Observational and Experimental Evidence for the Role of Physical Activity in Cancer Control

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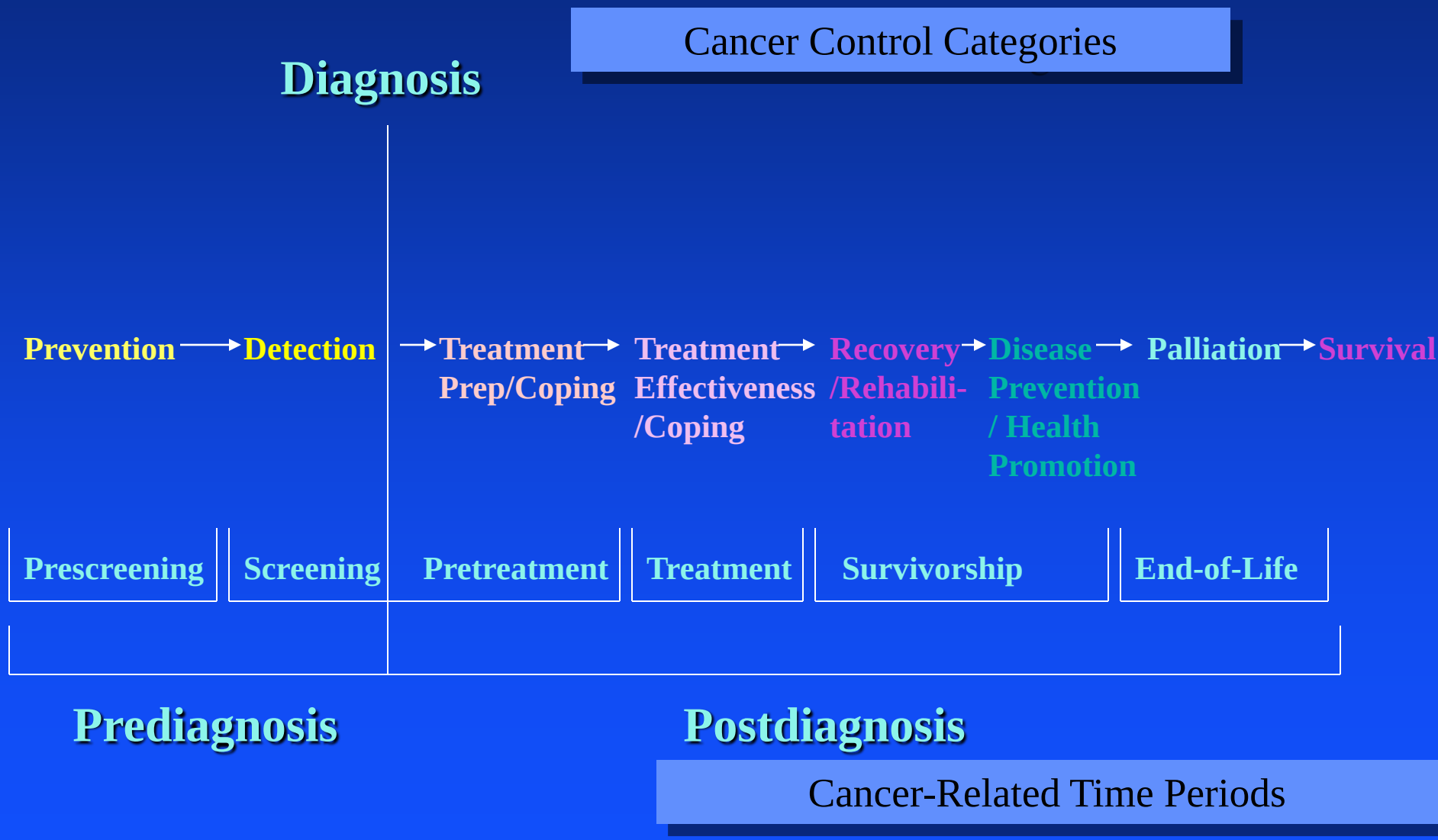
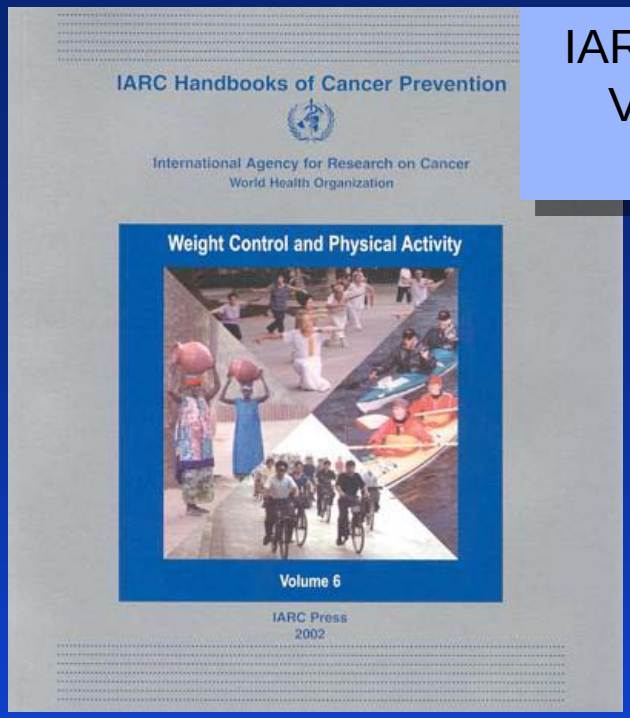
Overview

- Physical activity and cancer risk
  - Review of observational epidemiologic evidence
  - Biologic mechanisms
  - Randomized controlled exercise intervention trials
  - Population attributable risk for physical inactivity and cancer
  - Future research directions

Physical Activity in Cancer Control Framework

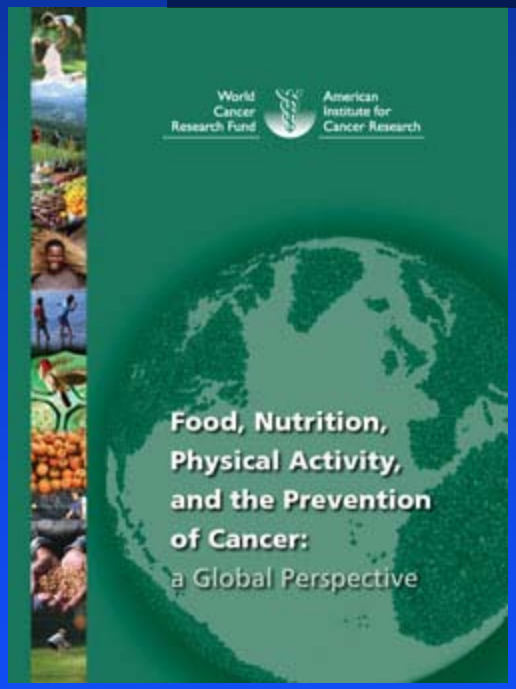
Courneya & Friedenreich (2001, 2007)

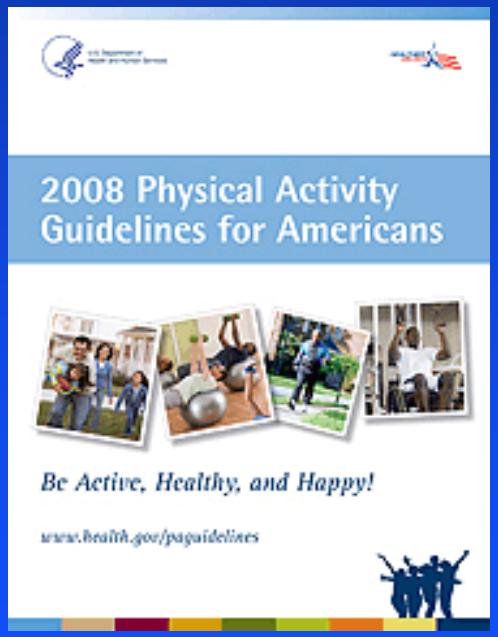




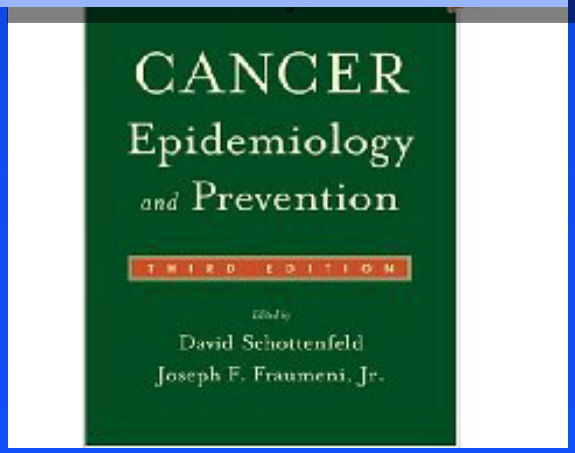
IARC Handbook of Cancer Prevention. Vol 6: Weight Control and Physical Activity, 2002

WCRF/AICR Report on Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective, 2007





Chapter 23: Physical Activity, 2006



US Dept Health & Human Services 2008 Physical Activity Guidelines for Americans

Physical Activity and Cancer

Courneya and Friedenreich, editors

- Topics:
  - Physical Activity and Cancer Prevention
  - Physical Activity and Cancer Survivorship
  - Physical Activity and Cancer Special Topics

Recent Results in Cancer Research, Springer-Verlag, 2011

Methodologic Issues in Physical Activity and Cancer Research

- Difficulty in assessing physical activity
  - Need to assess all:
    - *Types* of activity (occupational, household, recreational, transportation)
    - *Parameters* of activity (frequency, duration, intensity)
    - *Time periods* in life (pre and post-diagnosis)
  - Validity and reliability of self-reported PA measurement
  - Need for objective measurement methods
- Difficulty of comparisons across studies
  - Different physical assessment methods used
  - Variable adjustments for confounders and effect modifiers
  - Not feasible to do meta-analyses since assessments are not uniform
- Insufficient sample sizes to explore all factors that relate to physical activity
  - Cancers of low incidence more difficult to study
- Histologic heterogeneity within cancer sites
  - Few studies have examined the risks associated with histologic sub-types
- Possible selection bias if healthier, more physically active individuals participate in research studies

Level of Evidence on Physical Activity and Cancer Risk Reduction

Convincing or Probable
Colon
Breast
Endometrial

Weaker evidence
Lung
Prostate
Ovarian

Insufficient or Null
Rectal *
Pancreatic
Gastric
Bladder
Testicular
Kidney
Hematologic cancers (non-Hodgkin lymphoma, Hodgkin lymphoma, leukemia, multiple myeloma)

** No association*

Friedenreich et al. *EJC*, 2010; 46:2593-2604

Physical Activity and Breast Cancer Risk

Lynch BM, Neilson HK, Friedenreich CM. Physical activity and breast cancer prevention.

In Courneya KS and Friedenreich CM (eds). Physical Activity and Cancer. Recent Results in Cancer Research. Heidelberg:Springer-Verlag, 2011.

Summary of Evidence on Physical Activity and Breast Cancer Risk

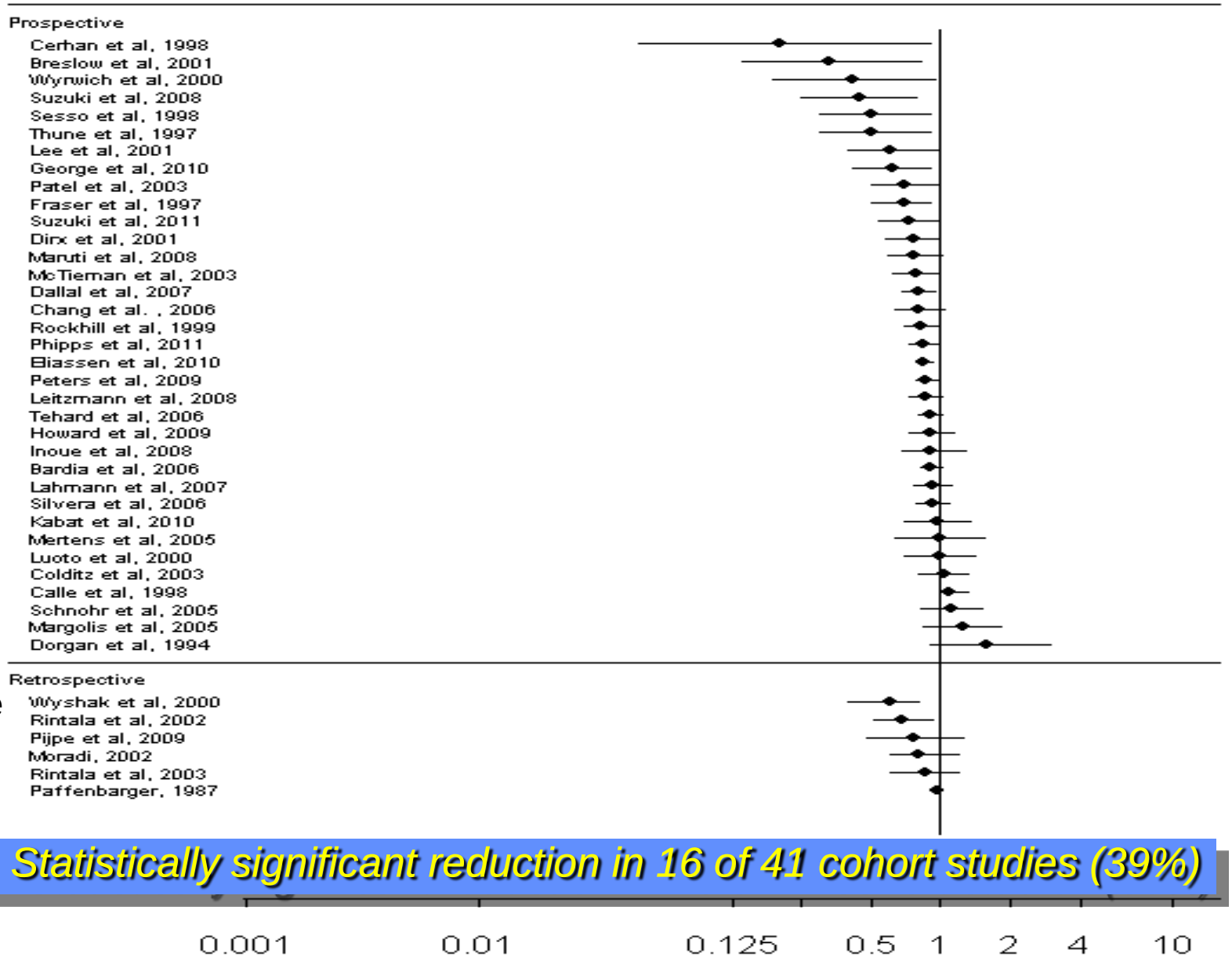
- Consistent evidence *(64 out of 86 observed decreased risk):*
  - 19 studies show no effect
  - 64 studies show decreased risk
  - 3 studies find increased risks
- Fairly strong risk reductions *(25% decrease for highest vs. lowest activity levels, on average)*
  - 29% average risk reduction in case-control studies
  - 20% average risk reduction in cohort studies
- Clear dose-response with increasing activity and decreasing risk *(40 of 50 studies)*
- Biologic plausibility exists *(several possible mechanisms)*
- Temporality exists

