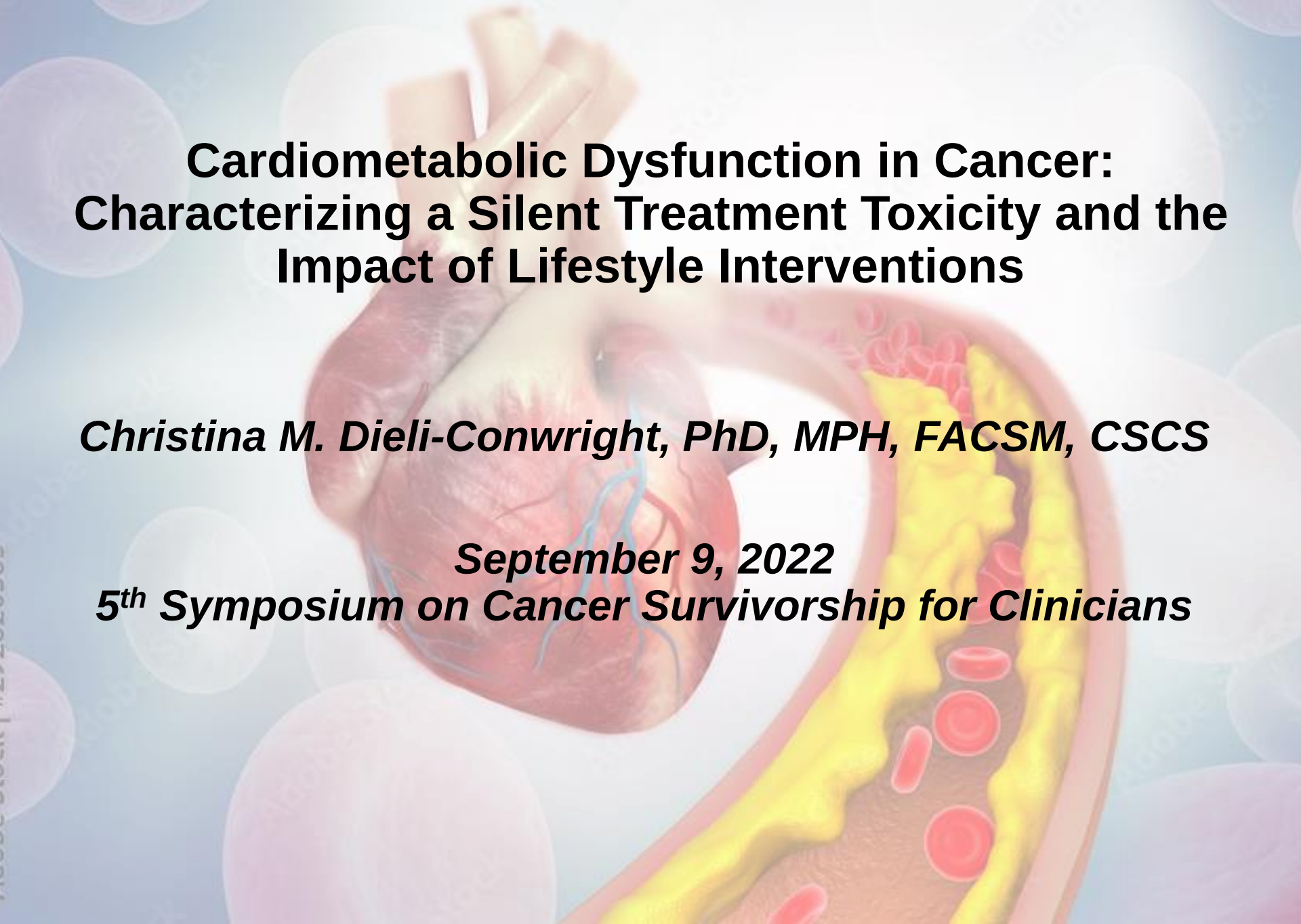
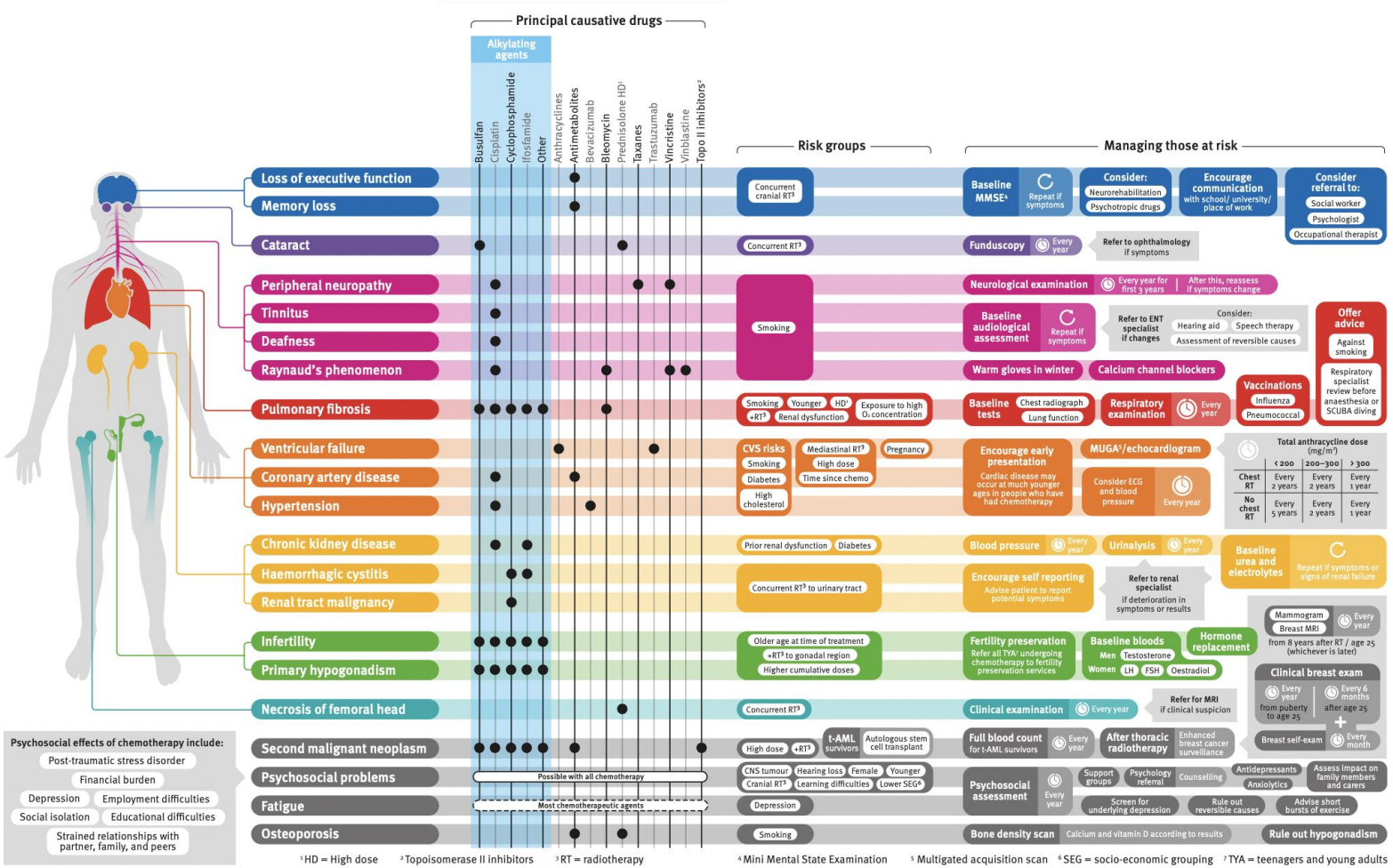
Cardiometabolic Dysfunction in Cancer: Characterizing a Silent Treatment Toxicity and the Impact of Lifestyle Interventions



Christina M. Dieli-Conwright, PhD, MPH, FACSM, CSCS

September 9, 2022
5th Symposium on Cancer Survivorship for Clinicians

Chemotherapy toxicities include and exacerbate metabolic toxicities.



