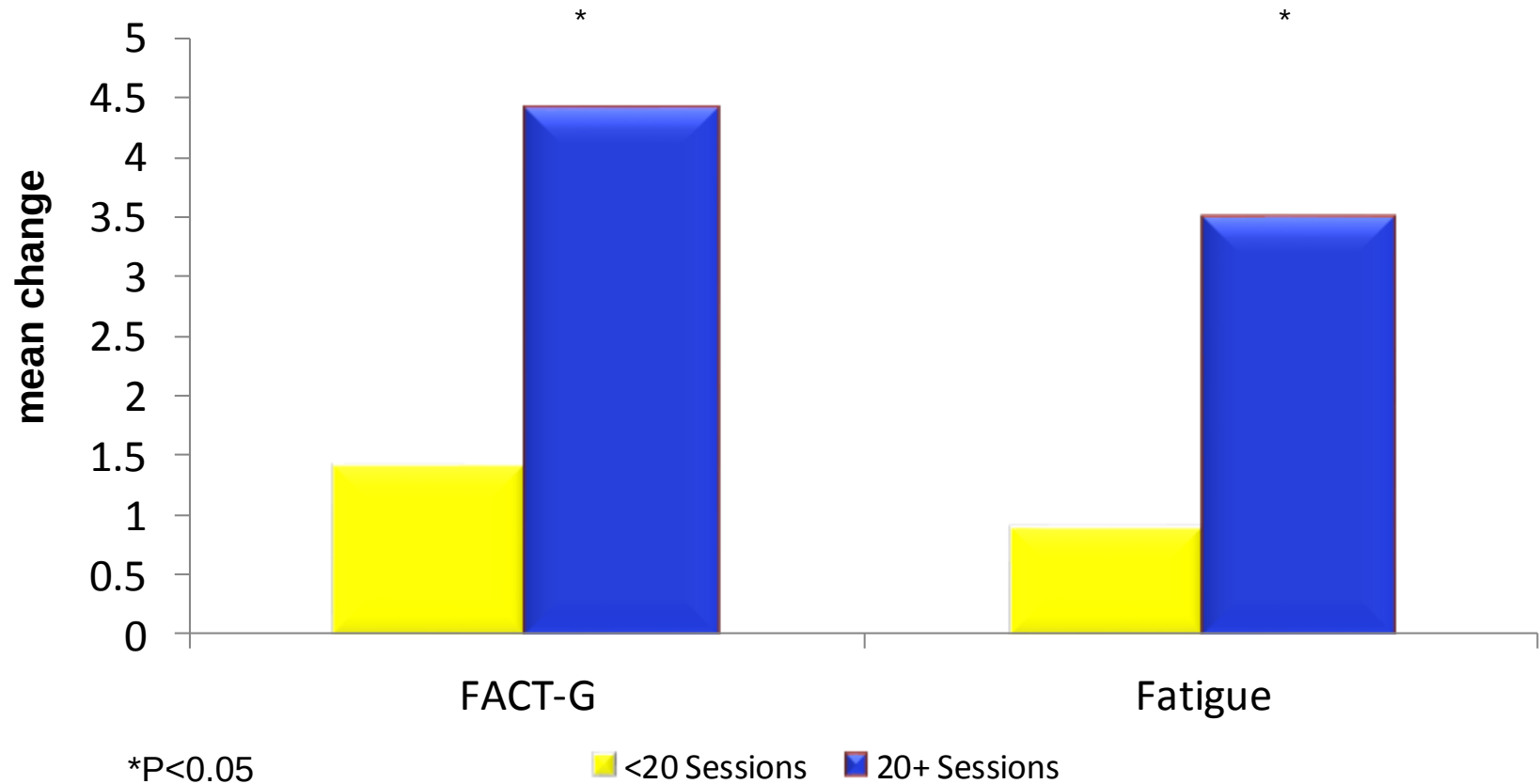
- Excellent adherence to exercise (166.0 ± 66.1 min/wk), with 84% exercising ≥ 120 min/wk
- Baseline QOL and fatigue were worse than healthy women and breast cancer survivors. Effects of exercise on QOL and fatigue were stronger among those with worse QOL and fatigue at baseline.
- 34% experienced recurrence during the trial, with no benefit of exercise on QOL and fatigue in women with recurrence.

Change in QOL and Fatigue

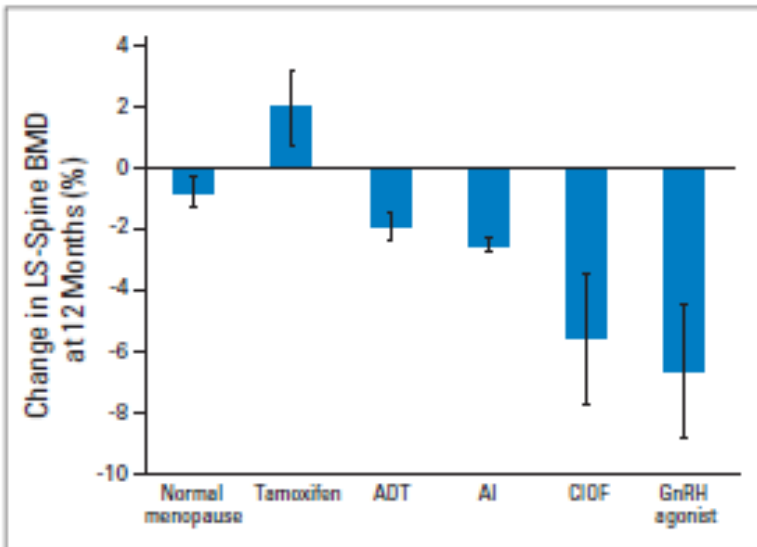


*P<0.05

Change in QOL and Fatigue by Exercise Attendance



Body Composition



- Weight gain and bone loss are common after some cancer diagnoses.
- Chemotherapy and endocrine therapy are associated with bone losses, osteoporosis and fractures.
 - Annual rates of bone loss at the spine from chemotherapy, AIs and ADT are 7%, 3% and 4%, respectively.
 - Fracture risk is increased by 15% in women with breast cancer compared with women without cancer (WHI), and by 20% in prostate cancer survivors on ADT compared with prostate cancer patients not on ADT.