Lynch et al. in Courneya and Friedenreich, Physical Activity and Cancer. Heidelberg: Springer-Verlag, 2011

Physical Activity and Breast Cancer Risk: Cohort Studies

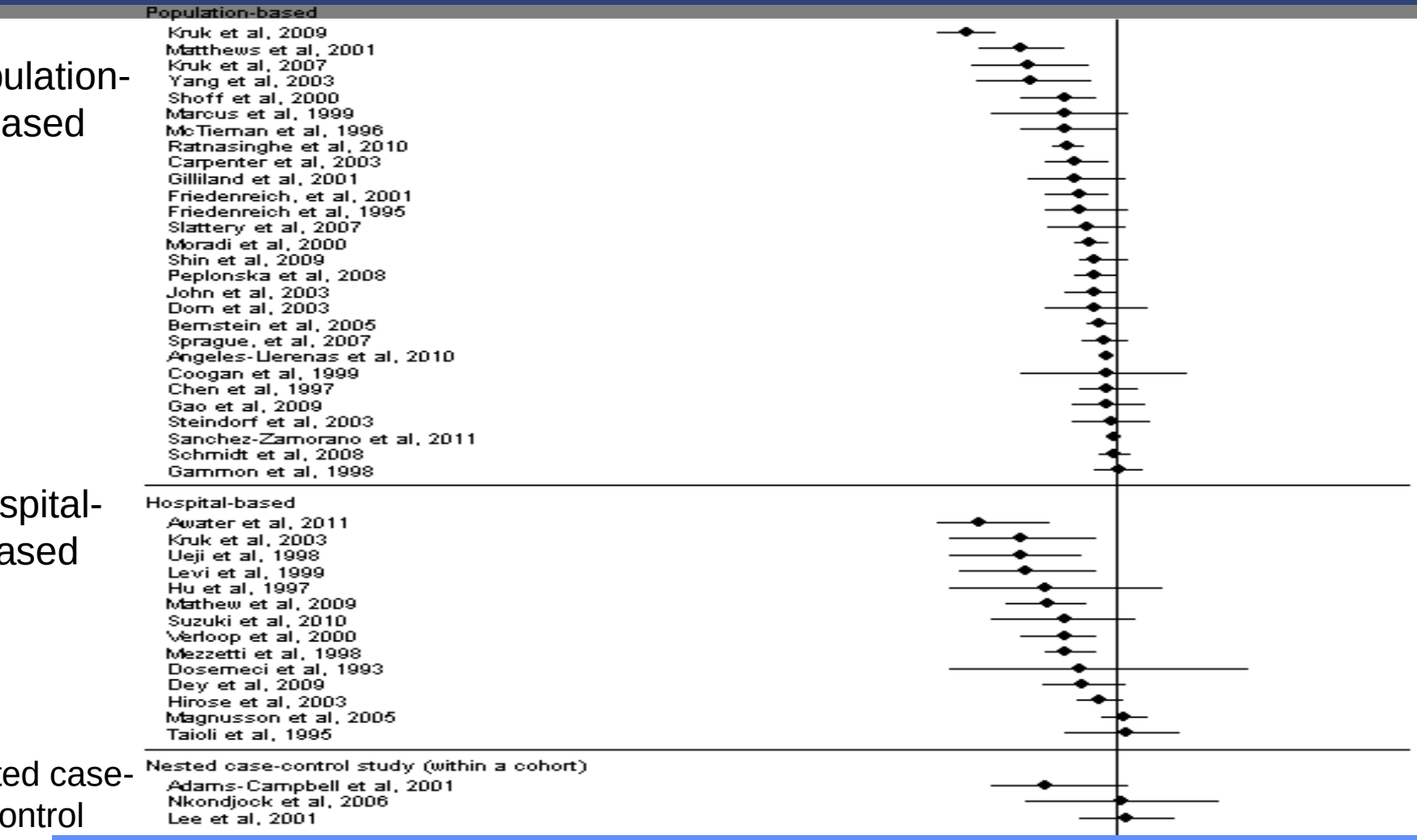
Prospective

Retrospective



Statistically significant reduction in 16 of 41 cohort studies (39%)

Physical Activity and Breast Cancer Risk: Case-control Studies



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Statistically significant reduction in 20 of 45 case-control studies (44%)

Type, Dose and Timing of Activity: Breast Cancer

- Type:
  - Of four types of activity, greatest risk decreases found for recreational and household activity (average 21% decrease), followed by walking/cycling (18% decrease) and occupational activity (13% decrease)
- Intensity:
  - Moderate activity – average 15% risk reduction
  - Vigorous activity – average **18%** risk reduction
- Duration:
  - 2-3 hours/week – 7%
  - 6.5+ hours/week – **28%**
- Timing:
  - Activity during 20s – 8%
  - Activity > 50 years – 17%
  - Adult lifetime – **27%**

Population Sub-groups: Breast Cancer

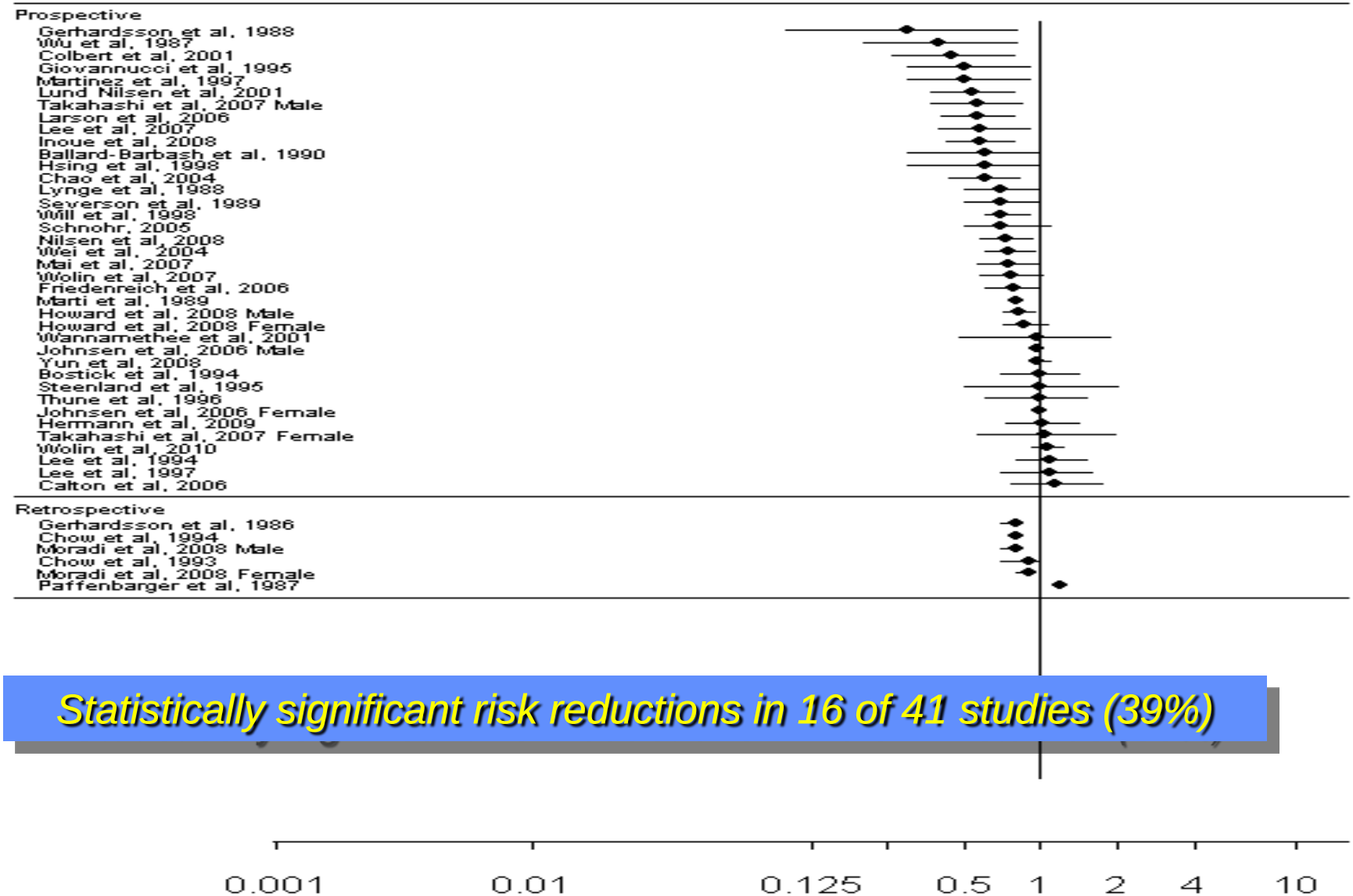
- Strongest associations seen in:
  - Menopausal status: Post-menopausal
  - Race / ethnicity: Non-white ethnicities
  - Body mass index: Low to medium BMI (≤ 25)
  - Family history: None
  - Parity: Parous
- No clear effect modification by hormone receptor status

Physical Activity and Risk of Colon Cancer

Summary of Evidence on Physical Activity and Colon Cancer Risk

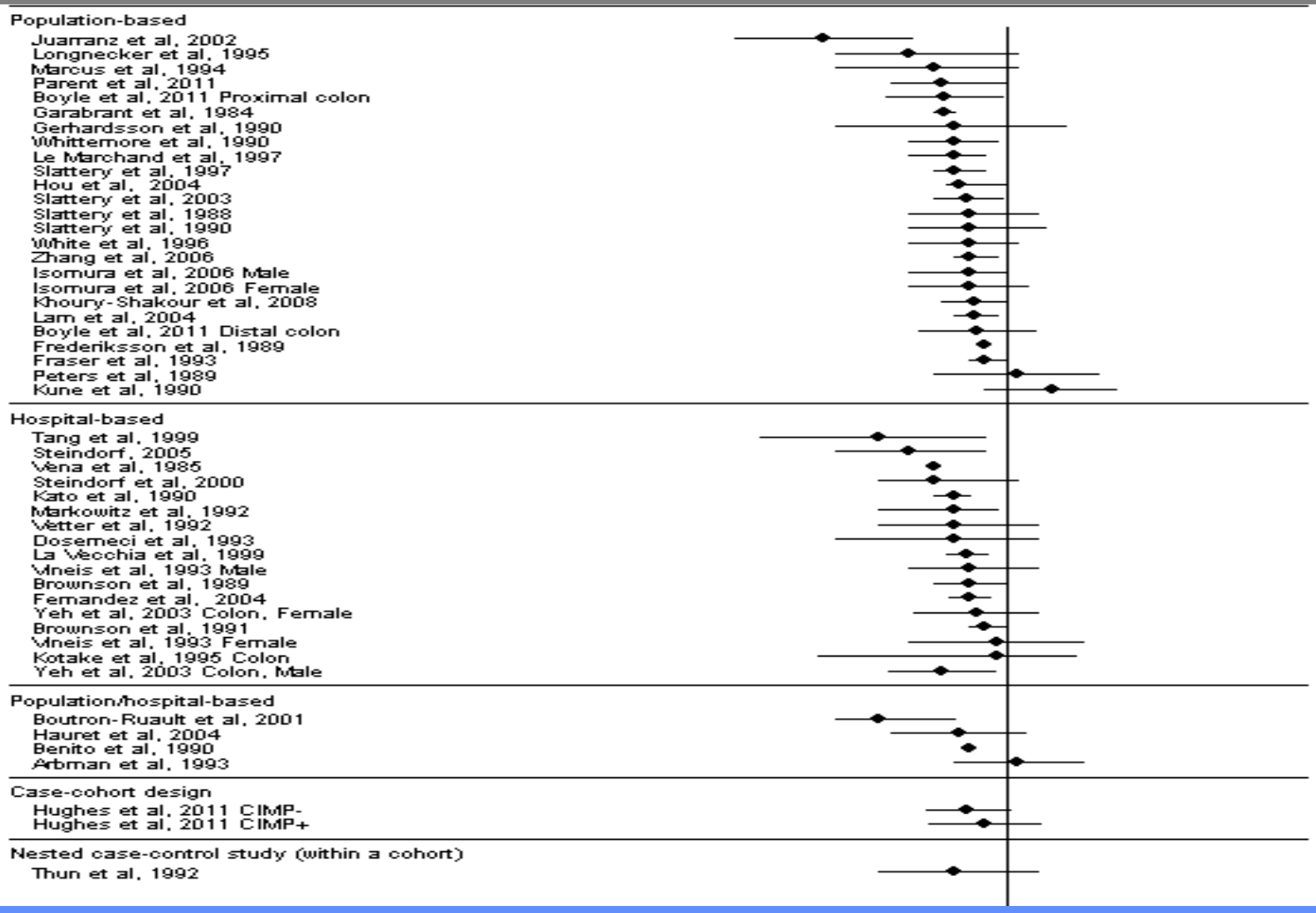
- Consistent evidence *(72 of 85 studies observe decreased risk)*
  - 14 show no effect and no studies find increased risk
- Fairly strong risk reductions *(~30% decreases for highest vs. lowest activity levels)*
  - 34% average risk reduction in case-control studies
  - 23% average risk reduction in cohort studies
- Clear dose-response *(41 of 47 studies)*
- Biologic plausibility exists
- Temporality exists

