

Randomized controlled trials of physical activity and clinical outcomes

Kristin L. Campbell, PhD

Post-Doctoral Fellow

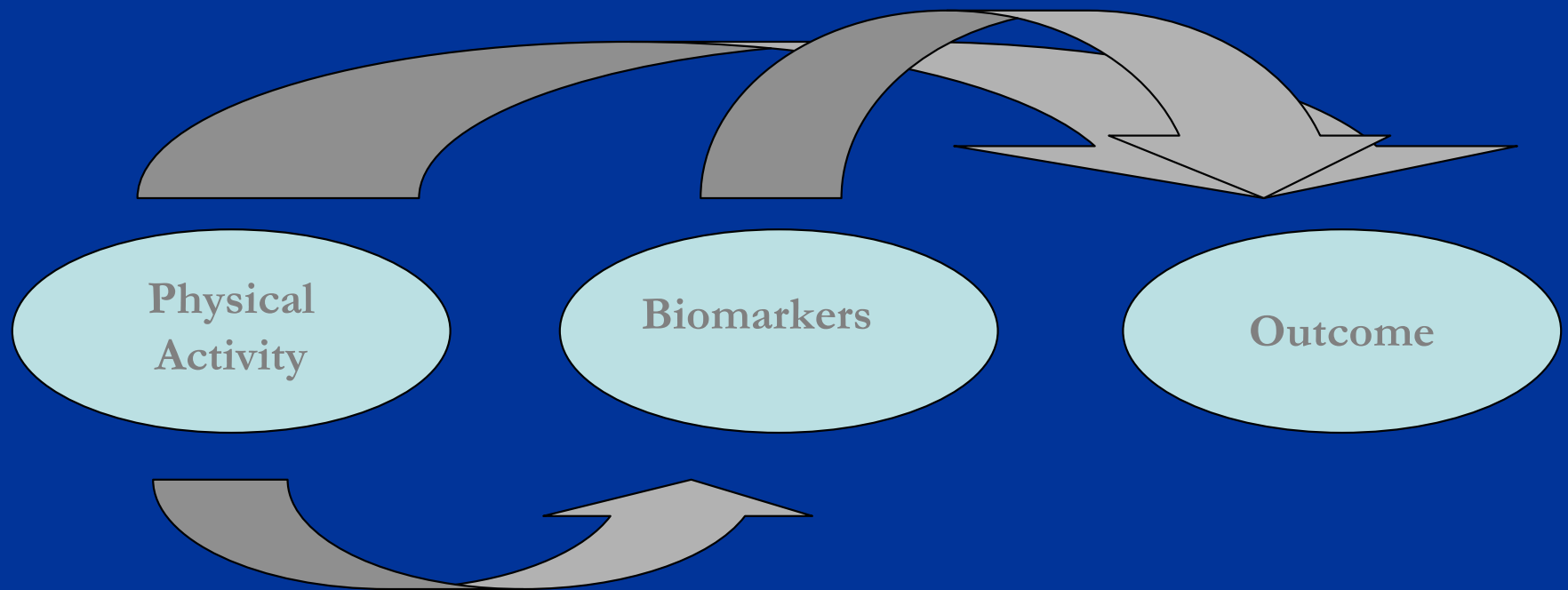
Fred Hutchinson Cancer Research Center

Seattle, WA

Outline

- Goals of RCT's using physical activity
- Example of a current RCT of PA and biomarkers of postmenopausal breast cancer risk
- Results from other RCT's of PA
 - PA and biomarkers of postmenopausal breast cancer
 - PA versus drug
 - Drug versus drug with PA on the side

Goals of RCT using PA



Goals of RCT using PA

- Examine the effect of PA on outcomes of interest
- Examine mechanisms for epidemiological findings
- Compared the effects of PA to those of diet or medications



To understand the mechanisms behind the epidemiological evidence suggesting a lower risk of certain cancers with higher levels of physical activity.



