Exercise is Regenerative Medicine:
Impact on Chronic Disease

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NIH National Rehabilitation Research Resource to Enhance Clinical Trials
NIH Medical Rehabilitation Research Resource Network Coordinating Center
Core Muscle Research Laboratory, GRECC, Birmingham VA Medical Center



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Moving Research into Medicine

Disclosures

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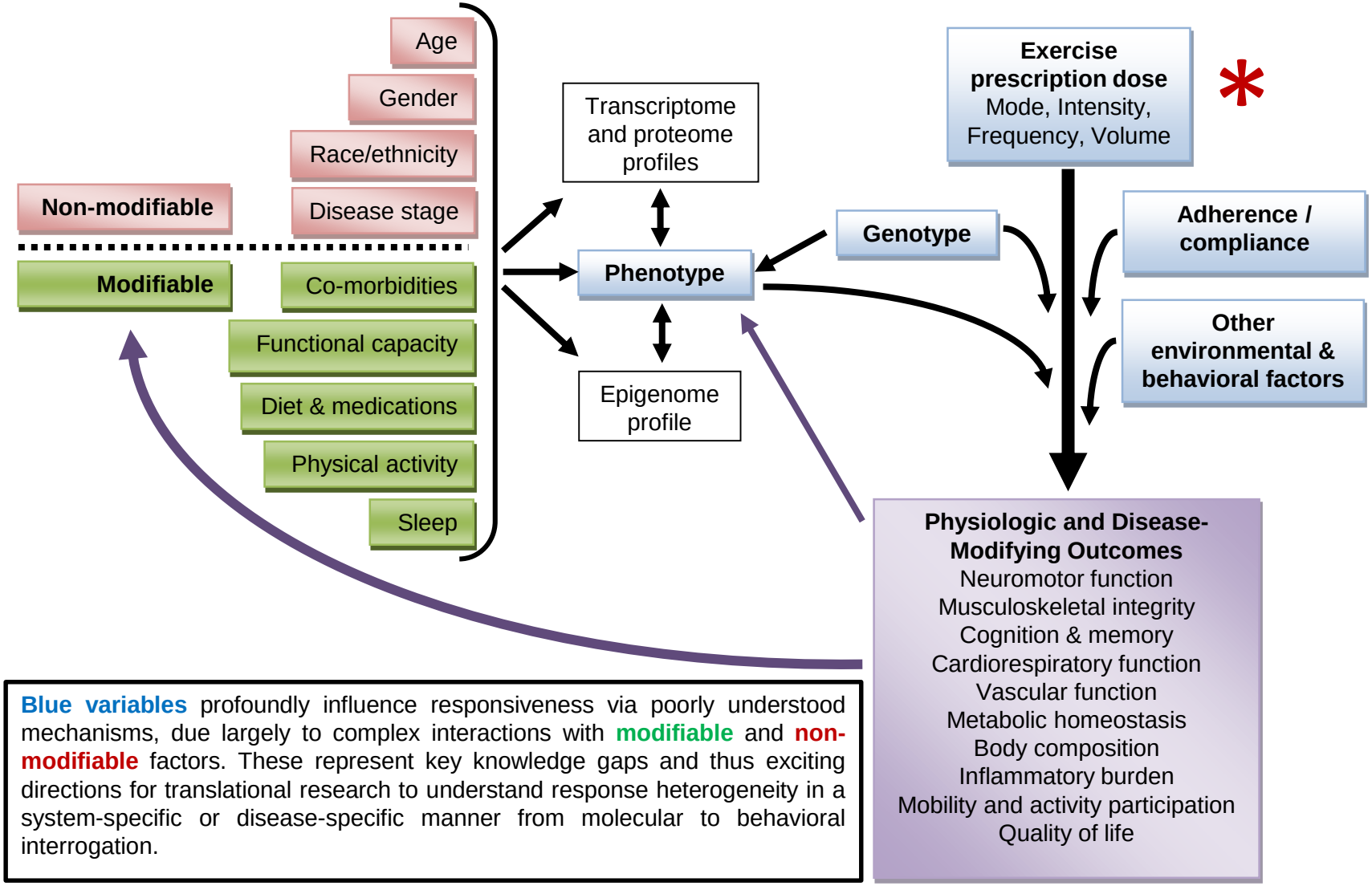
Key terms defined

- **Physical activity:** Any bodily movement produced by skeletal muscles that results in energy expenditure' above resting (basal) levels. Physical activity broadly encompasses exercise, sports, and physical activities done as part of daily living, occupation, leisure, and active transportation.
- **Exercise:** Physical activity that is planned, structured, and repetitive and that has as a final or intermediate objective the improvement or maintenance of physical fitness.
- **Physical fitness:** The ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy [leisure] pursuits and to meet unforeseen emergencies. Operationalized as a set of measurable health and skill-related attributes:
  - **cardiorespiratory fitness (VO2max)**
  - **muscular strength/endurance**
  - **body composition**
  - **flexibility**
  - **balance, agility, reaction time and power.**
- **Physical function:** The capacity of an individual to carry out the physical activities of daily living. Physical function reflects motor function and control, physical fitness, and habitual physical activity and is an independent predictor of functional independence, disability, morbidity, and mortality.
- **Energy expenditure:** The total amount of energy (gross) expended during exercise, including the resting energy expenditure (resting energy expenditure + exercise energy expenditure). Energy expenditure may be articulated in METs, kilocalories or kilojoules.
- **MET:** An index of energy expenditure. A MET is the ratio of the rate of energy expended during an activity to the rate of energy expended at rest. One MET is the rate of energy expenditure while sitting, and is equal to an oxygen uptake of 3.5 mL/kg/min.
- **Inactivity:** Sedentary behavior or activity that involves little or no movement or physical activity, having an energy expenditure of about 1–1.5 METs. Examples are sitting, watching television, playing video games, and using a computer.

ACSM Position Stand 2011

Factors influencing exercise adaptation: key research priorities



Blue variables profoundly influence responsiveness via poorly understood mechanisms, due largely to complex interactions with **modifiable** and **non-modifiable** factors. These represent key knowledge gaps and thus exciting directions for translational research to understand response heterogeneity in a system-specific or disease-specific manner from molecular to behavioral interrogation.

Primary modes of exercise, and current HHS guidelines for the general population

Endurance (aerobic) training

HHS Guidelines (2008 PAGC)

150 min/wk moderate intensity (via exercise on most days)
OR
75 min/wk vigorous intensity (across ~3 days/wk)

Resistance (strength) training

HHS Guidelines (2008 PAGC)

Strengthening exercise for each major muscle group
2 days/wk

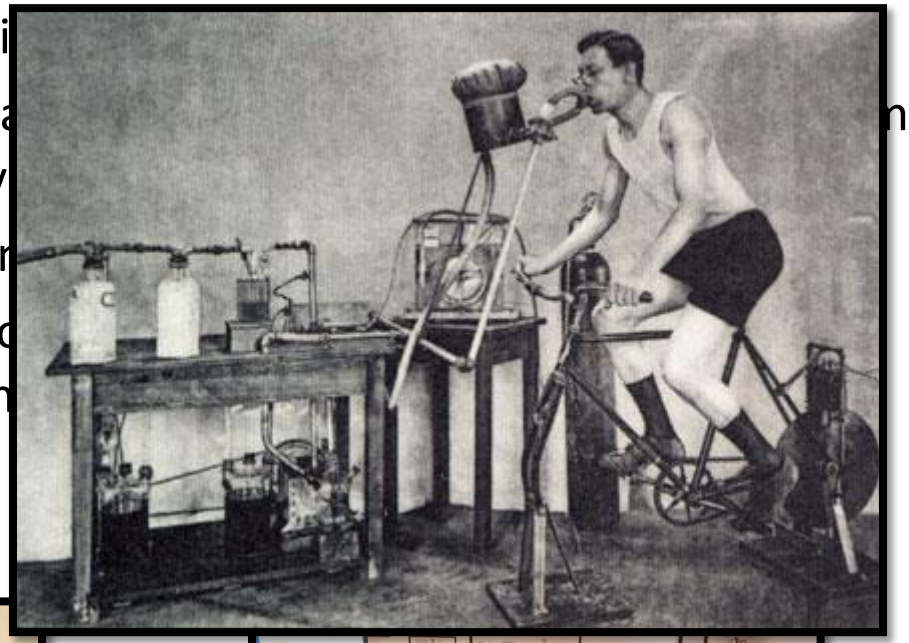
Endurance Training (e.g. 70% HRR)	
Cardiorespiratory	
VO2max	↑↑
Cardiac muscle	Preload hypertrophy
Resting HR	↓↓
Resting SV	↑
Resting SBP	↓ in hypertensives
Resting DBP	↓ in hypertensives
Skeletal Muscle	
Type I myofiber hypertrophy	↔
Type II myofiber hypertrophy	↔
Type IIx to IIa myofiber shift	↑↑
Capillary density	↑↑
Mitochondrial content	↑↑
Anaerobic enzymes	↑
Oxidative enzymes	↑↑
PC stores	↔ or slight ↑
Glycogen stores	↑
Intramyocellular lipid stores	↑