Physical Activity and Colon Cancer Risk: Cohort Studies



Statistically significant risk reductions in 16 of 41 studies (39%)

Physical Activity and Colon Cancer Risk: Case-control Studies



Statistically significant risk reductions in 18 of 44 studies (41%)

Type, Dose and Timing of Activity: Colon Cancer

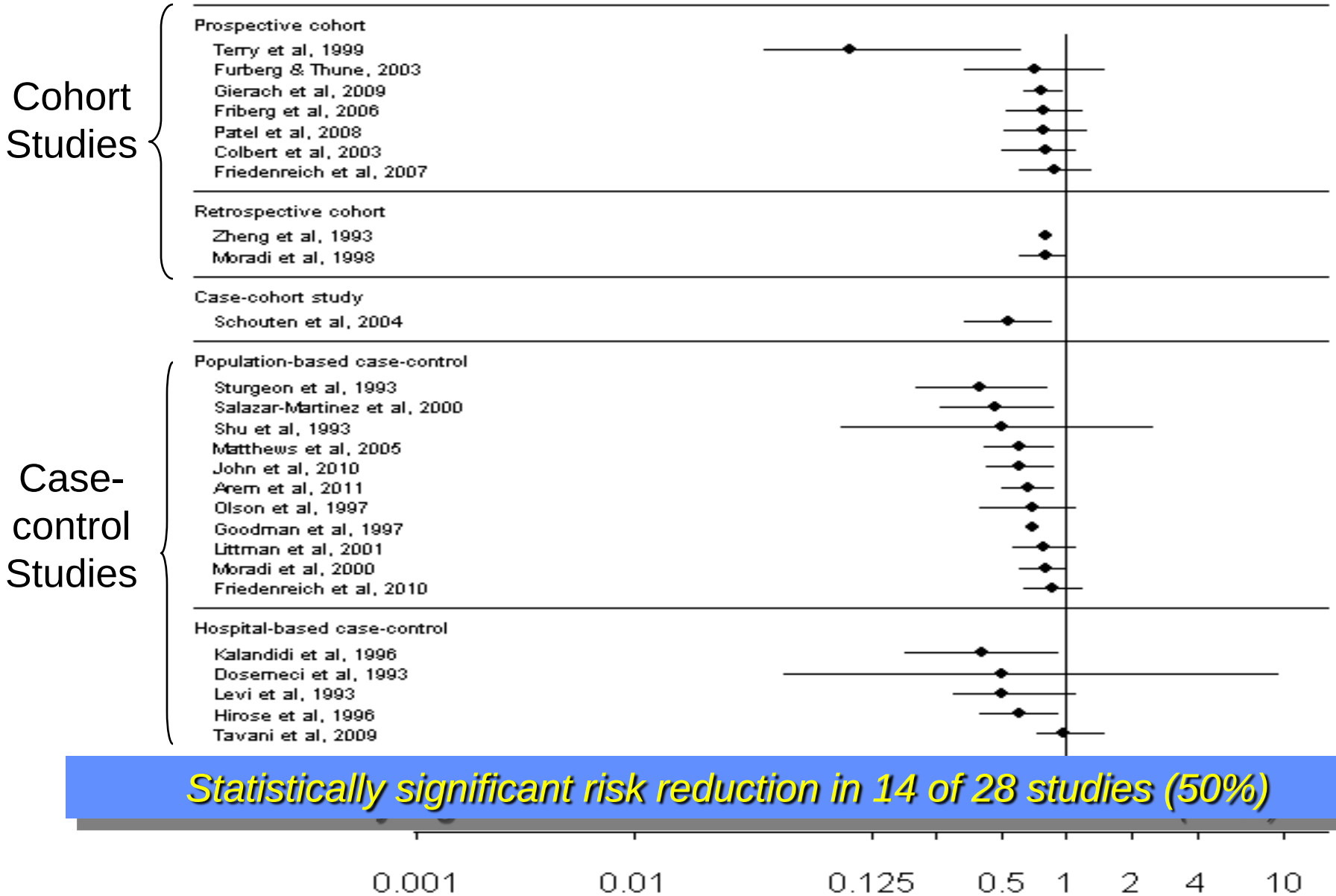
- Type of Activity:
  - All types may be effective for lowering risk
    - e.g., occupational activity (22% decrease in risk), recreational (23%)
  - Sedentary behaviour may increase risk
- Intensity:
  - Vigorous or moderate activity decrease risk
- Timing of Activity:
  - Inconsistent findings
- Population Sub-groups:
  - Relatively constant effects across BMI categories
  - Association may vary by tumour sub-site
    - i.e., proximal or distal
  - Benefit for men and women
  - Unclear effects of race/ethnicity, dietary intake, HRT use

Physical Activity and Risk of Gynecologic Cancer

Summary of Evidence on Physical Activity and Endometrial Cancer Risk

- Consistent evidence *(23 of 28 studies)*
  - Nearly all of studies show risk reductions
- Fairly strong risk reductions *(30-35% decreases for highest vs. lowest activity levels)*
  - 25% average risk reduction in cohort studies
  - 33% average risk reduction in case-control studies
- Evidence of dose-response *(12 of 19 studies)*
- Biologic plausibility exists
- Sedentary behaviour emerging as possibly important

Physical Activity and Endometrial Cancer Risk

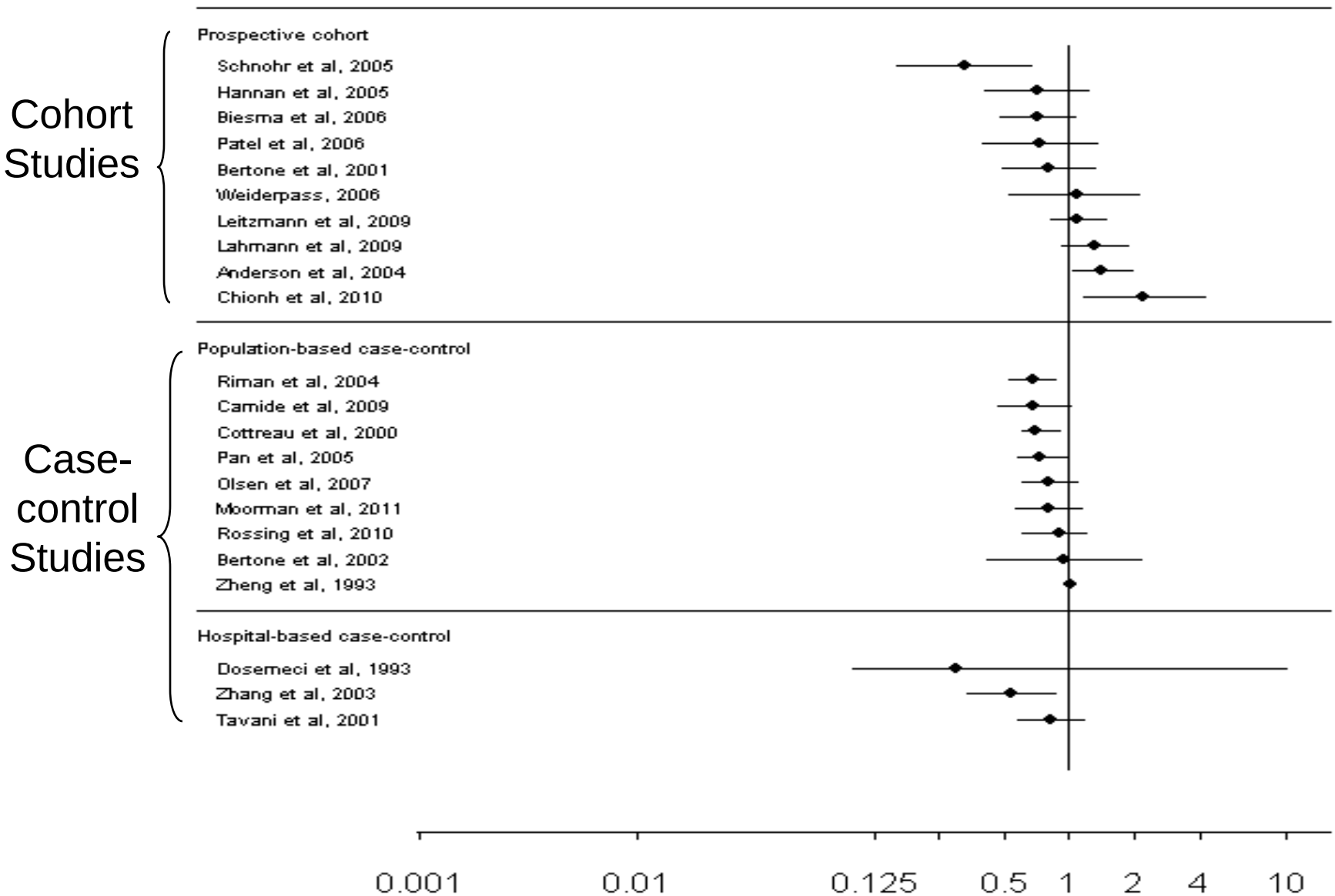


Statistically significant risk reduction in 14 of 28 studies (50%)

Summary of Evidence on Physical Activity and Ovarian Cancer Risk

- Moderately consistent evidence *(12 of 23 studies)*
  - Half studies show risk reductions
  - 3 studies show increased risk (1 is statistically significant)
- Weak risk reductions *(<10% average decreases for highest vs. lowest activity levels)*
  - Average 10% increased risk in cohort studies
  - Average 25% decreased risk from case-control studies
- Some evidence of dose-response *(9 of 11 studies)*