Table 2 Summary of Fractures in Breast Cancer Adjuvant Studies With AIs

Trial	No. of Patients	Median Duration of Follow-Up (months)	Fractures (%)		P
			AI	TAM	
AI v TAM					
ATAC ⁵⁹	6,186	120	14.5	11.3	< .001
ATAC post-treatment ^{59*}	6,186	120	3.5	3.6	.9
BIG 1-98 ⁶⁰	4,895	51	8.6	5.8	< .001
AI after 2-3 years of TAM					
IES ⁶¹	4,742	58	4.3	3.1	.03
ABCSGB/ARNO ⁶¹	3,224	28	2.0	1.0	.015
AI after 5 yrs of TAM					
MA.17 ⁶²	5,187	30	5.3	4.6	.25

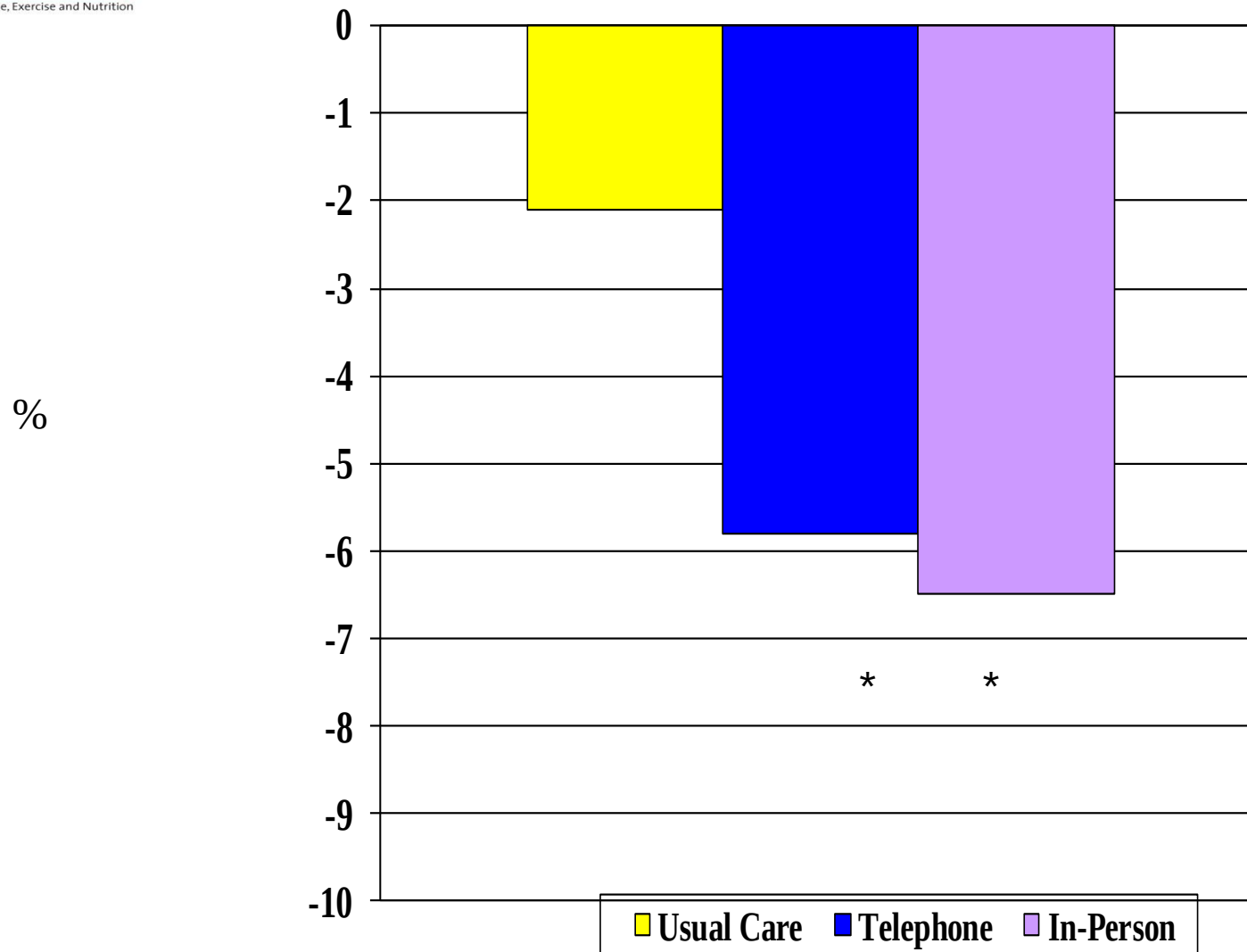
Abbreviations: ABCSG, Austrian Breast and Colorectal Cancer Study Group; AI, aromatase inhibitor; ARNO, Arimidex-Nolvadex; ATAC, Arimidex, Tamoxifen Alone or in Combination; BIG, Breast International Group; IES, Inter-Group Exemestane Study; TAM, tamoxifen.

*After 60 months of AI use, fracture rates decrease after stopping AI.