Resistance Training (e.g. 75% 1RM)	
Cardiorespiratory	
VO2max	↔ or slight ↑
Cardiac muscle	Afterload hypertrophy
Resting HR	↓
Resting SV	↑
Resting SBP	↔ or slight ↓ in HTN
Resting DBP	↔ or slight ↓ in HTN
Skeletal Muscle	
Type I myofiber hypertrophy	↑
Type II myofiber hypertrophy	↑↑
Type IIx to IIa myofiber shift	↑↑
Capillary density	↔
Mitochondrial content	↔
Anaerobic enzymes	↑↑
Oxidative enzymes	↔ or slight ↑
PC stores	↑
Glycogen stores	↑
Intramyocellular lipid stores	?

Functional	**ET**	**RT**
Strength performance	↔	↑↑↑
Specific strength (per unit muscle)	↔	↑
Endurance capacity	↑↑↑	↑
Steady state exercise HR	↓	↓
Steady state exercise Ve	↓	↓
Steady state exercise RER	↓	↓
Body Composition		
Lean mass	↔	↑
Subcutaneous fat mass	↓	↓
Visceral fat mass	↓	↓
Bone mineral density	↔	↑ (mechanically loaded regions)
Metabolic		
Insulin sensitivity	↑↑	↑
HDL cholesterol	↑↑	↑↑
LDL cholesterol	slight ↓	↔ or slight ↓
Triglycerides	↓	↓

Cardiorespiratory fitness defined

- CRF = aerobic capacity, or maximum rate of oxygen consumption/utilization (i.e. VO_2max)
- Hallmark measure of fitness
- Major predi
- Assessed via np protocol (ty
- Total test tir
- Highly respo decondition



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IMPACT OF PHYSICAL INACTIVITY ON MORBIDITY AND MORTALITY

Diabetologia (2012) 55:2895–2905
DOI 10.1007/s00125-012-2677-z

META-ANALYSIS

Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis

E. G. Wilmot · C. L. Edwardson · F. A. Achana · M. J. Davies · T. Gorely · L. J. Gray · K. Khunti · T. Yates · S. J. H. Biddle