Physical Activity and Ovarian Cancer Studies

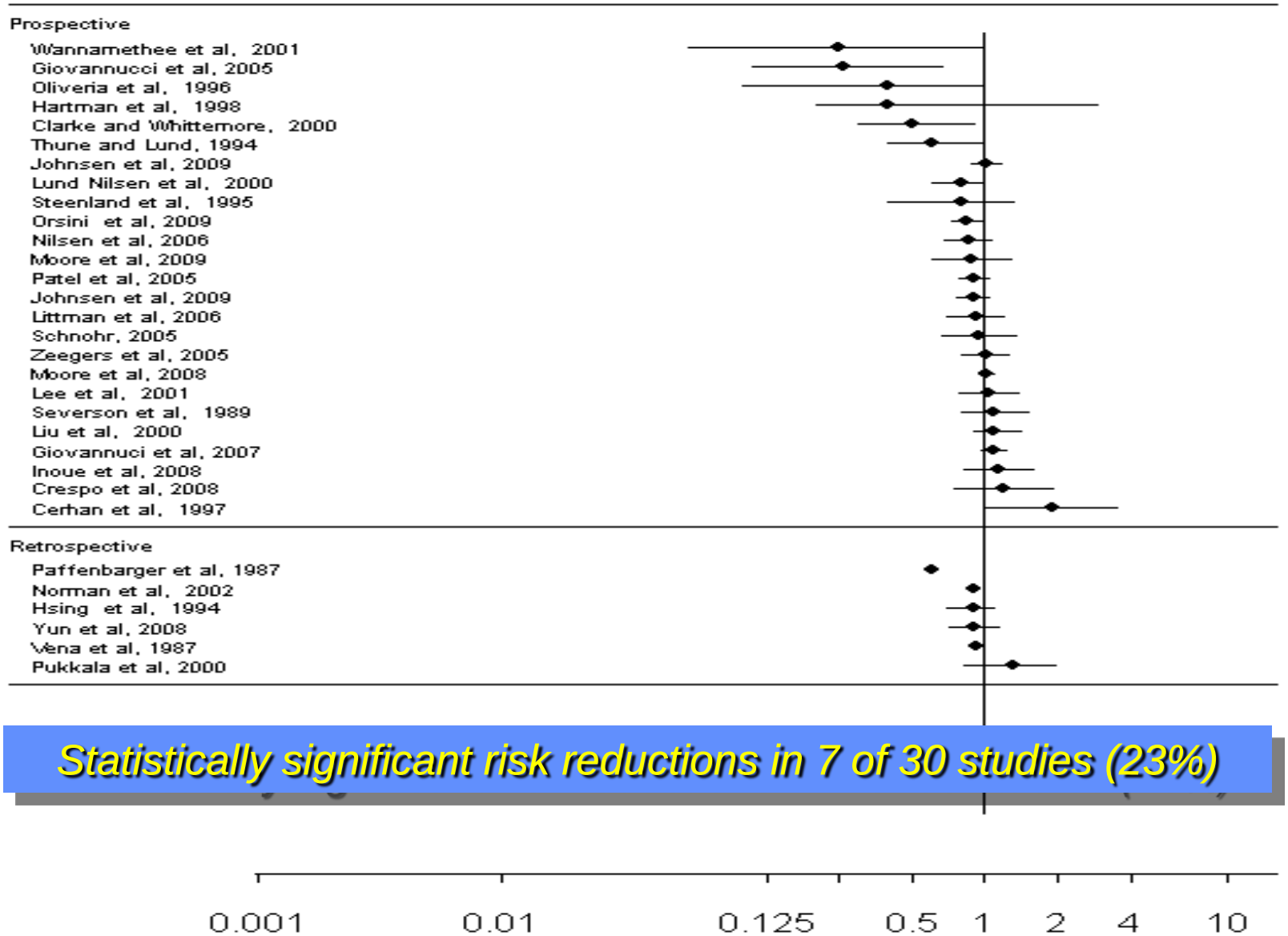


Physical Activity and Risk of Prostate Cancer

Summary of Evidence on Physical Activity and Prostate Cancer Risk

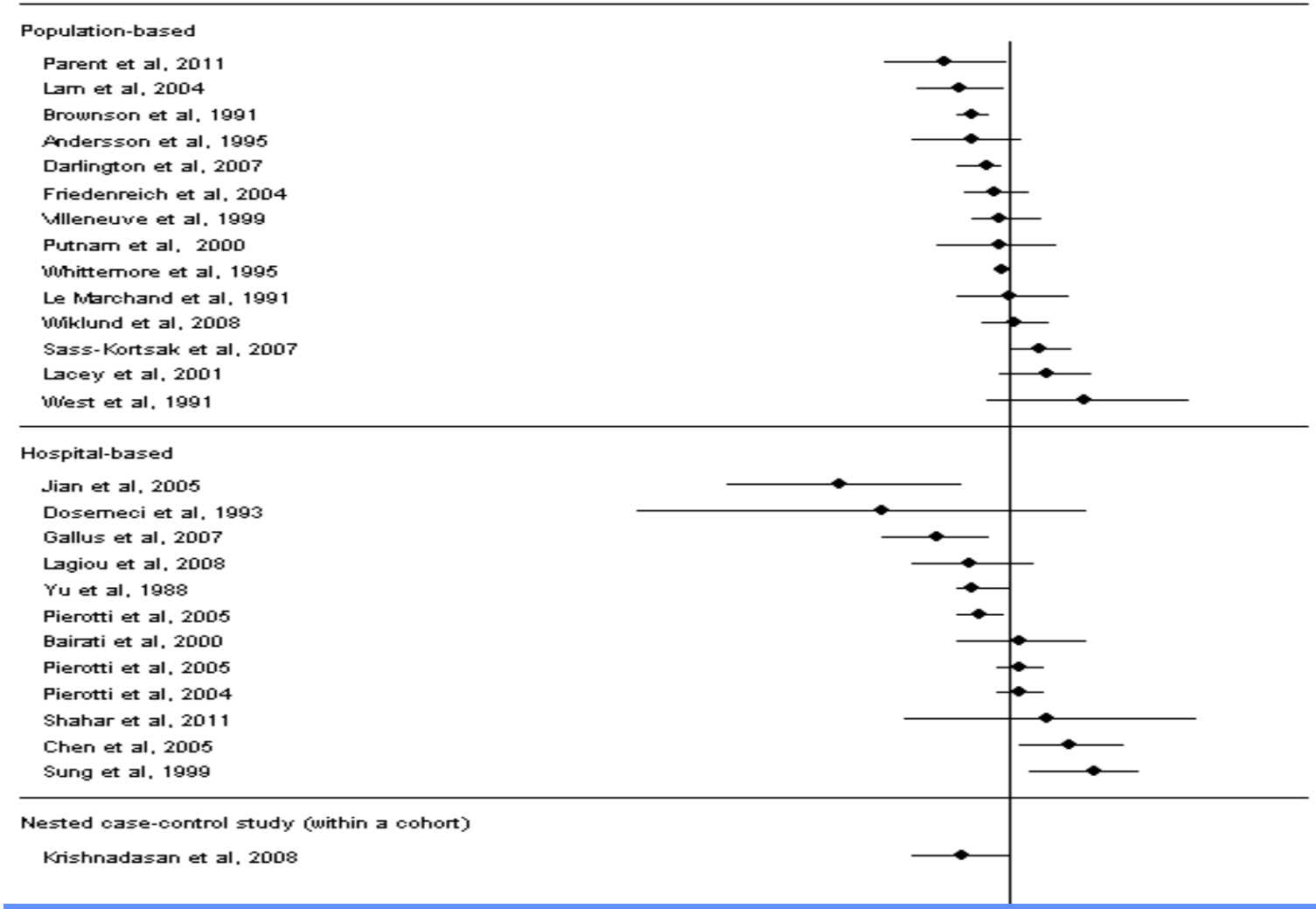
- Less consistent evidence *(26 of 56 studies)*
  - 25 studies find no effect
  - 26 studies find decreased risk
  - 5 studies find increased risk
- Weak risk reductions *(10% decreases for highest vs. lowest activity levels)*
- Evidence of dose-response *(12 of 18 studies)*
  - about half of the studies that examined these trends
- Some biologic plausibility exists

Physical Activity and Prostate Cancer: Cohort Studies



Statistically significant risk reductions in 7 of 30 studies (23%)

Physical Activity and Prostate Cancer: Case-control Studies



Statistically significant risk reductions in 8 of 26 studies (30%)

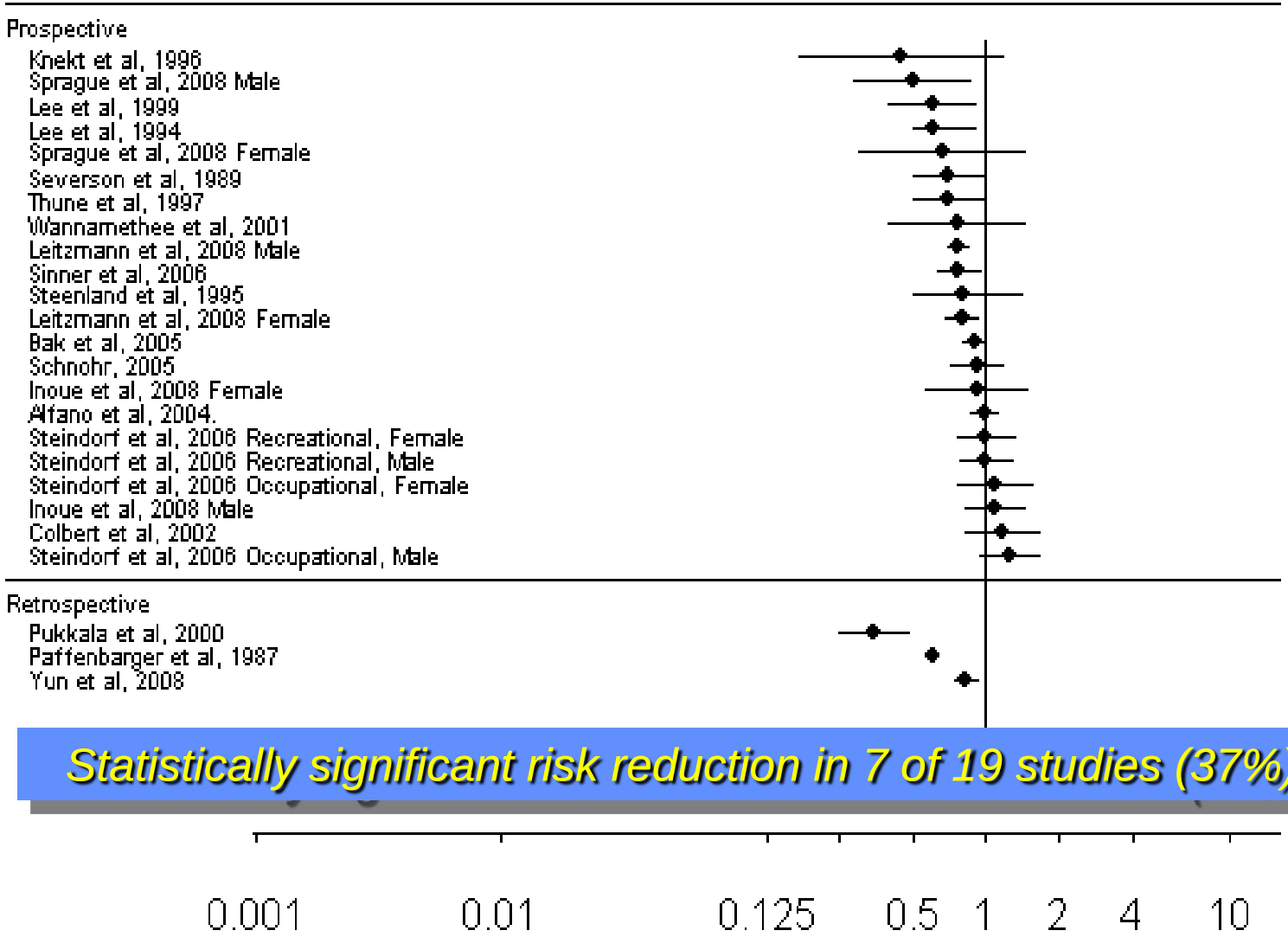
0.001 0.01 0.125 0.5 1 2 4 10

Physical Activity and Risk of Lung Cancer

Summary of Evidence on Physical Activity and Lung Cancer Risk

- Consistent evidence *(19 of 27 studies)*
  - 7 show no effect
  - 19 show decreased risks
- Fairly strong risk reductions *(25% decreases for highest vs. lowest activity levels)*
- Evidence of dose-response *(9 of 11 studies)*
  - about half of the studies that examined these trends
- Weaker evidence for biologic plausibility exists
- Effect of smoking needs to be considered

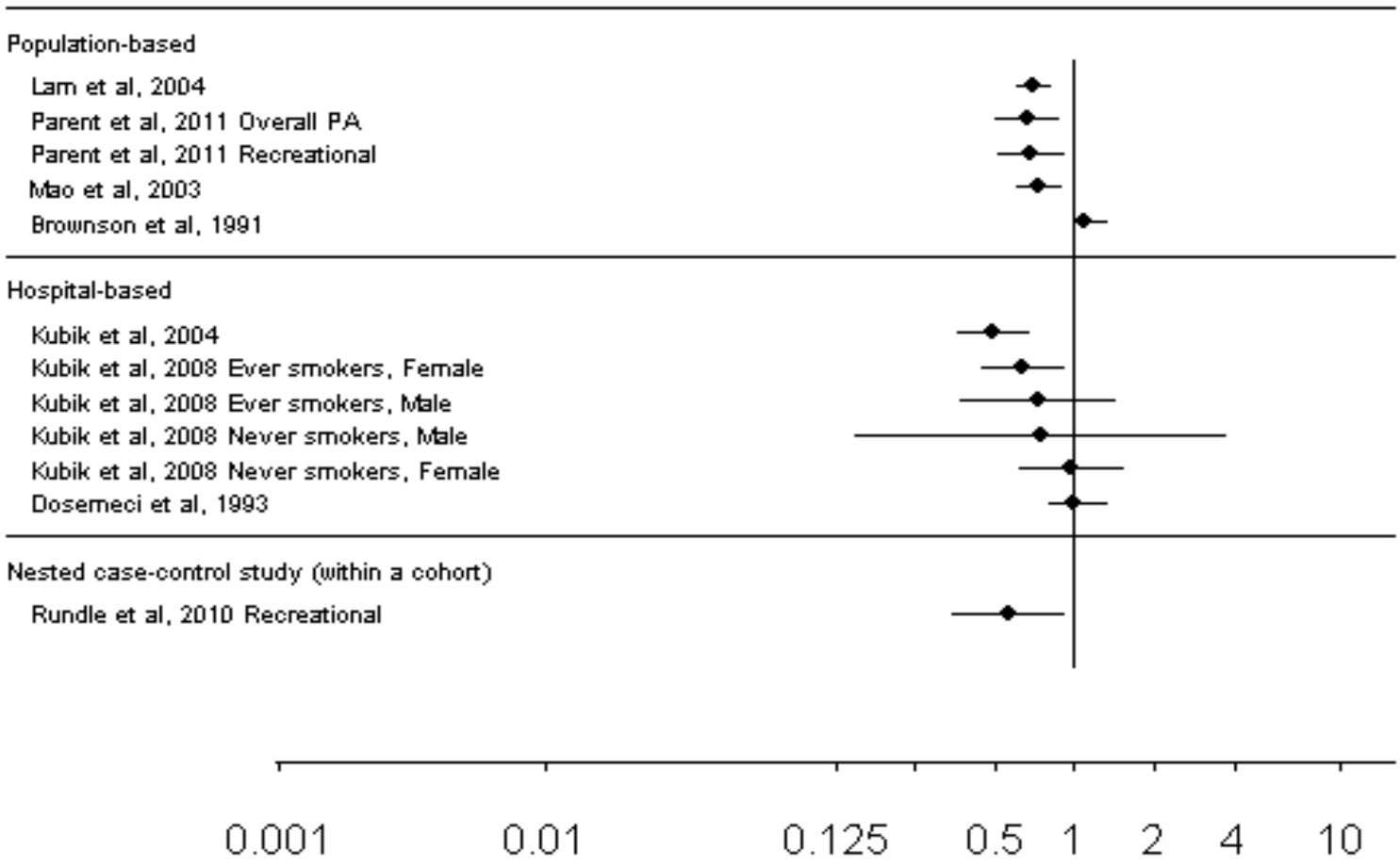
Physical Activity and Lung Cancer: Cohort Studies



Statistically significant risk reduction in 7 of 19 studies (37%)

Physical Activity and Lung Cancer: Case-Control Studies

Statistically significant risk reduction in 6 of 8 studies (75%)