Weight Loss Trials in Breast Cancer Survivors

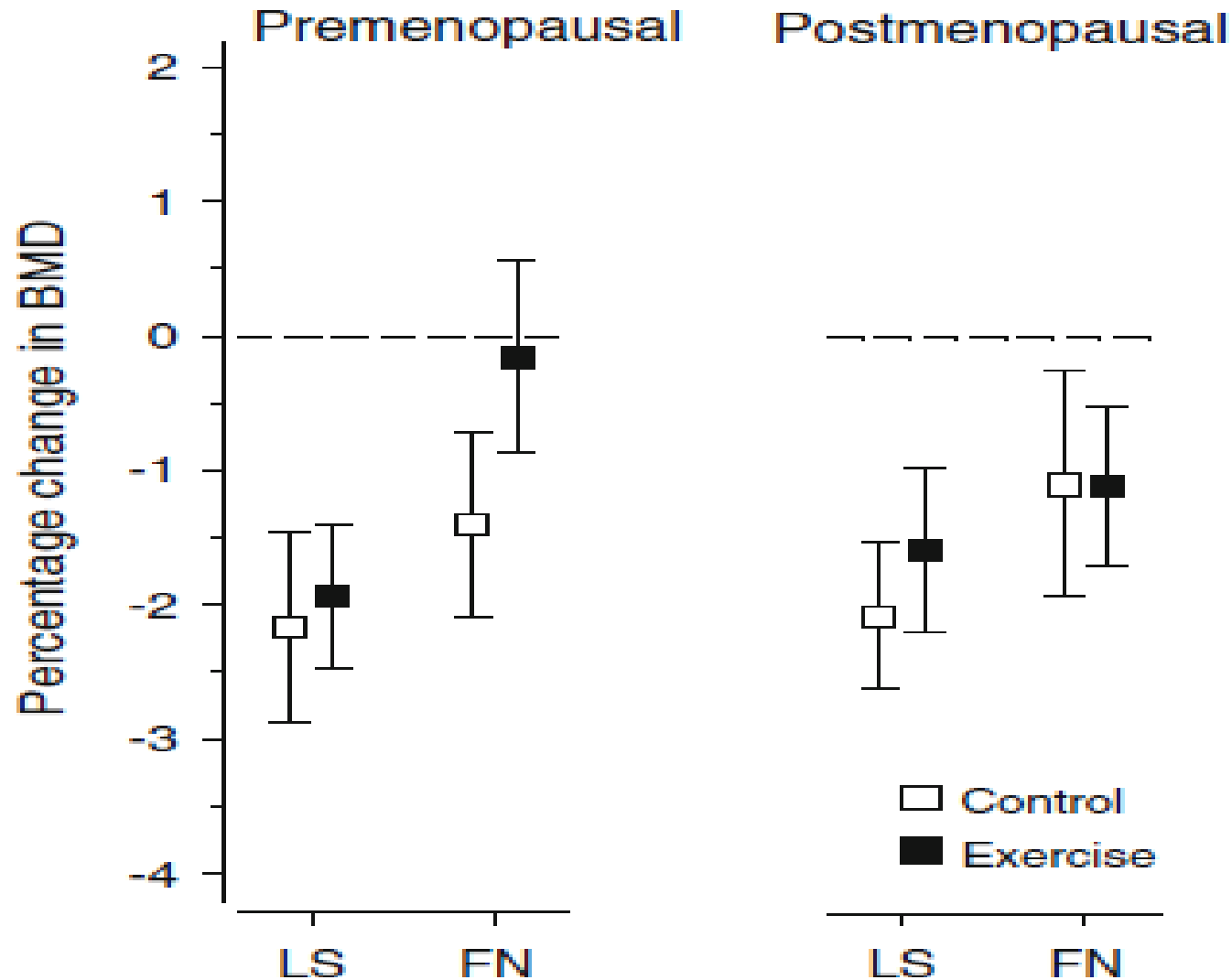
- **ENERGY Trial:**
 - 2-year **GROUP-based** weight loss trial in 692 breast cancer survivors
 - 6% weight loss in intervention vs. 1.5% weight loss in control, $p < .001$
- **LISA Trial:**
 - 2-year **telephone-based** weight loss trial in 338 breast cancer survivors
 - 5.3% weight loss in intervention vs. 0.7% in control, $p < .01$)
- **Rural Health Trial:**
 - 6-month bi-weekly phone-based group counseling in 210 breast cancer survivors living in a rural area
 - 14% weight loss at 6 months
 - At 18 months, 75% maintained $\geq 5\%$ weight loss compared to 58% in newsletter, $p = .02$

Weight Changes by Telephone vs. In-Person



* p < .05 compared to usual care

1-Year BMD Changes with Exercise in Breast Cancer Survivors (N = 573)



Resistance Training and Breast Cancer-Related Lymphedema

Table 3. Lymphedema Outcomes at 12 Months, According to Study Group.*

Variable	Weight Lifting		Control		Cumulative Incidence Ratio or Mean Difference (95% CI) [†]	P Value [‡]
	no. of patients with data	value	no. of patients with data	value		
Change in interlimb volume difference						
≥5% increase — no. (%)	70	8 (11)	69	8 (12)	1.00 (0.88 to 1.13)	1.00
≥5% decrease — no. (%)	70	13 (19)	69	15 (22)	0.96 (0.81 to 1.14)	0.68
Mean interlimb volume discrepancy between baseline and 12 mo (percentage points)	70	−0.69±5.87	69	−0.98±7.31	−0.29 (−1.94 to 2.51)	0.80
Exacerbation — no. (%)	65	9 (14)	65	19 (29)	0.47 (0.23 to 0.97)	0.04
Change in no. of symptoms reported between baseline and 12 mo [§]	70	−1.81±2.16	69	−1.17±1.94	−0.63 (−1.32 to 0.06)	0.07
Change in severity of symptoms between base- line and 12 mo [§]	70	−0.51±0.80	69	−0.22±0.71	−0.29 (−0.54 to −0.03)	0.03

Resistance Training and Prevention of Lymphedema

Table 3. Lymphedema Onset Outcomes at 12 Months^a

	Weight Lifting Intervention		Control		Cumulative Incidence Ratio (95% CI)	P Value ^b
	No./Total No. (%)	Mean (SD)	No./Total No. (%)	Mean (SD)		
All participants						
Defined by $\geq 5\%$ increase in arm swelling ^c	8/72 (11)		13/75 (17)		0.64 (0.28-1.45)	.003
Clinician-defined onset	1/66 (1.5)		3/68 (4.4)		0.34 (0.04-3.22)	.12
Participants who had ≥ 5 lymph nodes removed						
Defined by $\geq 5\%$ increase in arm swelling ^c	3/45 (7)		11/49 (22)		0.30 (0.09-1.00)	.001
Clinician-defined onset	1/42 (2.4)		3/46 (6.5)		0.37 (0.04-3.38)	.13
	Total No.		Total No.		Mean (SD) Difference	
All participants						
Δ in No. of symptoms reported	72	-0.51 (1.57)	75	-0.42 (2.26)	-0.10 (0.32)	.77
Δ in symptom severity ^d	72	-0.27 (0.97)	75	-0.28 (0.86)	0.003 (0.15)	.99
Participants who had ≥ 5 lymph nodes removed						
Δ in No. of symptoms reported	45	-0.63 (1.86)	49	-0.83 (1.52)	0.21 (0.35)	.55
Δ in symptom severity ^d	45	-0.30 (1.06)	49	-0.41 (0.88)	0.12 (0.20)	.56

Abbreviation: CI, confidence interval.

