Physical activity and cancer

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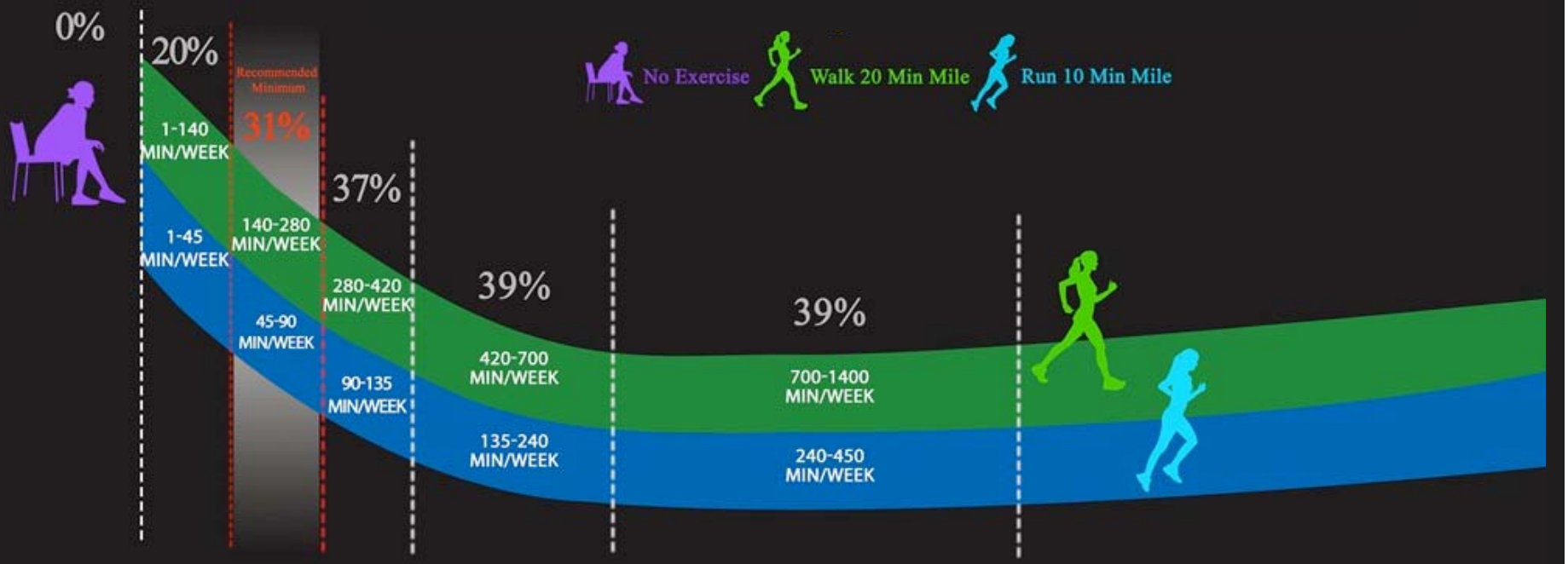
NIH NATIONAL CANCER INSTITUTE

June 21, 2016

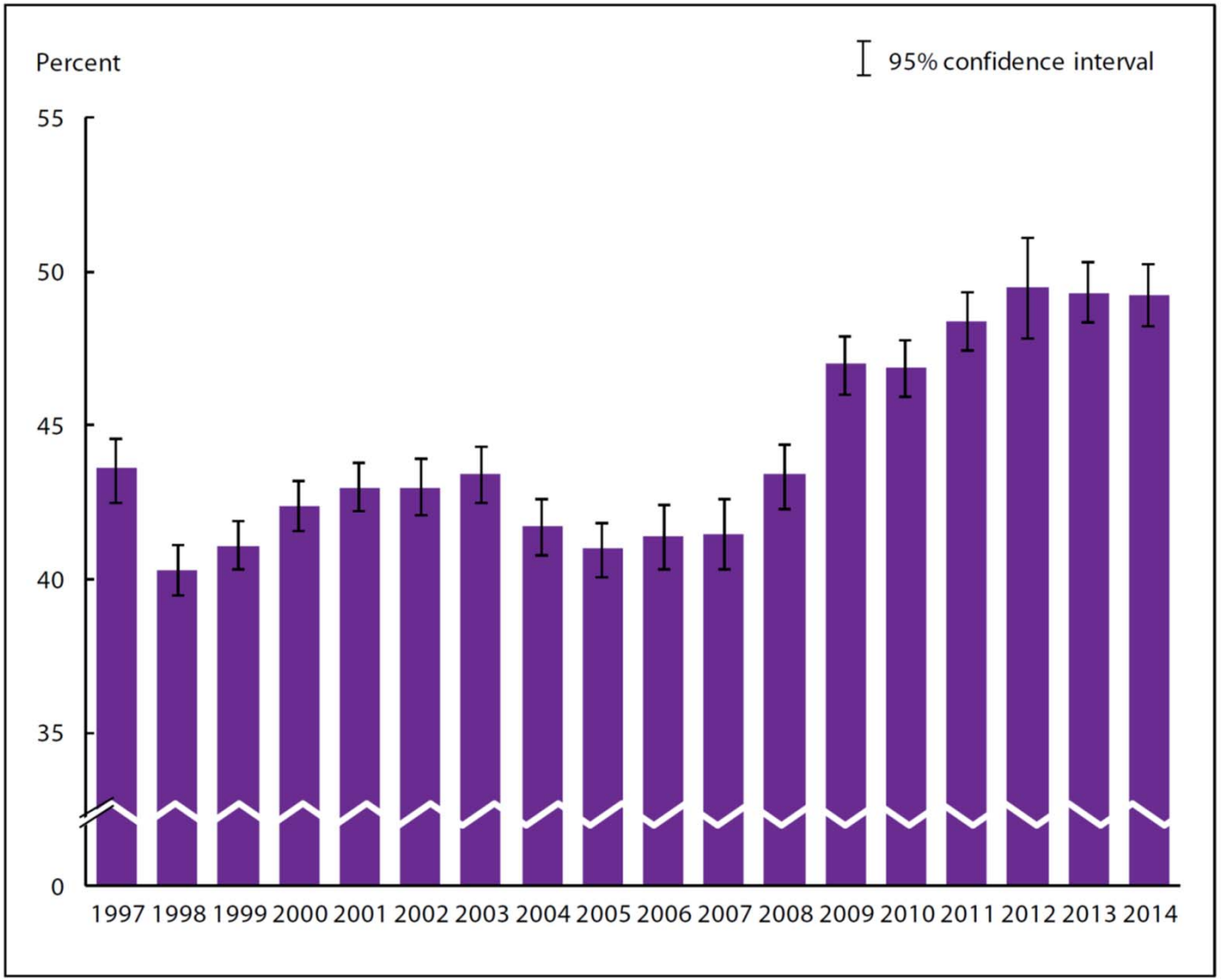
Physical activity reduces risk of death
Results of the NCI Cohort Consortium
660,000 participants



This infographic summarizes the findings as reported in the manuscript published by Arem, et.al. *JAMA Internal Medicine* 2015

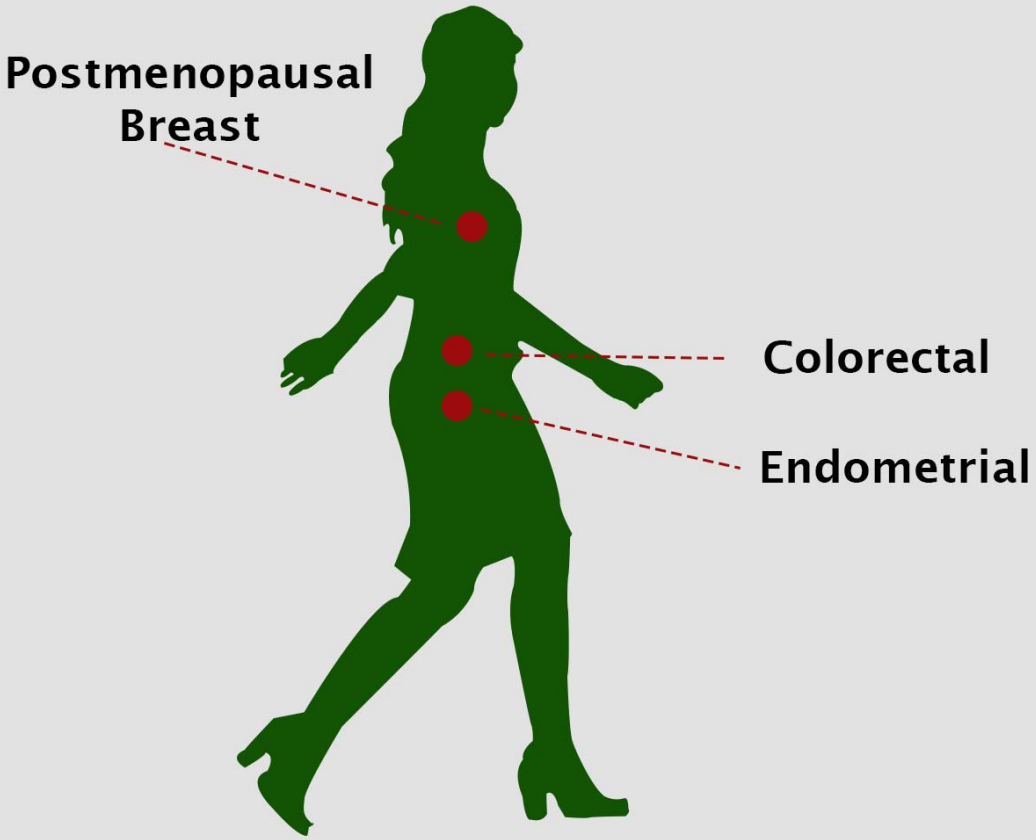
@NCIEpiTraining

Percent of US adults meeting recommended activity levels



CDC Faststats 2014

Physical activity is associated with lower risk of:



World Cancer Research Fund, 2007 and World Cancer Research Fund continuous update project

Original Investigation

Association of Leisure-Time Physical Activity With Risk of 26 Types of Cancer in 1.44 Million Adults

Steven C. Moore, PhD, MPH; I-Min Lee, MBBS, ScD; Elisabete Weiderpass, PhD; Peter T. Campbell, PhD; Joshua N. Sampson, PhD; Cari M. Kitahara, PhD; Sarah K. Keadle, PhD, MPH; Hannah Arem, PhD; Amy Berrington de Gonzalez, DPhil; Patricia Hartge, ScD; Hans-Olov Adami, MD, PhD; Cindy K. Blair, PhD; Kristin B. Borch, PhD; Eric Boyd, BS; David P. Check, BS; Agnès Fournier, PhD; Neal D. Freedman, PhD; Marc Gunter, PhD; Mattias Johannson, PhD; Kay-Tee Khaw, MD, MsC, PhD; Martha S. Linet, MD; Nicola Orsini, PhD; Yikyung Park, ScD; Elio Riboli, MD; Kim Robien, PhD; Catherine Schairer, PhD; Howard Sesso, ScD, MPH; Michael Spriggs, BS; Roy Van Dusen, MS; Alicja Wolk, DMSc; Charles E. Matthews, PhD; Alpa V. Patel, PhD

IMPORTANCE Leisure-time physical activity has been associated with lower risk of heart-disease and all-cause mortality, but its association with risk of cancer is not well understood.

OBJECTIVE To determine the association of leisure-time physical activity with incidence of common types of cancer and whether associations vary by body size and/or smoking.

DESIGN, SETTING, AND PARTICIPANTS We pooled data from 12 prospective US and European cohorts with self-reported physical activity (baseline, 1987-2004). We used multivariable Cox regression to estimate hazard ratios (HRs) and 95% confidence intervals for associations of leisure-time physical activity with incidence of 26 types of cancer. Leisure-time physical activity levels were modeled as cohort-specific percentiles on a continuous basis and cohort-specific results were synthesized by random-effects meta-analysis. Hazard ratios for high vs low levels of activity are based on a comparison of risk at the 90th vs 10th percentiles of

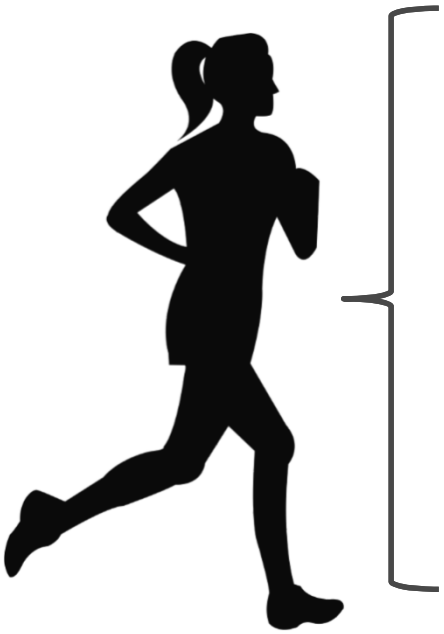
Invited Commentary
page 826

Supplemental content at
jamainternalmedicine.com

Moore et al. JAMA Intern Med 2016.