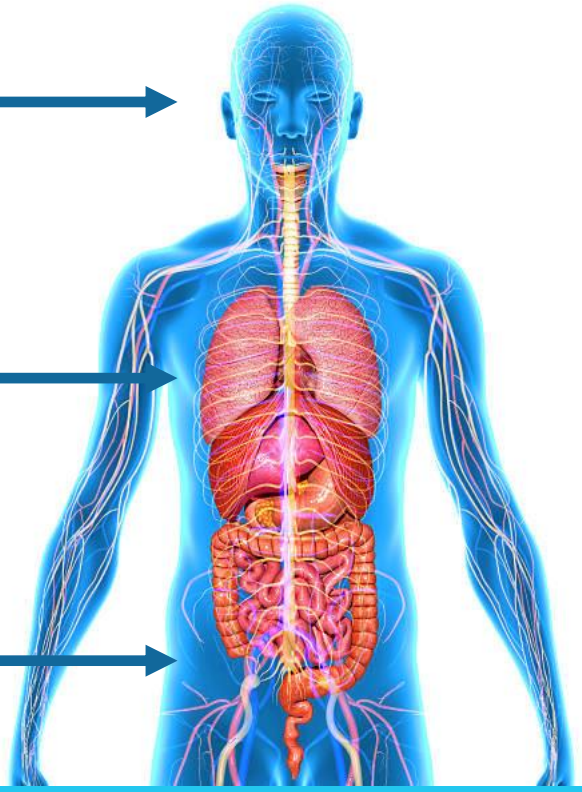
Pre-existing conditions at diagnosis in combination with treatment promote metabolic toxicity in cancer survivors.

Multiple-Hit Hypothesis

Direct Hit-
Cancer Cancer Treatments

Indirect Hit-
Modifiable Lifestyle Factors

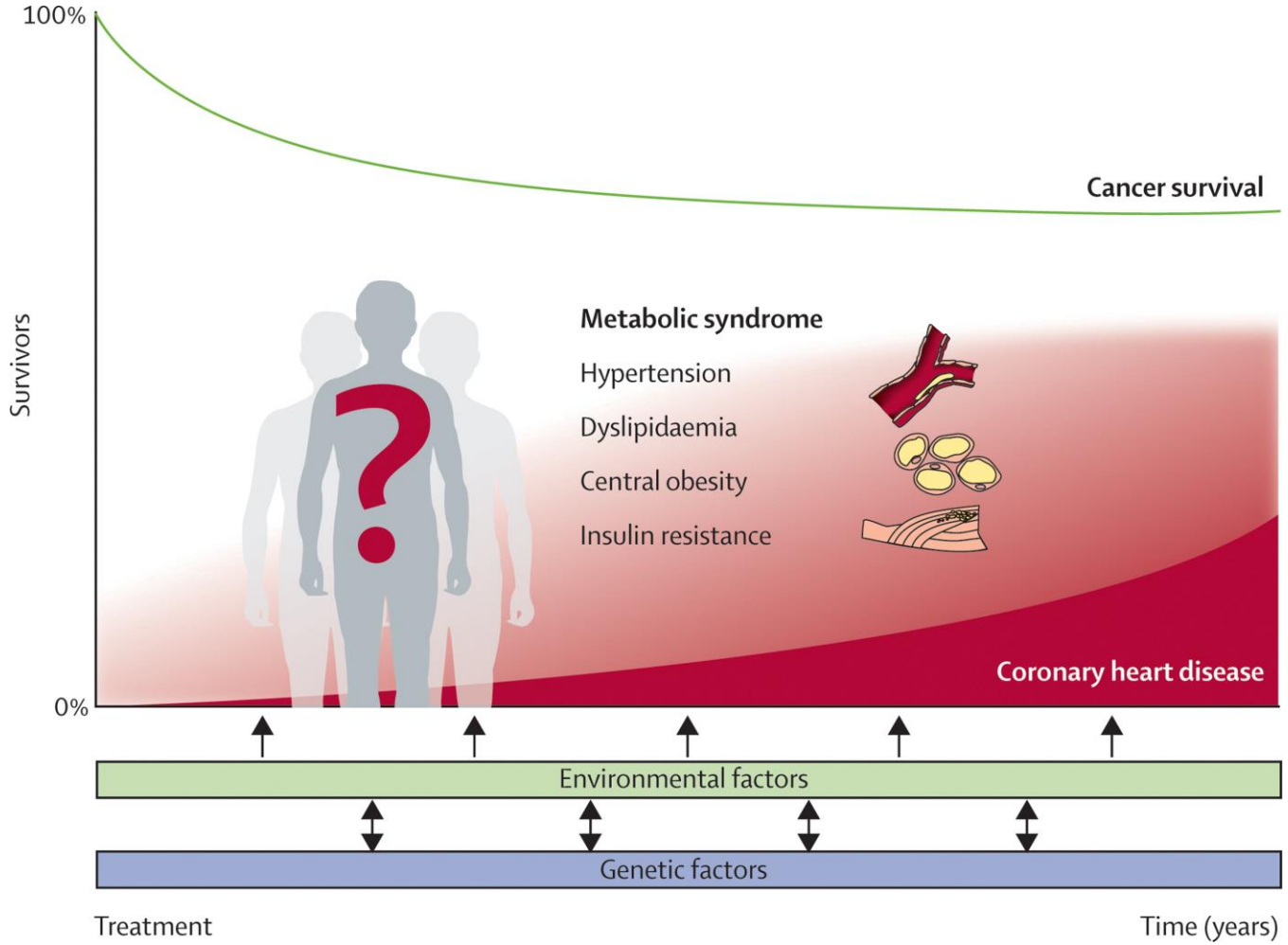
Baseline Status-
Age, Smoking, Comorbidities



- Poor brain health
- Immune impairments
- Blood disorders
- Cardiovascular events
- Respiratory problems
- Gastrointestinal disease
- Weakened bones
- Muscle breakdown

Cancer Patient

Metabolic toxicities may develop into metabolic syndrome (MSY) and lead to the onset of severe comorbidities.

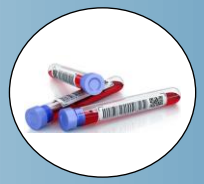


De Haas et al., 2010 Lancet Oncology

Metabolic syndrome (MSY) is associated with a 2-fold increase in CVD and Type 2 Diabetes.

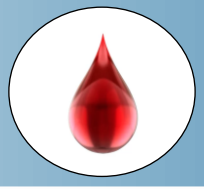
Blood Pressure
≥ 130/85 or medication

HDL
< 40 mg/dL (men)
< 50 mg/dL (women)