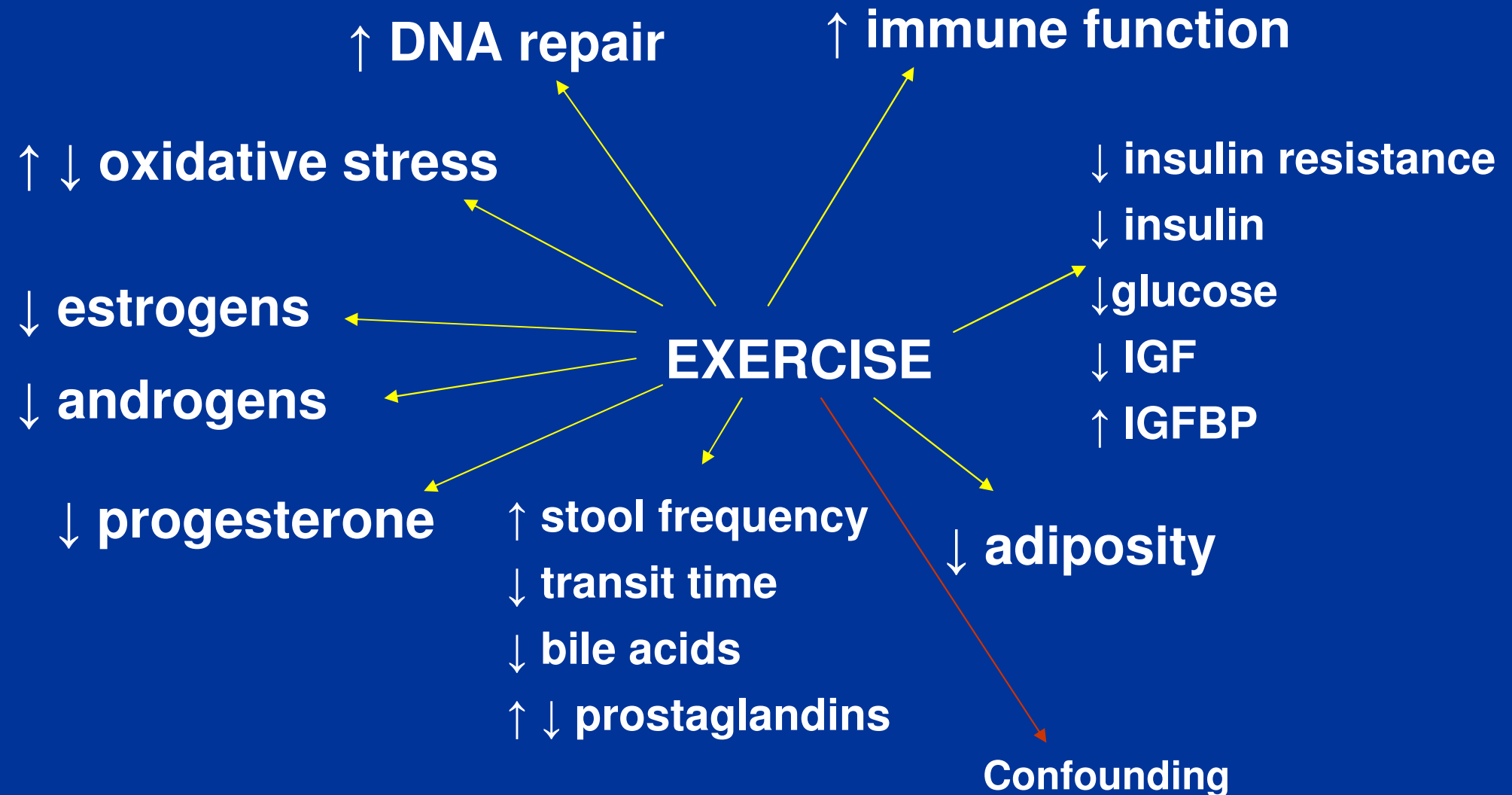
Post menopausal breast cancer



Energy balance and cancer



Link between physical activity and cancer





- 503 postmenopausal women
- 12-month intervention
- Randomized controlled clinical trial

- AIM:

Assess effects of a moderate-intensity exercise program, weight reduction diet, and both exercise + diet in postmenopausal women on serum estrogens and other breast cancer biomarkers

Table D.1: Study Inclusion and Exclusion Criteria

Inclusion Criteria

- Age 50-75
- Postmenopausal (no periods for past 12 months); check FSH levels for women between the ages of 50-59 that do not have an intact uterus, to determine menopausal status
- No menopausal HRT use of any type including vaginal X 6 months and willing to avoid use for study duration
- BMI > 25.0 kg/m² (If Asian or Asian-American BMI > 23.0 kg/m²)
- Physically able to undertake a moderate exercise or calorie reduction program
- Able to come for clinic visits, classes, and measurements, fill out questionnaires and logs in English
- Gives informed consent, agrees to be randomly assigned