Types of physical activity included:

Leisure-time



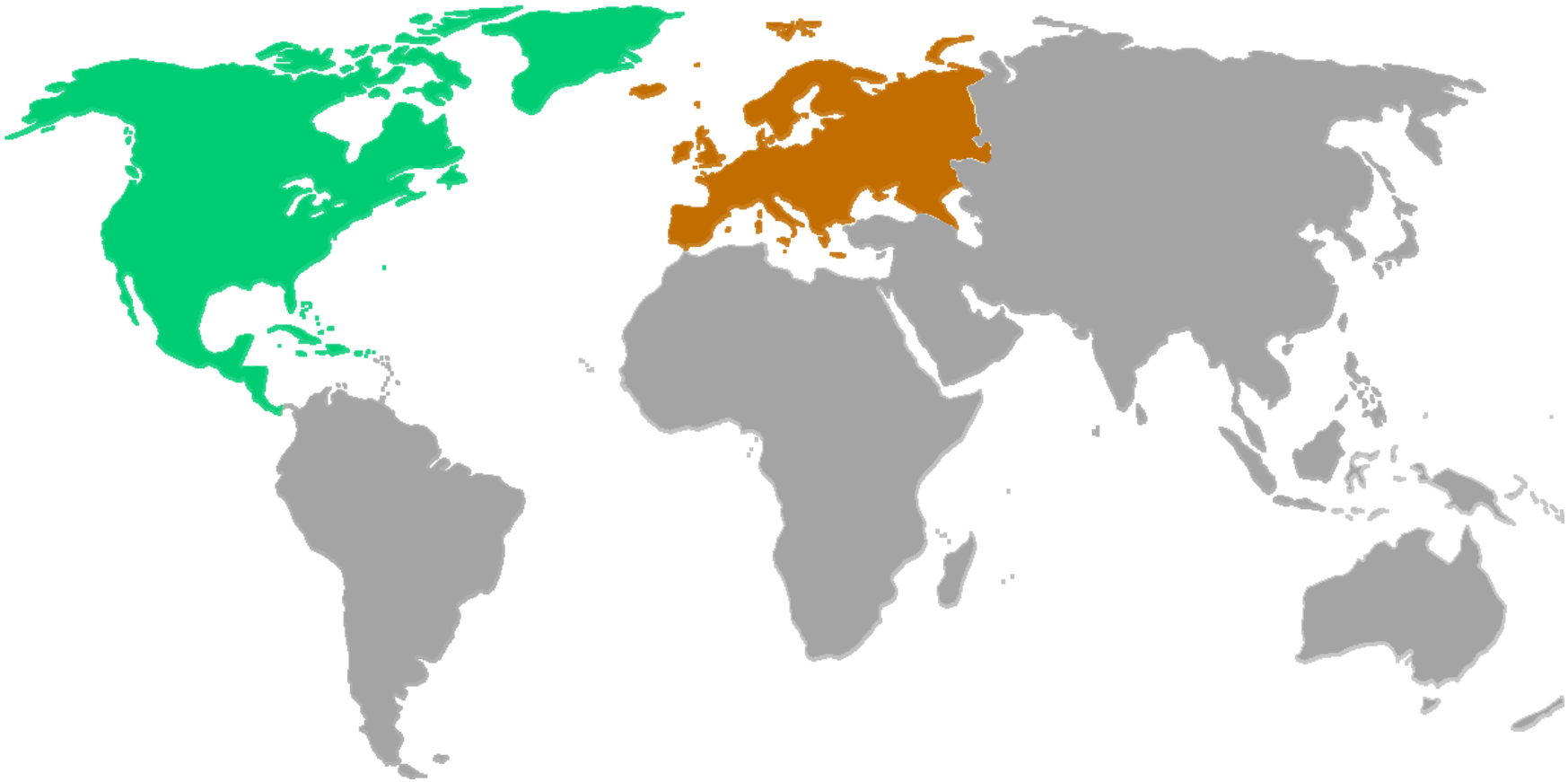
Moderate intensity
e.g. walking

Vigorous intensity
e.g. hiking, jogging

The Physical Activity Collaboration of the NCI Cohort Consortium

8 US Cohorts

4 European Cohorts



The Physical Activity Collaboration of the NCI Cohort Consortium

8 US Cohorts

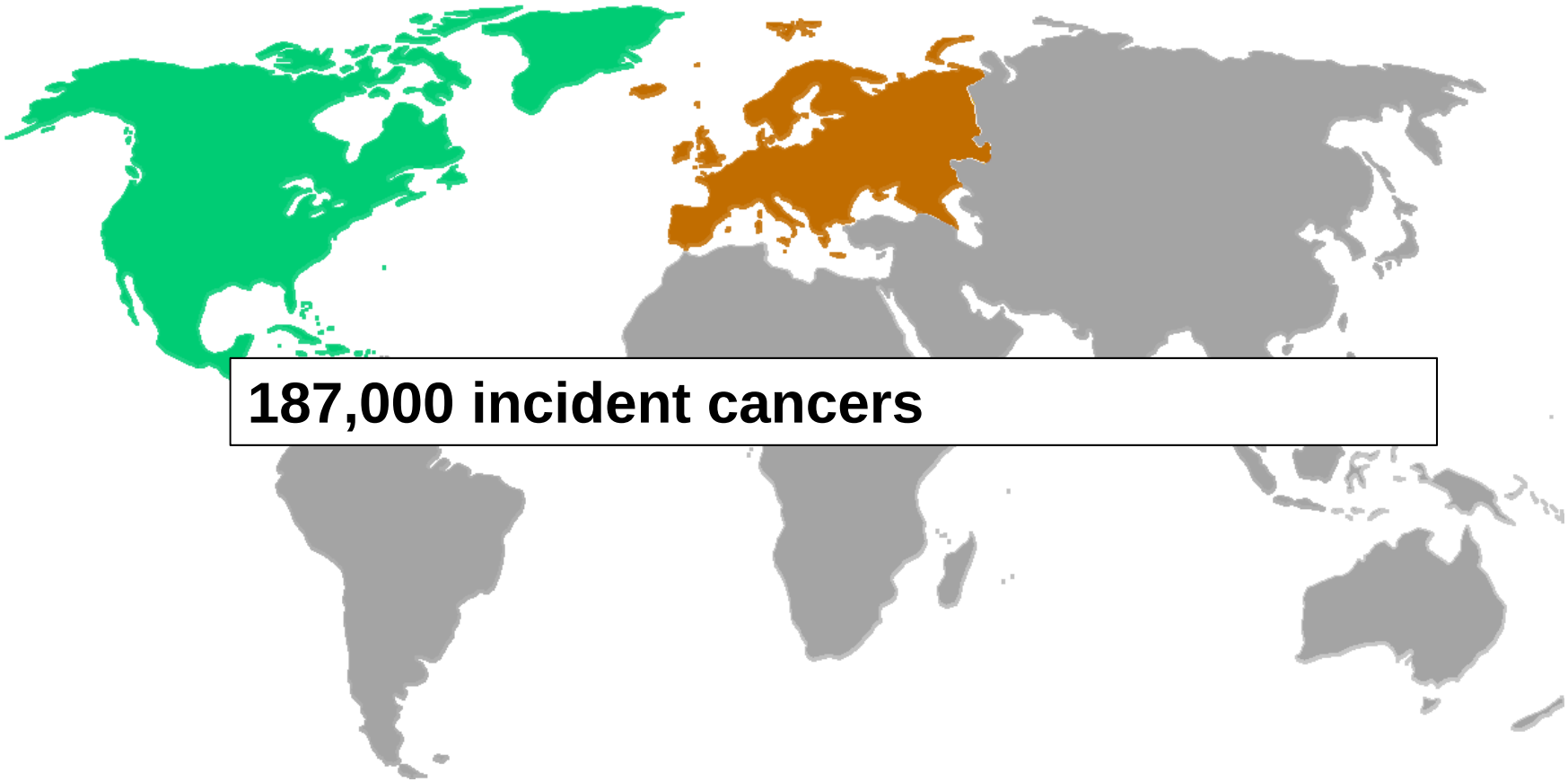
4 European Cohorts

1.44 million participants
55% women
Age 50-65 years
Activity levels comparable to U.S. population
~ 2.5 hrs/wk walking or
~ 1 hr/wk jogging