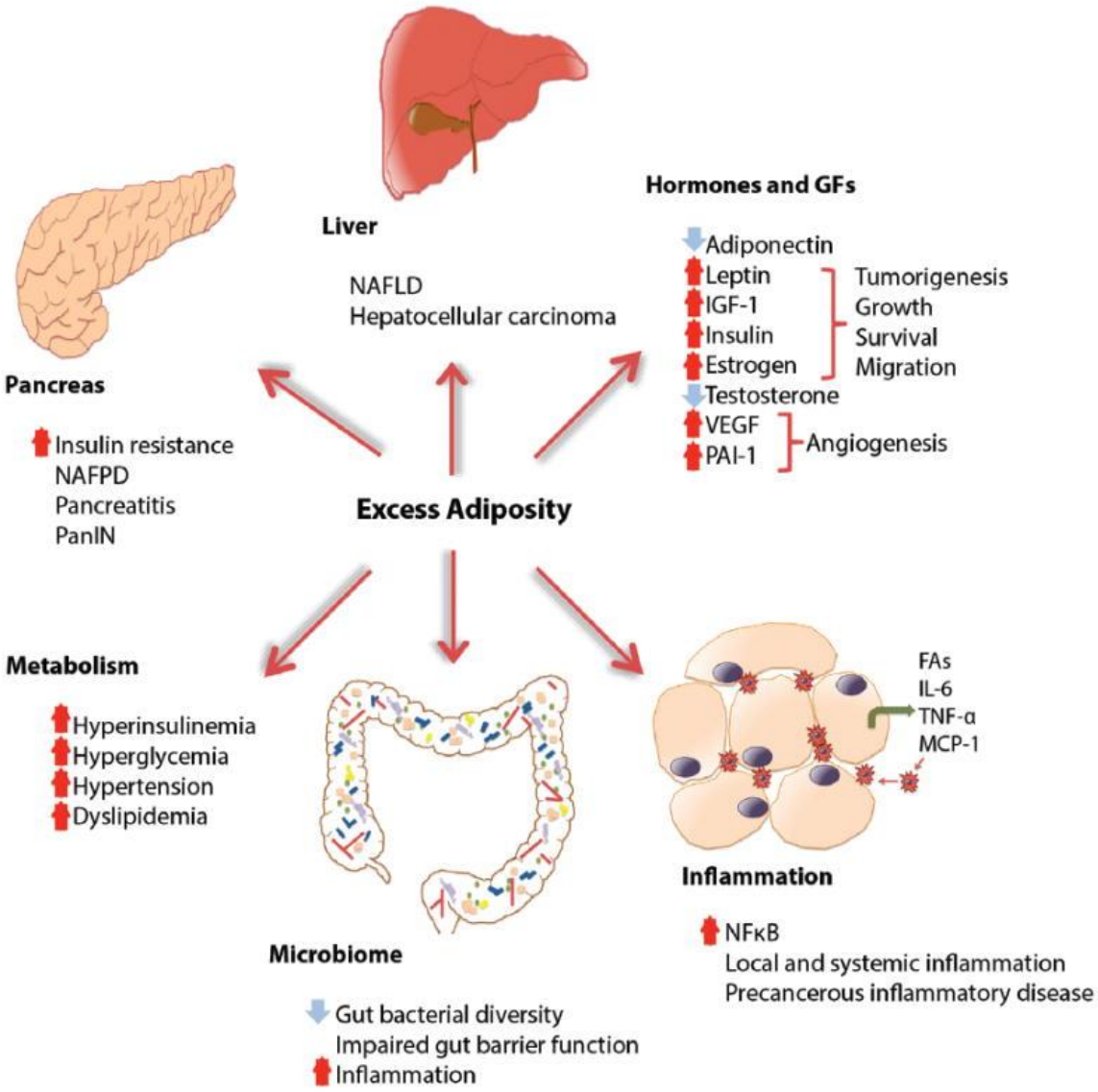
Waist Circumference
> 40 in (men)
> 35 in (women)

Glucose
≥ 100 mg/dL or medication



Triglycerides
≥ 150 mg/dL or medication

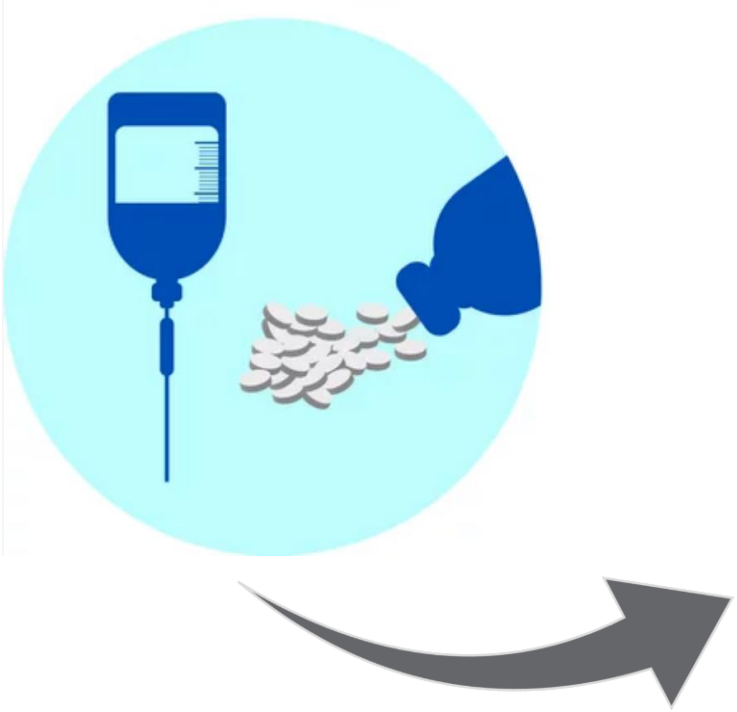
MSY is linked to poor cancer outcomes.



O'Flanagan et al., 2015, Horm Mol Bio Clin Investig

The Silent Treatment Toxicity:

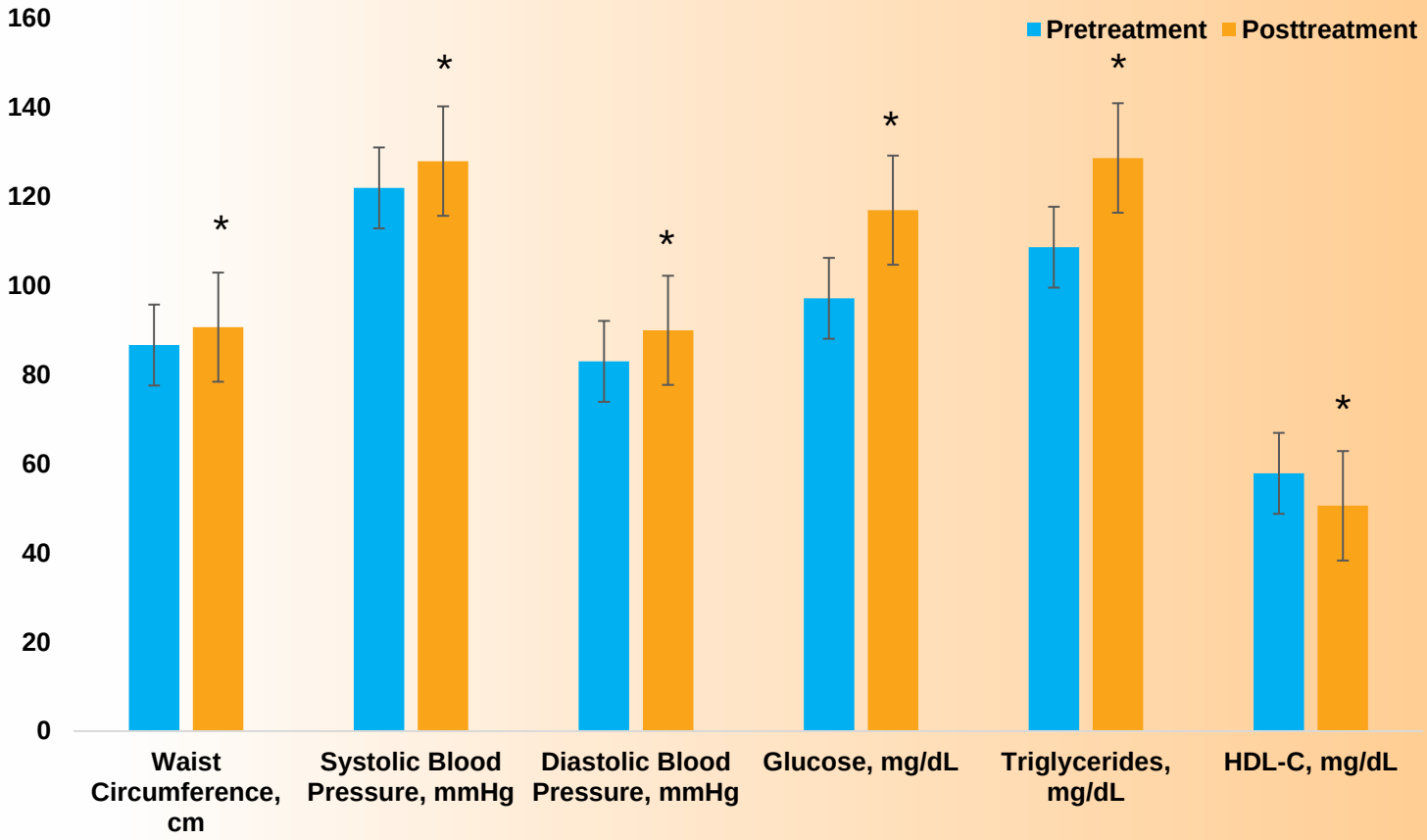
Chemotherapy may contribute to the onset of MSY among women diagnosed with early-stage breast cancer.