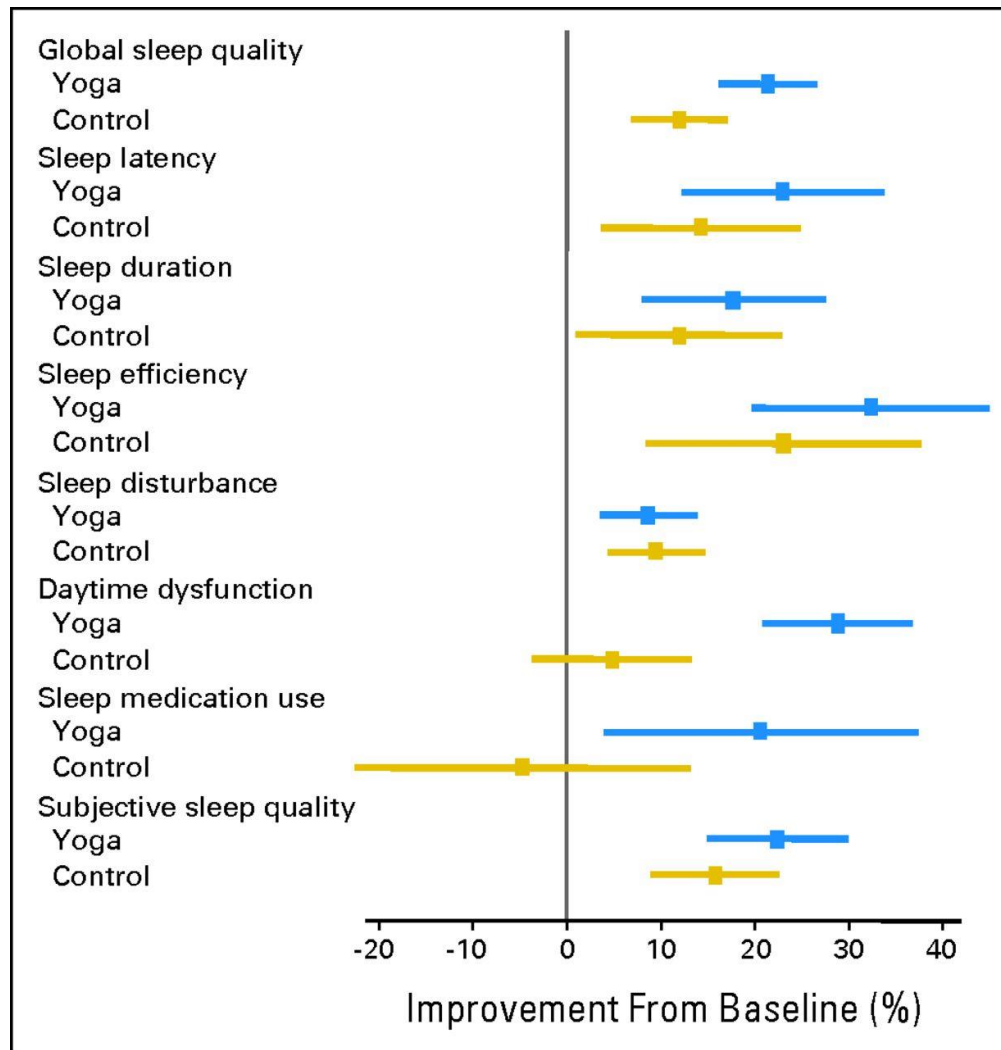
^aResults for arm swelling and symptoms include imputed data.

^bTest for equivalence, using Fisher exact test for arm volume changes and Wilcoxon rank sum 2-sample test for change in symptoms.

^cArm swelling = [(affected arm volume - unaffected arm volume)/unaffected arm volume] (eg, interlimb volume difference).

^dPossible values were 0 (did not have symptom) to 4 (very severe) for each item; outcomes reported are average changes in symptom severity across all 14 possible symptoms (rings too tight, watch too tight, bracelets too tight, clothing too tight, puffiness, could not see knuckles, could not see veins, skin felt leathery, arm felt tired, pain, pitting, swelling after exercise, difficulty writing, or other).