794,577 participants

Relative Risks

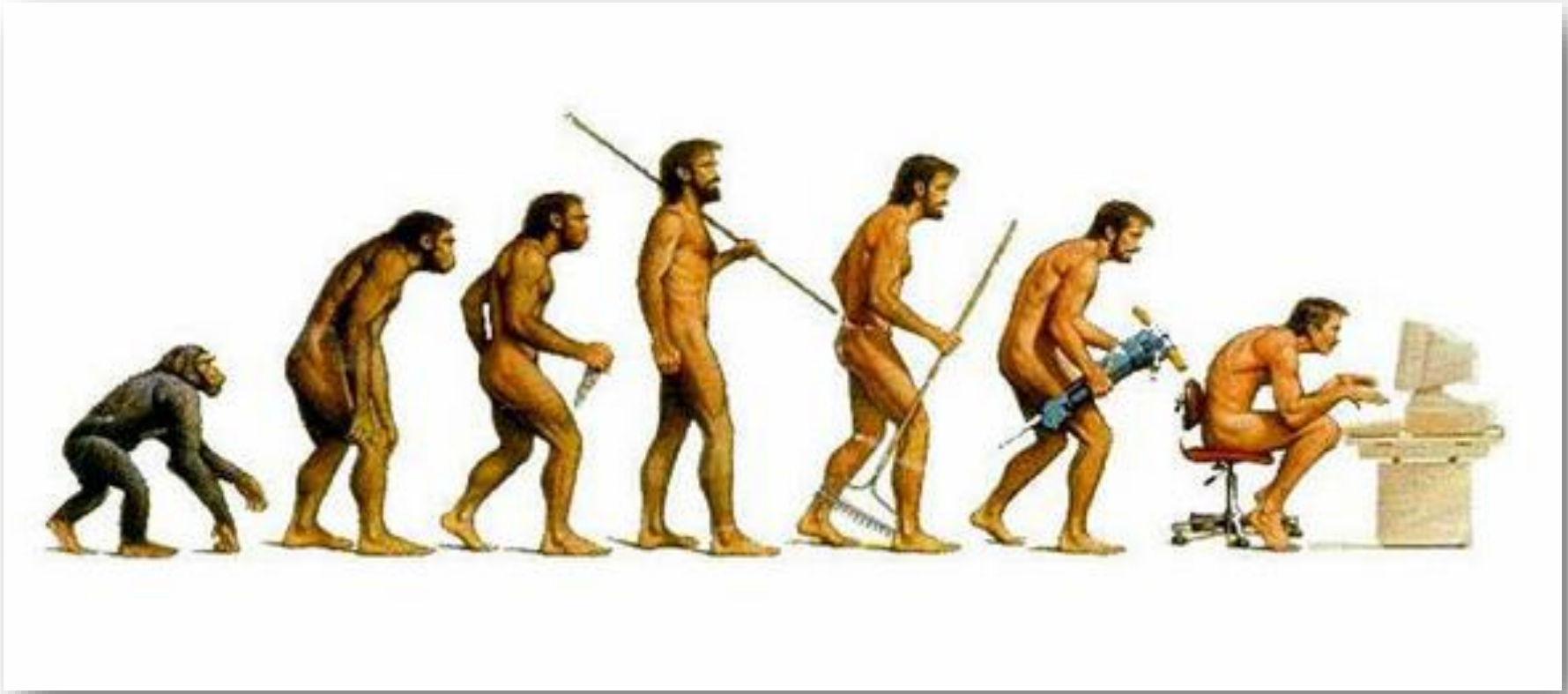
Diabetes RR 2.12

CV Events RR 2.47

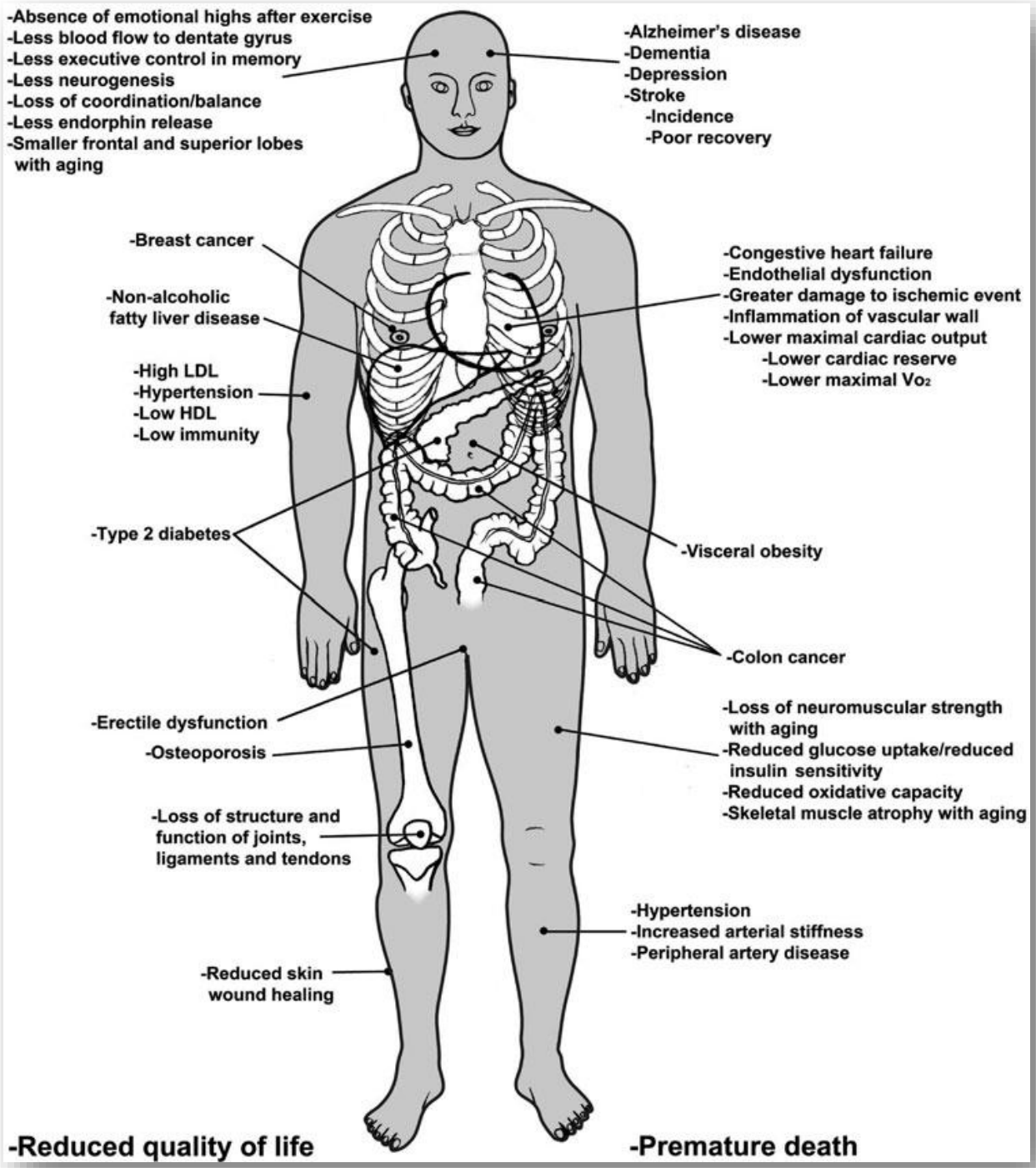
Hazard Ratios

CV Mortality HR 1.90

All-Cause Mortality HR 1.49

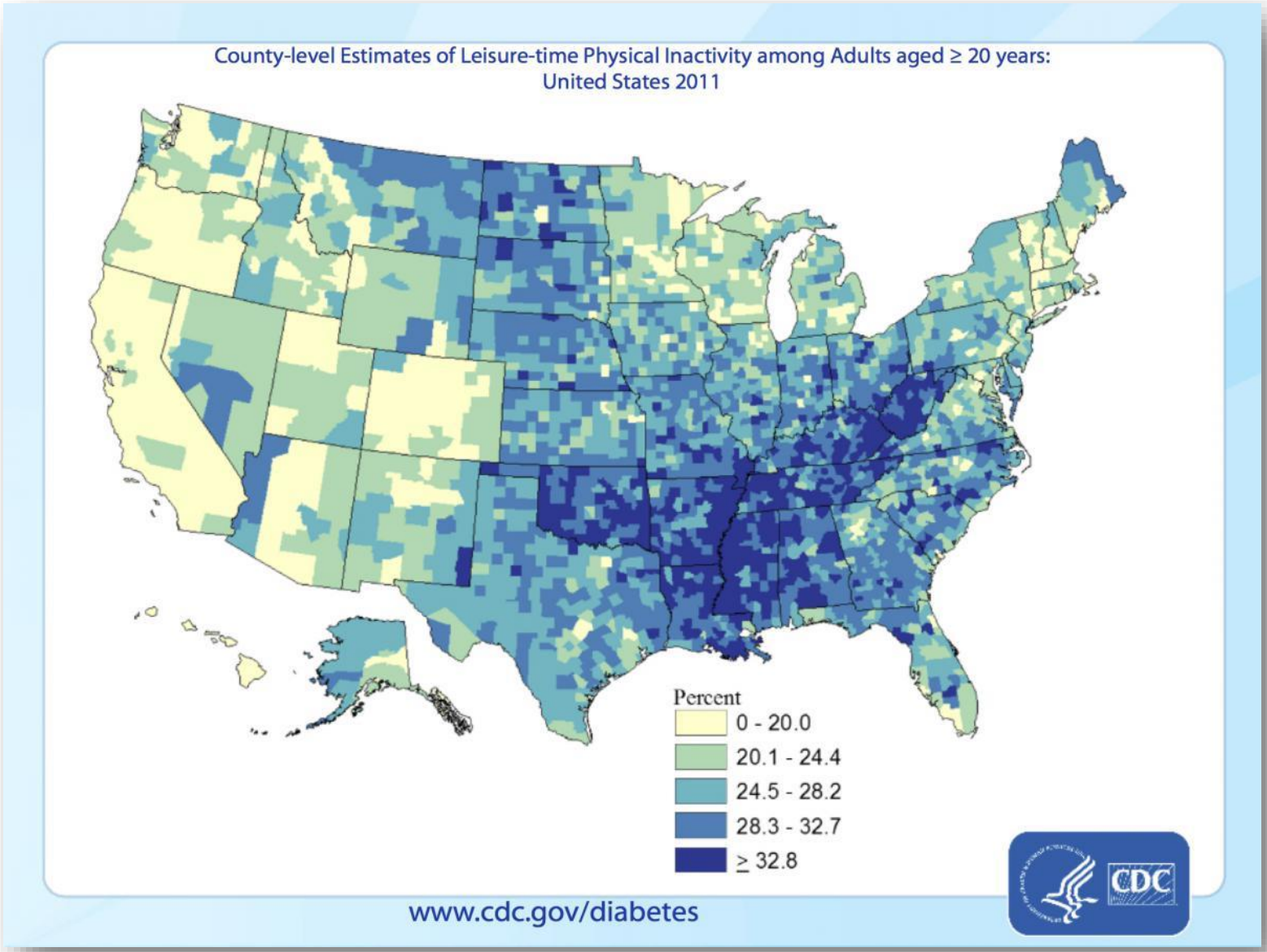