CHARACTERISTIC N (%)	MEAN (±Standard Deviation)	N (%)
Age, years	48.2 (10.1)	
Menopausal status	Premenopausal Postmenopausal	46 (53) 40 (47)
Race/ethnicity	Caucasian Asian Hispanic African American Other	38 (44) 6 (7) 26 (30) 7 (8) 9 (11)
Tobacco use	Never Current Past	42 (49) 4 (4) 40 (47)
Partner status	Married Single/divorced Widowed	68 (79) 13 (15) 5 (6)
Education level	High school or equivalent College or postgraduate degree Other	30 (35) 47 (55) 8 (10)
Employment status	Full-time Part-time Retired	57 (66) 16 (18) 13 (16)
Cancer stage	I II III	34 (40) 42 (49) 10 (11)
Surgery type	Mastectomy Lumpectomy N/A (Neoadjuvant chemo)	39 (45) 29 (34) 18 (21)
Chemotherapy type	Doxorubicin/Cyclophosphamide + Paclitaxel Docetaxel/cyclophosphamide Carboplatin +Paclitaxel Doxorubicin/Cyclophosphamide Docetaxel/Cyclophosphamide/trastuzumab	36 (42) 31 (36) 8 (9) 6 (7) 5 (6)

The Silent Treatment Toxicity:

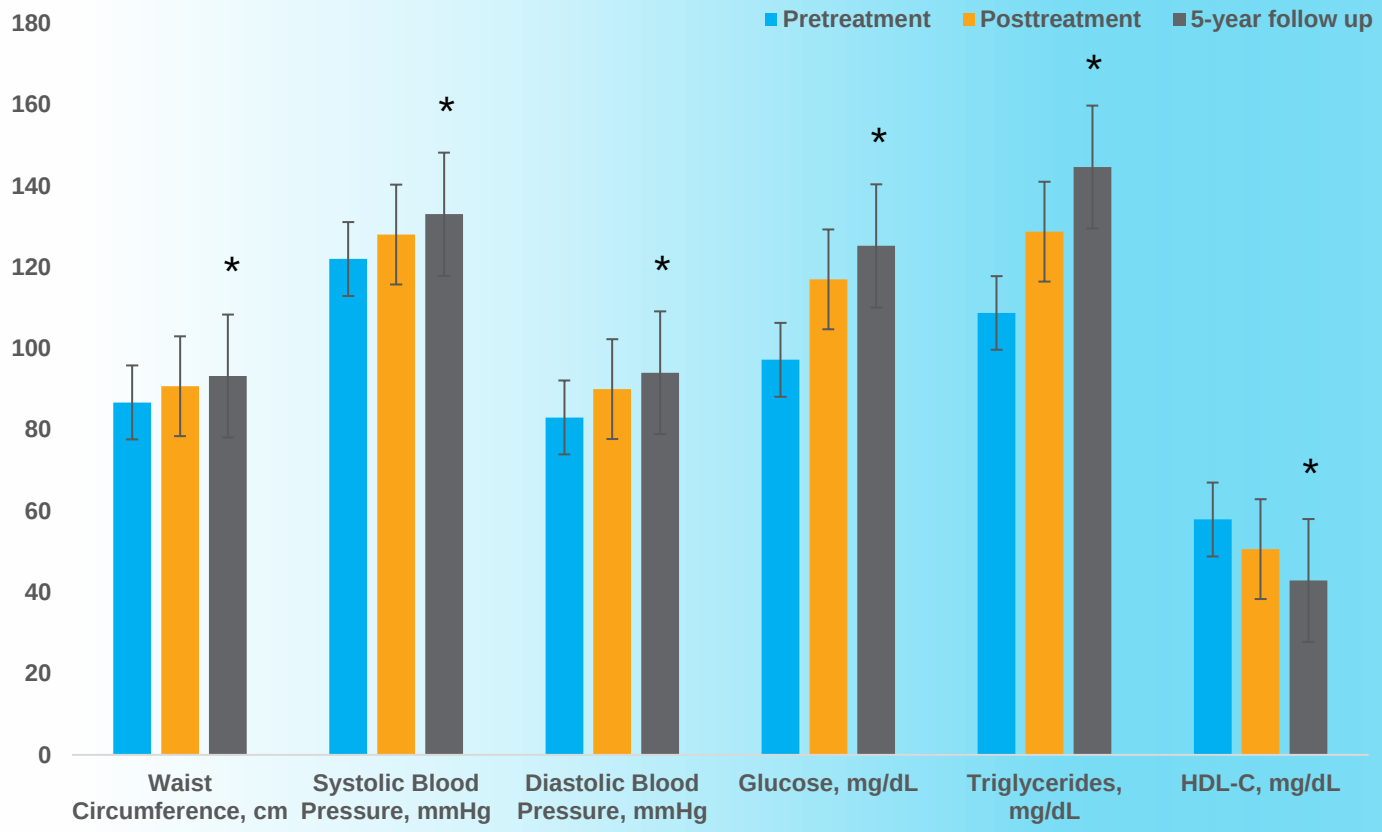
Chemotherapy may contribute to the onset of MSY among women diagnosed with early-stage breast cancer.



* P<0.01; significantly different from baseline

The Silent Treatment Toxicity:

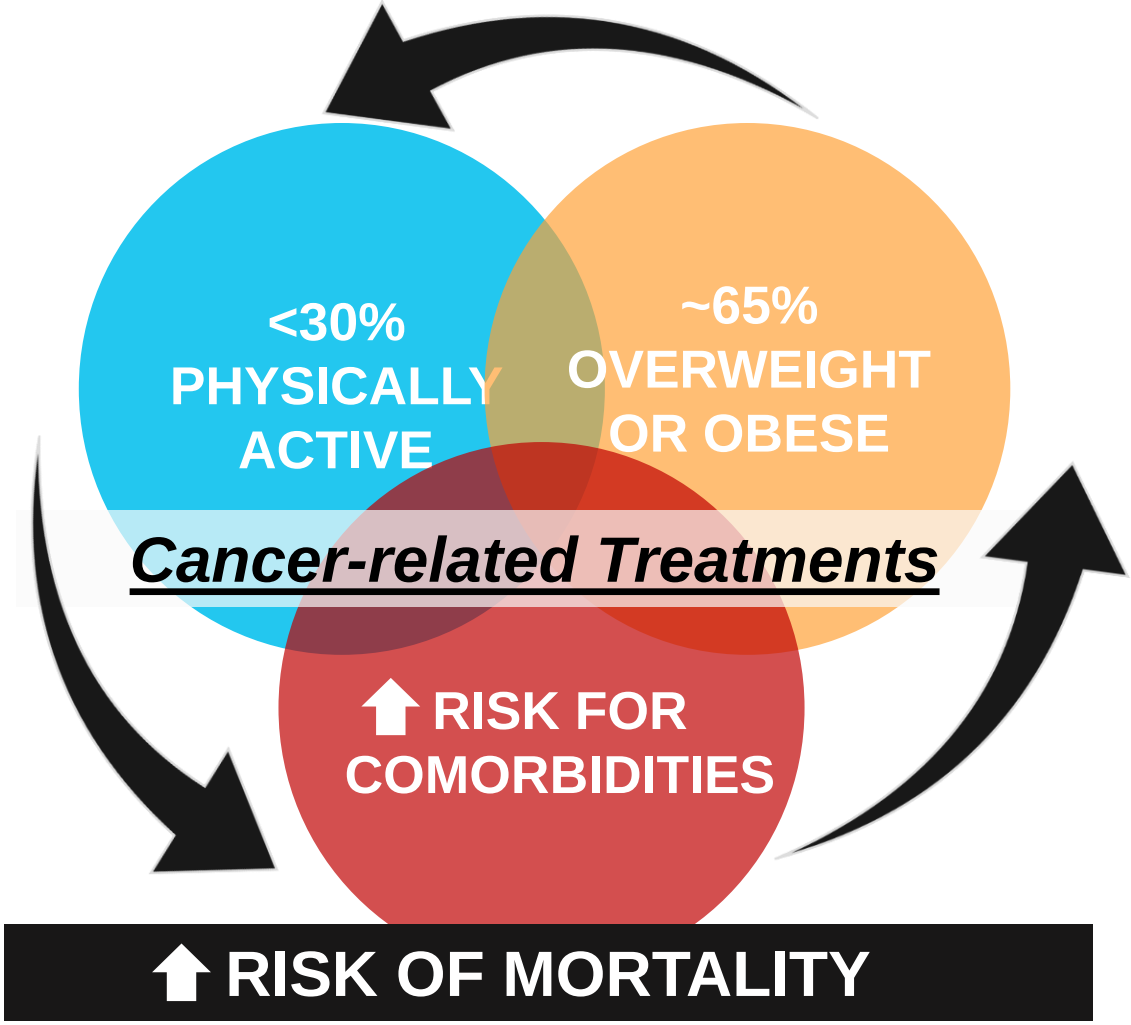
MSY **worsens** 4-5 years post-chemotherapy among women diagnosed with early-stage breast cancer.