Exclusion Criteria

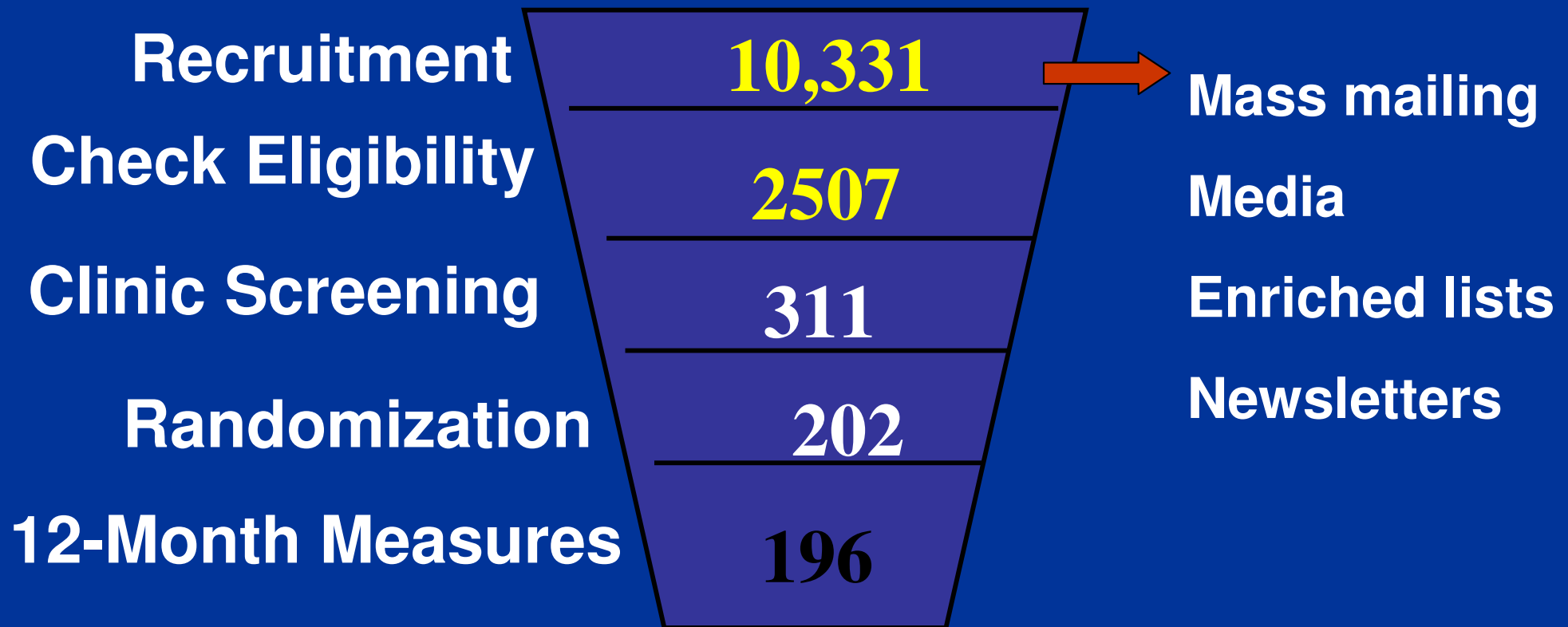
- Plans to leave the study area within the follow-up period
- Plans to join another organized weight loss or exercise program or take appetite suppressant medication during the study period
- Current use of medications likely to interfere with adherence to interventions or study outcomes
 - Moderate to high alcohol intake (more than 2 drinks per day)
- Current smoker (Has not smoked for 12 months)
- Personal history of invasive or in situ breast cancer; any other invasive cancer within the past 10 years (simple basal or squamous cell carcinoma okay)
- DM mellitus or taking medications commonly used to treat Diabetes (i.e. insulin sensitizers)
- Abnormal screening labs (hematocrit < 32 or > 48, WBC < 3.0 or > 15.0, potassium < 3.5 or > 5.0, FBS > 126 (on 2 occasions), creatinine > 2.0), or abnormalities on screening physical that contraindicate participation
- Contraindications for treadmill testing or entry into a training program: recent (within 6 months) MI, pulmonary edema, myocarditis, pericarditis, unstable angina, PE/DVT; uncontrolled hypertension (syst > 200, diast > 100), orthostatic hypotension, mod/severe AS, uncontrolled arrhythmia, uncontrolled CHF, 3rd degree heart block, left bundle branch block, myocarditis, thrombophlebitis, ST displacement > 3 mm at rest, history of cardiac arrest or stroke
- Abnormal exercise tolerance test (≥ 1.5 mm ST depression > 1 lead, to 1 min recovery, or ≥ 1.1 mm ST depression > 1 lead after 1 min recovery, or reading of positive test by study MD) (A follow-up neg ETT thallium or ETT echo will allow eligibility)
- Alcohol or drug abuse, significant mental illness (as assessed by study staff impression)

N.E.W. Eligibility Criteria

- Healthy women, 50 to 75 years
- Postmenopausal
- Overweight (BMI ≥ 25 m/kg² or ≥ 23 m/kg² if Asian-American)
- Physically inactive (< 60 min/wk moderate or vigorous exercise)
- No hormone therapy x 6 months
- Non smoker, < 2 alcohol drinks/day
- No cancer, diabetes, heart disease
- Normal exercise tolerance test

Recruitment and Screening

Number of participants



Measure	Screening	Baseline	6- mo.	12- mo.
Eligibility, baseline, and follow-up questionnaires	X	X	X	X
Food Frequency Questionnaire (FFQ), Physical Activity Interview (PAI), Pedometer log		X	X	X
Physical exam	X			
Blood pressure, resting pulse	X			X
Screening bloods (CBC, electrolytes, glucose)	X			
Anthropometrics (height, weight, waist and hip circumferences, and BMI)	X	X	X	X
DEXA scan		X		X
VO2 max (also as screen for exercise tolerance)	X			X
Serum hormones (12 hour fasting) (also serum, plasma, DNA, collected and stored)		X		X
Mammogram density		X		X

Intervention

- 4 arms:
 - Exercise
 - Diet
 - Diet + Exercise
 - Control (usual lifestyle)

Exercise Intervention

- 12 months' duration
- 45 minutes/day, 5 days/week
 - 3 d/week facility (FHCRC Prevention Center)
 - 2 d/week home
- Moderate-intensity aerobic activity (walking, elliptical, biking, other sports)
 - 60-75% VO_2max
- 8 weeks progression to full program
 - Start at 15 minutes; 40% VO_2max

Diet Intervention

- 12 months duration
- Modified from Diabetes Prevention Program diet
- Individual goal 10% weight loss (group goal 7% weight loss)
- < 25% calories/fat
- Daily weighing
- Individual meeting with nutritionist, followed by weekly, then monthly group sessions
- Intensive program 1st 6 months, maintenance thereafter