Risks of low physical activity

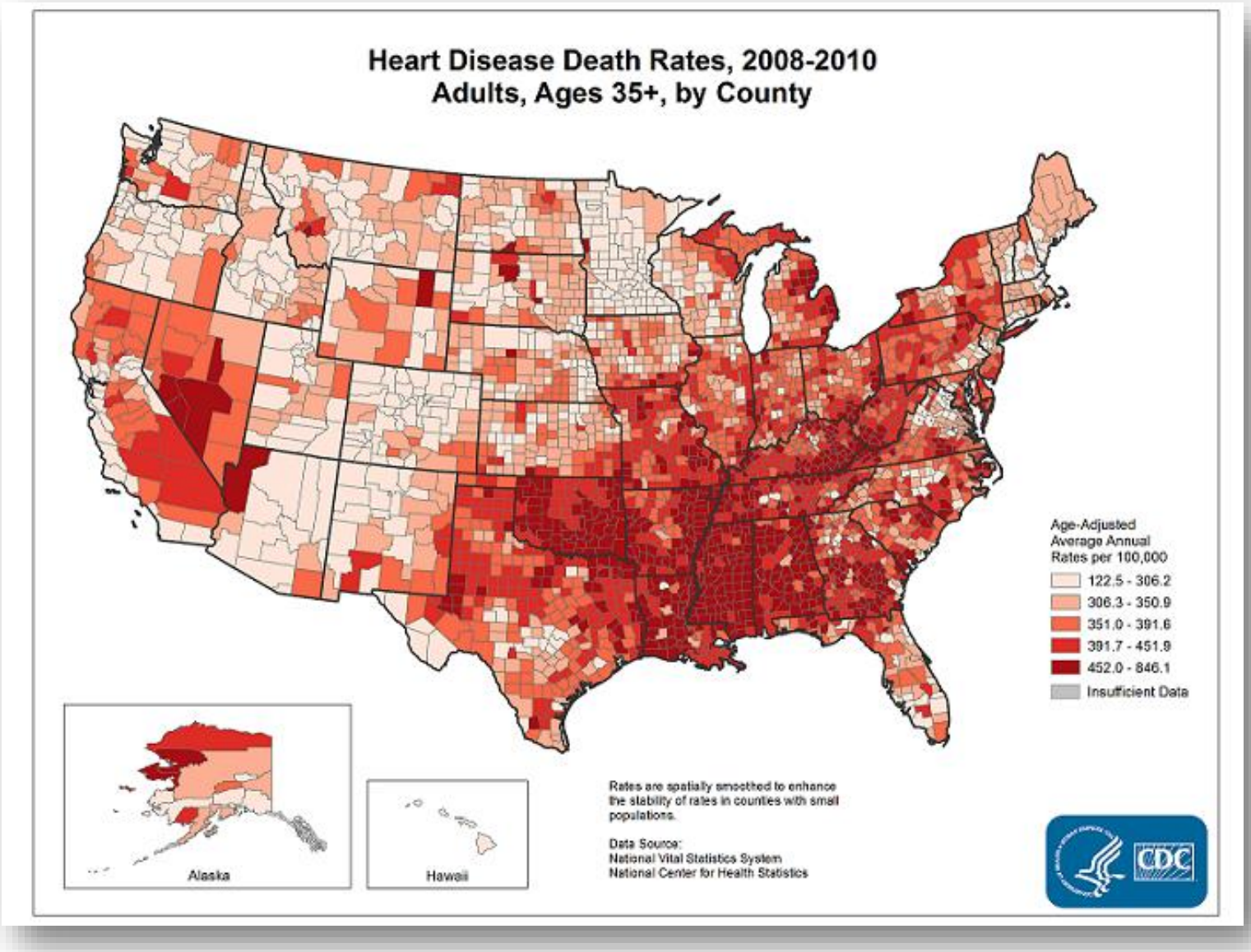


Booth FW and MJ Laye. J Physiol 587.23 (2009) pp 5527–5540

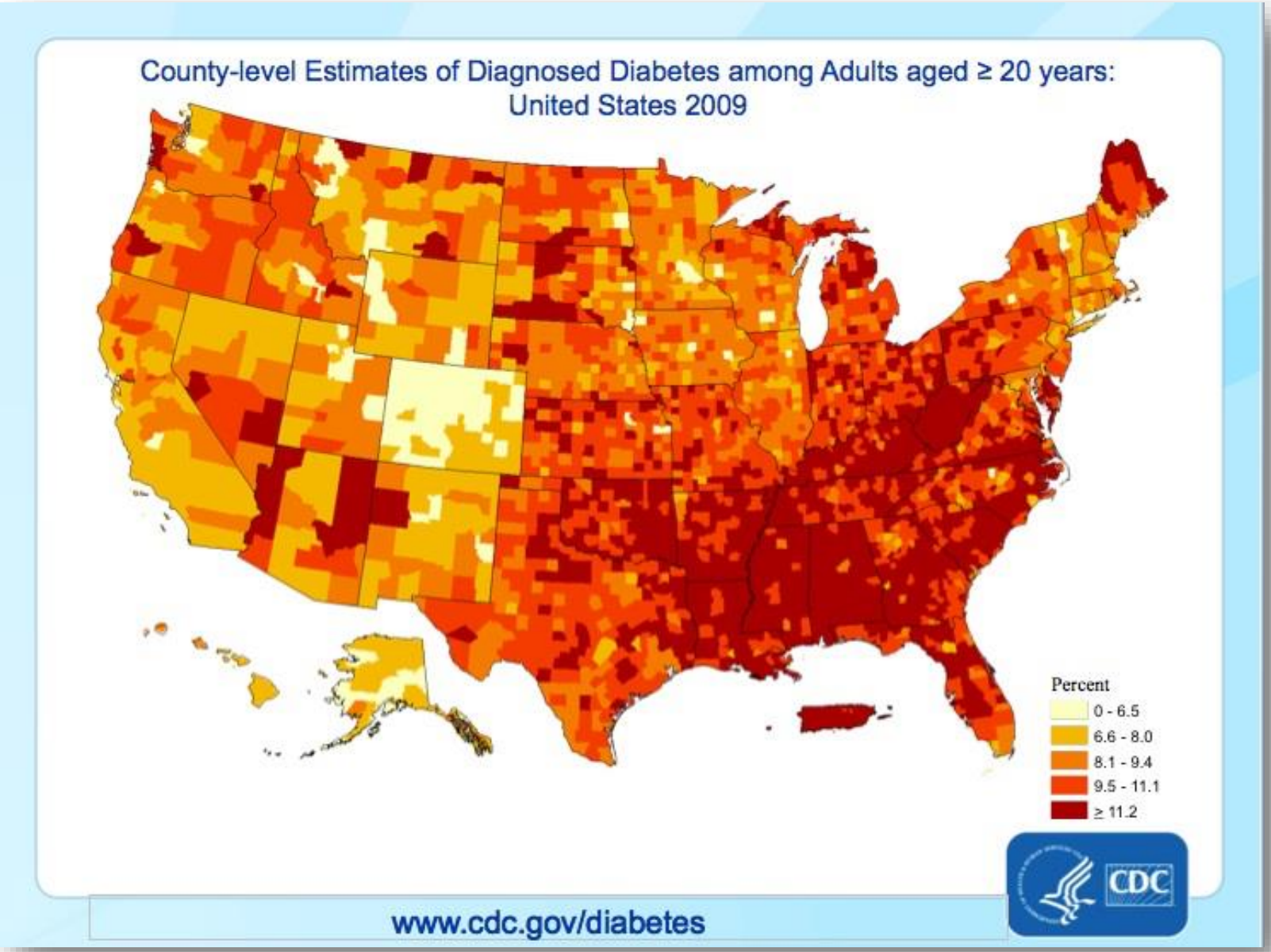
Physical inactivity by county



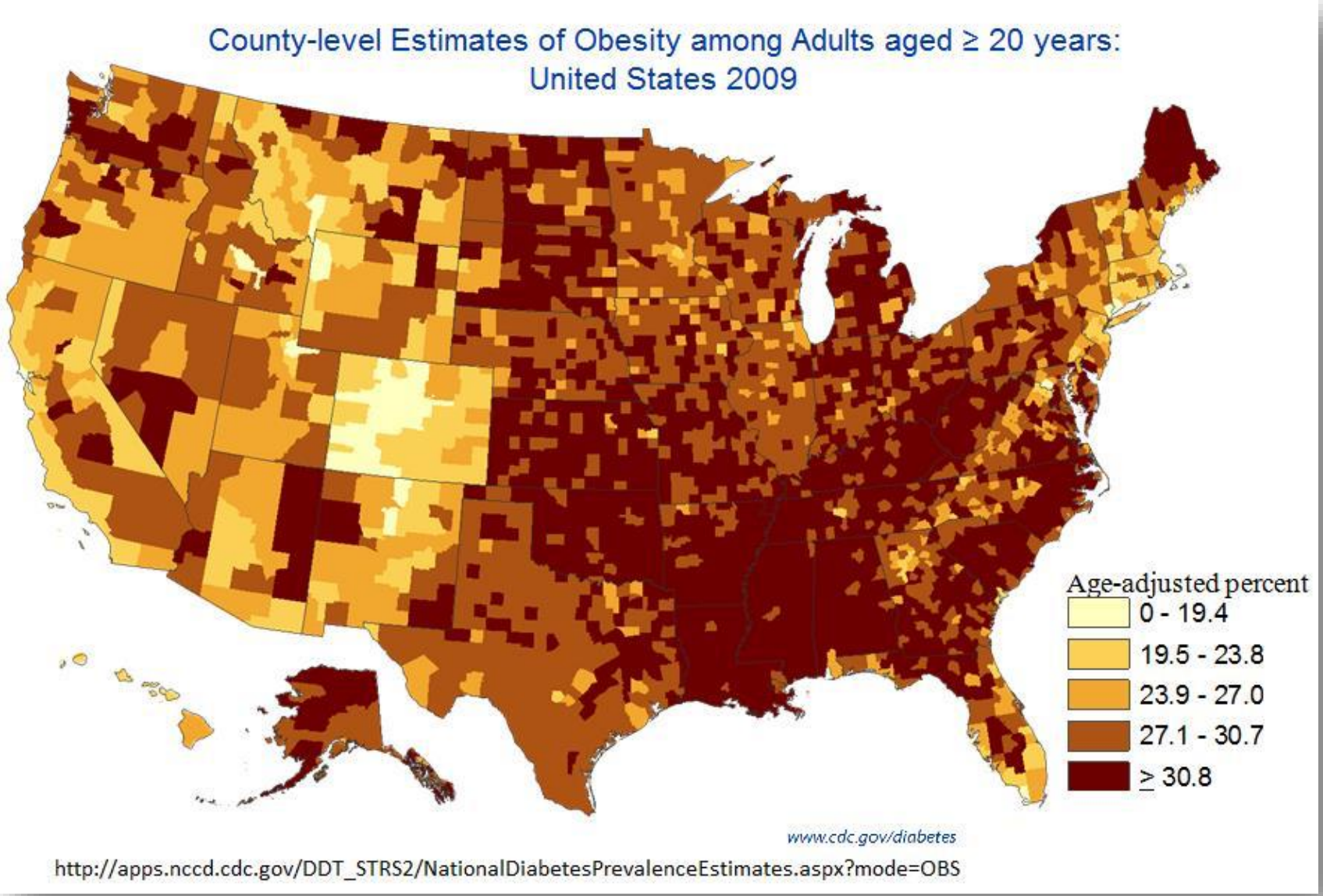
Heart disease mortality by county