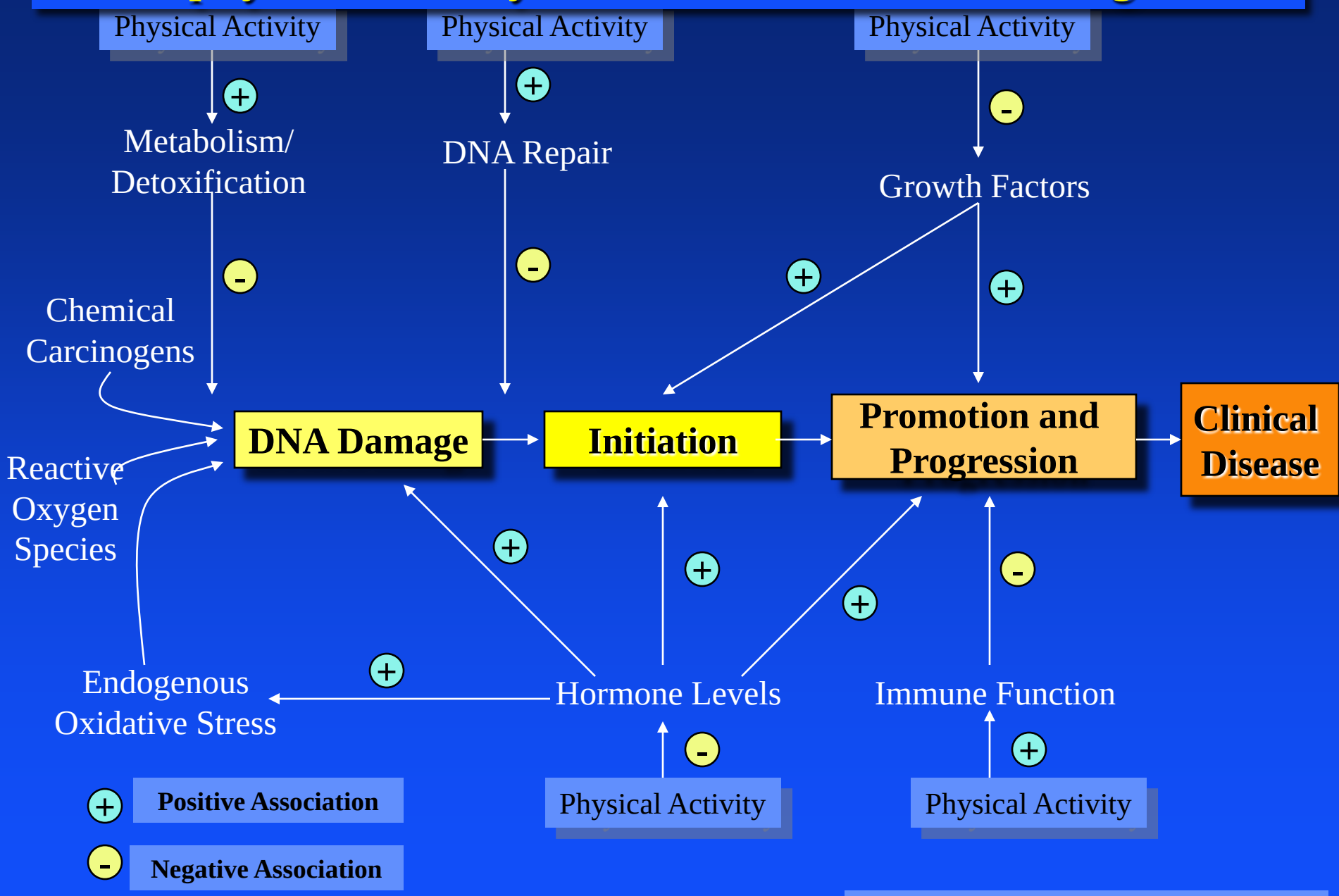


Summary of Evidence on Physical Activity and Cancer Risk by Site

Cancer Site	Number of Studies	Studies found reduced risk	Consistency of evidence	Magnitude of risk reduction	Dose-response effect
Colon	85	72	Yes	30%	Yes
Breast	86	64	Yes	25%	Yes
Endometrial	28	23	Yes	30-35%	Yes
Lung	27	19	Some	25%	Some
Prostate	56	26	No	10%	Limited
Ovarian	23	12	No	<10%	Limited
All Others	Insufficient or Null				

Biologic Mechanisms

How physical activity could interact with carcinogenesis



Adapted from Rundle A. CEBP 2005;14:227-36

Biologic Mechanisms: Stronger Evidence of Effect of PA

Mechanism	Possible effect of Physical Activity	Cancer Sites
Body fat	* Reduces fat → lowers adipokines, inflammatory markers, estrogens, testosterone * Improves insulin sensitivity, ↑ SHBG levels	Colon Postmenopausal breast Endometrium Ovaries
Insulin resistance	* Improves insulin sensitivity, ↓ plasma insulin, C-peptide, glucose levels since body fat reduced and skeletal muscle increased * Increased glucose transport into muscle and decreased fatty acid synthesis	Colon Breast Endometrium Ovaries Prostate
Improved pulmonary function	* Lowers concentration of carcinogens in lungs * Shortens exposure time b/w lung tissue and carcinogens	Lung
Sex hormones	* Postmenopause: Body fat loss ↓ aromatase & 17β-dehydrogenase levels in adipose tissue → can lower estrone, estradiol and testosterone synthesis * Hepatic synthesis of SHBG increases with lower insulin levels, ↓estradiol and testosterone	Breast Endometrium Ovaries

Biologic Mechanisms: Emerging Evidence of Effect of PA

Mechanism	Possible effect of Physical Activity	Cancer Sites
Vitamin D	• Associated with higher 25-hydroxyvitamin D blood levels	Colon, Breast
Insulin-like growth factors	• Might ↓IGF-1 and ↑IGFBP-3	Colon, Premenopausal breast, Endometrium, Ovaries, Prostate, Lung
Sex hormones	• Pre-menopause: Ovarian production of estrogens may decrease → delay menarche, menstrual dysfunction, anovulation	Breast, Endometrium, Ovaries, Prostate
Adipokines	• Decreases body fat (main source of leptin) •↑ Adiponectin levels by ↓IL-6 and TNF-α but possibly only with weight loss	Colon, Breast, Endometrium, Prostate, Lung
Chronic low-grade inflammation	• May ↓ inflammatory markers (CRP, IL-6, TNF- α) partly through fat loss	Most cancers

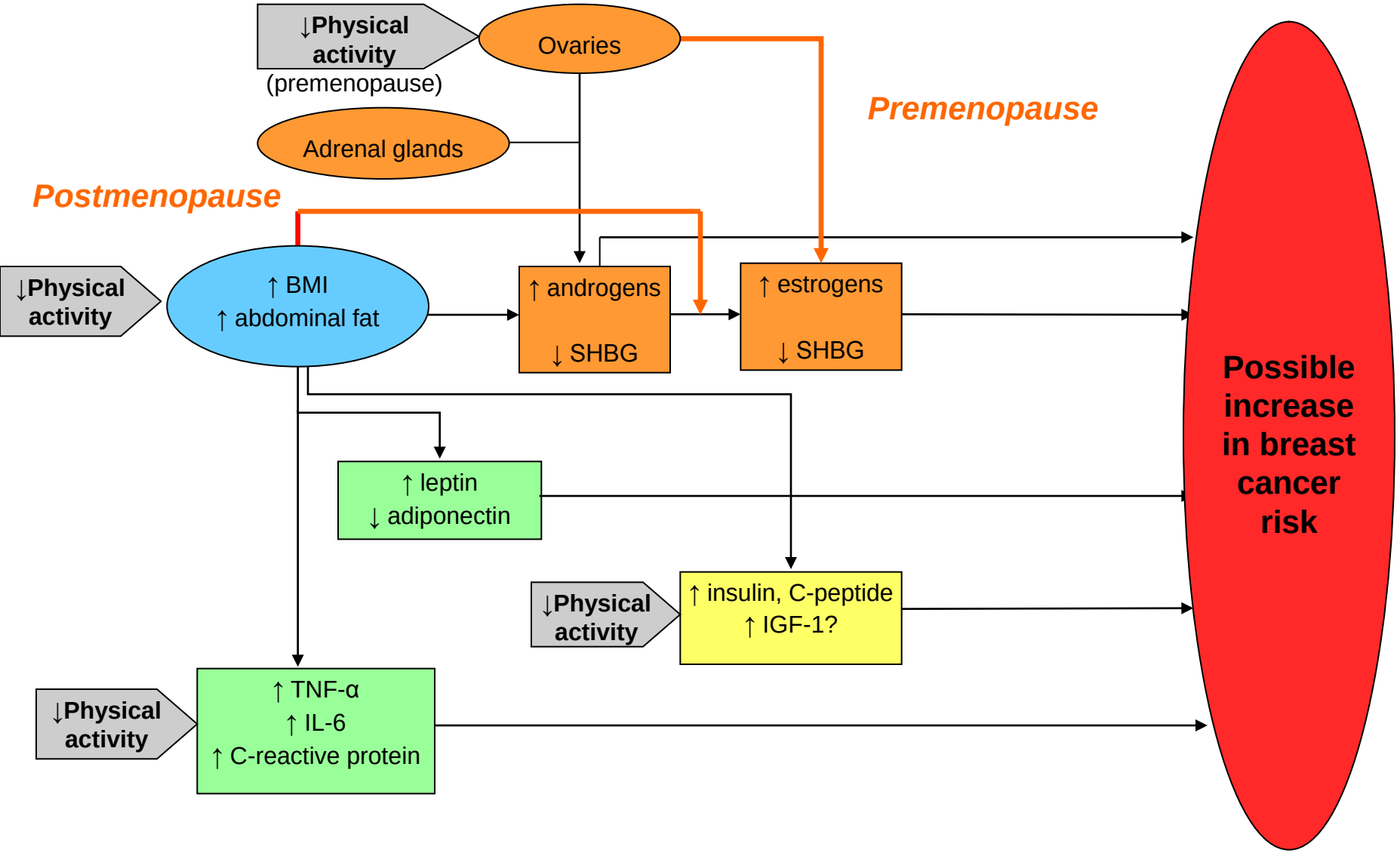
Biologic Mechanisms: Emerging Evidence of Effect of PA

Mechanism	Possible effect of Physical Activity	Cancer Sites
Immune function	•May improve innate and acquired immune responses to recognize and eliminate cancer cells •Effects of long-term, moderate intensity PA on humans at risk not well understood	Most cancers
Oxidative stress, anti-oxidant defense and DNA repair	• May reduce oxidative stress, increase anti-oxidant enzymes (e.g. superoxide dismutase), and/or enhance DNA repair	Most cancers
Prostaglandins	• May inhibit synthesis of prostaglandins synthesis	Colon
Gastrointestinal transit time	• ↑ gut motility and may ↓ transit time → less interaction between mucosa and carcinogens but changes may not be large enough to alter risk	Colon

Randomized Controlled Exercise Intervention Trials for Breast Cancer Prevention

- Three year-long RCTs conducted to date on aerobic exercise and breast cancer biomarkers among postmenopausal, inactive, 50-75 yr old healthy women:
  - McTiernan et al. (***P**hysical **A**ctivity for **T**otal **H**ealth Trial*) (N=173)
  - Monninkhof et al. (***S**ex **H**ormones and **P**hysical **E**xercise **T**rial*) (N=189)
  - Friedenreich et al. (***Al**berta **Ph**ysical **A**ctivity and Breast Cancer Prevention Trial*) (N=320)

Hypothesized Biologic Mechanisms Between Physical Activity and Breast Cancer



Friedenreich CM, Neilson HK, Lynch BM. *Eur J Cancer*. 2010; 46:2593-2604

Main Findings on Exercise and Breast Cancer Biomarkers

Endpoint	PATH Trial	SHAPE Trial	ALPHA Trial
Sex hormones	↓estrone and estradiol restricted to women who lost >2% body fat	No effect on estrogens or androgens	↓estradiol and ↑SHBG
Obesity	↓ all adiposity measures	↓ body fat but no effect on weight, BMI or hip circumference	↓all adiposity measures
Insulin resistance	↓insulin, leptin, HOMA score	Not reported	↓ insulin, HOMA-IR, leptin, adiponectin/leptin ratio
Inflammation	↓C-reactive protein	Not reported	↓ C-reactive protein
Publications	Irwin 2003; McTiernan 2004; Frank 2005; Campbell 2009	Monninkhof 2009; Velthuis, 2009	Friedenreich 2010a; Friedenreich 2010b, Friedenreich 2011

ALPHA Trial: Design

- **Study design:** Two-armed, two-centered RCT
- **Intervention:** Year-long, 5 days/week, 45 mins/session (3 supervised, 2 unsupervised), aerobic exercise only, no change in diet
- **Eligibility criteria:** Postmenopausal, 50-74 yrs, no previous cancer, healthy, BMI=22-40, no HRT use, non-smoker, non-excessive alcohol, inactive
- **Control:** No change in exercise or diet
- **Sample size:** 320
- **Outcomes:** Sex hormones, adiposity, insulin resistance, inflammation, mammographic density

ALPHA Trial

ALPHA Trial Flow Chart

Recruitment

Assessed for eligibility (n=3454)

Did not meet inclusion criteria (n=1840)
Refused (n=798)
Other reasons (n=274)

Attend information session and remain eligible and interested (n=542)

Data Collection

Randomized (n=320)