Yoga and Sleep





JOURNAL OF CLINICAL ONCOLOGY

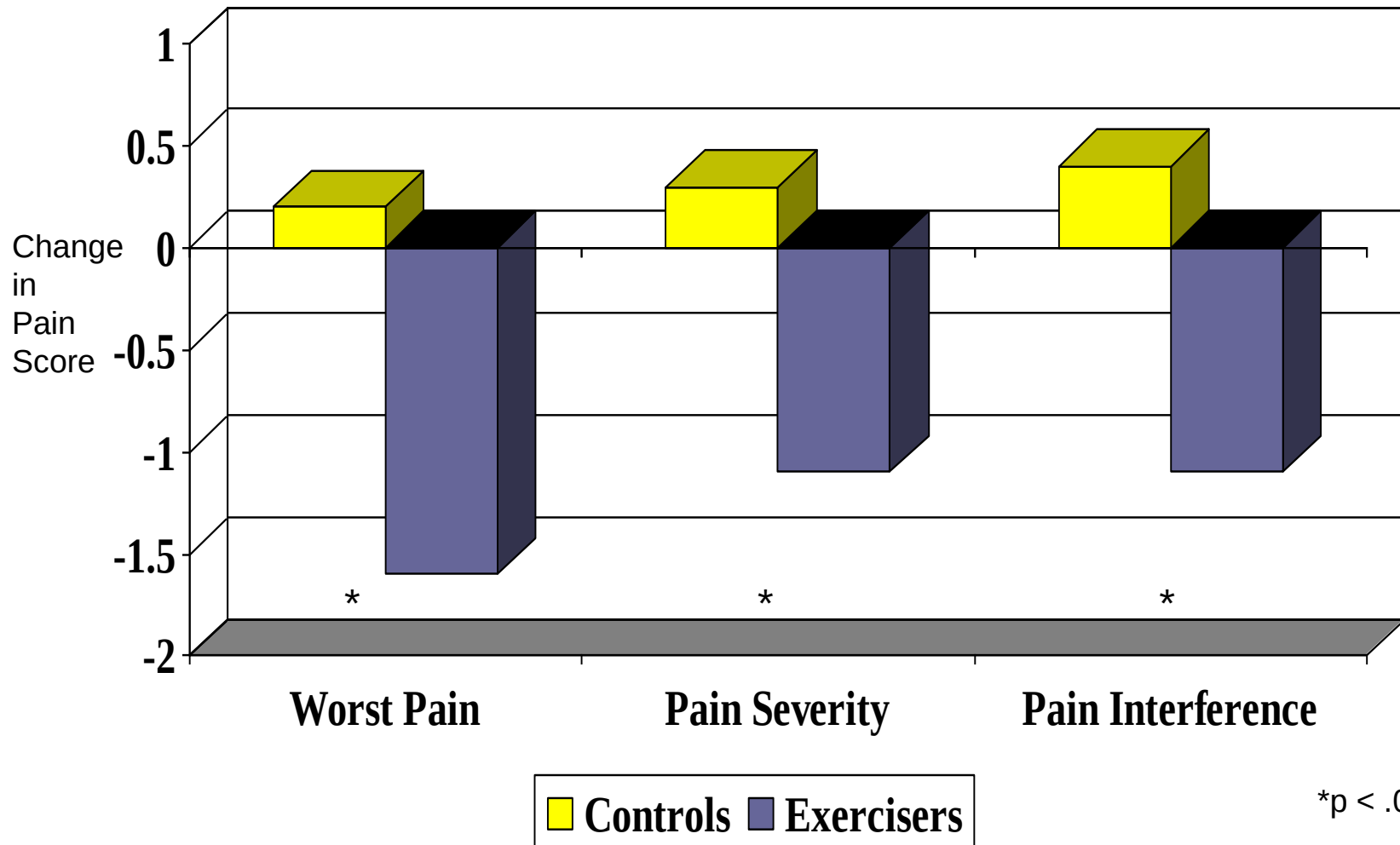
ORIGINAL REPORT

Randomized Exercise Trial of Aromatase Inhibitor–Induced Arthralgia in Breast Cancer Survivors

Melinda L. Irwin, Brenda Cartmel, Cary Gross, Elizabeth Ercolano, Fangyong Li, Xiaopan Yao, Martha Fiellin, Scott Capozza, Marianna Rothbard, Yang Zhou, Maura Harrigan, Tara Sanft, Kathryn Schmitz, Tuhina Neogi, Dawn Hershman, and Jennifer Ligibel

Melinda L. Irwin, Brenda Cartmel, Cary Gross, Elizabeth Ercolano, Fangyong Li, Xiaopan Yao, Martha Fiellin, Scott Capozza, Marianna Rothbard, Yang Zhou, Maura Harrigan, and Tara Sanft, Yale University; Melinda L. Irwin, Brenda Cartmel, Cary Gross, Elizabeth

RCT of Exercise on 12 Month Change in Joint Pain in Breast Cancer Patients taking AIs



Comorbidities and the ENERGY Weight Loss Trial in Breast Cancer Survivors

Table 2 New medical conditions, prescription medications, hospital visits, and emergency room visits at baseline, 12- and 24-month time points among the ENERGY trial cohort

	Baseline (study entry)					12-month follow-up					24-month follow-up				
	Intervention <i>N</i> = 344		Control <i>N</i> = 348		<i>P</i> value ^a	Intervention <i>N</i> = 271		Control <i>N</i> = 245		<i>P</i> value ^a	Intervention <i>N</i> = 260		Control <i>N</i> = 250		<i>P</i> value ^a
	<i>N</i>	%	<i>N</i>	%		<i>N</i>	%	<i>N</i>	%		<i>N</i>	%	<i>N</i>	%	
Any new medical condition	—	—	—	—	—	53	19.6	79	32.2	0.001	68	26.2	55	22.0	0.27
Leading conditions in which non-cancer medications were prescribed															
Antihypertensives (%)	106	30.8	100	28.7	0.47	84	31.1	79	32.2	0.81	84	32.4	83	33.3	0.83
Lipid-lowering agents (%)	80	23.3	77	22.1	0.66	66	24.4	63	25.7	0.72	69	26.5	66	26.4	0.97
Diabetes medications (%)	21	6.1	19	5.5	0.69	19	7.0	17	6.9	0.88	15	5.8	19	7.6	0.48
Acid reflux medications (%)	75	21.8	68	19.5	0.43	65	24.1	60	24.5	0.54	53	20.5	55	22.1	0.52
Hospital visit ^b (%)	87	25.3	87	25.0	0.86	22	8.1	24	9.9	0.49	18	6.9	13	5.2	0.42
Emergency room visit ^b (%)	56	16.3	50	14.4	0.49	18	6.7	18	7.4	0.77	22	8.5	18	7.2	0.59

- 37% had a comorbidity at baseline (most common: HTN, depression, osteoporosis)
- Average of 2.3 comorbidities for which participants were taking non-cancer prescription medications

Exercise and Risk of CVD in Breast Cancer Survivors

- CVD is leading cause of mortality in women with non-metastatic breast cancer.
- Women with non-metastatic breast cancer may be at increased CVD risk compared with age-matched women without breast cancer.