The Physical Activity Collaboration of the NCI Cohort Consortium

8 US Cohorts

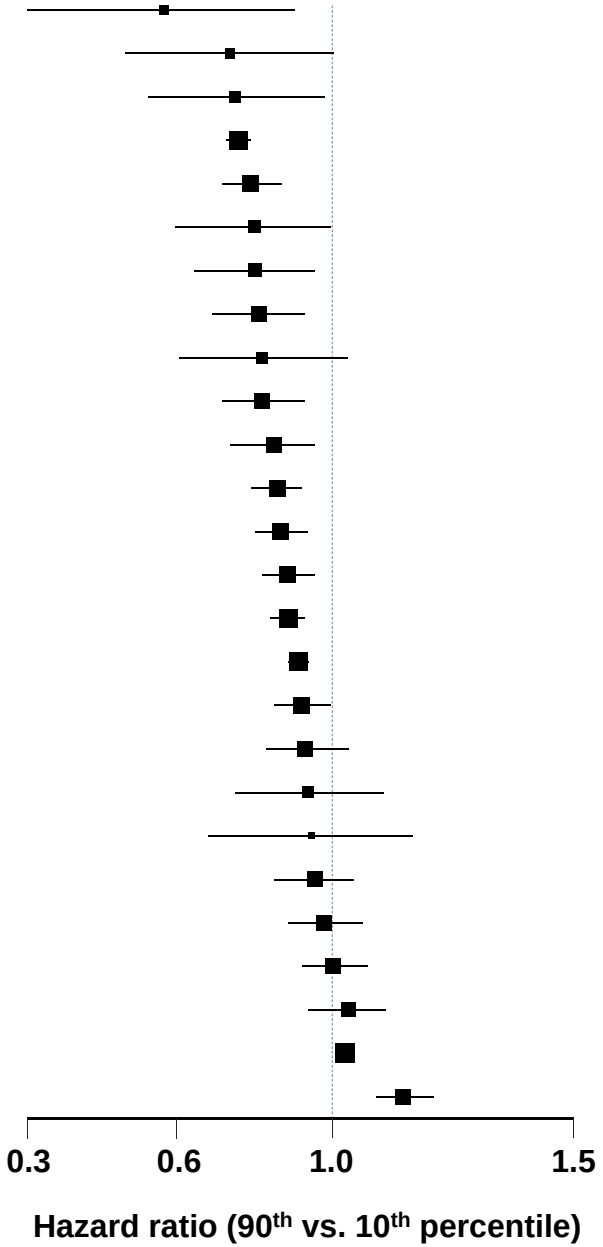
4 European Cohorts



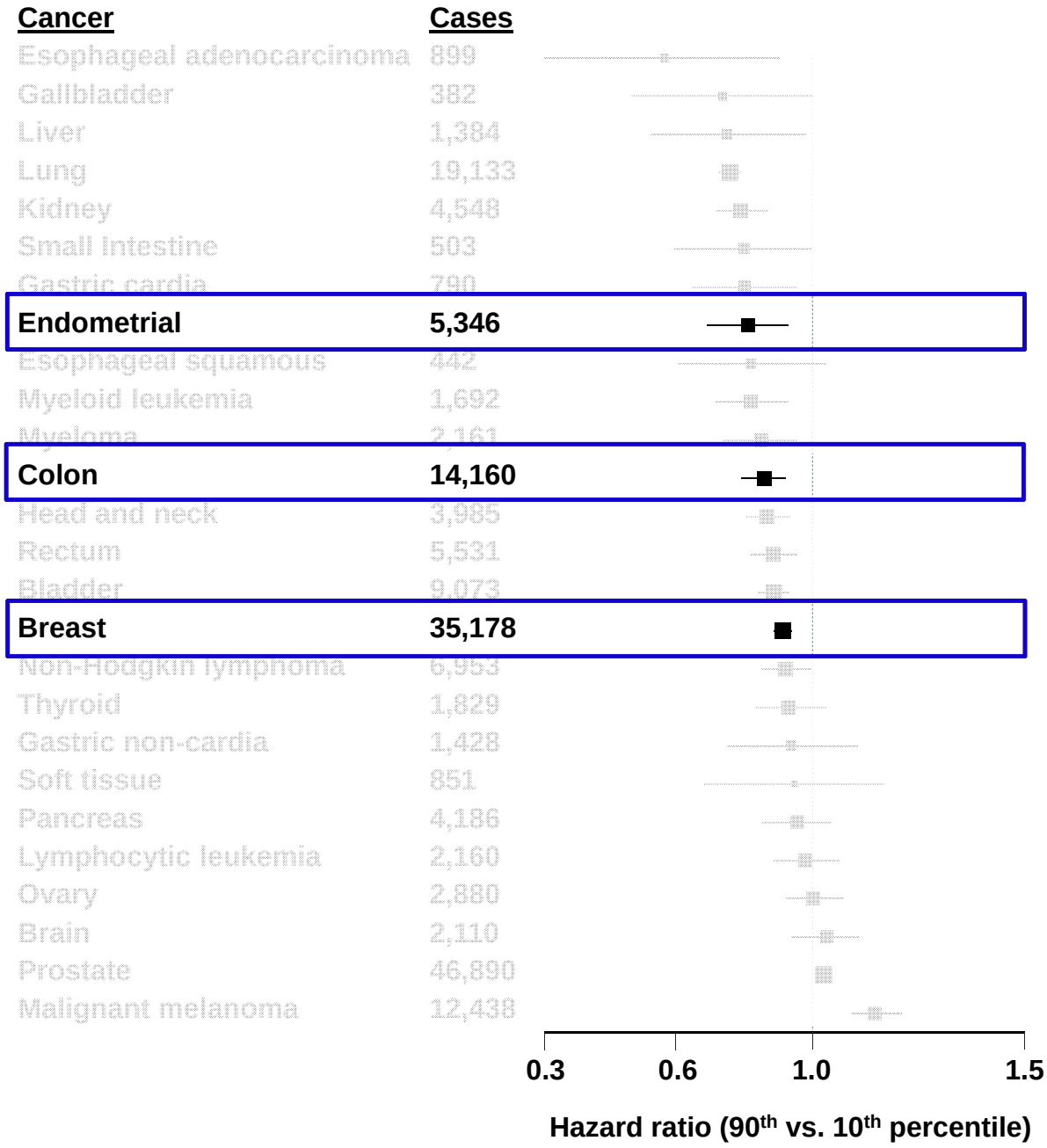
187,000 incident cancers

Main results

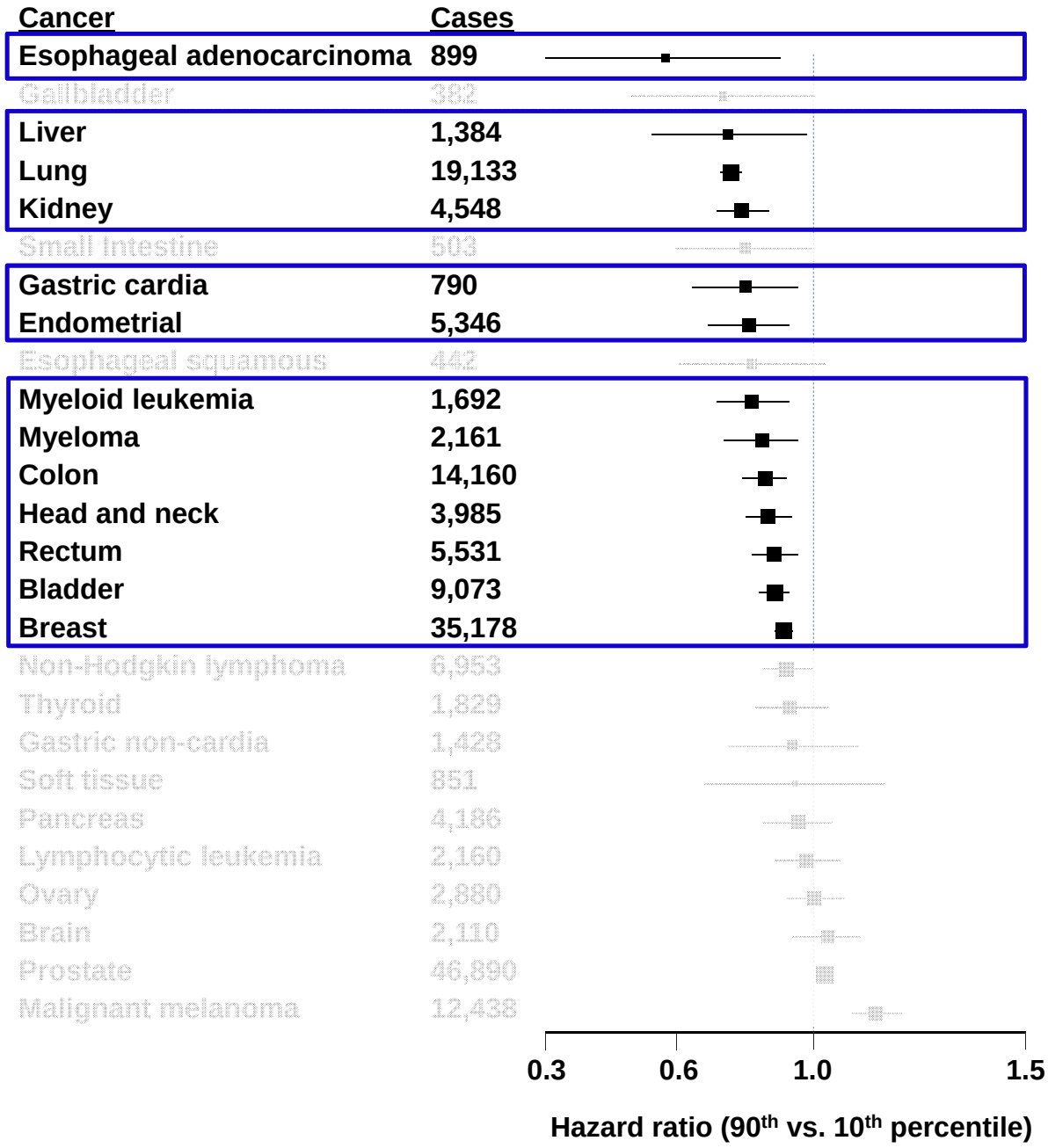
Cancer	Cases
Esophageal adenocarcinoma	899
Gallbladder	382
Liver	1,384
Lung	19,133
Kidney	4,548
Small Intestine	503
Gastric cardia	790
Endometrial	5,346
Esophageal squamous	442
Myeloid leukemia	1,692
Myeloma	2,161
Colon	14,160
Head and neck	3,985
Rectum	5,531
Bladder	9,073
Breast	35,178
Non-Hodgkin lymphoma	6,953
Thyroid	1,829
Gastric non-cardia	1,428
Soft tissue	851
Pancreas	4,186
Lymphocytic leukemia	2,160
Ovary	2,880
Brain	2,110
Prostate	46,890
Malignant melanoma	12,438



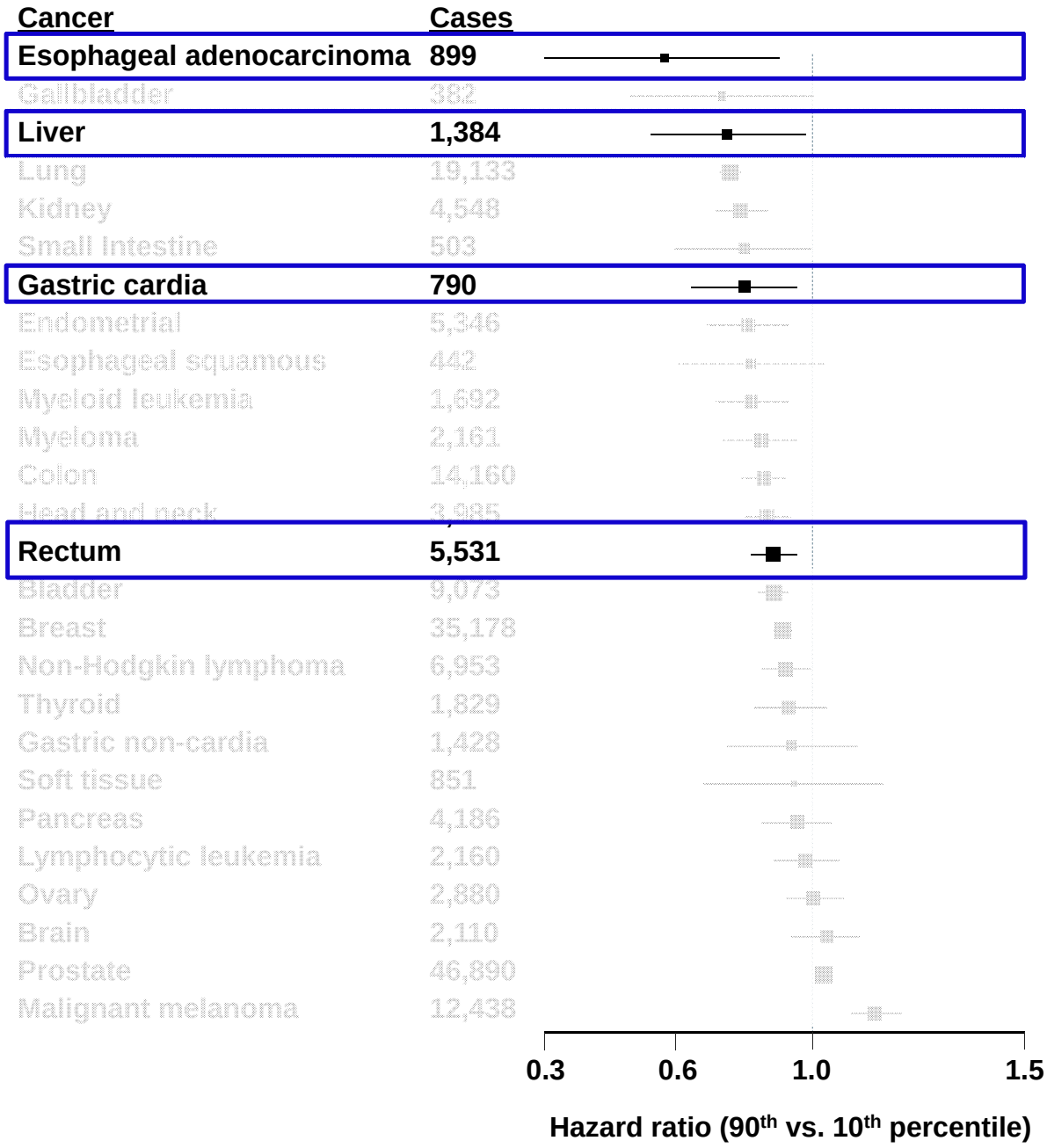
Previously established associations



Physical activity associated with lower risk of 10 additional cancers



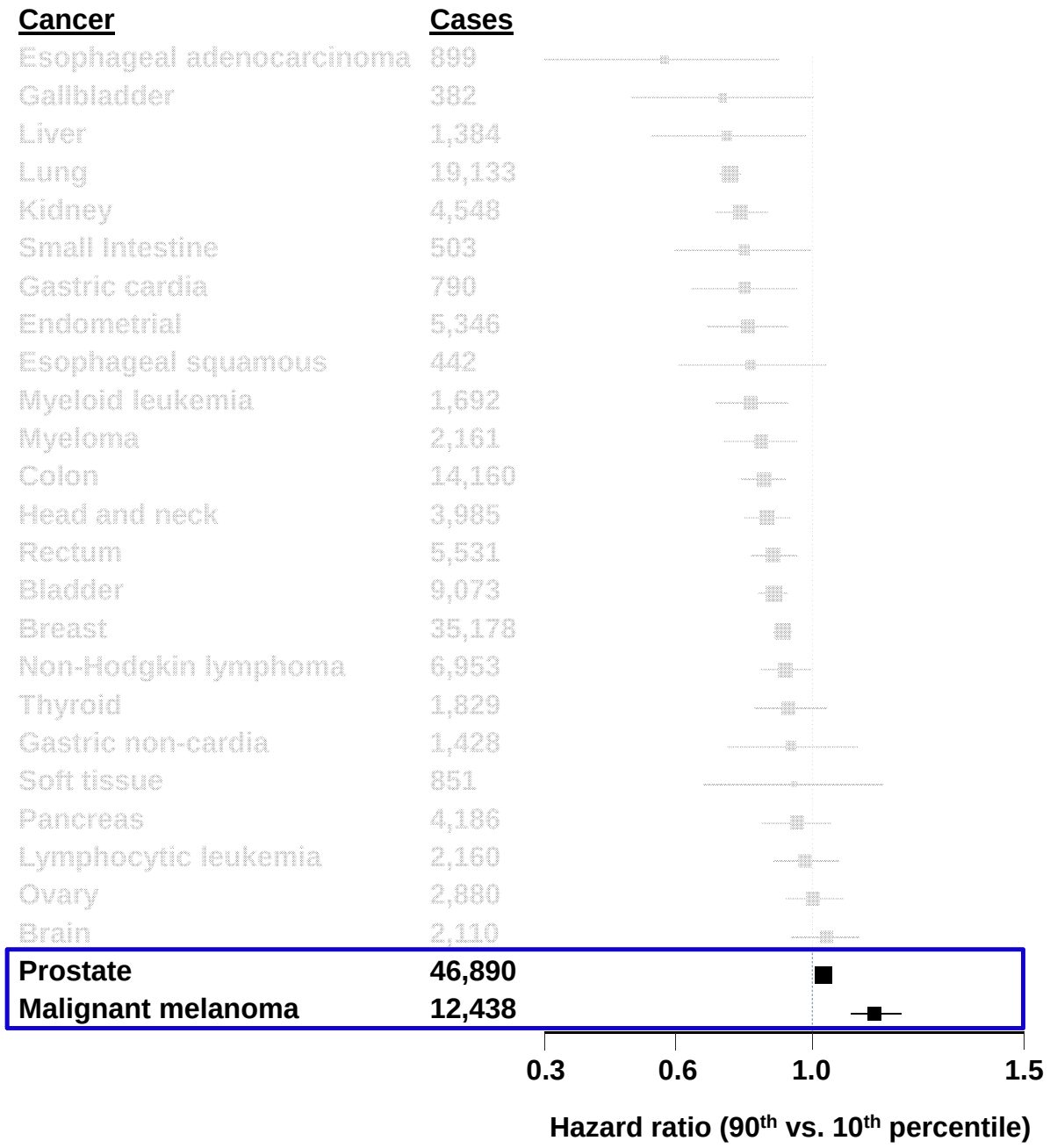
Physical activity associated with lower risk of digestive cancers