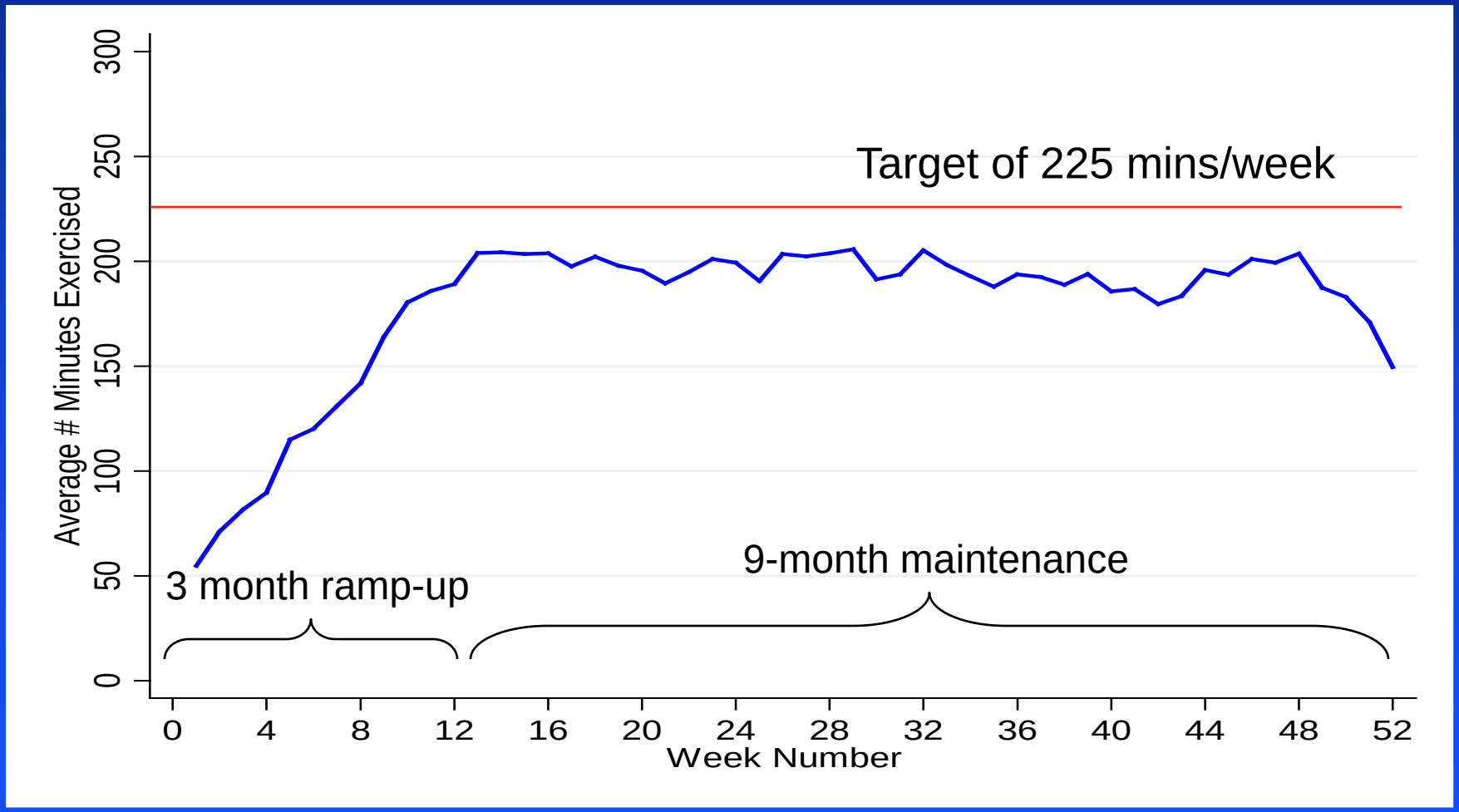
Exercise Group (n=160)

Control Group (n=160)

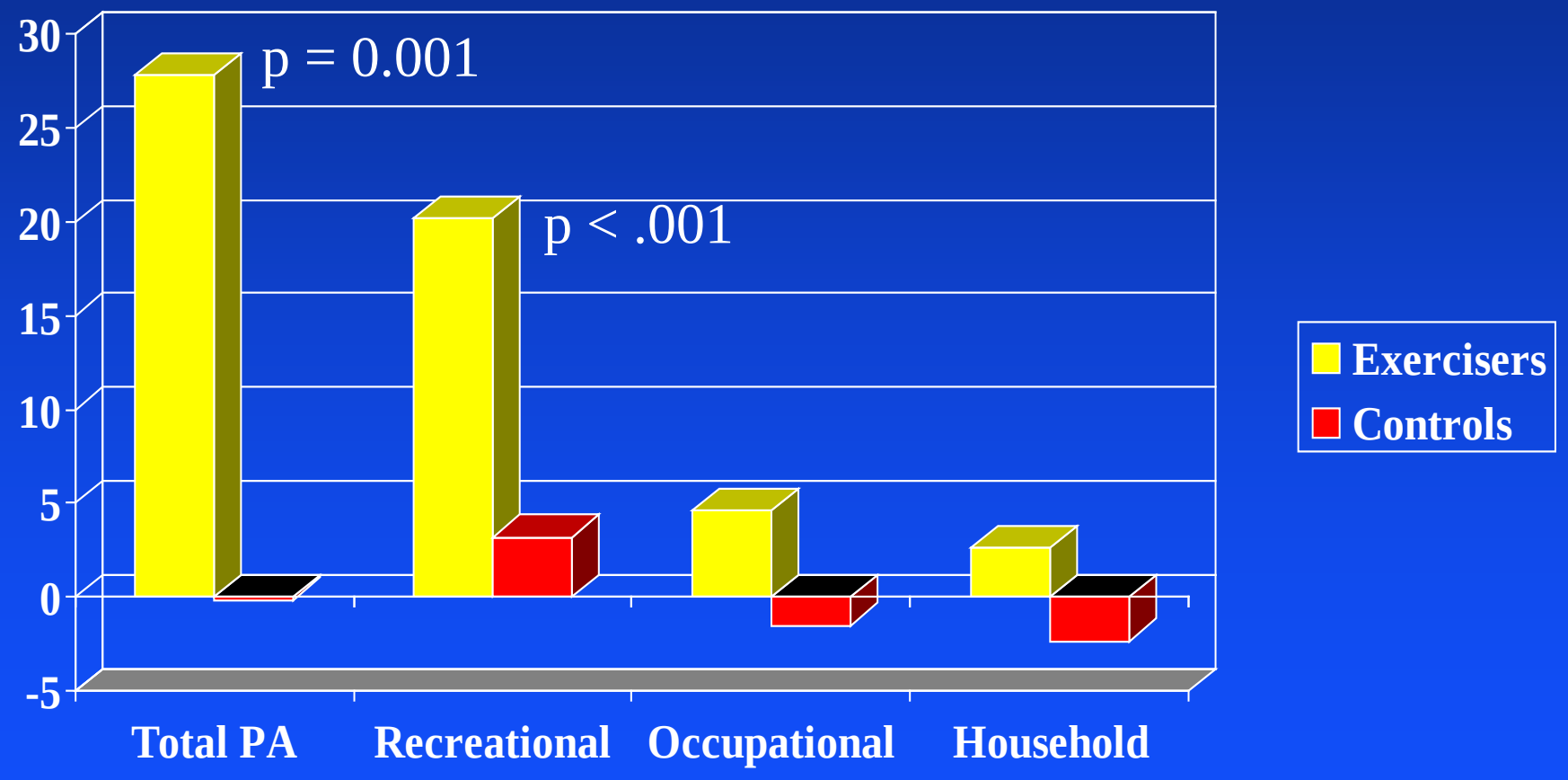
12 month blood samples (n=154)

12 month blood samples (n=156)

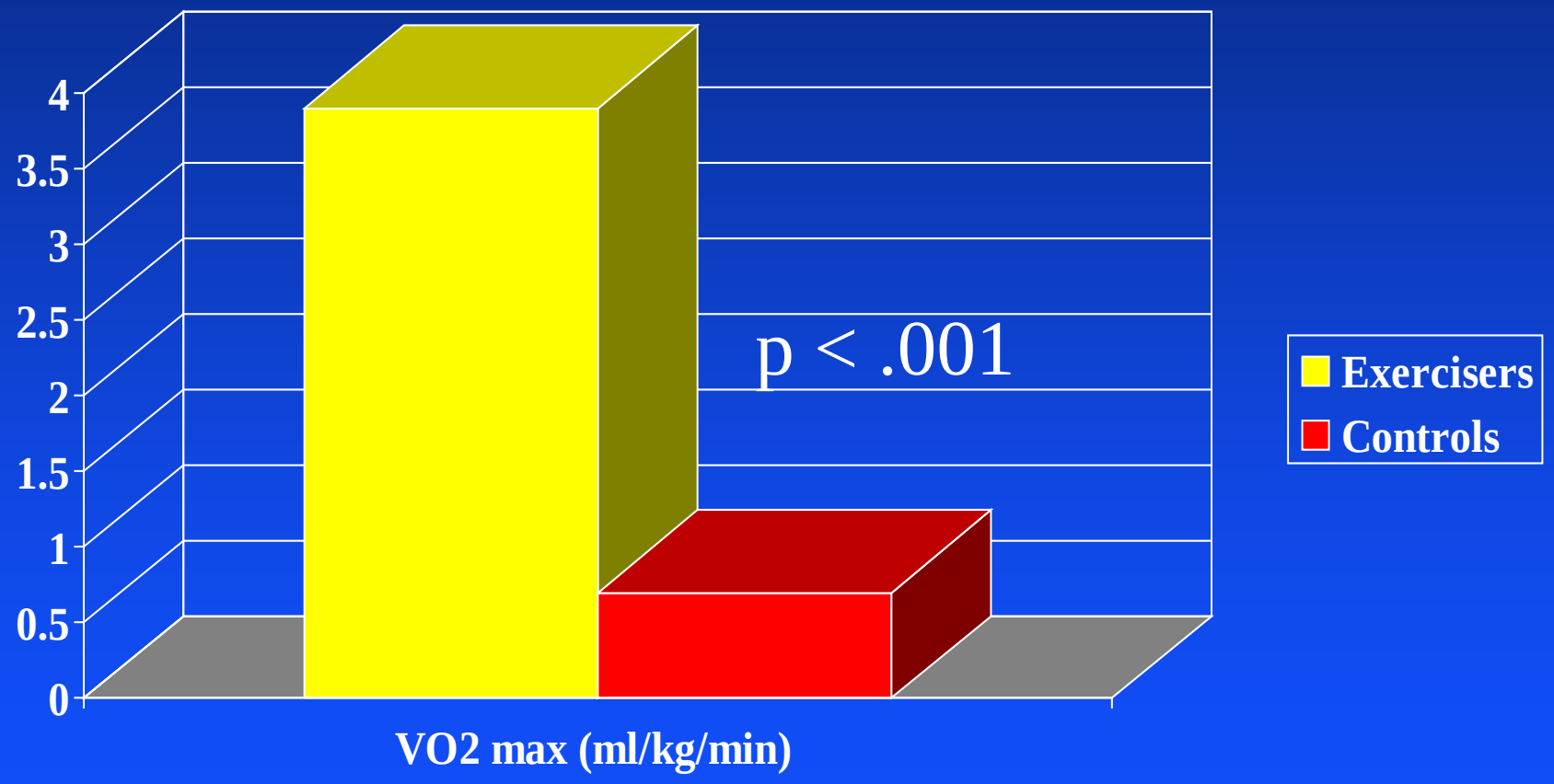
ALPHA Trial: Average Number of Minutes Exercised by Week on Trial



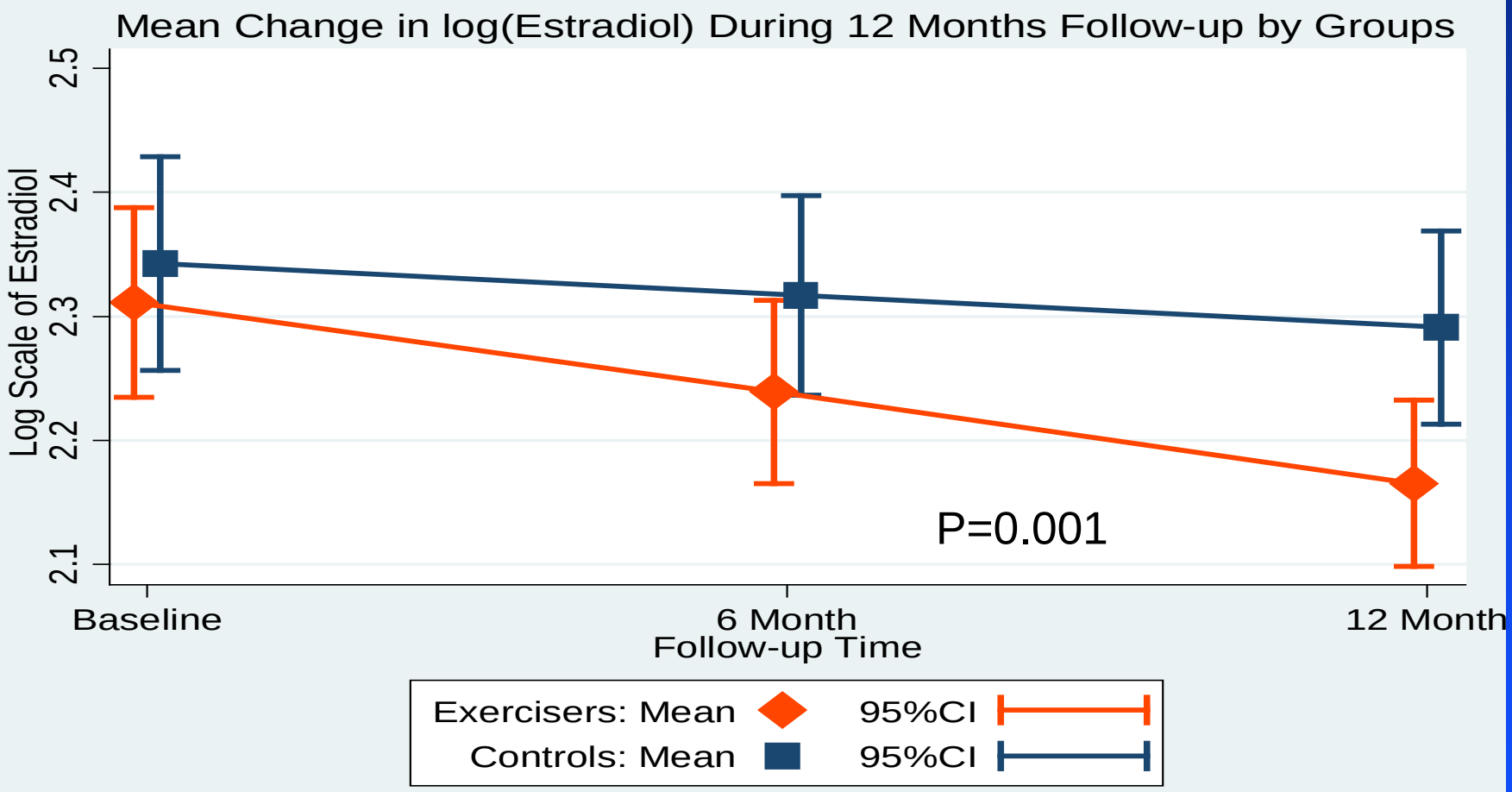
Change in Physical Activity Levels from Baseline to 12 Months (MET-hrs/wk)