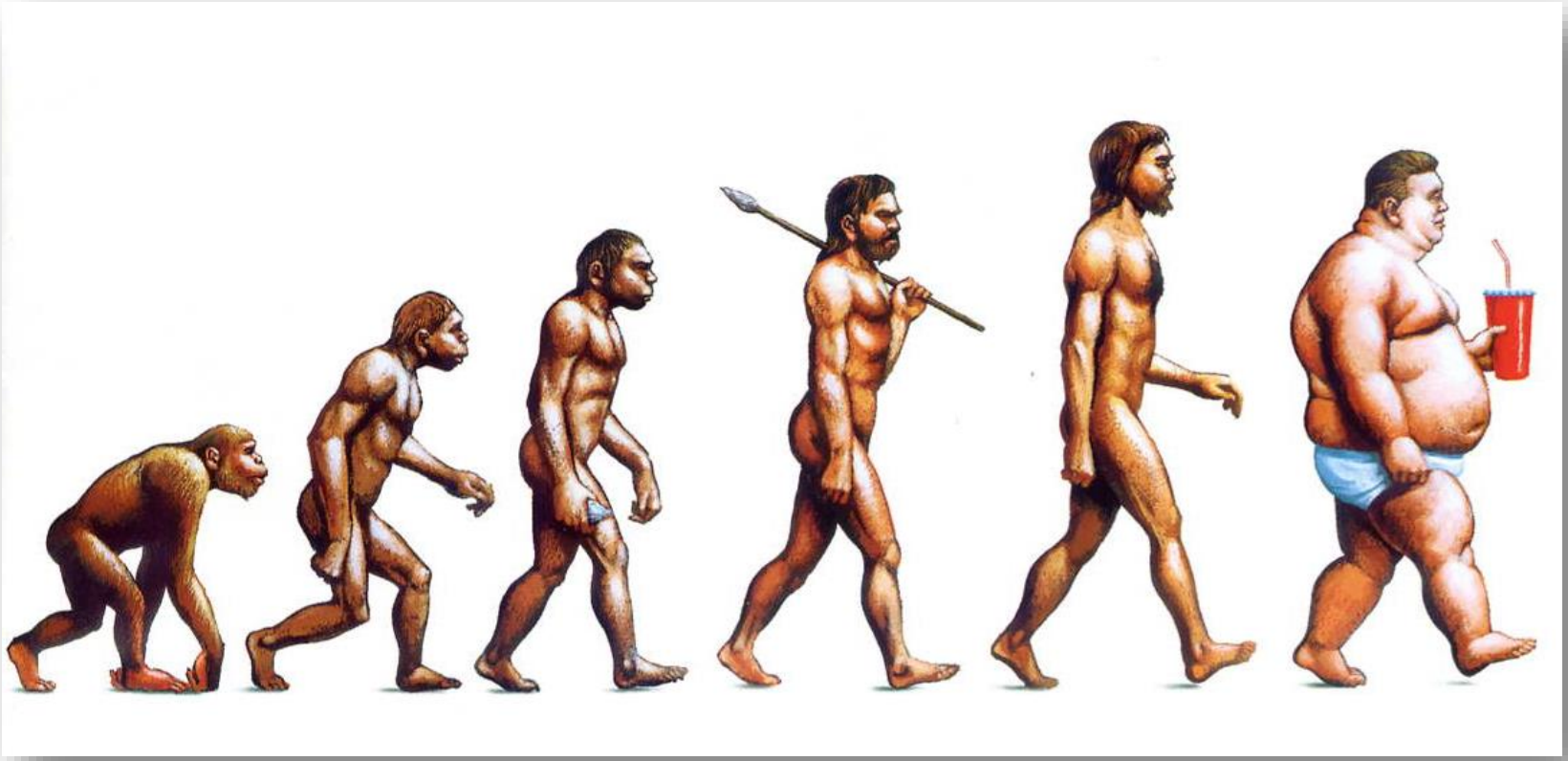


Diabetes by county

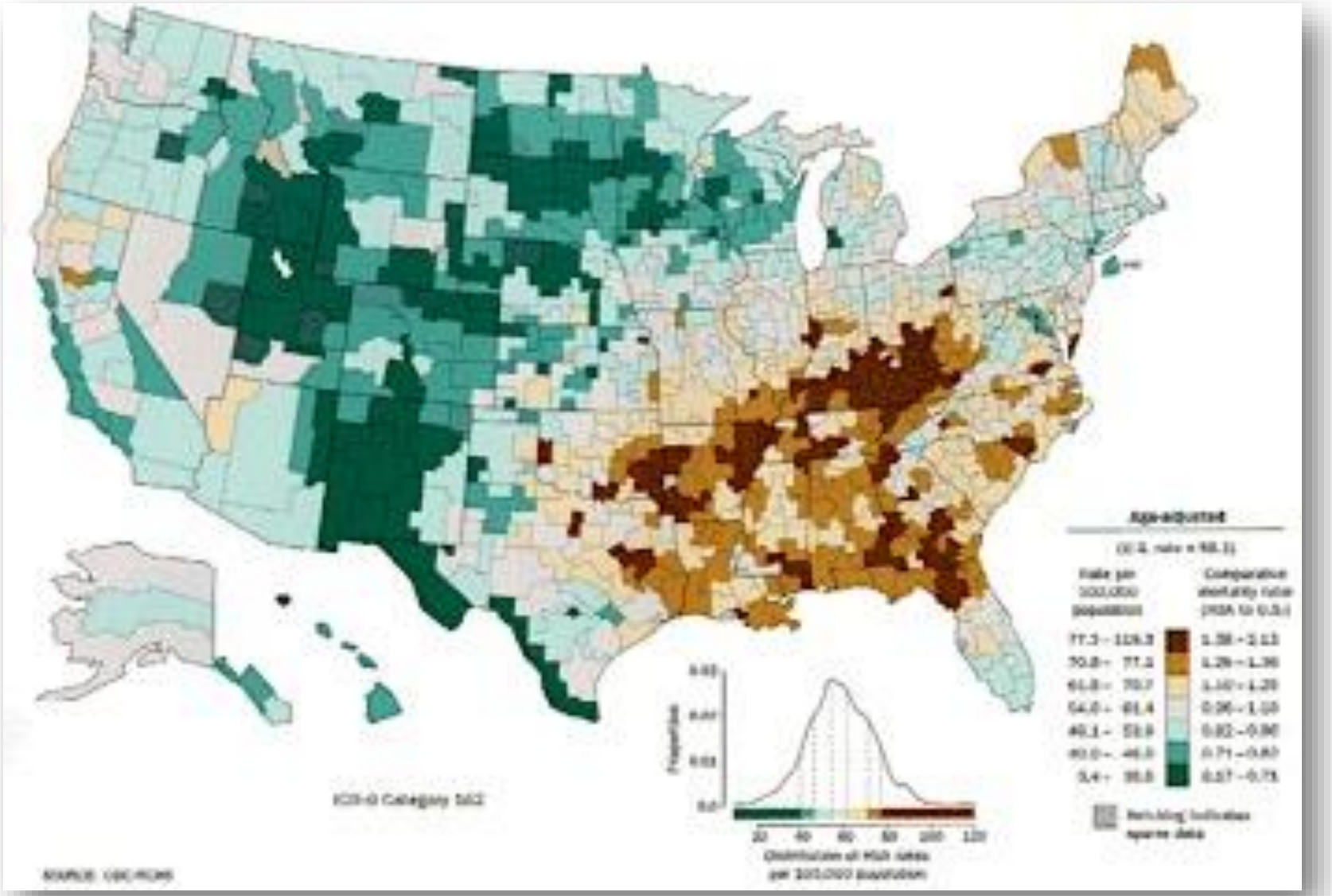


Obesity by county

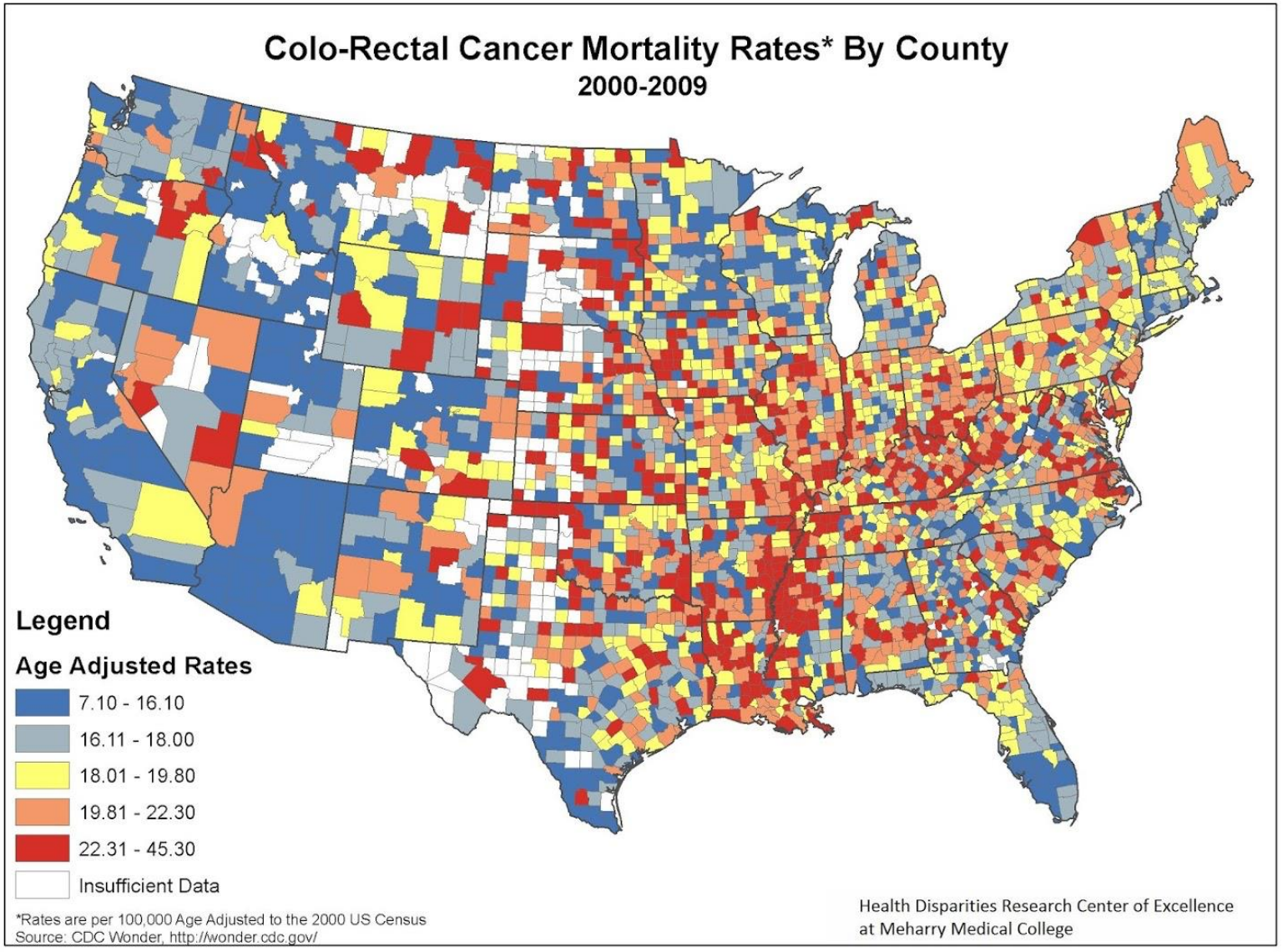




Lung cancer by county

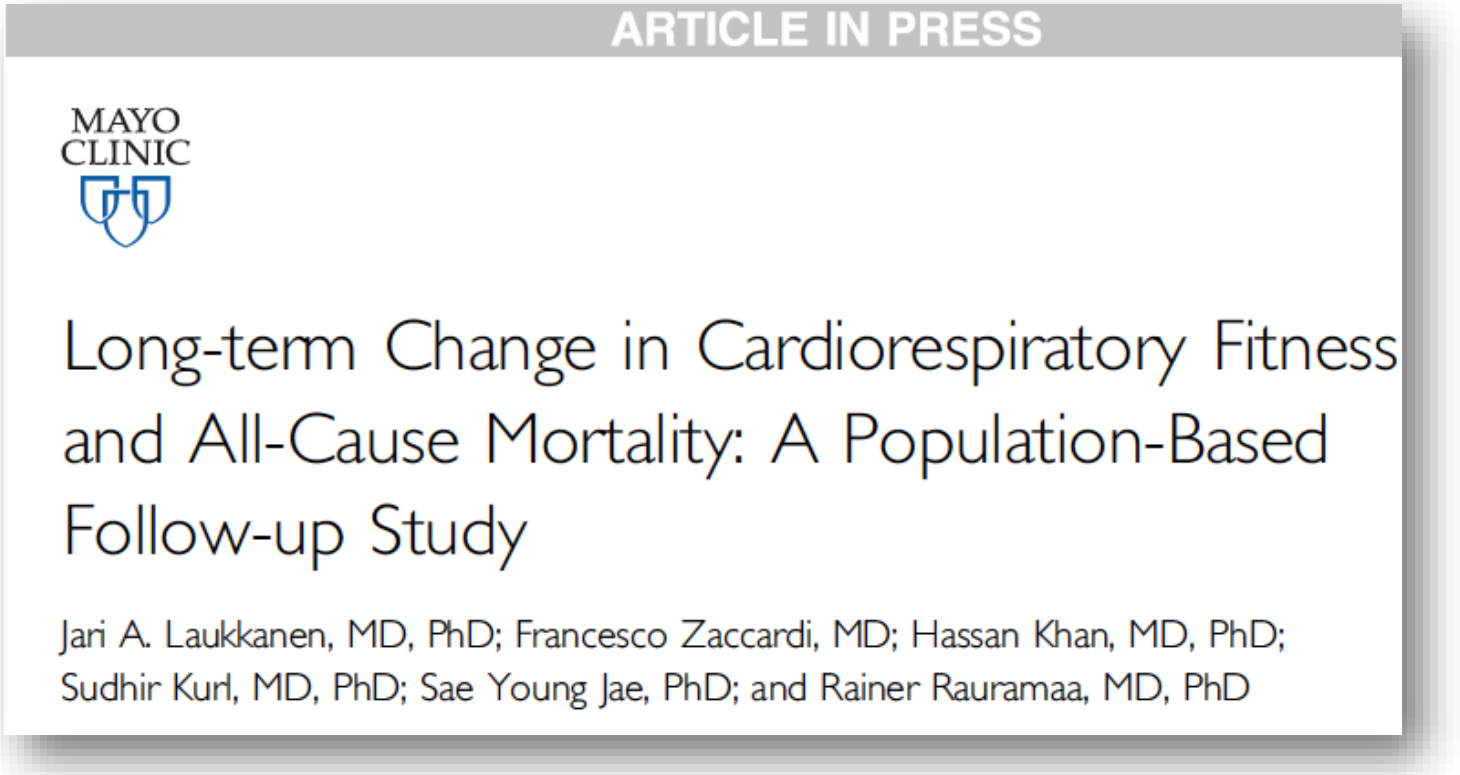


Colo-rectal cancer by county