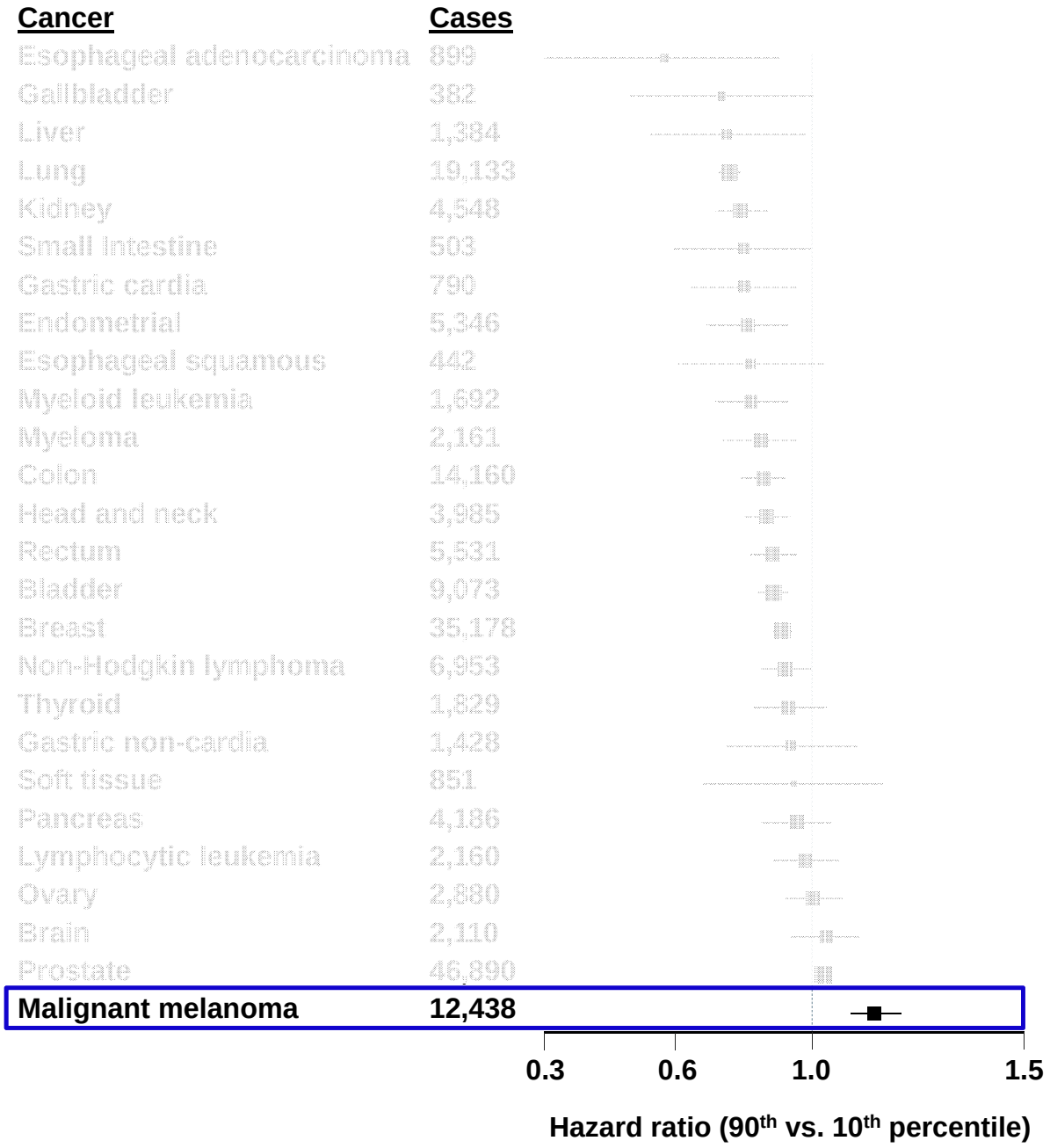
Physical activity associated with higher risk of prostate cancer and melanoma

..Advanced <u>prostate cancer</u>

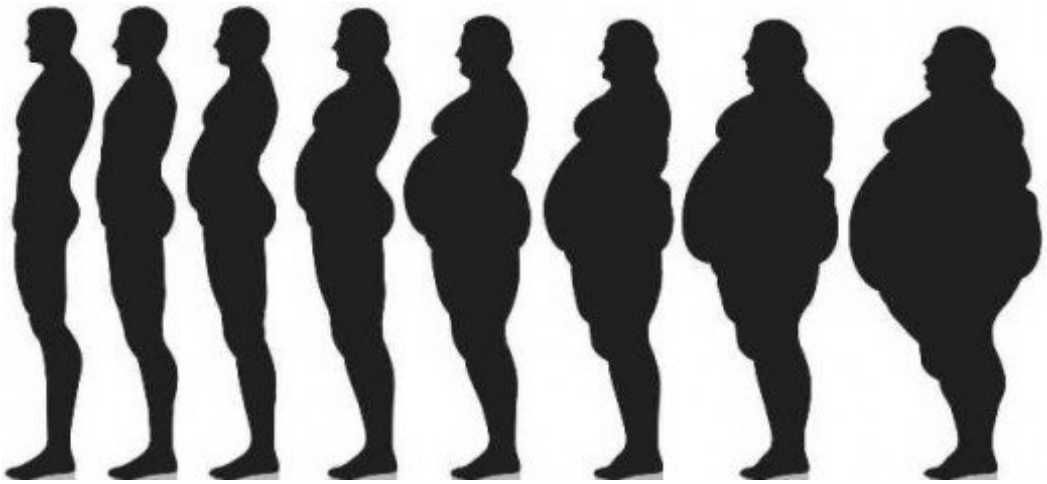
Hazard ratio=0.99
95% CI: 0.88-1.10



Physical activity associated with higher risk of prostate cancer and melanoma



Is it obesity?



Associations before BMI adjustment

Cancer	Cases
Esophageal adenocarcinoma	899
Liver	1,384
Lung	19,133
Kidney	4,548
Gastric cardia	790
Endometrial	5,346
Myeloid leukemia	1,692
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Rectum	5,531
Bladder	9,073
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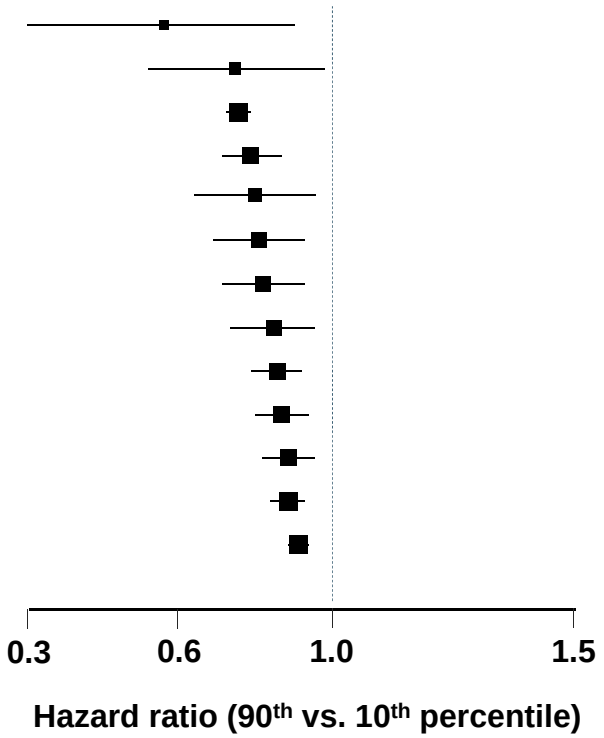
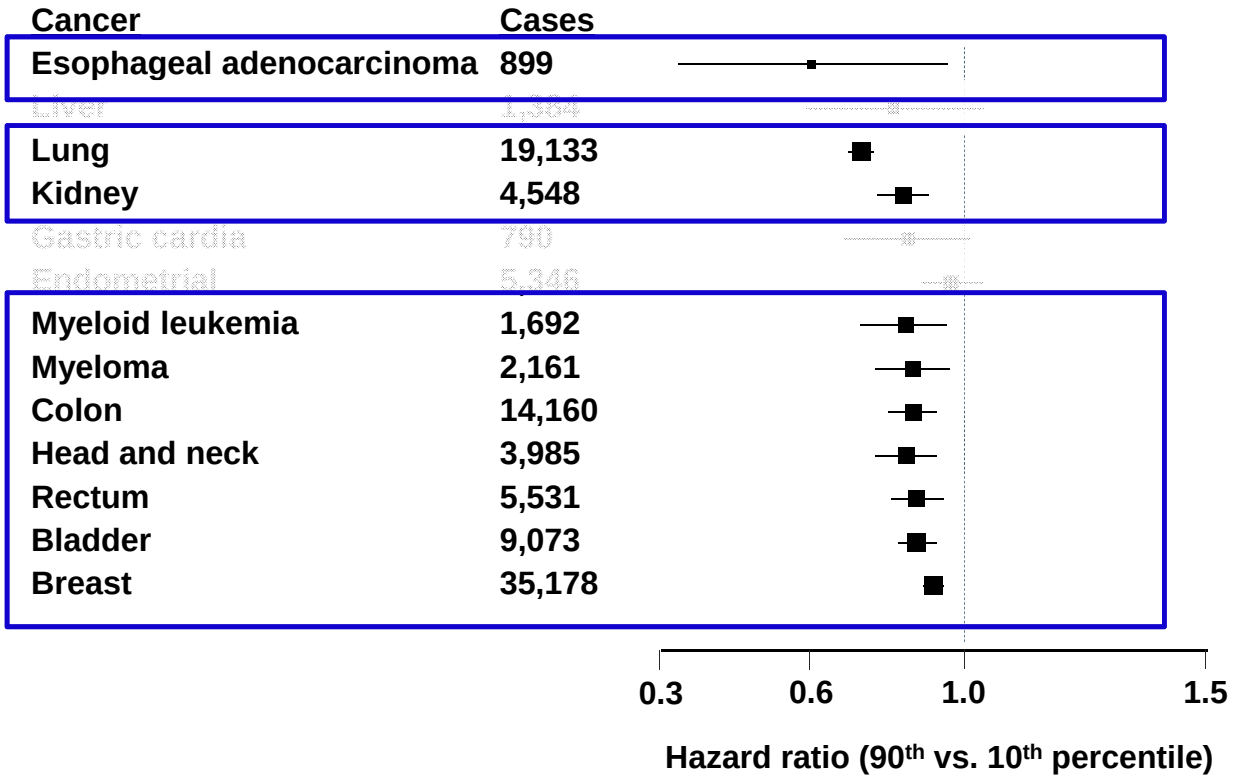
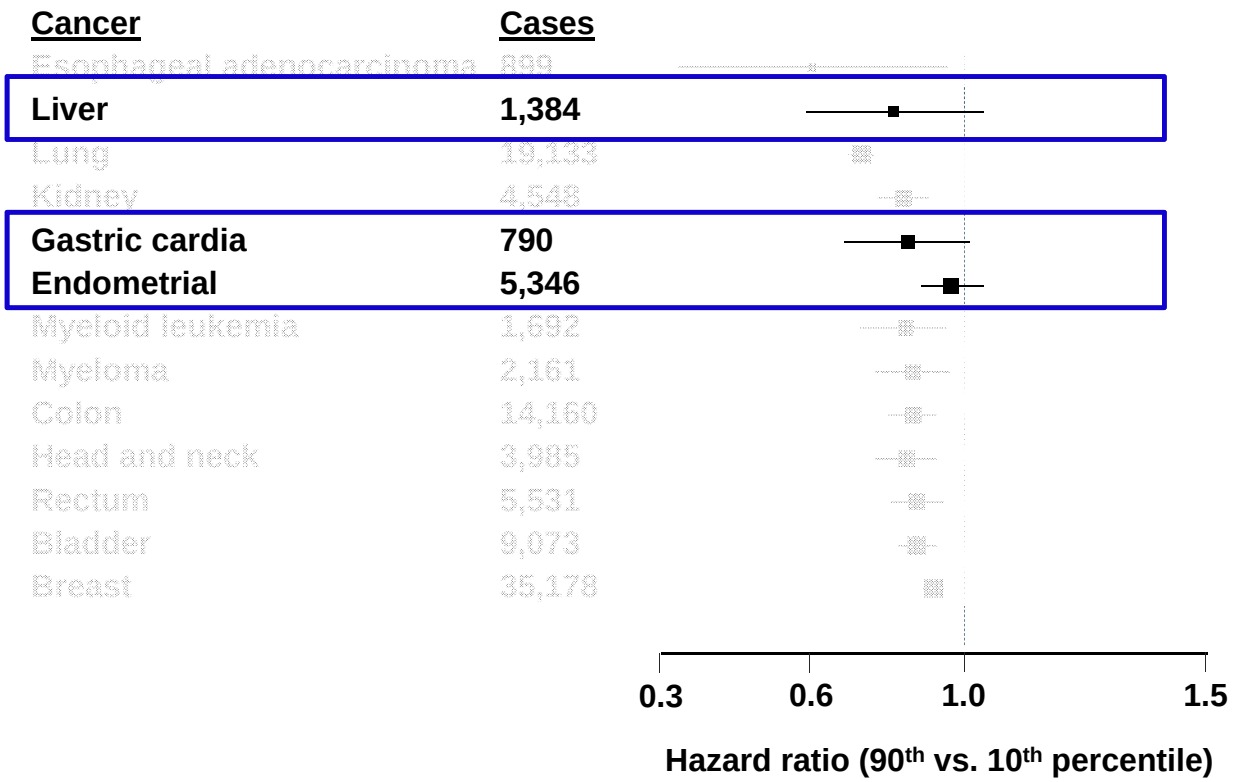


Associations after BMI adjustment



BMI-Independent associations

Associations after BMI adjustment



Associations with and without BMI adjustment

Cancer	HR (95% CI) Not BMI Adjusted	HR (95% CI) BMI Adjusted
Liver	0.73 (0.55-0.98)	0.81 (0.61-1.09)
Gastric cardia	0.78 (0.64-0.95)	0.85 (0.69-1.04)
Endometrial	0.79 (0.68-0.92)	0.98 (0.89-1.09)