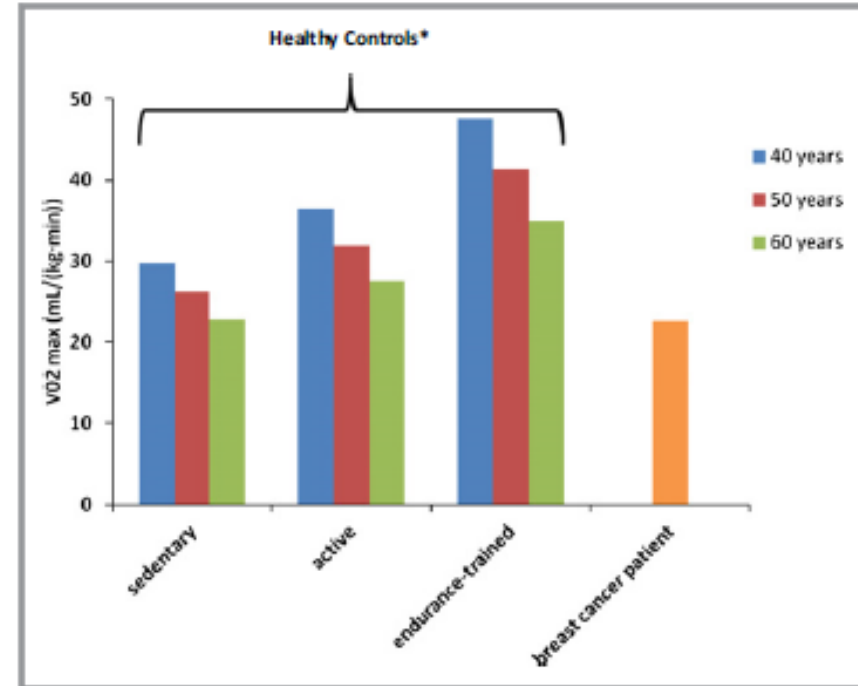
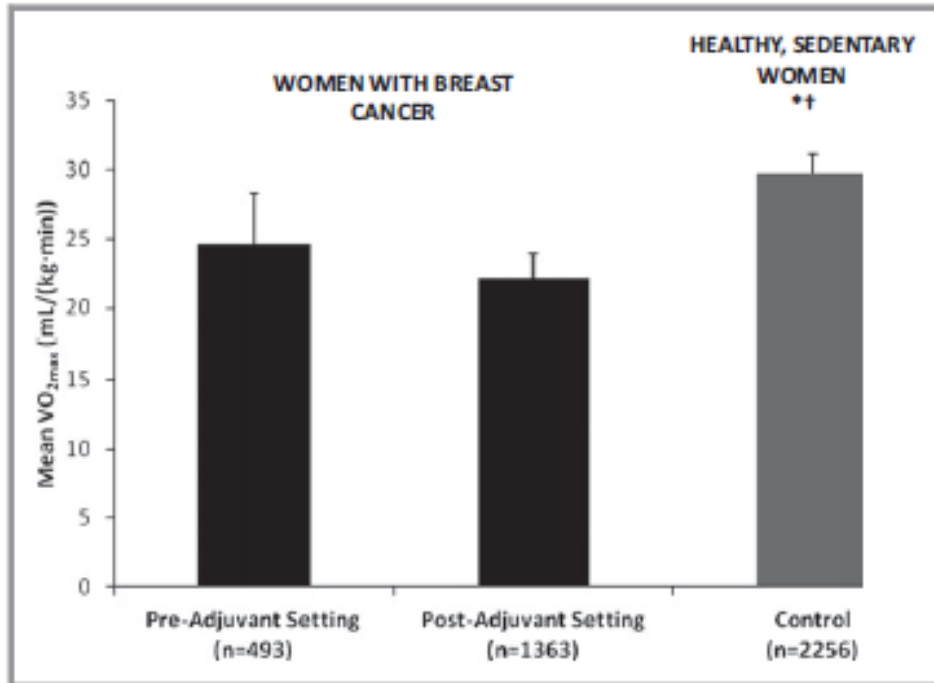
Table 2 Age-Adjusted and Multivariable-Adjusted HRs of Cardiovascular Events According to Quartile of Exercise (MET-h/wk)

	Total (N = 2,973)	≤ 2 (n = 741)	MET-h/wk			<i>P</i> _{trend}
			2.1-10.3 (n = 747)	10.4-24.5 (n = 741)	≥ 24.6 (n = 744)	
Median MET-h/wk	10.3	0.0	5.4	16.3	40.0	
Cardiovascular events*						
No. of events	862	262	243	198	159	
Age-adjusted HR (95% CI)		Ref	0.83 (0.70 to 0.99)	0.72 (0.60 to 0.86)	0.57 (0.47 to 0.69)	< .001
Multivariable-adjusted HR (95% CI)†		Ref	0.91 (0.76 to 1.09)	0.79 (0.66 to 0.96)	0.65 (0.53 to 0.80)	.001