IMPACT OF FITNESS ON MORTALITY

New Findings:
Longitudinal study with 11 yr follow-up



ARTICLE IN PRESS

MAYO CLINIC

Long-term Change in Cardiorespiratory Fitness and All-Cause Mortality: A Population-Based Follow-up Study

Jari A. Laukkanen, MD, PhD; Francesco Zaccardi, MD; Hassan Khan, MD, PhD; Sudhir Kurl, MD, PhD; Sae Young Jae, PhD; and Rainer Rauramaa, MD, PhD

Profound impact of change in cardiorespiratory fitness on all-cause mortality

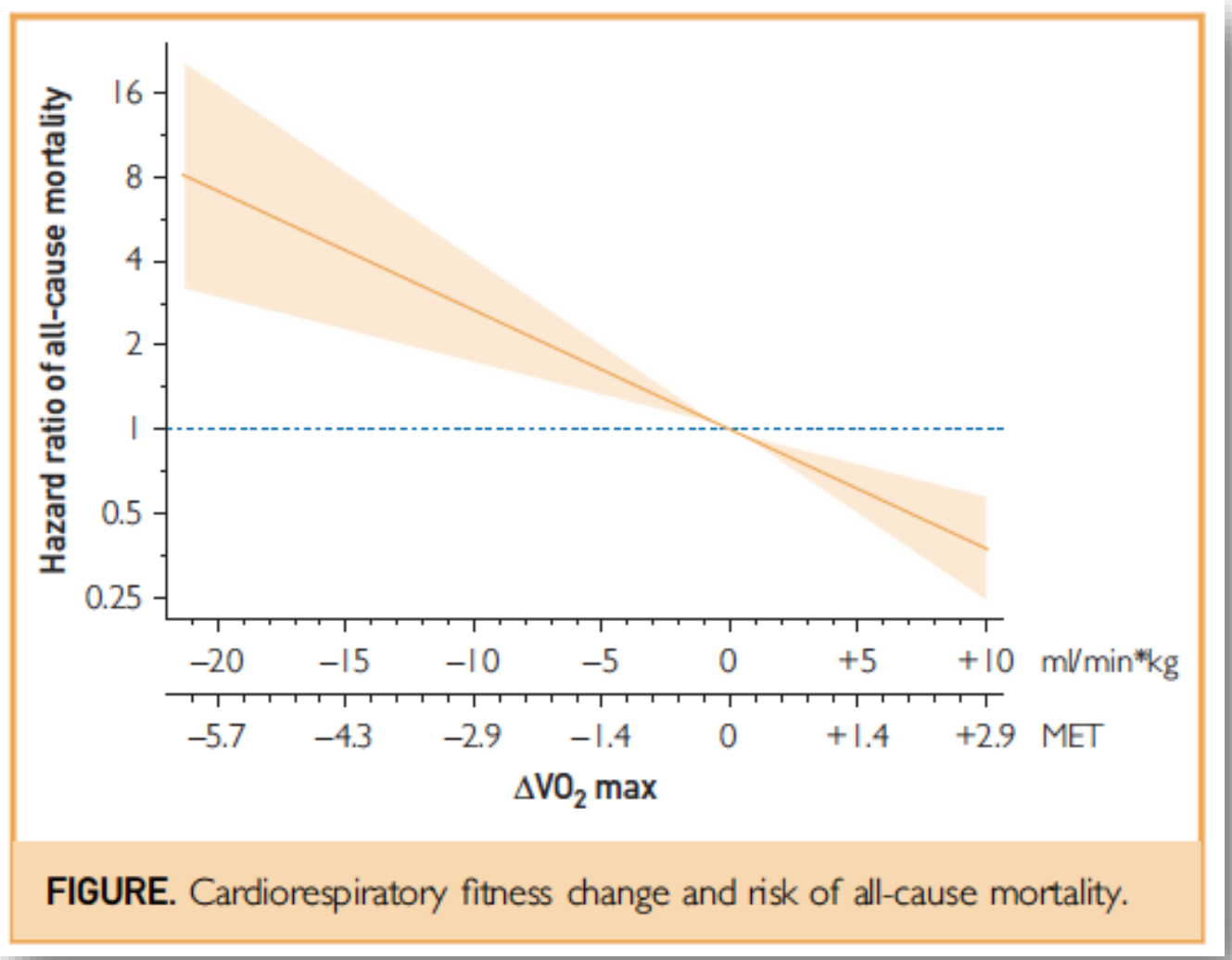


FIGURE. Cardiorespiratory fitness change and risk of all-cause mortality.