Associations with and without BMI adjustment

Cancer	HR (95% CI) Not BMI Adjusted	HR (95% CI) BMI Adjusted
Liver	0.73 (0.55-0.98)	0.81 (0.61-1.09)
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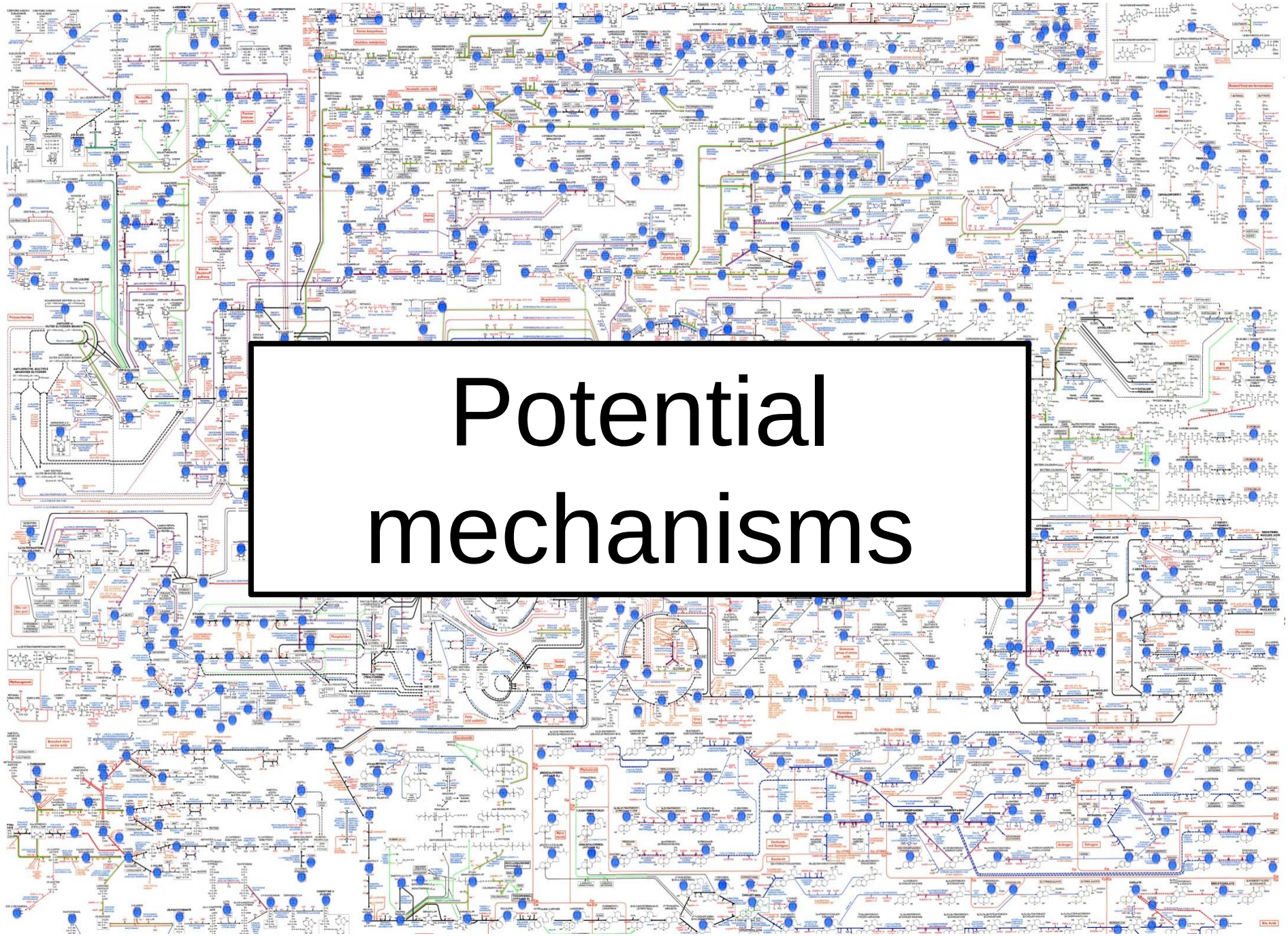
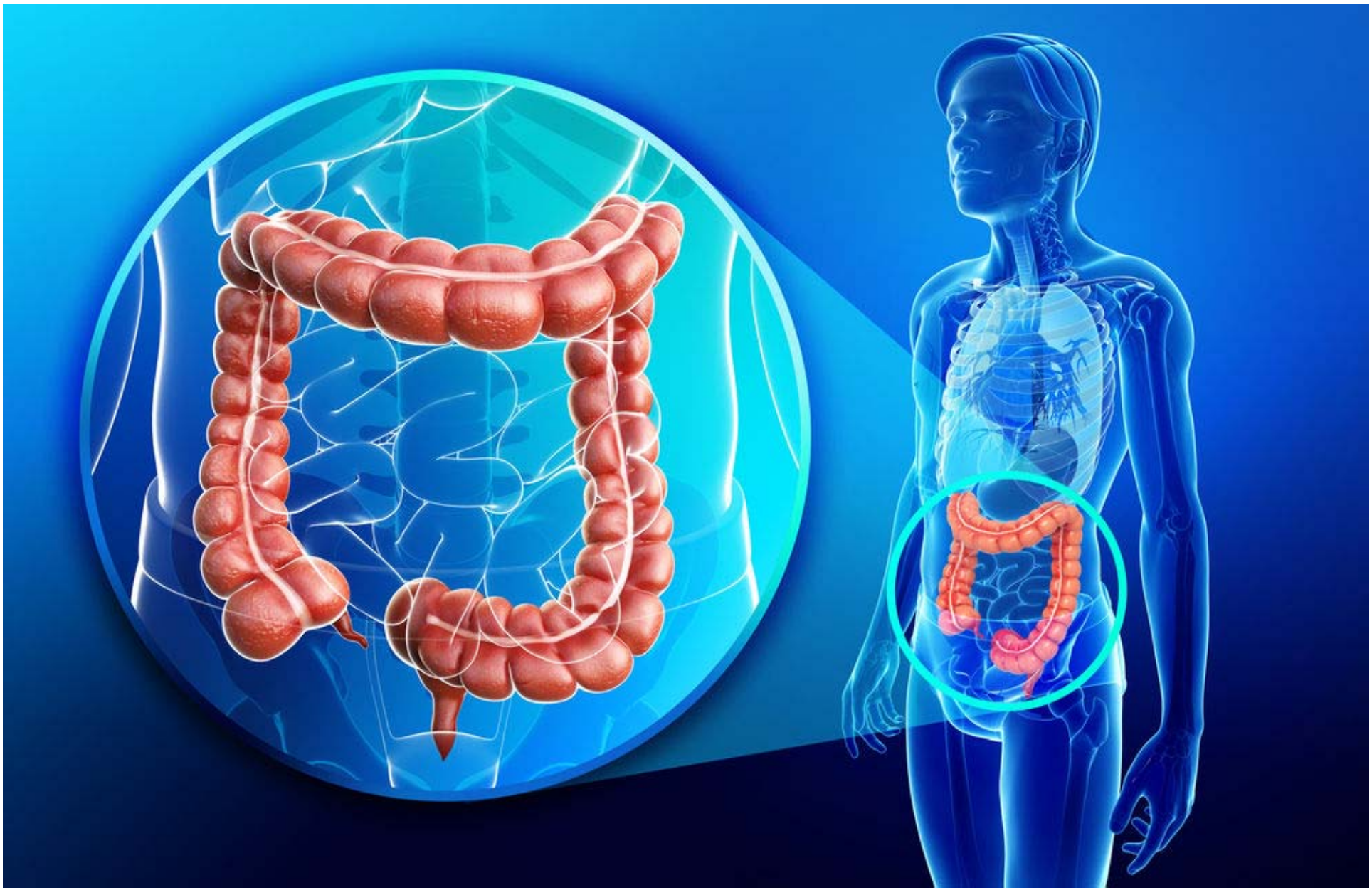
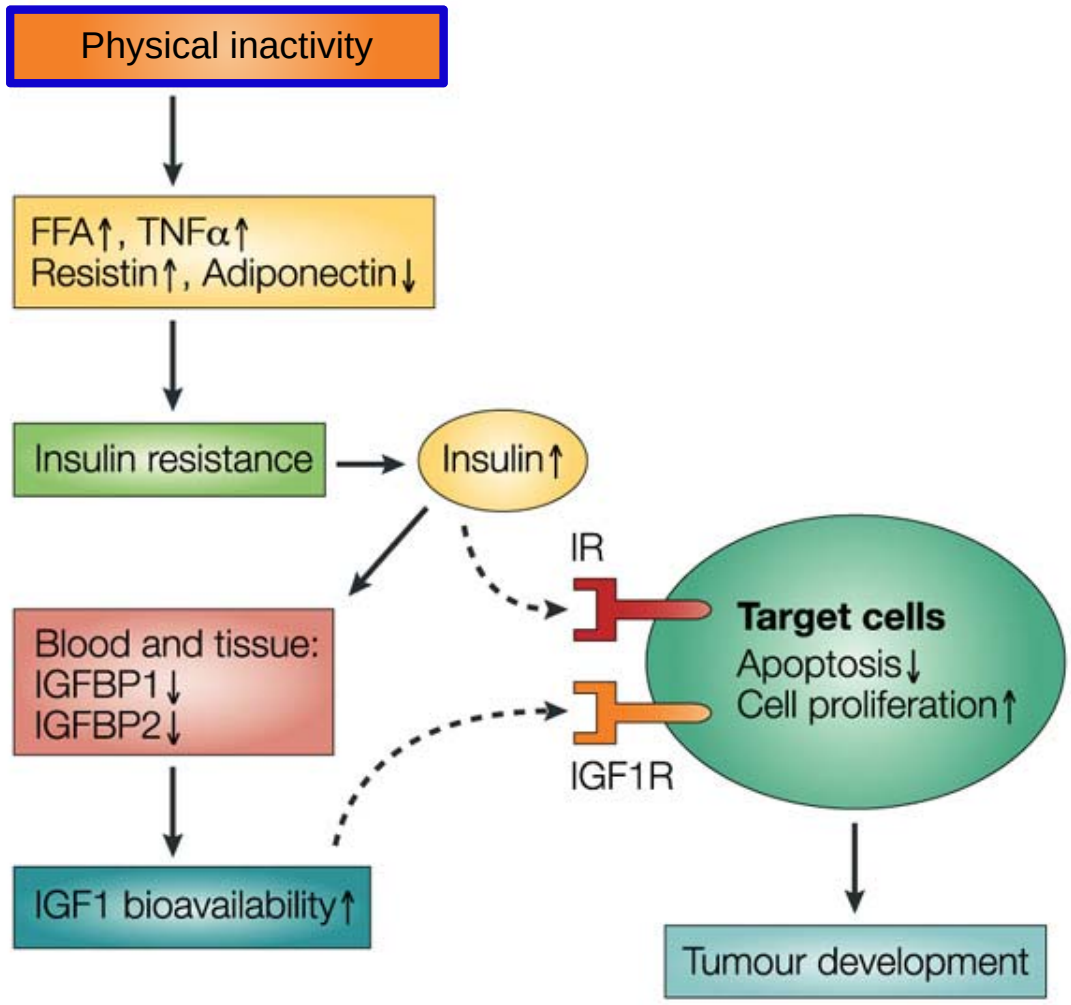