	All N=114	Exercise Only N=33	Diet Only N=33	Exercise + Diet N=26	Controls N=22
BMI (kg/m²)					
Baseline	30.7 (4.0)	30.1 (3.8)	31.1 (4.1)	29.8 (4.1)	31.9 (3.8)
Follow-up	28.4 (4.7)	29.2 (4.1)	27.1 (4.6)	26.8 (4.4)	31.6 (4.3)
Difference	-2.3	-0.9	-4.0	-3.0	-0.3
Weight (kg)					
Baseline	83.1 (12.3)	81.6 (13.9)	84.1 (11.9)	79.9 (10.4)	87.6 (11.6)
Follow-up	77.1 (13.5)	79.9 (14.4)	72.3 (12.0)	71.9 (11.0)	86.7 (11.5)
Difference	-6.0	-1.7	-11.8	-8.0	-0.9

	All N=114	Exercise Only N=33	Diet Only N=33	Exercise + Diet N=26	Controls N=22
% Body Fat					
Baseline	47.3 (6.3)	46.0 (6.4)	47.3 (6.2)	45.8 (6.4)	51.0 (5.1)
Follow-up	42.4 (9.2)	43.7 (6.9)	40.1 (8.4)	37.2 (10.6)	50.0 (6.1)
Difference	-4.9	-2.3	-7.2	-8.6	-1.0

N.E.W. Study Endpoints

- Estrone, estradiol, free estradiol
- Testosterone, free testosterone
- Insulin, glucose
- IGF-1, IGFBP-3
- Mammogram density
- Adiposity (weight, BMI, waist and hip circumferences, body composition - DEXA)

N.E.W. Study Additional Endpoints (TREC)

- Mutagen sensitivity
- DNA repair capacity
- Inflammatory markers (CRP, SAA, IL-6)
- Adipokines (leptin, adiponectin)
- Proteomics
- Genotypes (related to inflammation and IGF)

What you need to do an RCT of exercise/diet (N=500)

- \$\$\$\$\$\$\$\$
- 1 Fitness Facility + 3 Exercise trainers
- 2 Dieticians
- 1 Exercise Testing Facility + 1 Physician
- 1 Project coordinator
- 2 Clinic staff
- 1 Phlebotomist
- 3 Project Assistants
- 2 Data Coordinators

- All must be friendly, competent and good at keeping track of pieces of paper

Issues of Physical Activity in RCT

- Agree to randomization
- Blinding
- Compliance
 - Drop-outs
 - Drop-ins
- Screening
- External validity

Results of Physical Activity RCT's

- 1. Biomarkers of postmenopausal breast cancer risk**
- 2. Development of diabetes**
- 3. Weight loss**

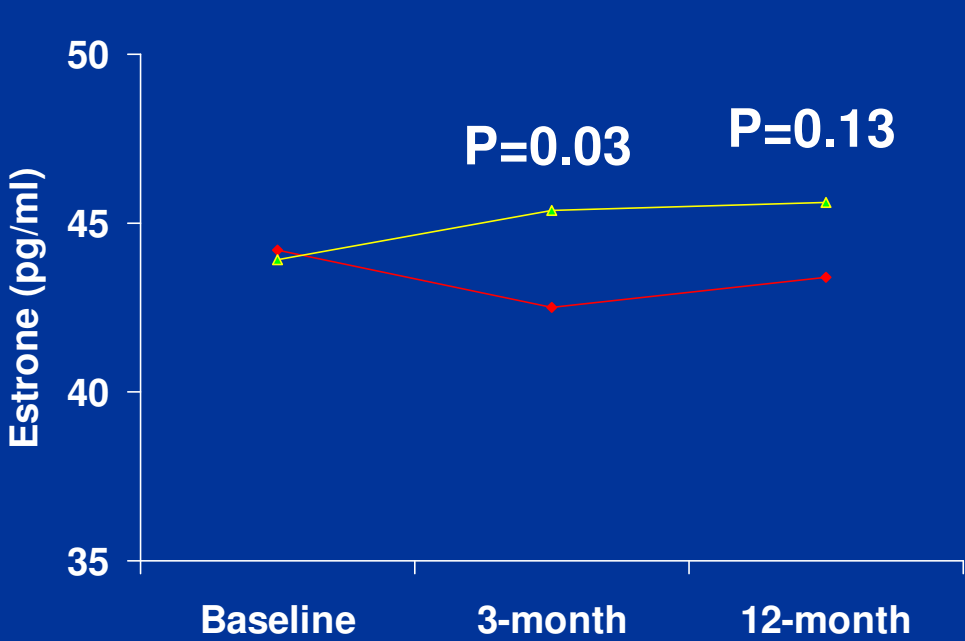
Physical Activity for Total Health Trial

- To test the effect of 12-month moderate/vigorous exercise on biomarkers of breast cancer risk in postmenopausal women.
- N= 173