Change in Fitness from Baseline to 12 Months

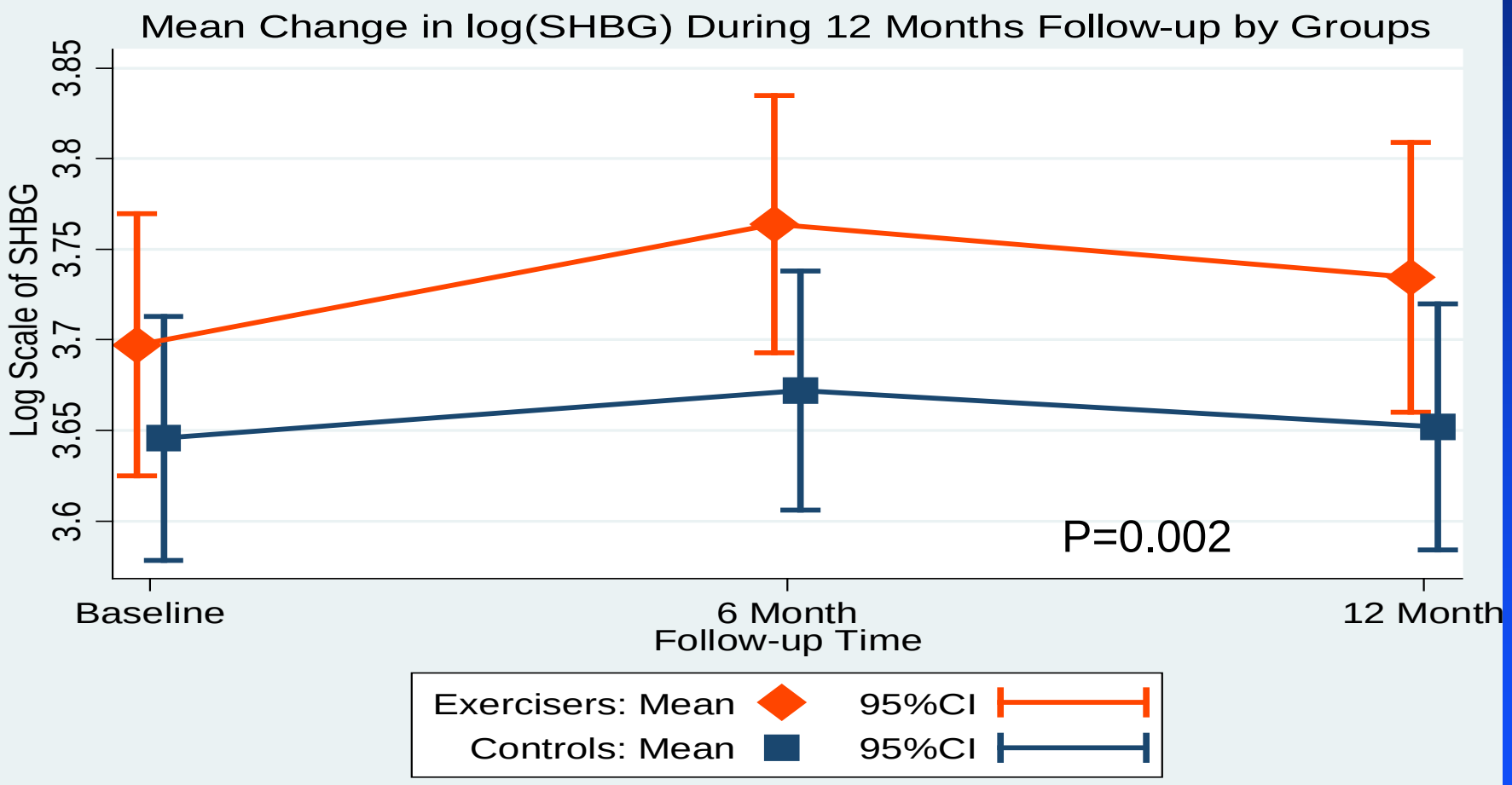


Impact of Exercise Intervention on Endogenous Estrogens: Estradiol



Friedenreich et al., *JCO*, 2010; 28:1458-66

Impact of Exercise Intervention on Sex Hormone Binding Globulin



Friedenreich et al., *JCO*, 2010; 28:1458-66

Impact of Exercise Intervention on Adiposity Outcomes

Change from Baseline	Exercisers	Controls	Difference	*p*-value
Weight (kg)	-2.3	-0.5	-1.8	<.001
Body mass index (kg/m^2)	-0.9	-0.2	-0.7	<.001
Waist circumference (cm)	-2.2	0.1	-2.3	<.001
Abdominal fat area (cm^2)	-48.5	-9.6	-38.9	<.001
Intra-abdominal fat area (cm^2)	-16.5	-1.6	-14.9	<.001

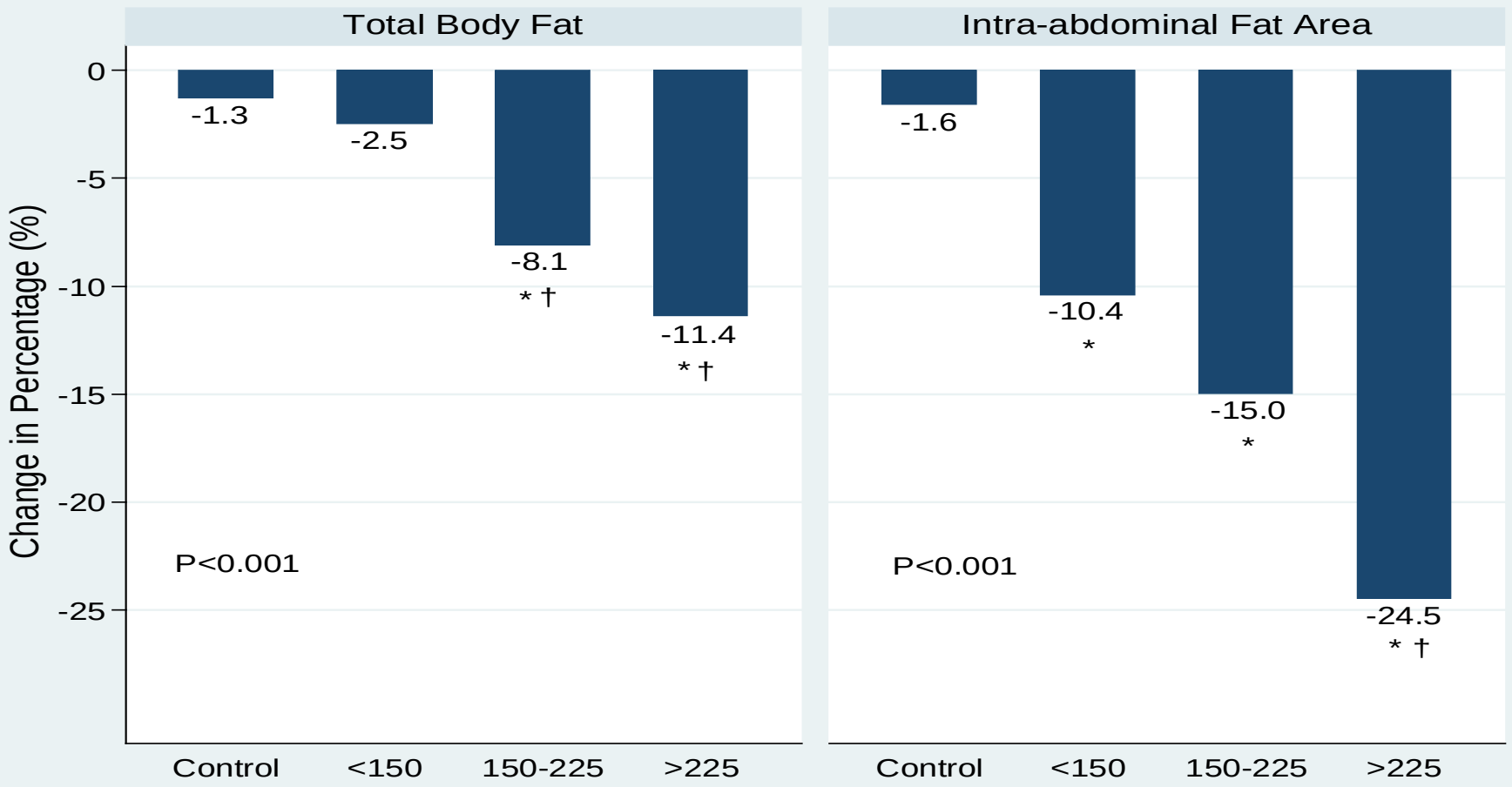
Friedenreich et al., *Int J Obes* 2010; 35:427-35

Impact of Exercise Intervention on Adiposity Outcomes

Change from Baseline	Exercisers	Controls	Difference	*p*-value
Subcutaneous fat area (cm^2)	-32.0	-7.9	-24.1	<.001
Percent body fat	-2.0	-0.2	-1.8	<.001
Fat mass (kg)	-2.4	-0.4	-2.0	<.001
Lean muscle mass (kg)	-0.0	-0.1	0.1	0.564

Friedenreich et al., *Int J Obes* 2010; 35:427-35

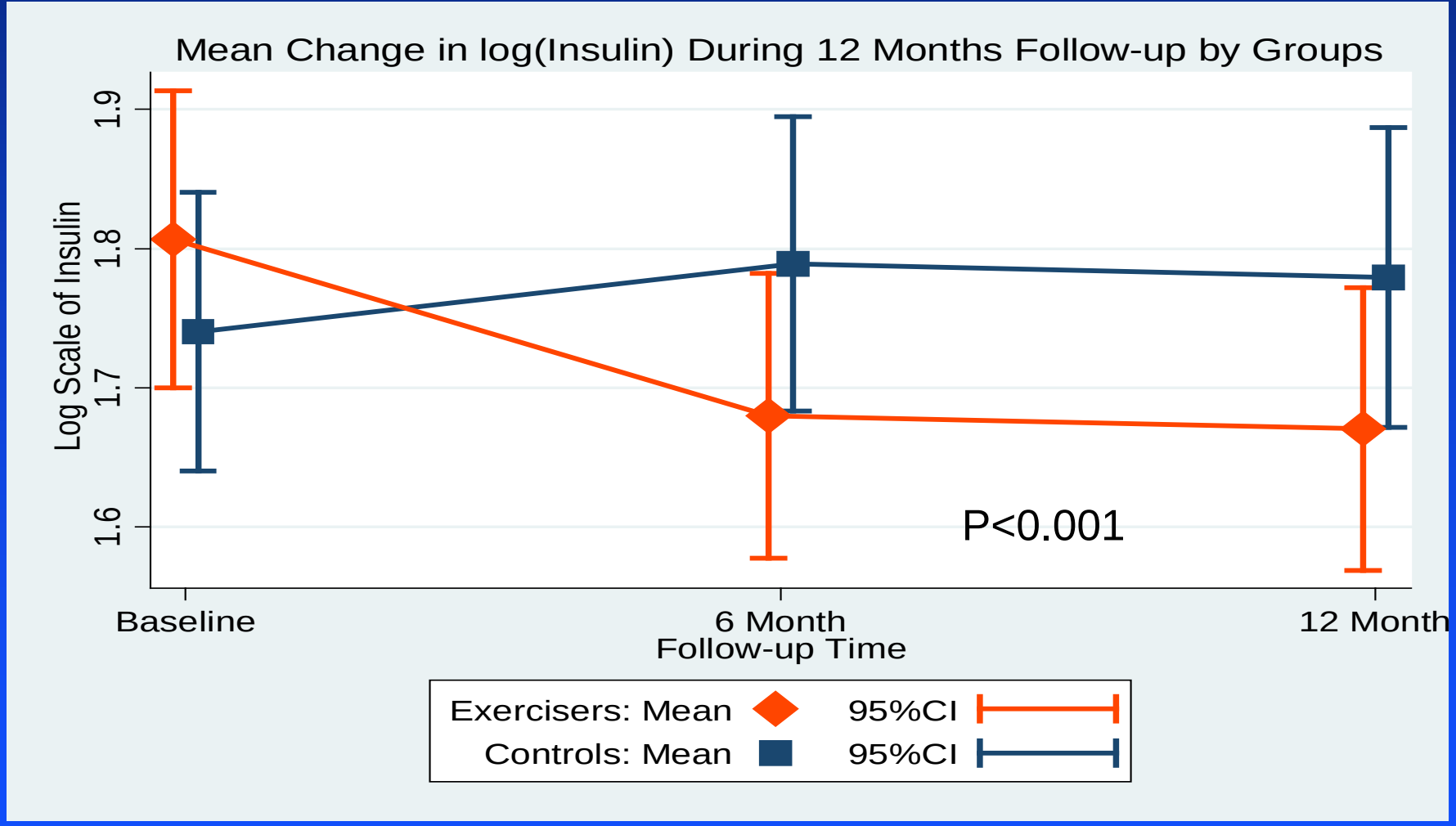
Percent Change of Total Body Fat and Intra-abdominal Fat by Average Weekly Duration of Exercise



*** Significant difference compared with control group (*P*<0.05).**
† Significant difference compared with low-active group (*P*<0.05).