Potential
mechanisms

Mechanism: Increased gut motility

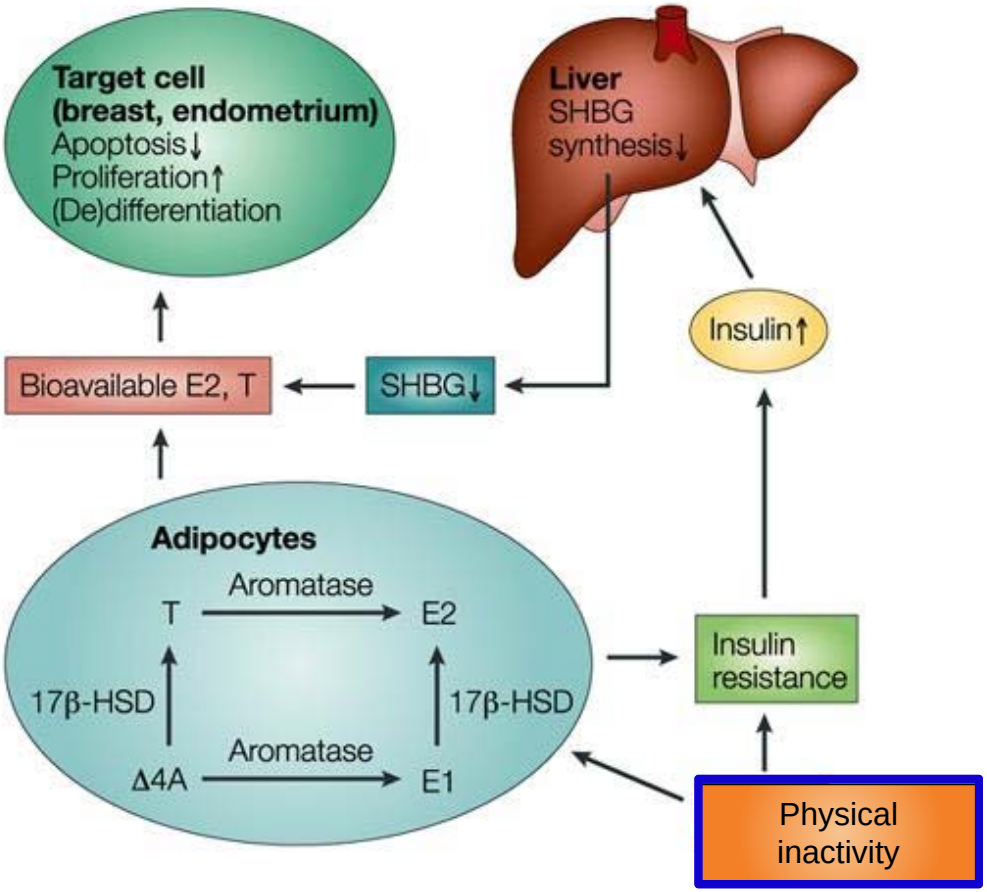


Mechanism: Insulin and metabolic effects



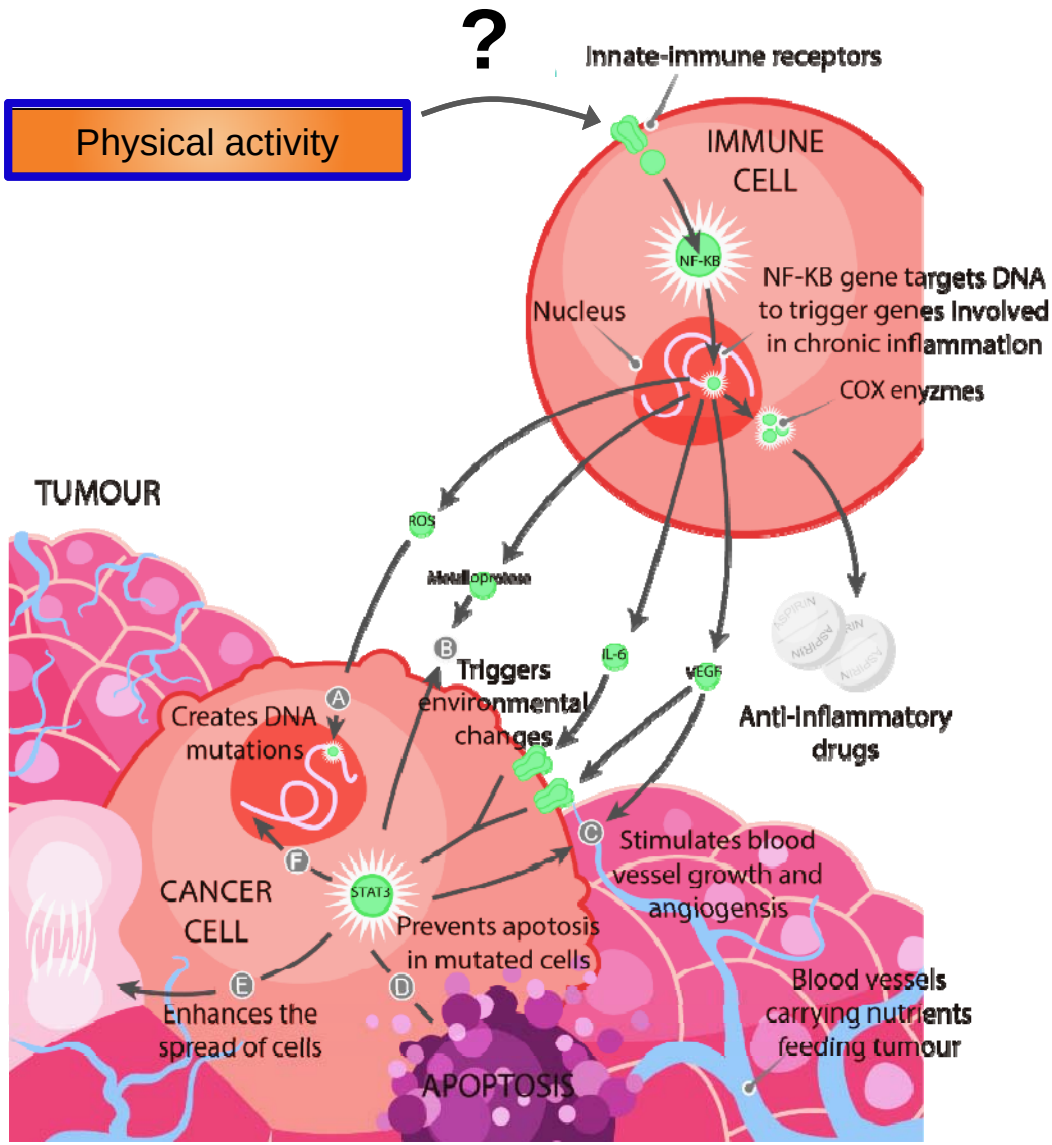
Calle and Kaaks. Nat Rev Cancer. 2004
Renehan et al. Nat Rev Cancer. 2015

Mechanism: Sex steroid hormones

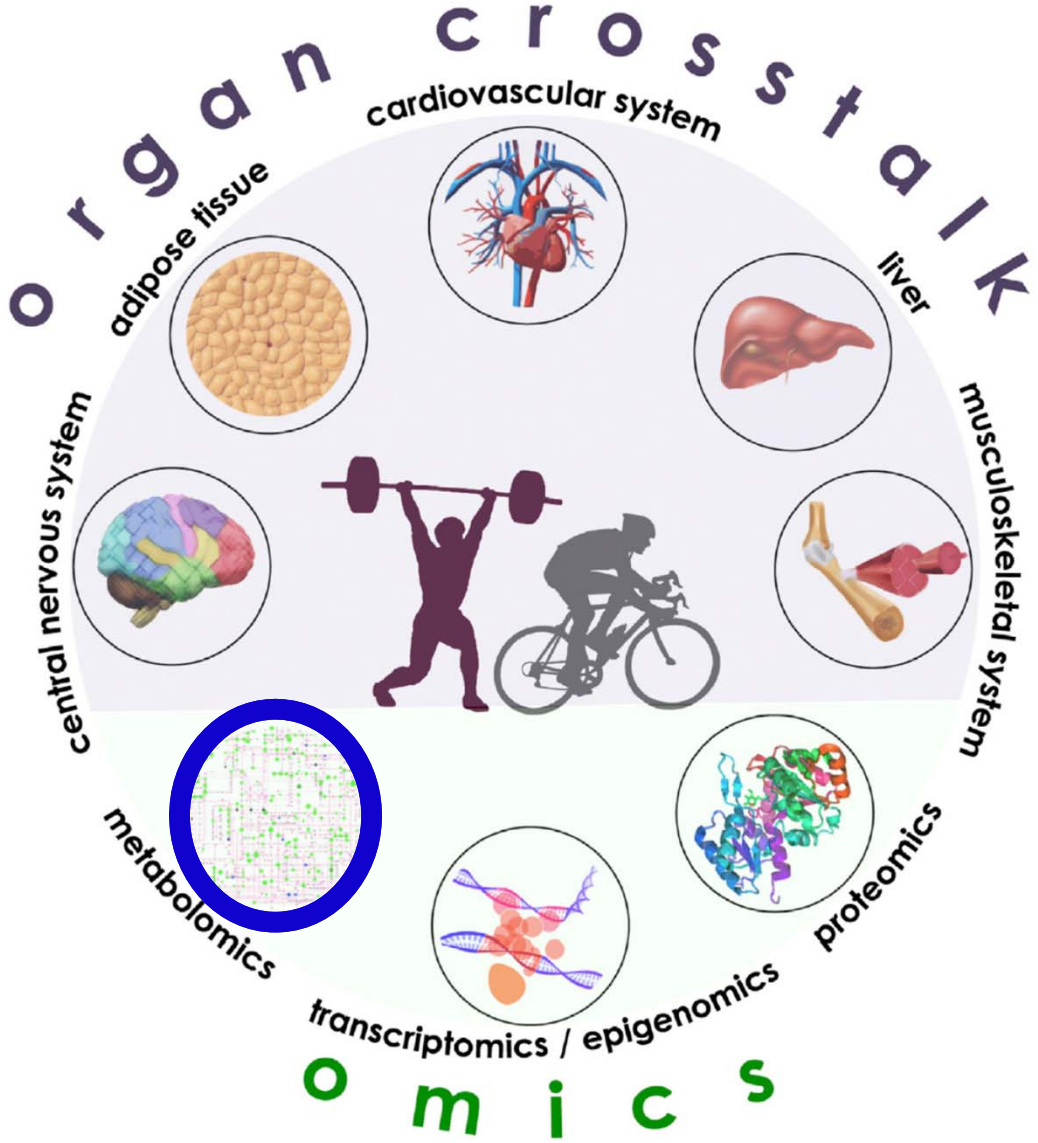


Calle and Kaaks. Nat Rev Cancer. 2004
Renehan et al. Nat Rev Cancer. 2015

Mechanism: Chronic inflammation



Physical activity mechanisms act at multiple levels

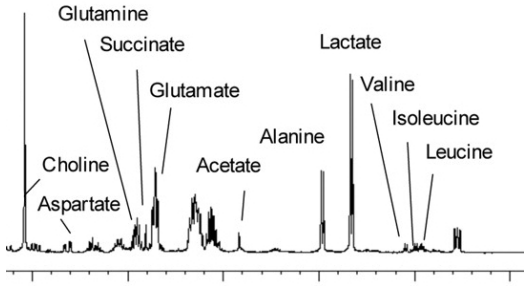


Zierath and Wallberg-Henriksson. Cell Metab 2015

Metabolomics

Blood

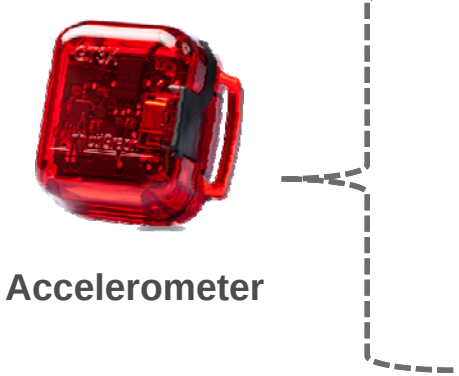
GC- and LC-
Mass spectrometry



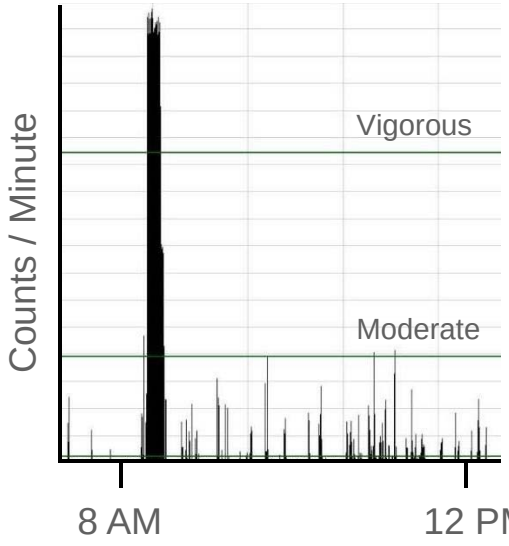
Hundreds of metabolites

Accelerometer-based physical activity study

- 339 Shanghai men and women (mean age 60)