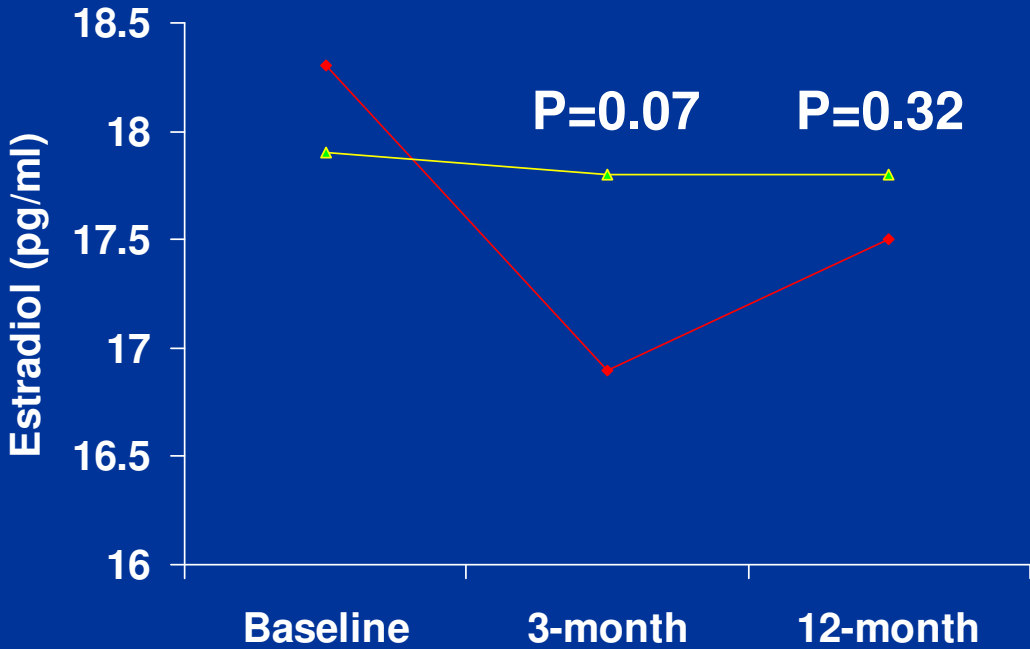
	EXERCISE	CONTROL	p
VO ₂ max, ml/kg/min	+ 2.4	+ 0.1	<.001
Body weight, kg	-1.3	+ 0.1	.01
BMI	-0.3	+ 0.3	.004
Body Fat, %	-1.2	-0.2	.003
Intra-abdominal fat, g/cm ²	-8.5	+ 0.1	.001