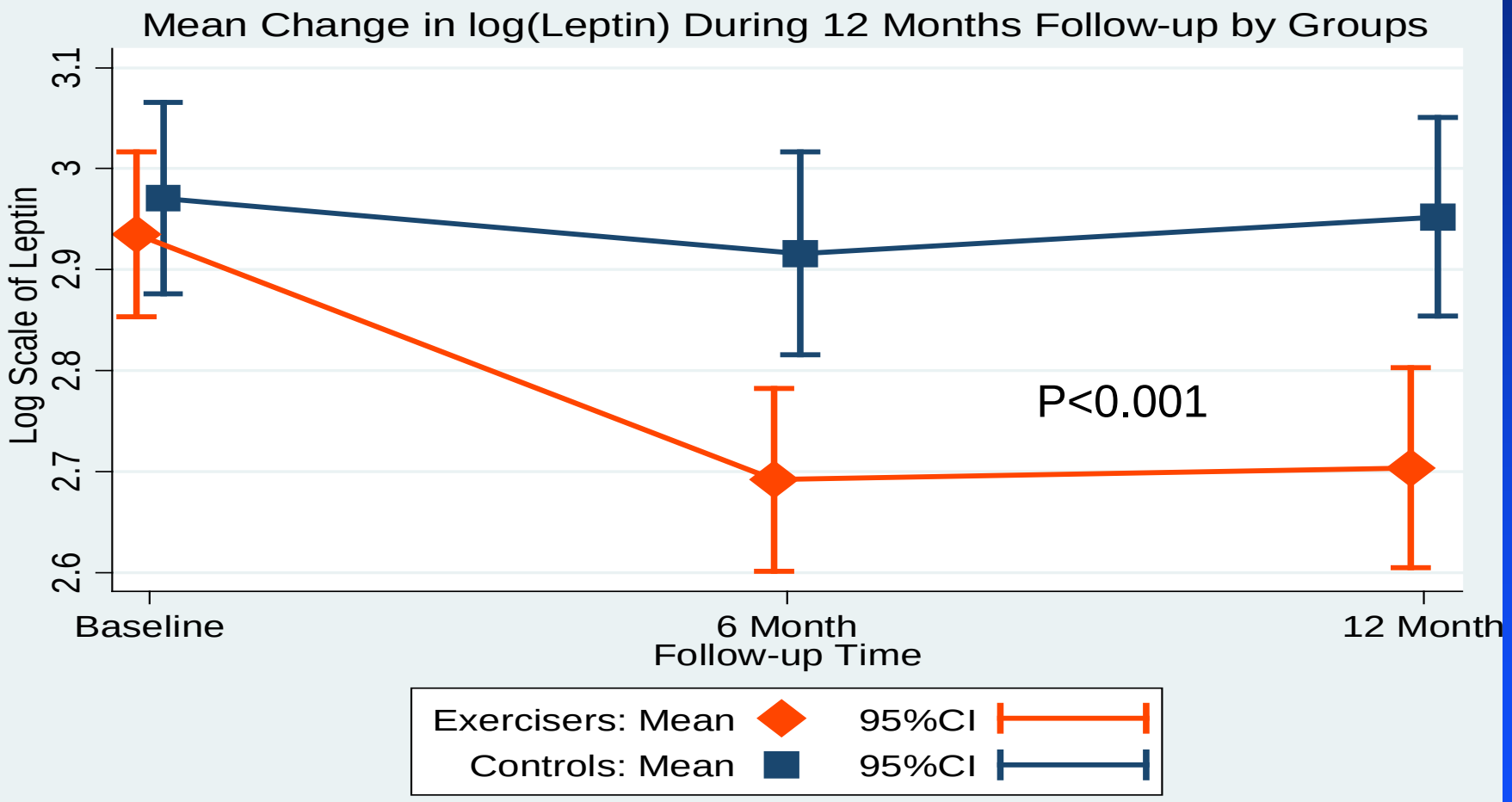
Friedenreich et al., *Int J Obes* 2010; 35:427-35

Impact of Exercise Intervention on Insulin



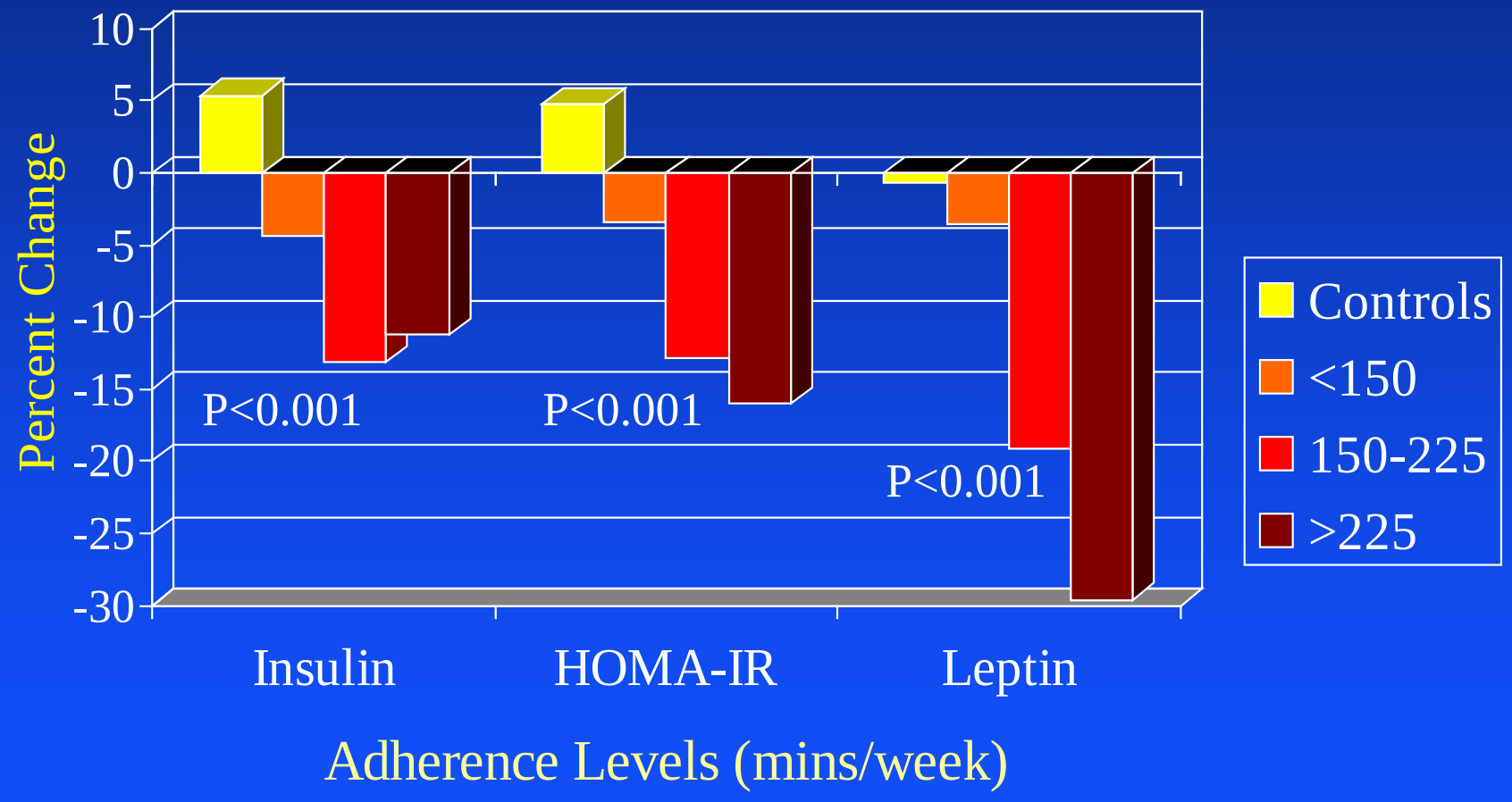
Friedenreich et al., *Cancer Prev Res* 2011;4 (epub)

Impact of Exercise Intervention on Leptin



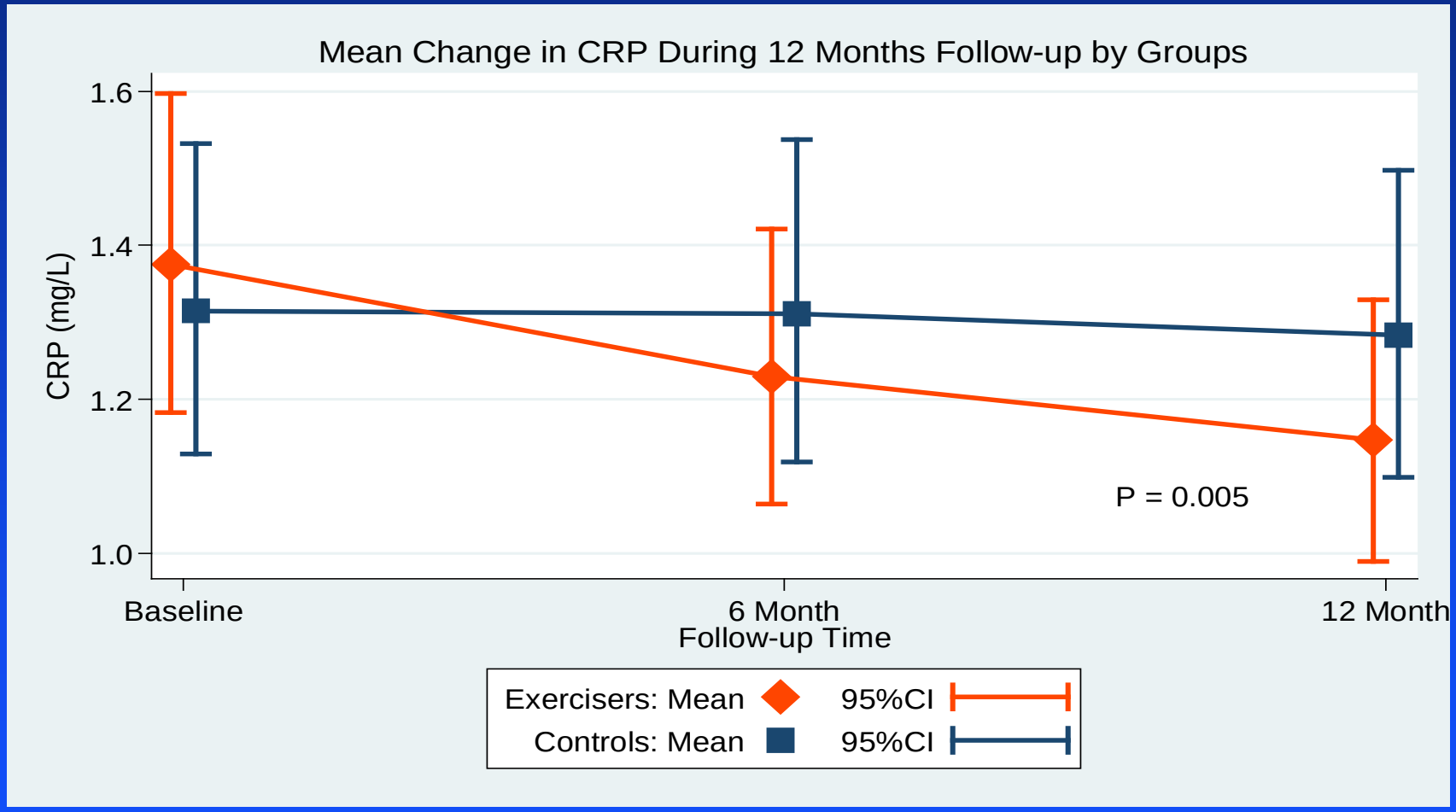
Friedenreich et al., *Endocrine Related Cancer* 2011

Percent Change in Insulin Biomarkers by Adherence Levels



Friedenreich et al., *Endocrine Related Cancer* 2011

Impact of Exercise Intervention on C-reactive Protein



Friedenreich et al. *Cancer Prev Research* 2011;4.

Breast Cancer and Exercise Trial in Alberta: Study Design

Recruit 330 postmenopausal women 50-74 years

Randomize

High volume exercise group (5 days/wk x 60 mins/session)

Moderate volume exercise group (5 days/wk x 30 mins/session)

Compare high vs moderate exercise groups on endogenous sex hormones, obesity and inflammatory markers, insulin, glucose

Estimated Preventable Cancers Associated with Physical Inactivity, USA, 2011

Cancer Site	No. of cancers in USA, 2011*	PAR for physical inactivity §	Estimated preventable cancers
Colon	141,210	30.4%	42,933
Breast	230,480	21.2%	48,948
Endometrial	46,470	25.8%	11,973
Prostate	240,890	12.7%	30,620
Lung	221,130	16.8%	37,200
Ovarian	21,990	8.2%	1,797
Total	**902,170**		**173,470**

*SEER Data for 2011 PAR=Pe(RR-1)/Pe(RR-1)+1 where Pe=0.754 from CDC PA data

Future Research Directions

- Investigate sedentary behaviour and light intensity activity as risk factors for cancers
- Improve PA measurements including objective assessments
- More precision on type, dose, timing of activity in relation to cancer risk
- Examine effect modification by other factors
- Conduct prospective observational studies of new biomarkers
- Need more mechanistic RCTs that evaluate different doses and types of PA
- Conduct RCTs of combined physical activity and diet for cancer prevention
- Ultimate objective: provide more quantitative data to enhance public health recommendations regarding PA type, dose, timing for cancer risk reduction

Conclusion

- Strong, consistent evidence worldwide that PA reduces colon, breast, endometrial cancer risks and possibly also prostate, lung and ovarian cancers by 10-30% with a dose-response effect and some sub-group effects
- Several plausible biologic mechanisms exist
- RCTs are finding support for these mechanisms
- 8-30+% of cancers may be attributable to physical inactivity

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