Accelerometer

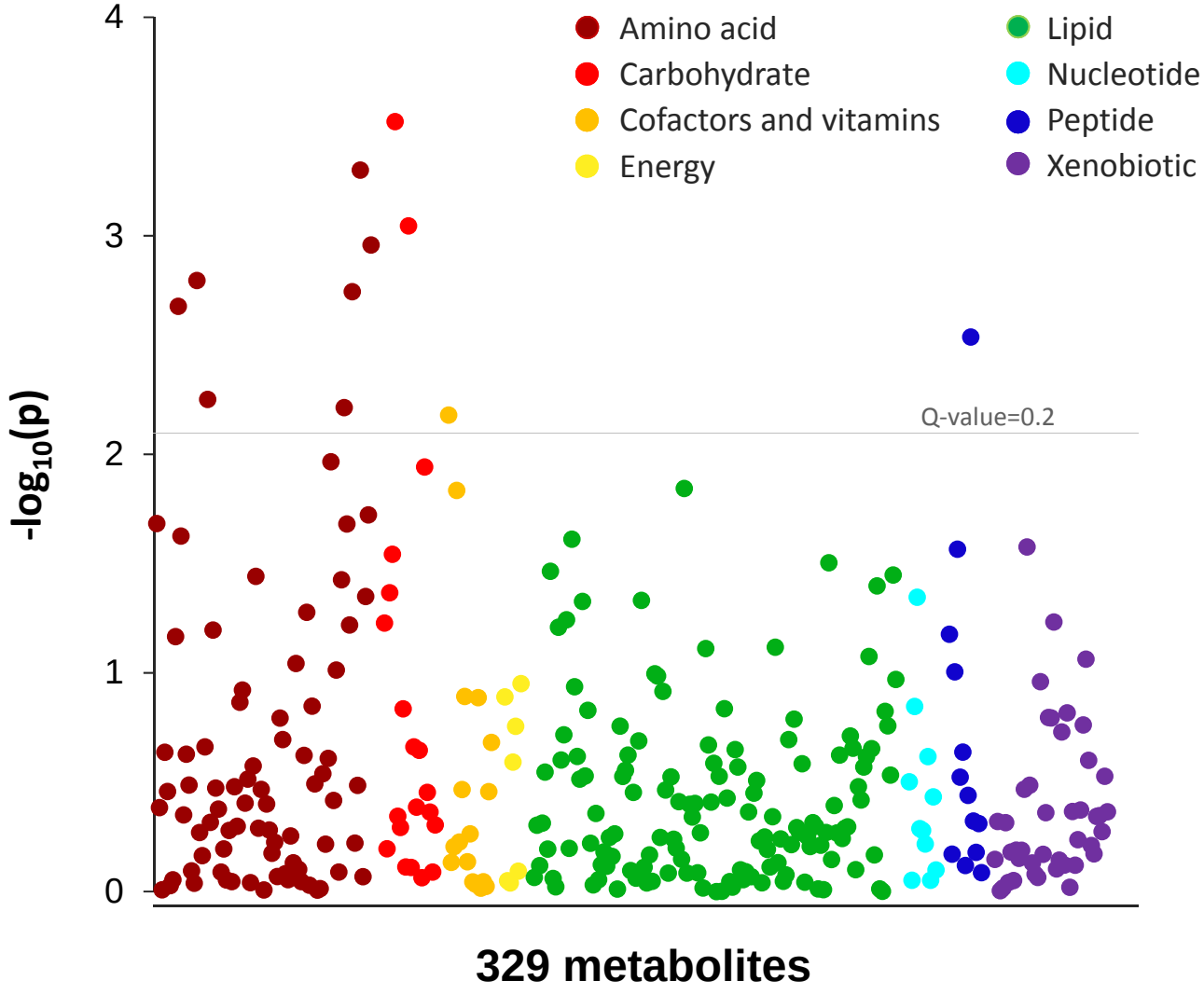


1 week in every 3 months during 1 year

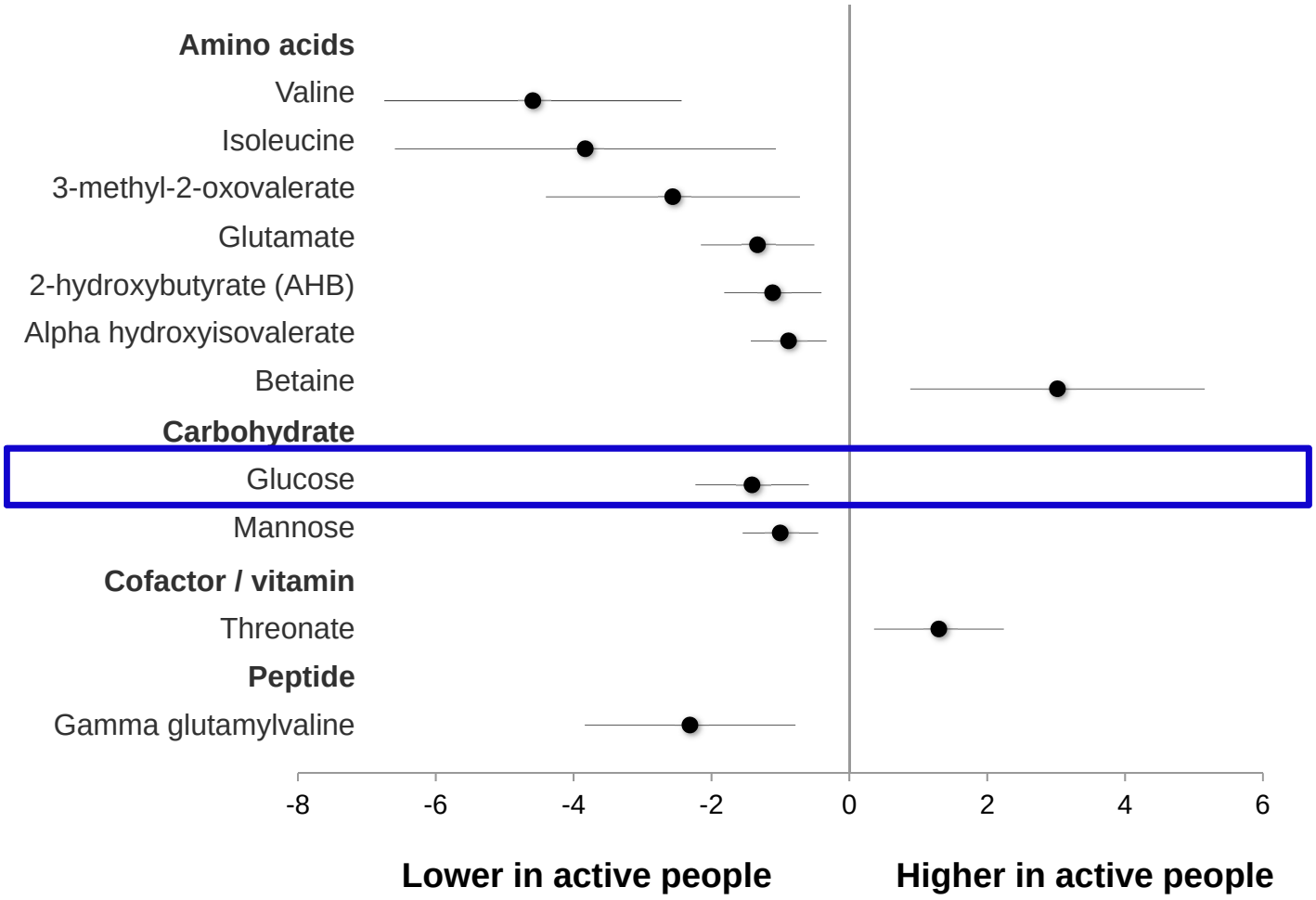
Average 1 year physical activity + fasting plasma

Xiao, Moore, et al. IJE 2016.

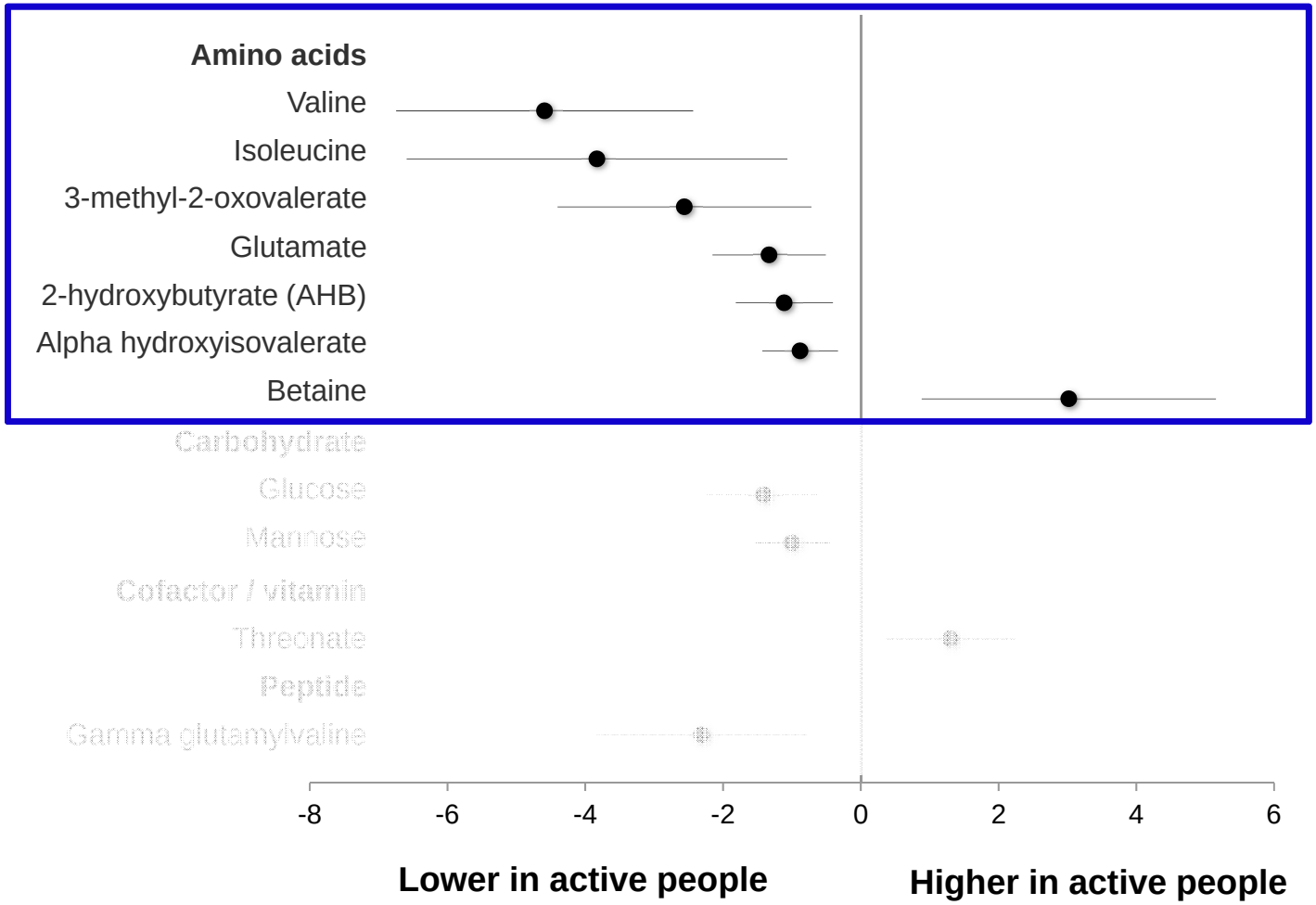
Manhattan plot of metabolite and physical activity associations



Physical activity is associated with 11 metabolites



Physical activity is associated with lower levels of amino acids

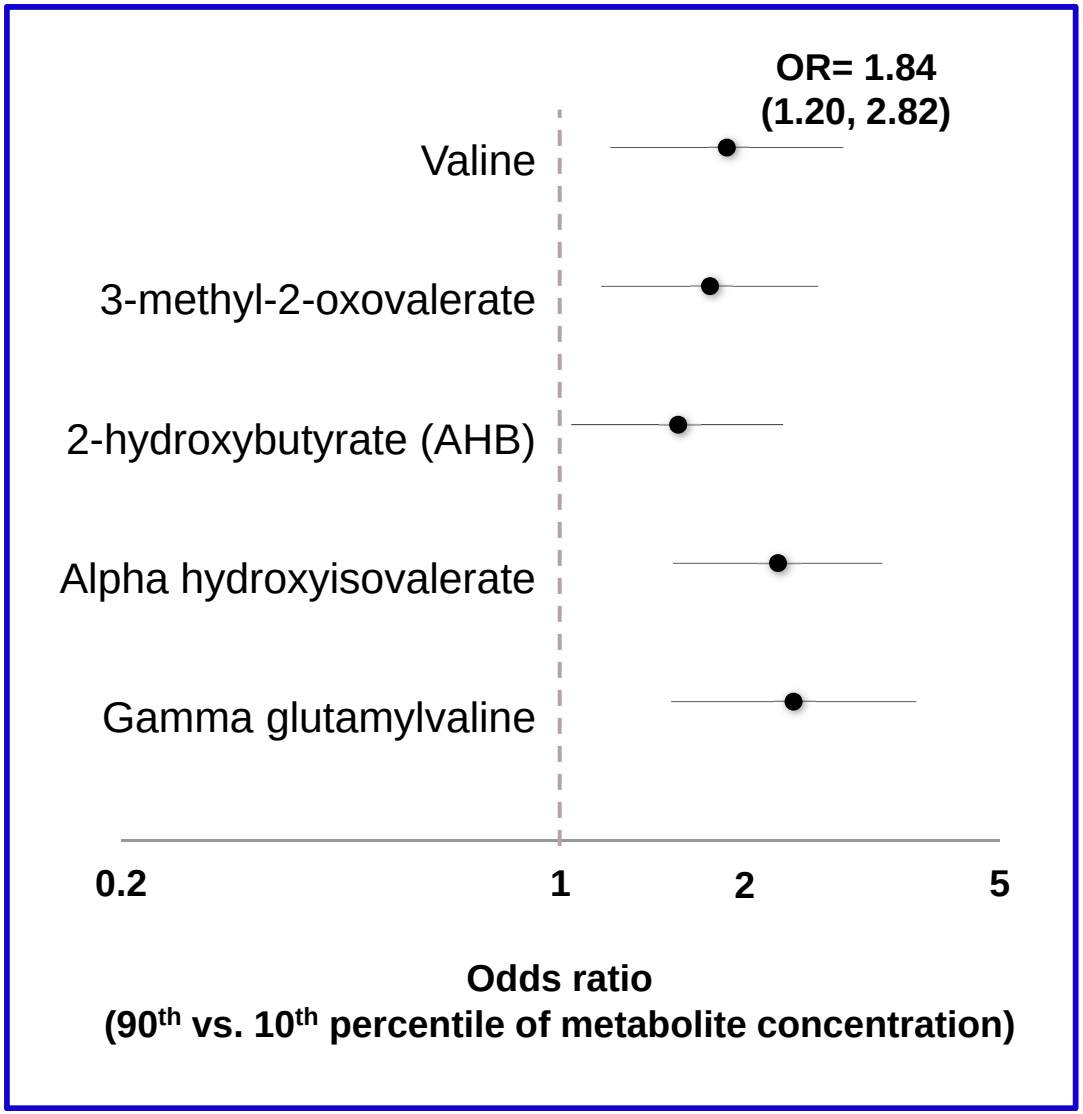


Metabolites and breast cancer risk

- Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
- 418 estrogen receptor positive cases and 418 controls
- Pre-diagnostic serum (median 7 yr follow-up)

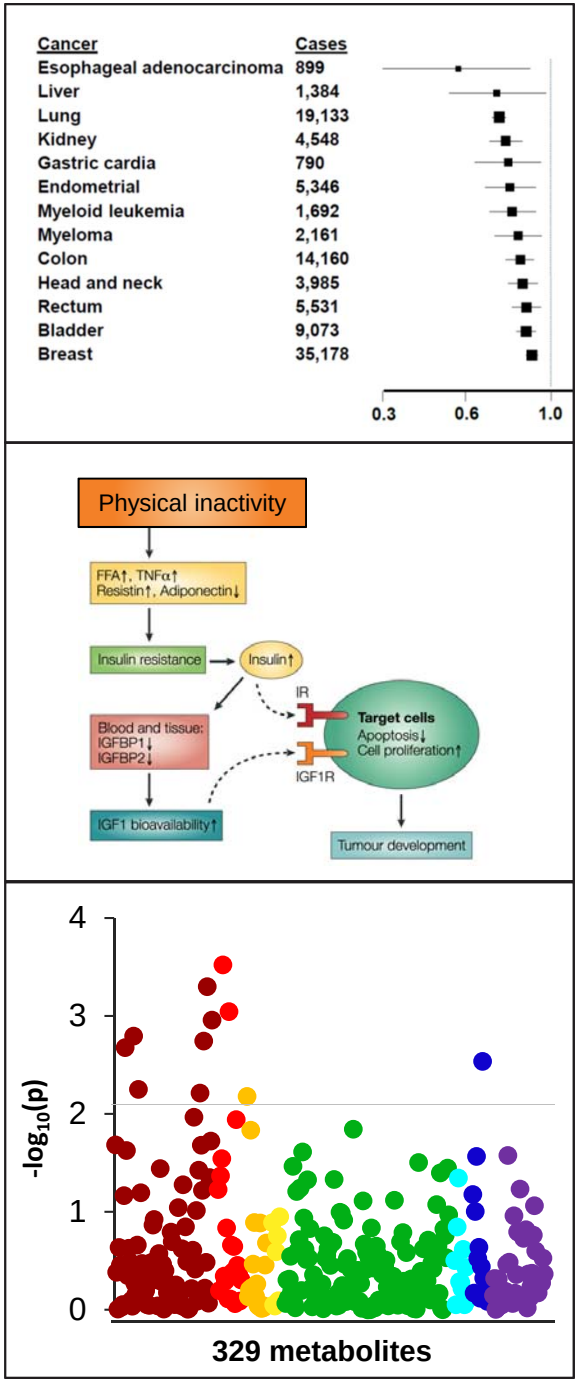
Moore et al. In preparation.