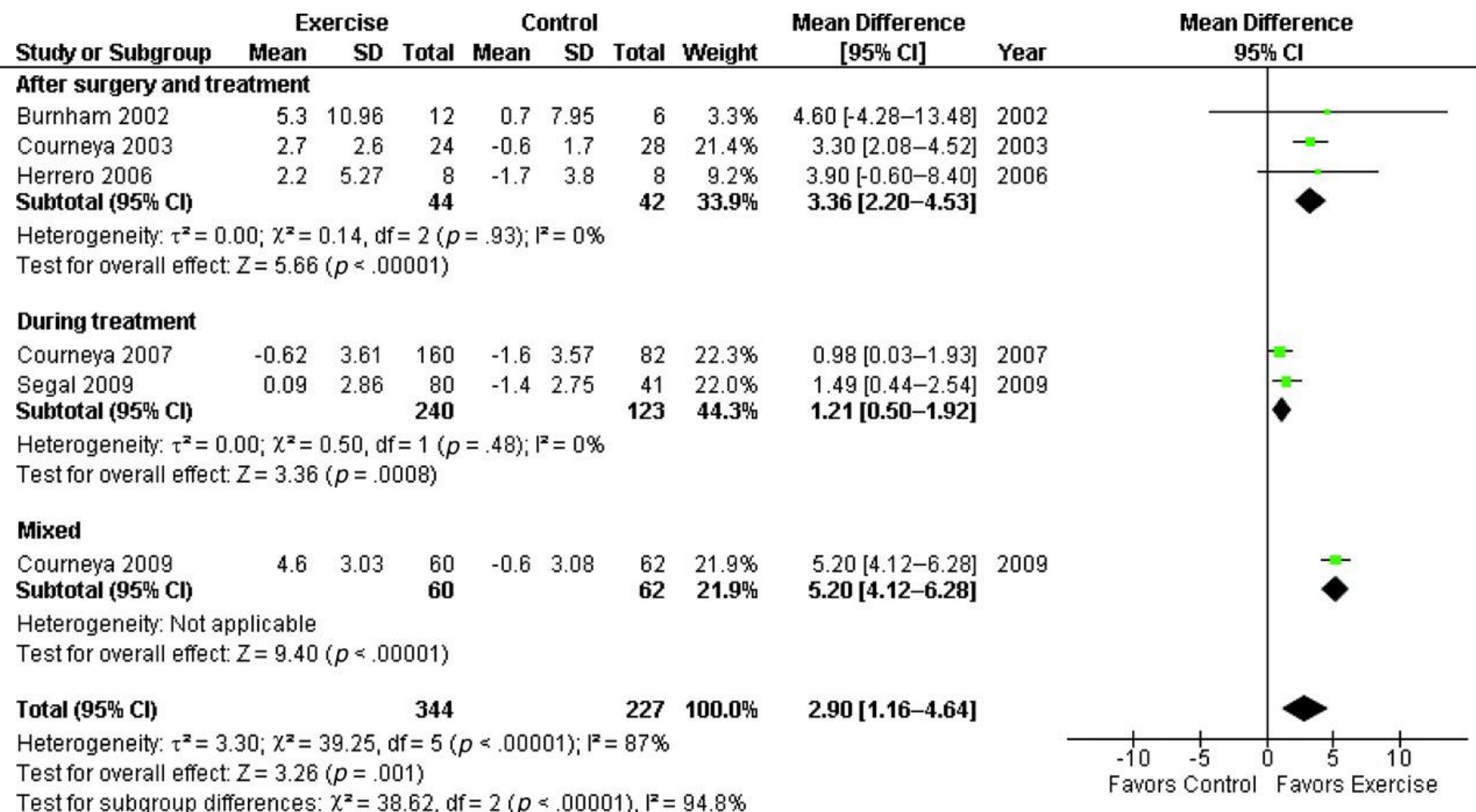
Cardiorespiratory Fitness

- Maximal oxygen consumption (VO₂max) provides the gold standard measure of cardiorespiratory fitness, and is a powerful predictor of mortality in healthy adults as well as those with CVD.
- Minimum VO₂max of 15 ml/kg/min in women and 18 ml/kg/min in men necessary for full and independent living
- Unfortunately, cancer patients have marked reductions in VO₂max.
 - ~30% below that of sedentary individuals without cancer
- VO₂max > 14 ml/kg/min associated with a 24% lower all-cause mortality rate compared to patients with <14 ml/kg/min
- Exercise improves VO₂max
 - Most studies used indirect measures
 - Usual care group has decreases; exercise group maintain or increase
 - Aerobic training better than resistance training; more improvement post-treatment