* P<0.01; significantly different from post-treatment

Dieli-Conwright et al., 2022, Diabet & Met Synd

Significance of *Metabolic Dysfunction* lies in increased risk of mortality in cancer survivors.



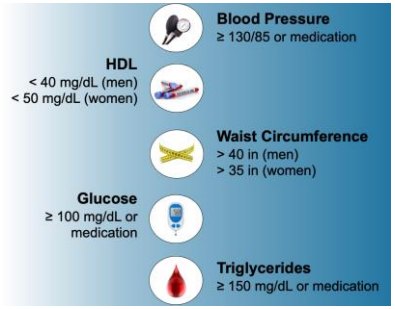
Chao et al., 2016, JCO; Murbabe et al., 2015, Supp Ca Care; ACS Facts & Figures 2020

NIH NATIONAL CANCER INSTITUTE

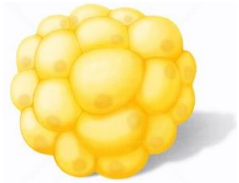
Can exercise reduce MSY in sedentary, overweight/obese breast cancer survivors?
The MSY Trial

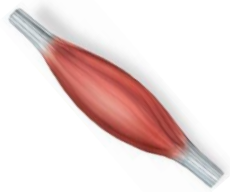
Exercise
(16 weeks)

Metabolic Syndrome



Sarcopenic Obesity





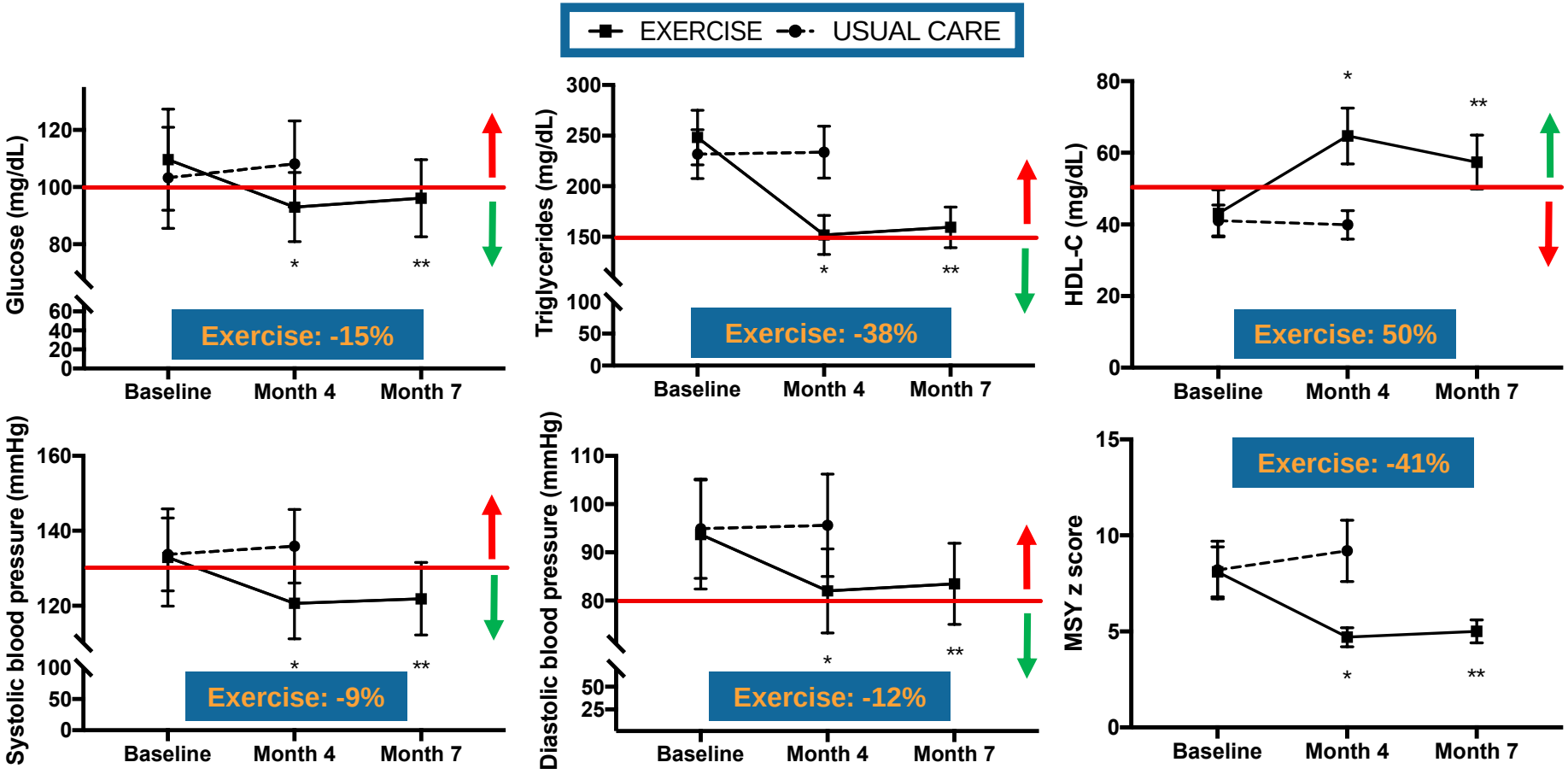
↓ Adipose tissue/ ↑ Skeletal muscle

The MSY Exercise Intervention

Supervised, Progressive Aerobic and Resistance Exercise

Day 1			Day 2		Day 3		
 					 		
Resistance Exercise			**No Resistance Exercise**		**Resistance Exercise**		
3 sets	15 repetitions	65-80% 1-rep max			3 sets	15 repetitions	65-80% 1-rep max
Aerobic Exercise			**Aerobic Exercise**		**Aerobic Exercise**		
50 minutes	65-80% VO_{2max}		50 minutes	65-80% VO_{2max}	50 minutes	65-80% VO_{2max}	

Exercise improves MSY in sedentary, overweight/obese breast cancer survivors.

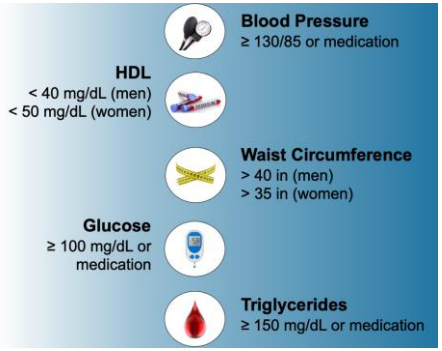


Data presented as mean±SD. *Significantly different from baseline and UC group post-intervention, p<0.05; **Significantly different from baseline, p<0.05.