Amino acid metabolites associated with higher ER+ breast cancer risk



Conclusions

- Physical activity was associated with lower risk of 13 different types of cancer
- Potential mechanisms include insulin, sex-steroid, and inflammatory pathways
- New high-throughput approaches may reveal novel mechanistic clues



Physical activity has a broad-based role in health

This infographic summarizes the findings as reported in the manuscript published by Arem, et.al. *JAMA Internal Medicine* 2015

@NCIEpiTraining

Acknowledgments

Writing group
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Trisha Hartge
Amy Berrington
Cari Kitahara

Cohort PIs
Breast Cancer Detection Demonstration
Cancer Prevention Study II
Cohort of Swedish Men
European Prospective Investigation into Cancer
Iowa Women’s Health Study
NIH-AARP Diet and Health Study
Physician’s Health Study
Prostate, Lung, Colon, and Ovarian Cancer
Swedish Mammography Cohort
U.S. Radiologist Technologists Study
Women’s Health Study
Women’s Lifestyle and Health Study

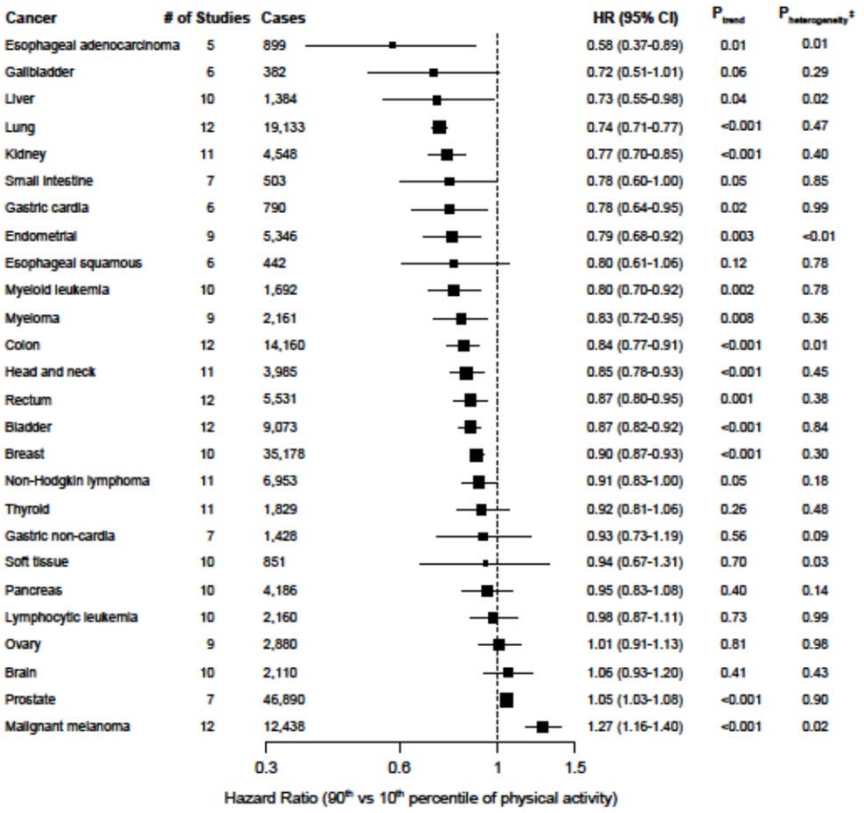
www.cancer.gov www.cancer.gov/espanol

Study design & methods: physical activity

Cohort	MET-hr/wk median	MET-hr/wk IQR
CPSII	8	4 – 18
COSM	8	4 – 16
PLCO	8	2 – 12
SMC	8	4 – 8
USRT	8	2 – 22
WHS	8	2 – 17
WLH	11	3 – 23

Complete results
(double-click figure)

Figure 1. Summary multivariable* hazard ratios (HR) and 95% confidence intervals (CI) for a higher (90th percentile) versus lower (10th percentile) level of leisure-time physical activity by cancer type†



* Multivariable models were adjusted for age, gender, smoking status (never, former, current), alcohol consumption (0, 0.1-14.9, 15.0-29.9 and 30.0+ g/day), education (did not complete high school, completed high school, post high-school training, some college, completed college), and race/ethnicity (white, black, other). Models for endometrial, breast, and ovarian cancers are additionally adjusted for hormone replacement therapy use (ever, never), oral contraceptive use (ever, never), age at menarche (<10 years, 10-11 years, 12-13 years, 14+ years), age at menopause (premenopausal, 40-44 years, 45-49 years, 50-54 years, 55+ years), and parity (0 children, 1 child, 2 children, 3+ children).

† The Surveillance Epidemiology and End Results site recode and the International Classification of Diseases for Oncology, Third Edition code corresponding to each cancer type are shown in Supplementary Table 1.

‡ $P_{heterogeneity}$ indicates the P-value for heterogeneity of hazard ratios across participating studies.

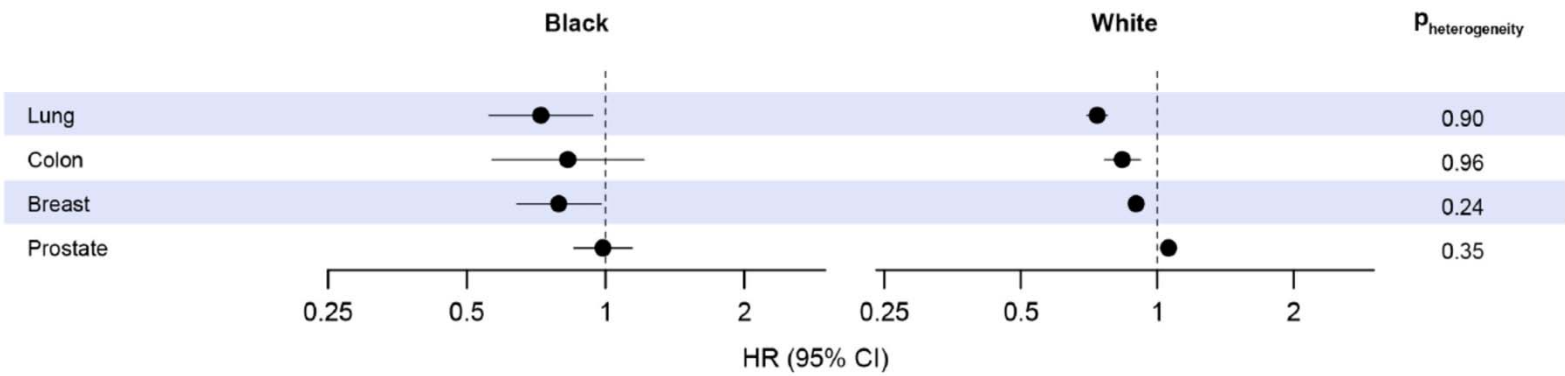
Physical activity association by smoking group

Cancer	HR (95% CI) Current smokers	HR (95% CI) Never smokers	$P_{interaction}$
Lung	0.73 (0.68-0.80)	1.03 (0.89-1.20)	<0.001
Head and neck	0.85 (0.65-1.10)	0.83 (0.68-1.02)	0.91

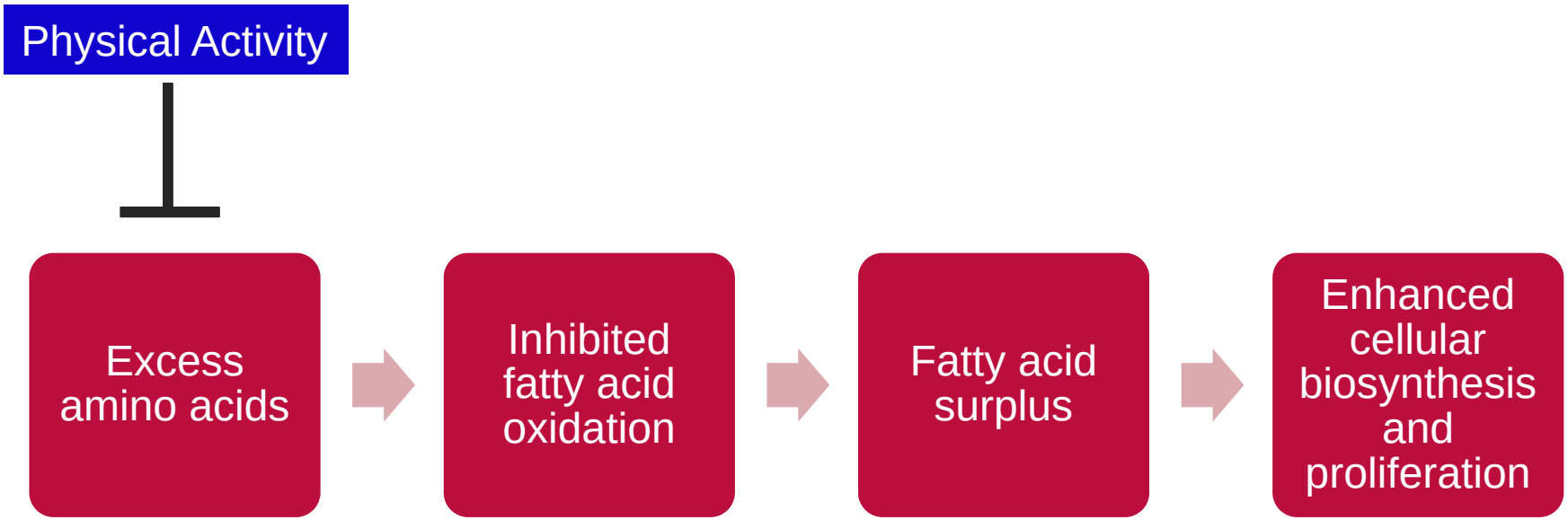
Effect modification by BMI (< vs. ≥ 25.0 kg/m^2)

Cancer type	P for interaction
Esophageal adenocarcinoma	.60
Gallbladder	.48
Liver	.51
Lung	.002
Kidney	.56
Small Intestine	.03
Gastric cardia	.02
Endometrial	<0.001
Esophageal squamous	.27
Myeloid leukemia	.68
Myeloma	.79
Colon	.81
Head and neck	.16
Rectum	.50
Bladder	.80
Breast	.92
Non-Hodgkin lymphoma	.33
Thyroid	.37
Gastric non-cardia	.68
Soft tissue	.90
Pancreas	.27
Lymphocytic leukemia	.26
Ovary	.76
Brain	.25
Prostate	.64
Malignant melanoma	.79

eFigure 7. Summary multivariable* hazard ratios (HR) and 95% confidence intervals (CI) for a higher (90th percentile) versus lower (10th percentile) level of leisure-time physical activity, by cancer type, stratified by race/ethnicity†.

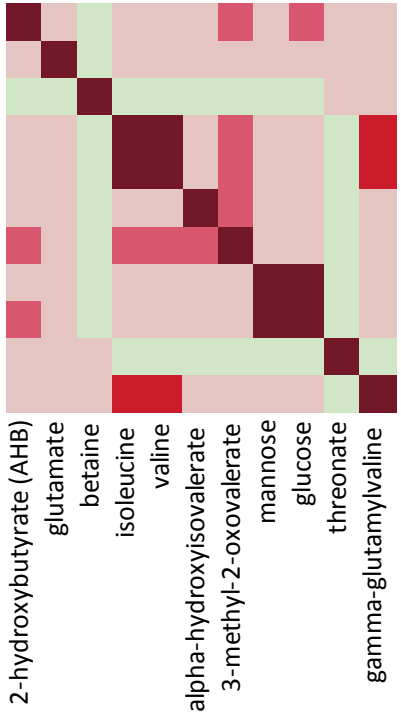


A simplified model



Physical activity and metabolite associations

Metabolite	Class	Pathway
2-hydroxybutyrate (AHB)	Amino acid	Cysteine, methionine, SAM, taurine metabolism
glutamate	Amino acid	Glutamate metabolism
betaine	Amino acid	Glycine, serine and threonine metabolism
isoleucine	Amino acid	Valine, leucine and isoleucine metabolism
valine	Amino acid	Valine, leucine and isoleucine metabolism
alpha-hydroxyisovalerate	Amino acid	Valine, leucine and isoleucine metabolism
3-methyl-2-oxovalerate	Amino acid	Valine, leucine and isoleucine metabolism
mannose	Carbohydrate	Fructose, mannose, galactose, starch, and sucrose metabolism
glucose	Carbohydrate	Glycolysis, gluconeogenesis, pyruvate metabolism
threonate	Cofactors and vitamins	Ascorbate and aldarate metabolism
gamma-glutamylvaline	Peptide	gamma-glutamyl



Breast cancer and metabolomics

Study Design

Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

621 incident invasive breast cancer cases

418 were ER+ cases

Median follow-up prior to dx: 6.7 years

Matched 1:1 to controls on age, date of blood draw, hormone use

Metabolites

Non-fasting serum

LC-MS/GC-MS (Metabolon Inc.)

672 metabolites

Statistical analysis

Conditional logistic regression (All cases and ER+ cases)

Adjusted for breast cancer risk factors, hormone use, body mass index

False discovery rate of 0.2