Estrone

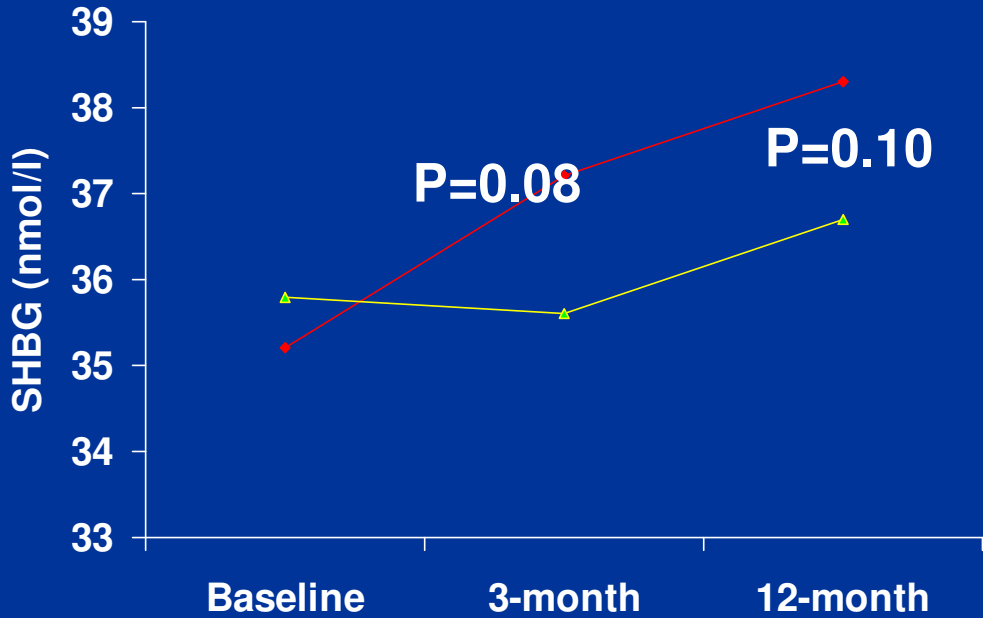


Estradiol

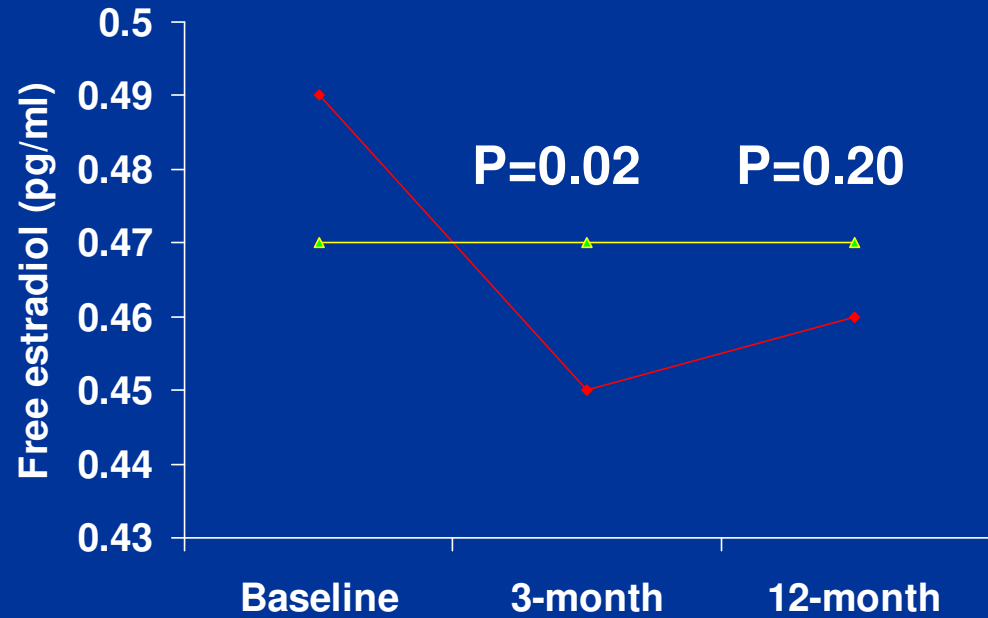




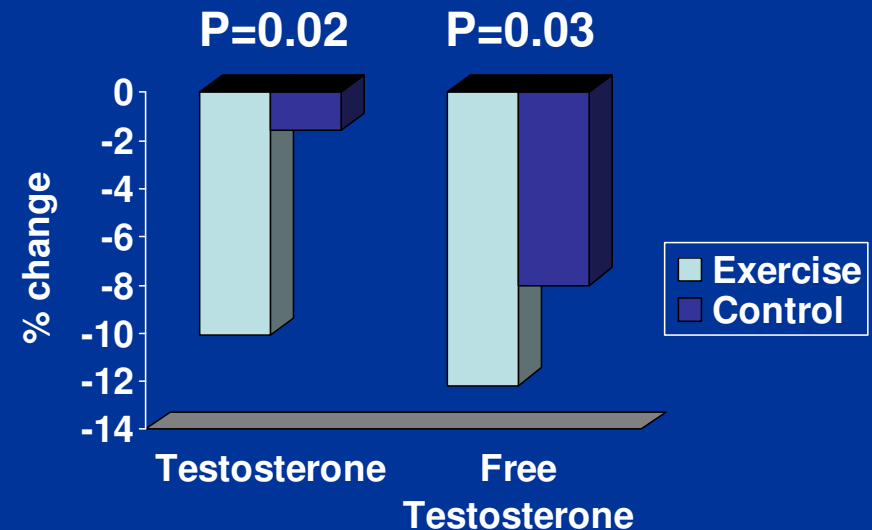
Sex hormone binding globulin



Free Estradiol



- No change in:
 - Androstenedione
 - DHEA or DHEA-S
 - Testosterone or Free Testosterone
- Change in testosterone with > 2% body fat loss



McTiernan et al. CEBP 2004; 13:1099-105

- No change in:
 - IGF-1
 - IGFBP-3
 - IGF-1/IGFBP-3
- No effect of change in body composition or VO_2 max

McTiernan et al. CEBP 2005; 14:1020-21

Summary

- A year-long moderate intensity PA RCT resulted in:
- Loss of body weight, body fat and intra-abdominal fat in the exercisers vs. controls
- Change in estrogens at 3-months in exercisers vs. controls
- Change in androgens associated with weight loss
- No change in insulin-like growth factors or binding proteins