Can HIIT improve MSY in sedentary, overweight/obese breast cancer patients receiving anthracycline chemotherapy? The HIIT Trial

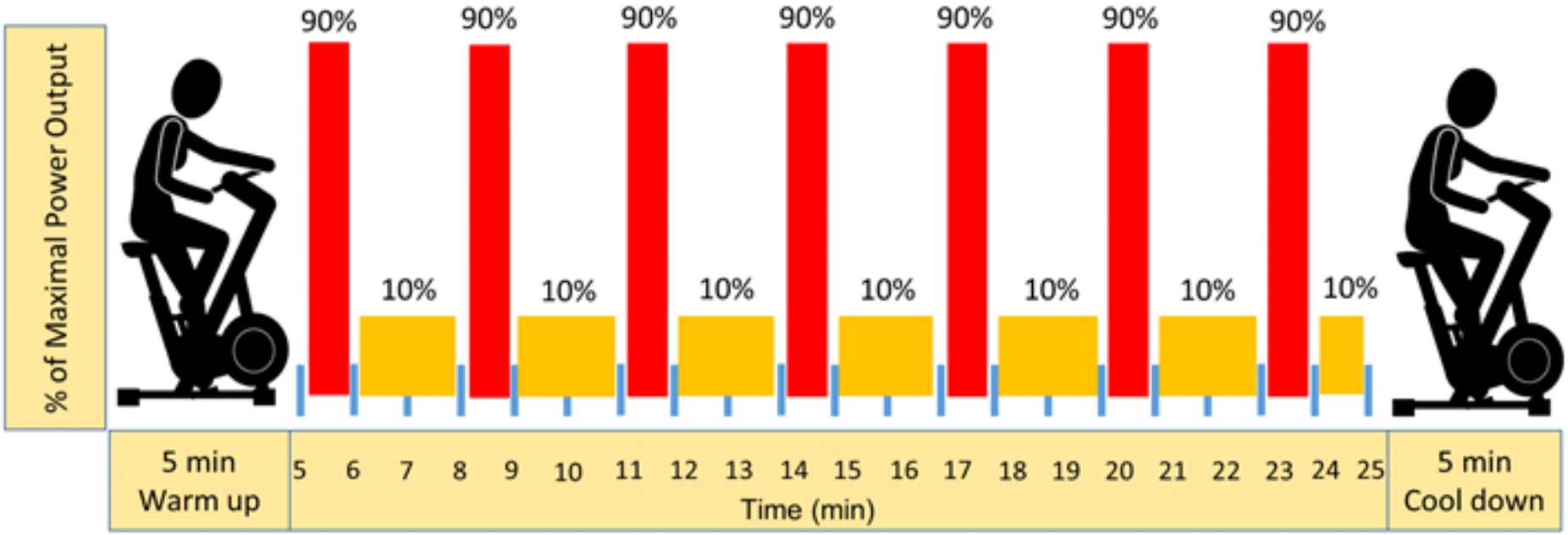
Chemotherapy (Anthracyclines)

High Intensity Interval Training (HIIT)



MSY

HIIT Intervention



Red bars indicate high intensity intervals at 90% peak power output and yellow bars indicate the 2 min active recovery at 10% peak power output.[1, 2]

HIIT improves MSY in breast cancer patients undergoing anthracycline-based chemotherapy.

	Baseline	Post-Intervention		Between Group Difference Post-Intervention	
Metabolic Syndrome	Mean (sd)	Mean (sd)	P[a]	Mean (95% CI)	P[b]
Waist Circumference (cm)				-1.88 (-4.40, 0.63)	0.14
HIIT	102.19 (17.66)	102.02 (17.46)	0.77		
Control	96.44 (11.48)	98.04 (13.25)	0.14		
Systolic Blood Pressure (mmHg)				-4.38 (-11.31, 2.55)	0.21
HIIT	120.93 (13.96)	119.00 (10.95)	0.50		
Control	127.27 (18.90)	128.60 (20.35)	0.51		
Diastolic Blood Pressure (mmHg)				-2.78 (-7.41, 1.84)	0.22
HIIT	72.40 (9.66)	74.07 (8.94)	0.42		
Control	76.67 (7.97)	80.00 (8.65)	0.01		
HDL-C (mg/dL)				27.51 (19.73, 35.30)	<0.001
HIIT	39.00 (7.04)	61.47 (10.98)	<0.001		
Control	38.27 (7.37)	33.73 (9.82)	0.005		
Triglycerides (mg/dL)				-80.89 (-109.69, -52.09)	<0.001
HIIT	135.07 (34.48)	90.13 (35.14)	<0.001		
Control	136.13 (34.14)	171.67 (49.64)	0.004		
Glucose (mg/dL)				-37.21 (-58.35, -16.07)	<0.001
HIIT	130.53 (59.41)	98.20 (9.86)	0.067		
Control	128.00 (47.99)	134.53 (46.16)	0.003		
MetS Z-Score				-7.60 (-9.08, -6.13)	<0.001
HIIT	0.68 (2.69)	-4.37 (2.70)	<0.001		
Control	1.24 (2.88)	3.62 (2.72)	<0.001		
ATP III Score				-2.05 (-2.69, -1.40)	<0.001
HIIT	3.13 (1.13)	1.53 (1.13)	<0.001		
Control	3.53 (1.36)	3.87 (3.27)	0.136		

Does a 12-week periodized resistance training intervention affect health outcomes in prostate cancer survivors on ADT?

Frequency	• 3x/week
Intensity	• Progressed through periodization
Time	• 45 min/session; 3 months
Type	• Machine-based, total body exercises

Periodization is a safe, feasible approach to resistance training among prostate cancer survivors.

Mesocycle	Muscular Endurance /Hypertrophy				Hypertrophy							
Microcycle (Wk)	1	2	3	4	5	6	7	8	9	10	11	12
Intensity	60% 1RM		65-67%1RM		70% 1RM		75% 1RM		80% 1RM		83% 1RM	
Volume	15 x3		12 x3		10 x3		10 x3		8 x3		8 x3	
Rest	1 min		1 min		1 min		1 min		1 min		1 min	

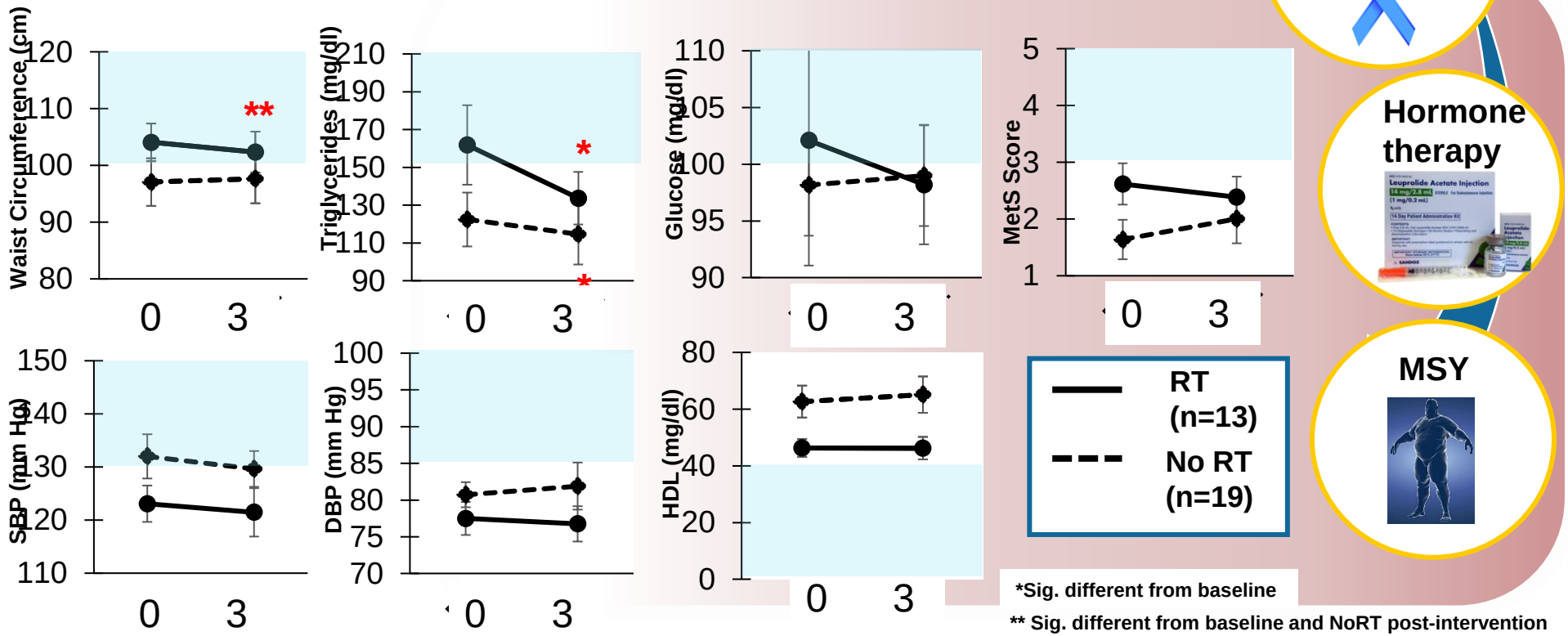
Training split:

Lower Body

Upper Body

Lower + Upper Body

Periodized Resistance Exercise Improves Waist Circumference and Triglycerides in Prostate Cancer Survivors on ADT

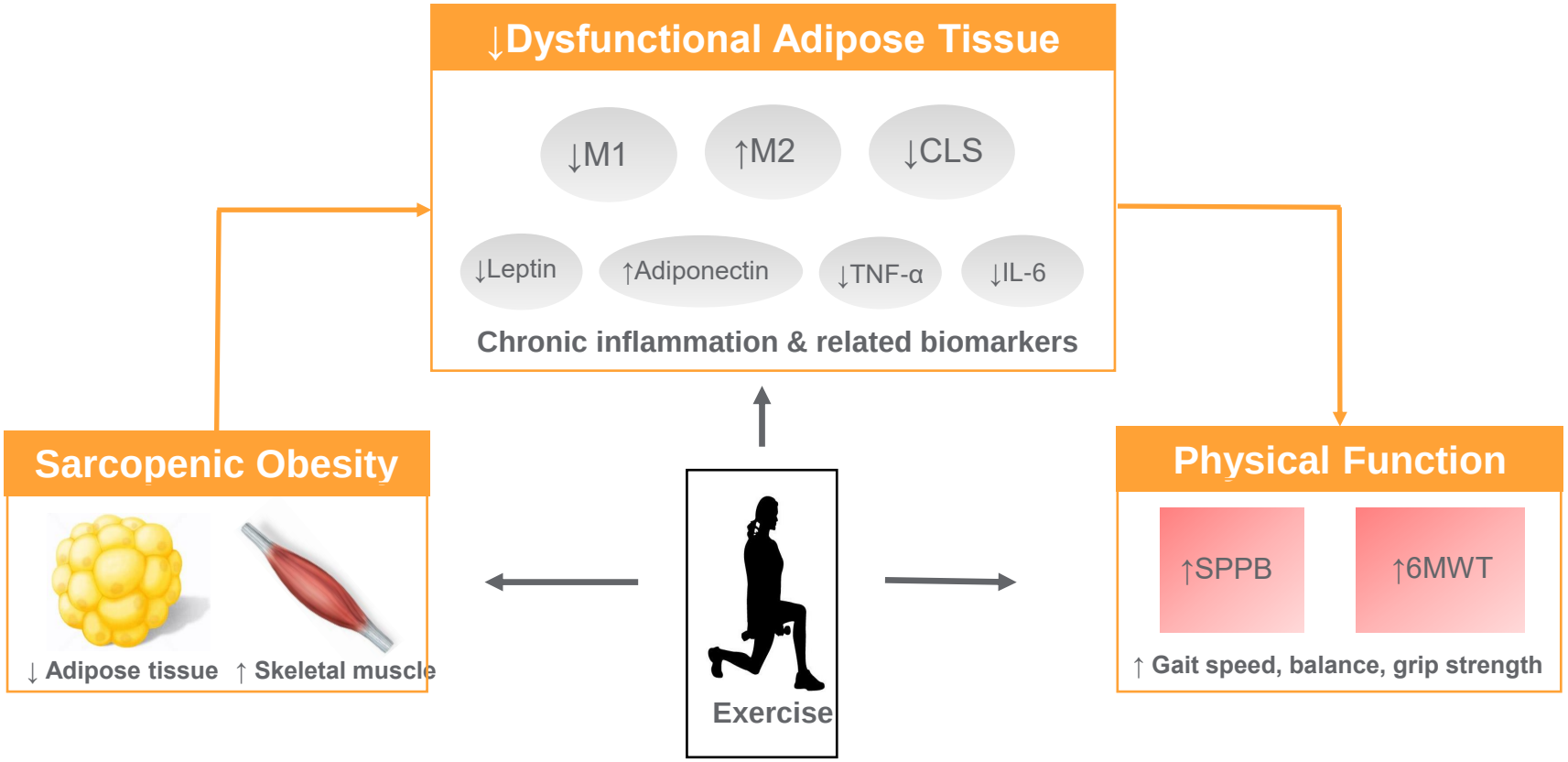


SUMMARY

"Exercise is Medicine" to Target Metabolic Dysfunction in Cancer Survivors

NIH NATIONAL CANCER INSTITUTE

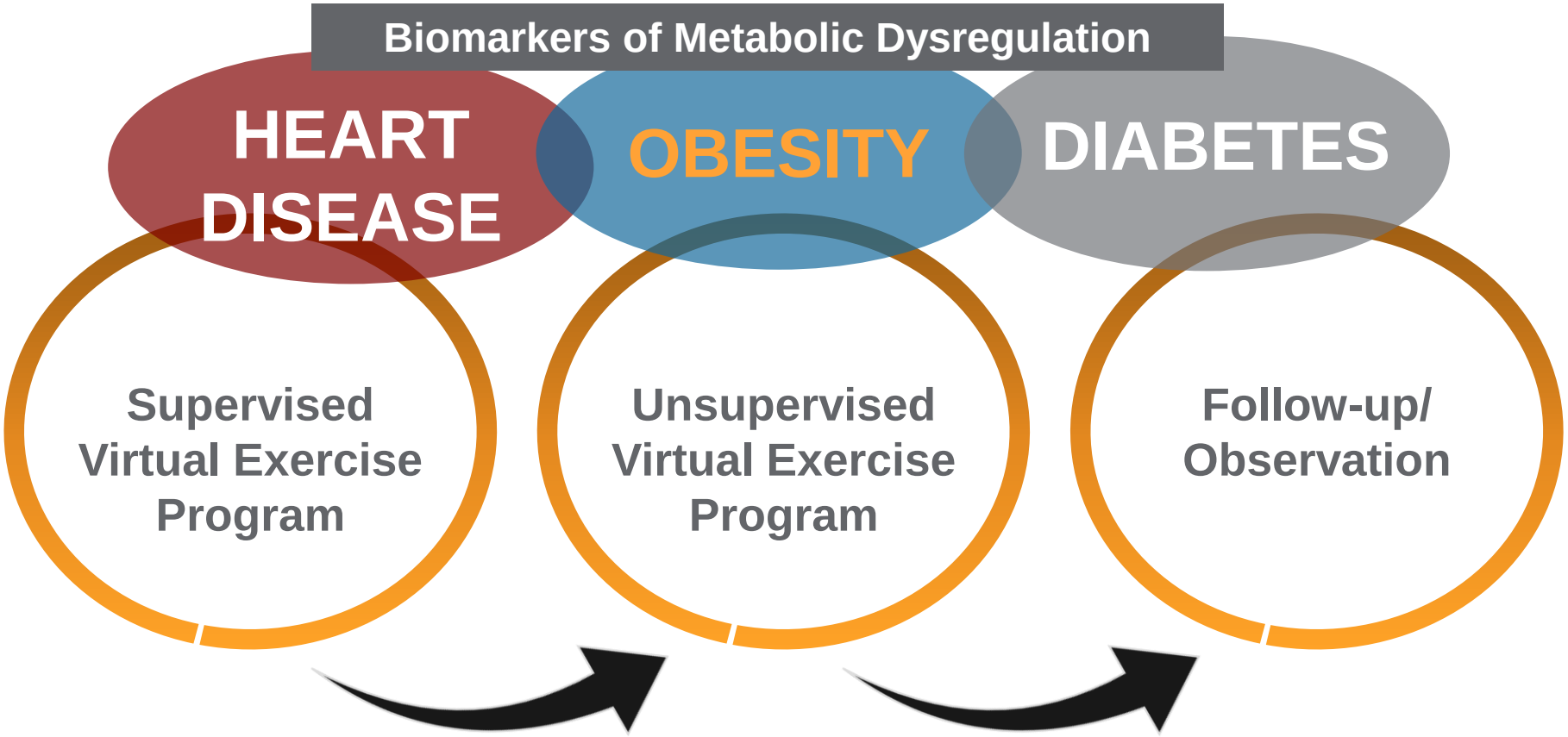
Taking AIM at Breast Cancer: Targeting Adiposity and Inflammation with Movement to Improve Prognosis in Breast Cancer Survivors