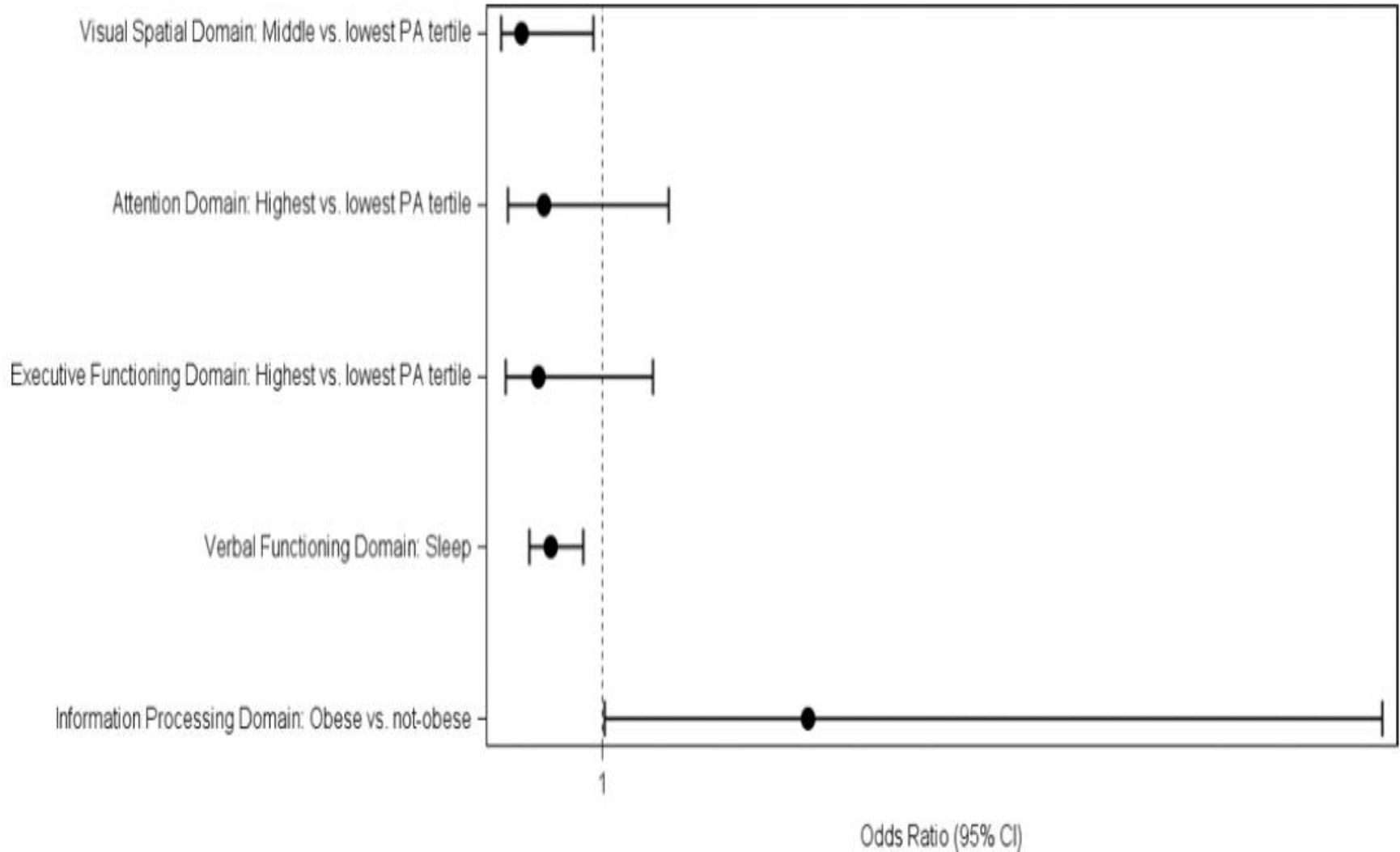
Normative Values of VO₂max



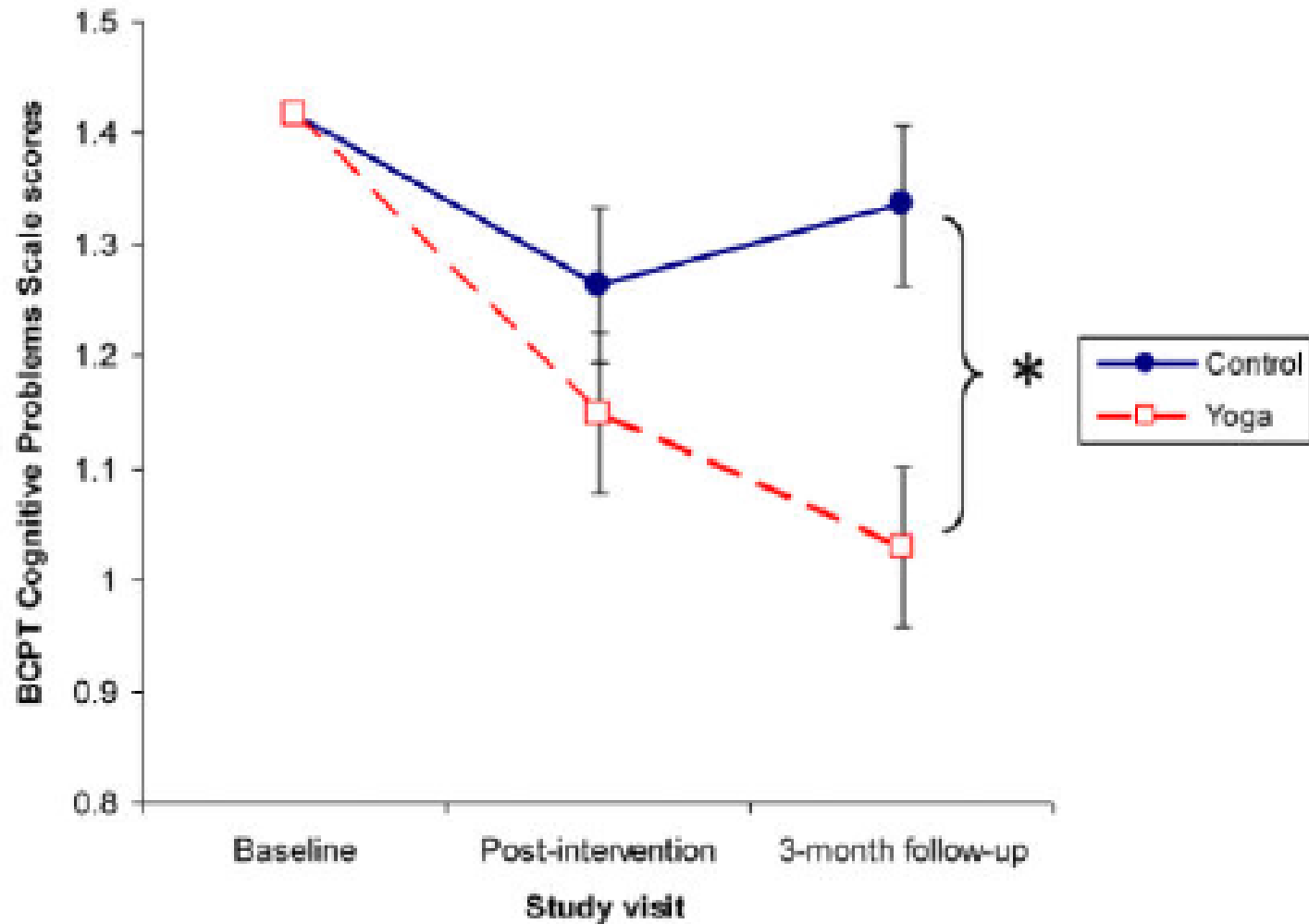
Meta-Analysis of Exercise on VO₂peak



Cognitive Function in Breast Cancer Survivors



Yoga and Cognitive Function in Breast Cancer Survivors



Limitations of Exercise and Weight Management Studies

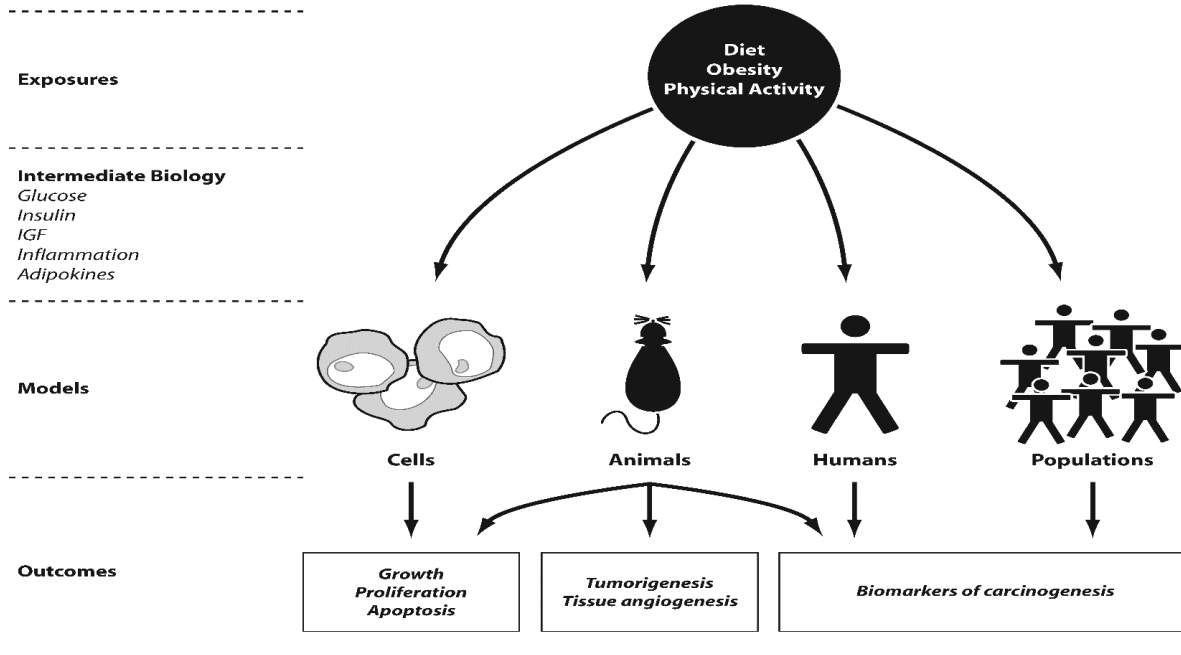
- Many trials focus on breast cancer
- Many trials enroll healthy patients without side effects
- Few trials control for attention effect
- Few trials in patients with metastatic disease
- Limited studies examining BMD, cognitive function and peripheral neuropathy
- Few trials focus on adherence to adjuvant treatments and drug +/- lifestyle interventions
- Promising studies in older patients, rural communities, racial/ethnic minorities
- Growing number of studies comparing different approaches of delivering interventions

Transdisciplinary Research on Energetics and Cancer

NCI R25 Education/Training Course



- To offer an annual weeklong energetics (i.e., physical activity, diet and obesity) and cancer course for 100 postdocs/junior faculty (20 trainees per year over 5 years)
- Goal is to increase the number of researchers who have expertise and successful careers in energetics and cancer, leading to dissemination and implementation of research findings into the clinic and community.



Summary

- Exercise and weight management trials improve QOL, fatigue, fitness, body weight, lymphedema, sleep and joint pain in cancer survivors.
- Uncertain effects of exercise and weight management on BMD, cognitive function, peripheral neuropathy and CVD biomarkers.
- More studies needed in individuals with treatment-related symptoms or high risk groups.
- More studies needed of lifestyle interventions on adjuvant treatment adherence and efficacy, and in combination with cancer therapies to attenuate toxicity.