The New England Journal of Medicine

Copyright © 2002 by the Massachusetts Medical Society

VOLUME 346

FEBRUARY 7, 2002

NUMBER 6



**REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE
INTERVENTION OR METFORMIN**

DIABETES PREVENTION PROGRAM RESEARCH GROUP*

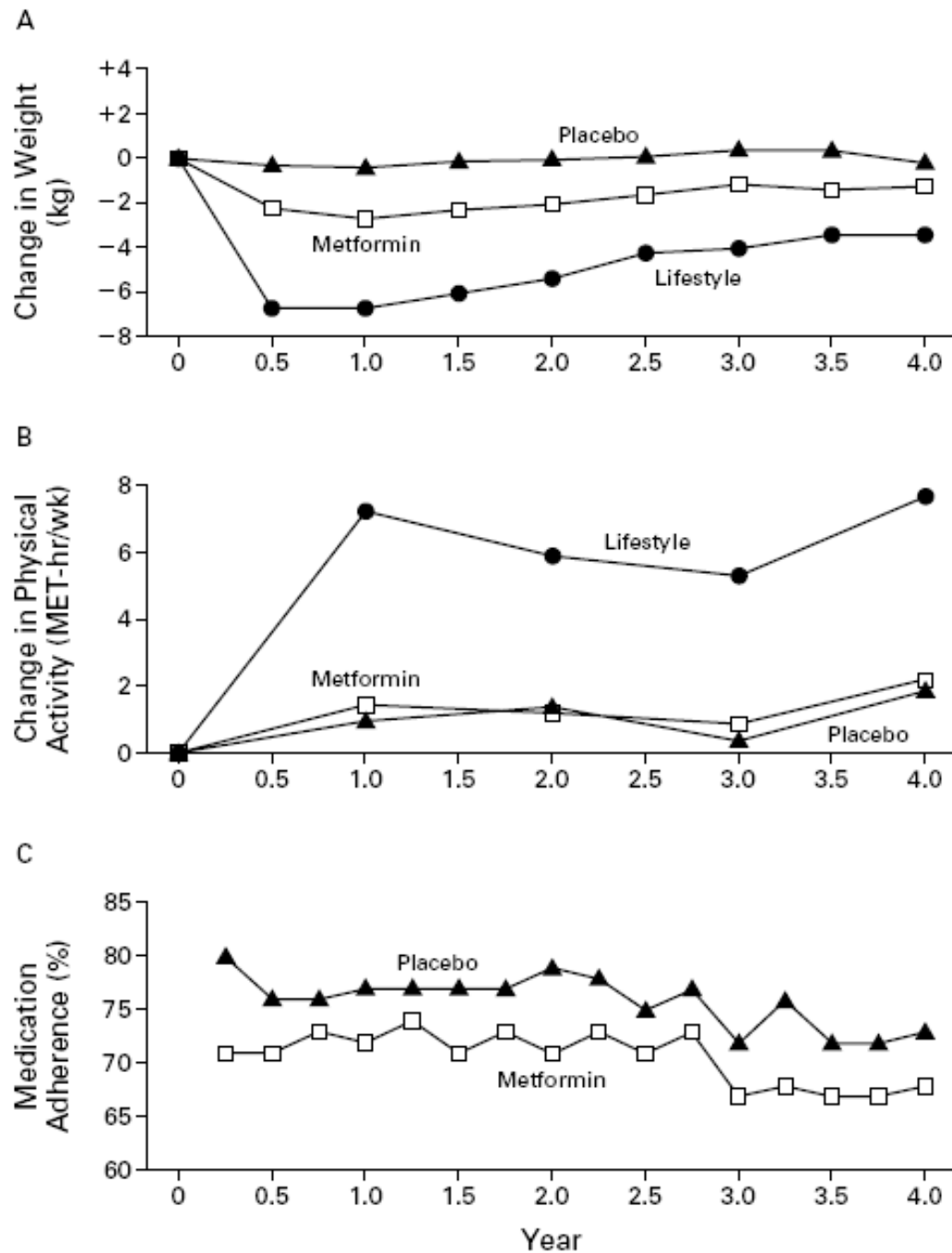
Methods

- Non-diabetic, with elevated blood glucose
- Men and women
- Mean age 51 yrs
- N=3234
 1. Metformin (N=1073)
 - 850 mg twice daily
 2. Lifestyle (N=1079)
 - Diet and at least 150 min of PA/week; 7% weight loss
 3. Placebo (N=1082)
 - Standard lifestyle + placebo pill

Research questions

- Does a lifestyle intervention or treatment with metformin prevent or delay the onset of diabetes?
- Do these two interventions differ in effectiveness?