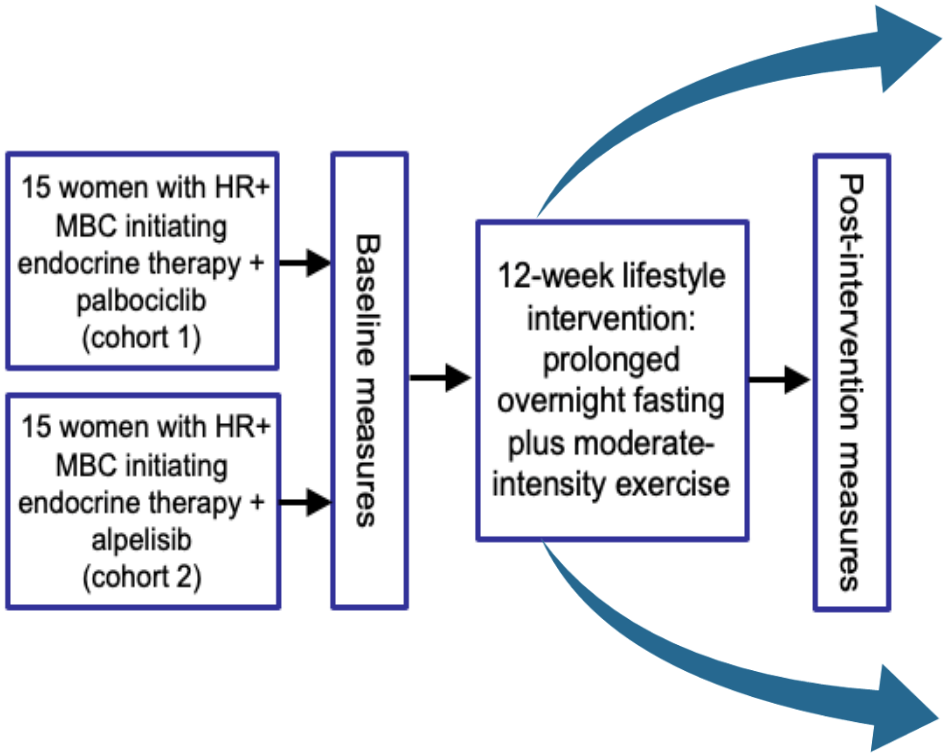
"Traditional" vs High-intensity circuit training

SPPB, Short Physical Performance Battery; 6MWT, 6-Minute Walk Test

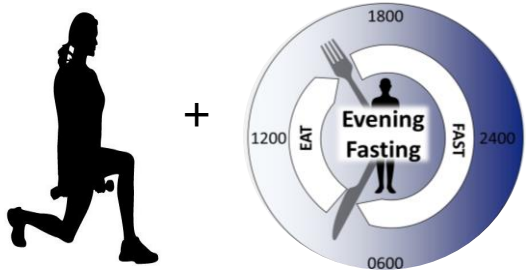
Reducing Metabolic Dysregulation in Obese Latina Breast Cancer Survivors using Physical Activity



Impact of a Combined Intermittent Fasting and Exercise Intervention on Metabolic Markers in Patients with Advanced Breast Cancer

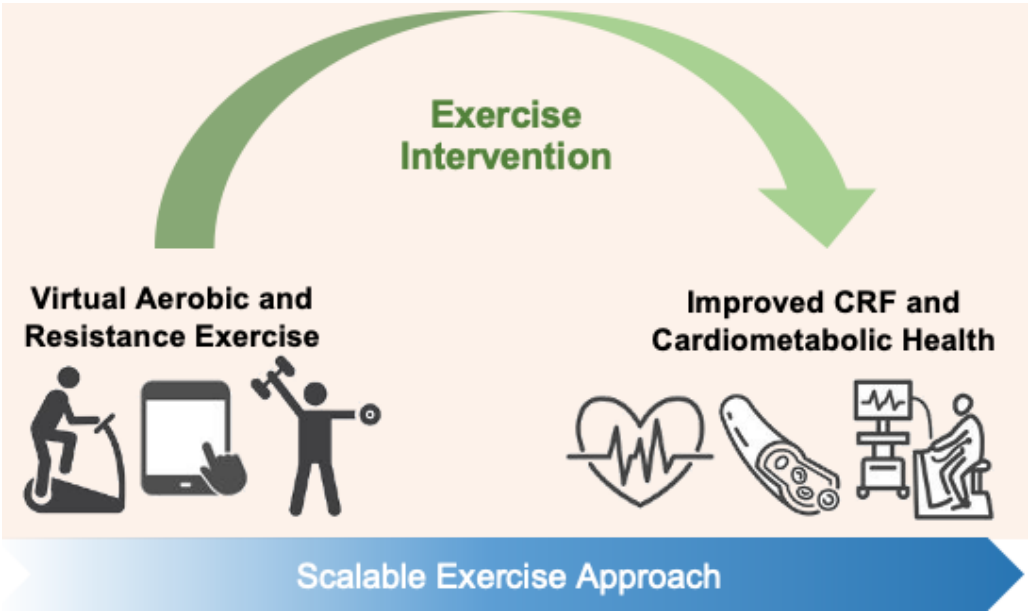


Feasibility



Hyperglycemia

Impact of Exercise on the Complications of Corticosteroids in Patients with Graft-Versus-Host Disease following Allogeneic Stem Cell Transplantation: the RESTART Trial



SUMMARY
The Silent Treatment Toxicity

Cancer treatments accelerate metabolic toxicity.

Observational studies are needed to better classify the onset of metabolic toxicity during treatment.

Exercise during and after treatment effectively improves metabolic dysfunction.

This strategy may reduce reduce the onset and exacerbation of metabolic dysfunction.

Acknowledgements:

Rebekah Wilson
Paola Gonzalo-Encabo
Derek Kang
Cami Christopher
Amber Normann
Mary Norris
Danny Nguyen
Jackie Dawson
Kyuwan Lee
Marybeth Hans
Deb Schrag
Jennifer Ligibel
Tim Rebbeck
Rachel Freedman
Marilyn Hammer
Hajime Uno
Corey Cutler
Steve Mittelman

Funding:

NIH NATIONAL CANCER INSTITUTE
American Cancer Society®
American Institute for Cancer Research
TREC Transdisciplinary Research on Energetics and Cancer Centers
NSCA®
SC CTSI

We thank the study participants for their time & dedication that make our research possible!

ChristinaM_Dieli-Conwright@DFCI.Harvard.edu