Results



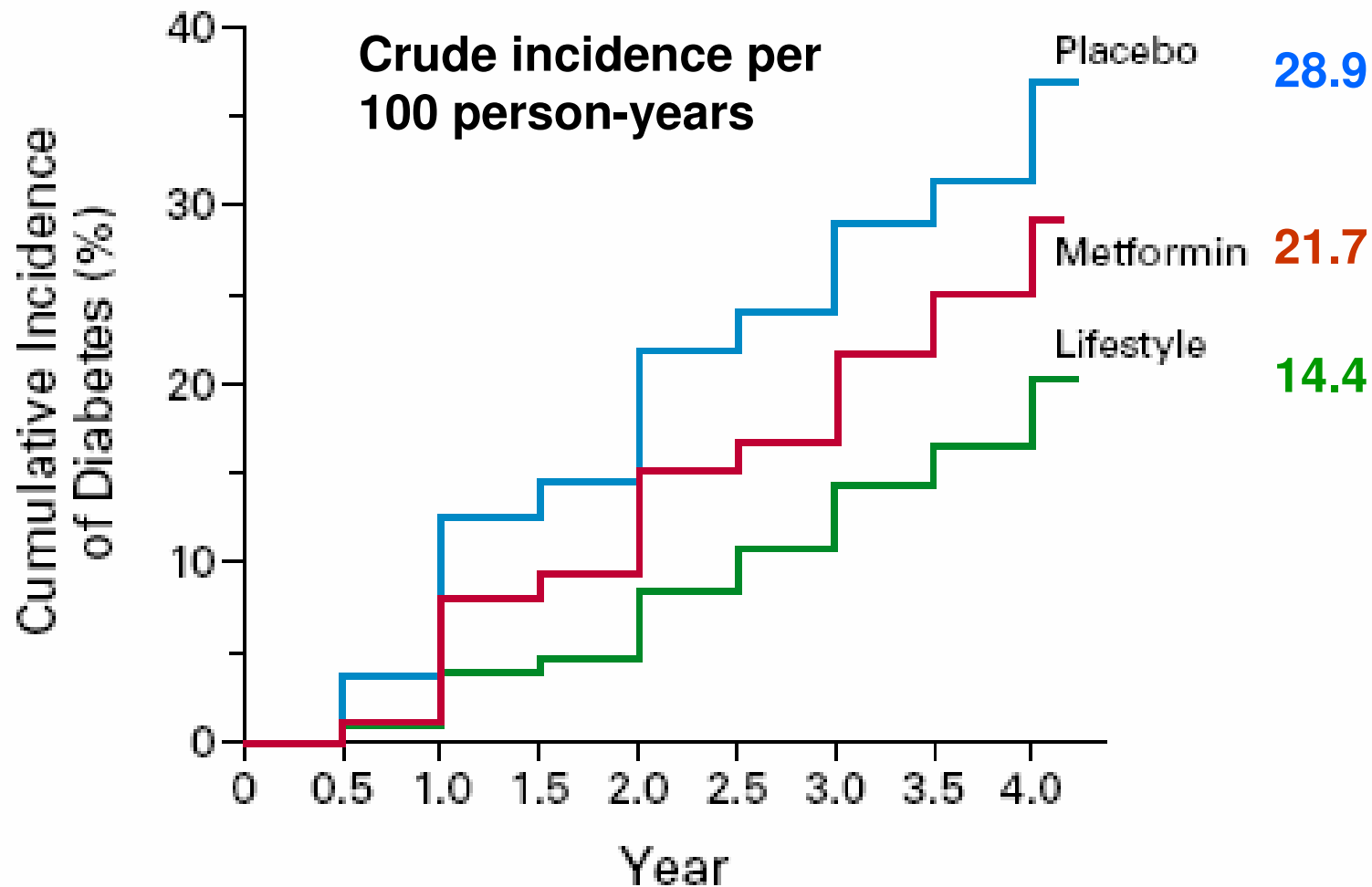


Figure 2. Cumulative Incidence of Diabetes According to Study Group.


The diagnosis of diabetes was based on the criteria of the American Diabetes Association.¹¹ The incidence of diabetes differed significantly among the three groups ($P < 0.001$ for each comparison).

Results

- Incidence of diabetes:
 - 58% lower in lifestyle intervention
 - 31% lower in metformin intervention
- Number needed to treat to prevent one case of diabetes (3 years of treatment)
 - 6.9 for the lifestyle intervention
 - 13.9 for metformin
- Adverse events
 - GI symptoms highest in metformin group
(77.8 (M) vs 30.7 (P); 12.9 (L) events /100 person years)
 - Musculoskeletal symptoms highest in lifestyle group
(24.1 (L) vs 20.0 (M); 21.1 (P) events/100 person years)

Summary

- “...our study showed that treatment with metformin and modification of lifestyle were two highly effective means of delaying or preventing type 2 diabetes.”

➔  Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study

*André J Scheen, Nick Finec, Priscilla Hollander, Michael Dj Jensen, Luc F Van Gaal, for the RIO-Diabetes Study Group**

The Lancet 2006; 368: 1660-1672

Methods

- Overweight/obese; Type 2 Diabetes
(already on metformin or sulphonylurea)
 - Men and women
 - Mean age 51 yrs
 - N=1047
 1. Rimonabant; 5 mg/day (N=360)
 2. Rimonabant; 20 mg/day (N=339)
 3. Placebo (N=348)
- All = mild hypocaloric diet (600 kcal deficit/day) and advice to ↑ PA level

Research Question

- “...to assess the efficacy and safety of rimonabant in combination with a mild hypocaloric diet and advice for increased physical activity in overweight or obese patients with type 2 diabetes...”
- Weight reduction and CVD risk factors
- Weight and cardiometabolic risk factors

Results*

	Placebo	5 mg/day	20 mg/day	p-value 5 mg vs. placebo	p-value 20 mg vs. placebo
N	345	355	336		
Weight change (kg)	-1.4 (3.6)	-2.3 (4.2)	-5.3 (5.2)	0.01	<0.0001
≥ 5% Weight loss	50 (14.5%)	77 (21.7%)	166 (49.4%)	0.02	<0.0001
≥ 10% weight loss	7 (2.0%)	22 (6.2%)	55 (16.4%)	0.01	<0.0001

* 1 Year

Mean (SD) or n/N (%)

Weight loss was significantly greater with both doses of rimonabant vs. placebo

Results

	Placebo (n=348)	5 mg/day (n=358)	20 mg/day (n=339)
Overall Drop out	117 (34%)	126 (35%)	110 (32%)
Any adverse event	276 (79%)	293 (82%)	288 (85%)
Any serious adverse event	15 (4%)	27 (8%)	27 (8%)
Discontinuation due to adverse event	19 (5%)	28 (8%)	51 (15%)

Most common adverse events:

- **Nausea, diarrhea, vomiting, dizziness, hypoglycemia, fatigue, and anxiety**
- **Discontinuation due to adverse events were more frequent in the rimonabant groups vs. placebo.**

Summary

- “These findings support the use of 20 mg/day rimonabant in addition to diet and exercise, as a new approach to improved glucose control and reduced number of cardiovascular and metabolic risk factors in overweight/obese patients with type 2 diabetes...”

Conclusions

RCT of Physical Activity

- Significant undertaking
- Limited external validity
- Intervention not feasible on population level
- Give good mechanistic data
- Can not answer some important questions on the impact of PA on health

What is special about PA

- Numerous health benefits
- Shown to help with weight loss, metabolic profile, cardiovascular disease risk factors, mental health, immune system, bone health....
- Few side effects
- So while drugs may be also be effective, the possible side effects potentially limit their use on a population level

Current Guidelines



Canadian Cancer Society
Société canadienne du cancer

“Be physically active on a regular basis. This will also help you maintain a healthy body weight”

American Cancer Society

Adults:

- moderate activity
- 30 minutes or more
- 5 or more days/week

Children & adolescents:

- moderate to vigorous activity
- 60 minutes per day
- 5 or more days/week

- *Further reduce the risk of breast and colon cancer*
- 45 minutes or more
- moderate to vigorous activity
- 5 or more days/week



World Health Organization

Exercise to maintain weight

Questions?

klcampbe@fhcrc.org