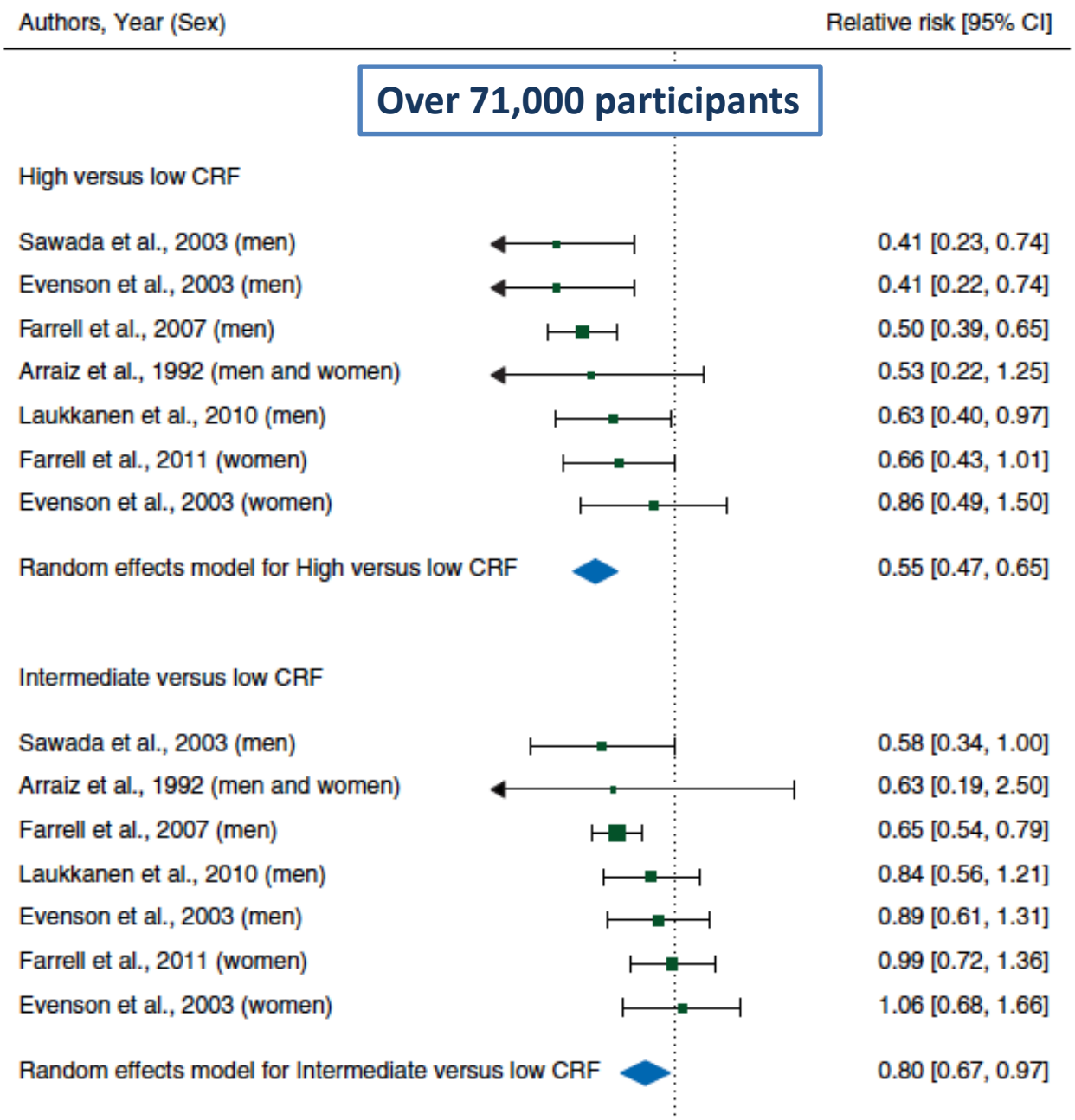
Annals of Oncology

Annals of Oncology 26: 272–278, 2015
doi:10.1093/annonc/mdu250
Published online 9 July 2014

Cardiorespiratory fitness as predictor of cancer mortality: a systematic review and meta-analysis

D. Schmid* & M. F. Leitzmann

Department of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany



High vs Low CRF
45% lower risk

Intermediate vs Low CRF
20% lower risk

Reduced Disability and Mortality Among Aging Runners

Arch Intern Med. 2008;168(15):1638-1646

A 21-Year Longitudinal Study

Eliza F. Chakravarty, MD, MS; Helen B. Hubert, PhD; Vijaya B. Lingala, PhD; James F. Fries, MD

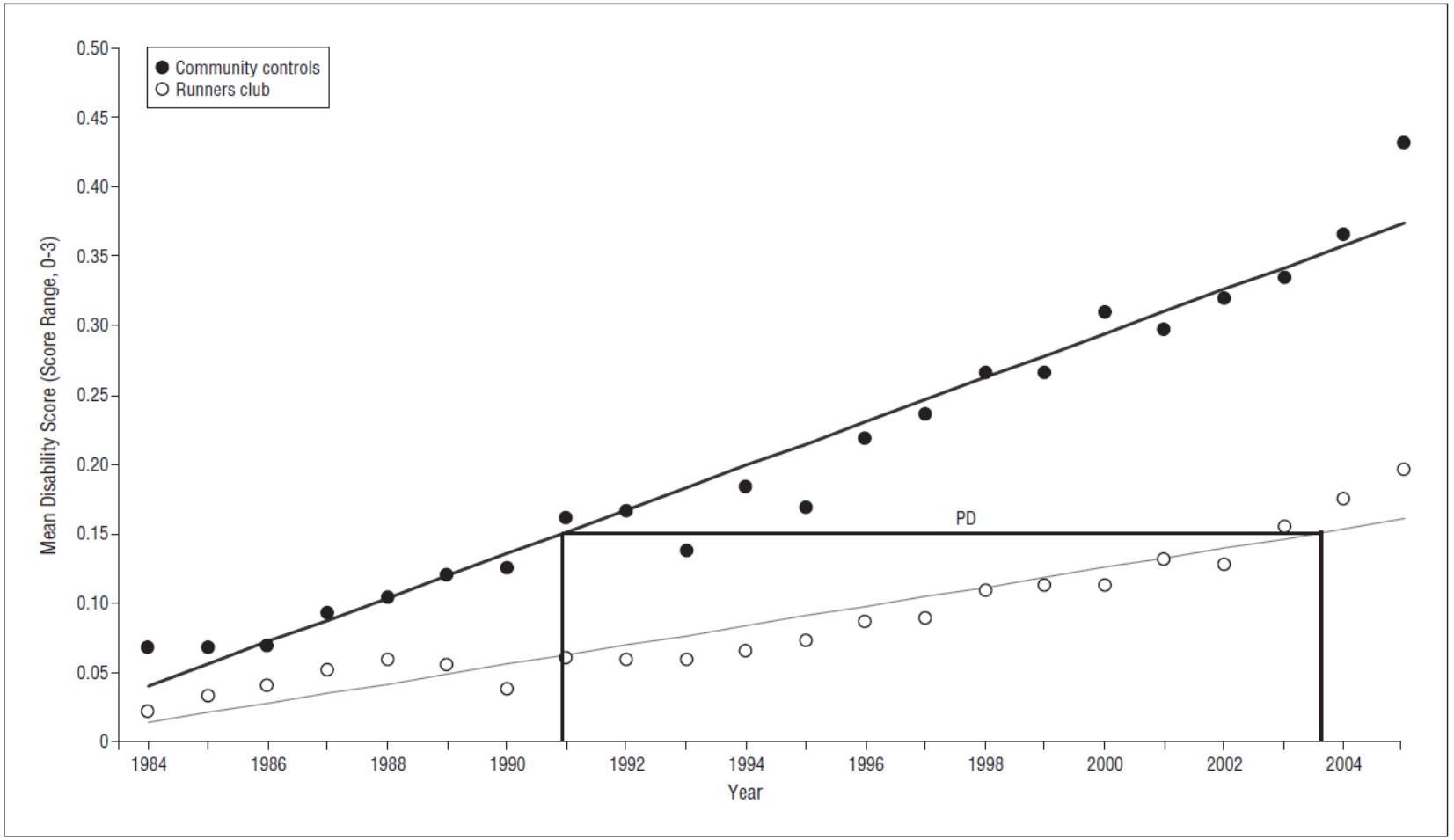


Figure 3. Progression of disability (PD). Linear mixed models of PD and postponement of disability. Regression lines are derived from linear mixed models and adjusted for the following covariates: age, sex, body mass index, smoking, and initial disability level. The PD is defined as the absolute difference between the 2 groups in the time required to cross a given level of disability. The example shown is to reach a Health Assessment Questionnaire Disability Index score of 0.15.

Reduced Disability and Mortality Among Aging Runners

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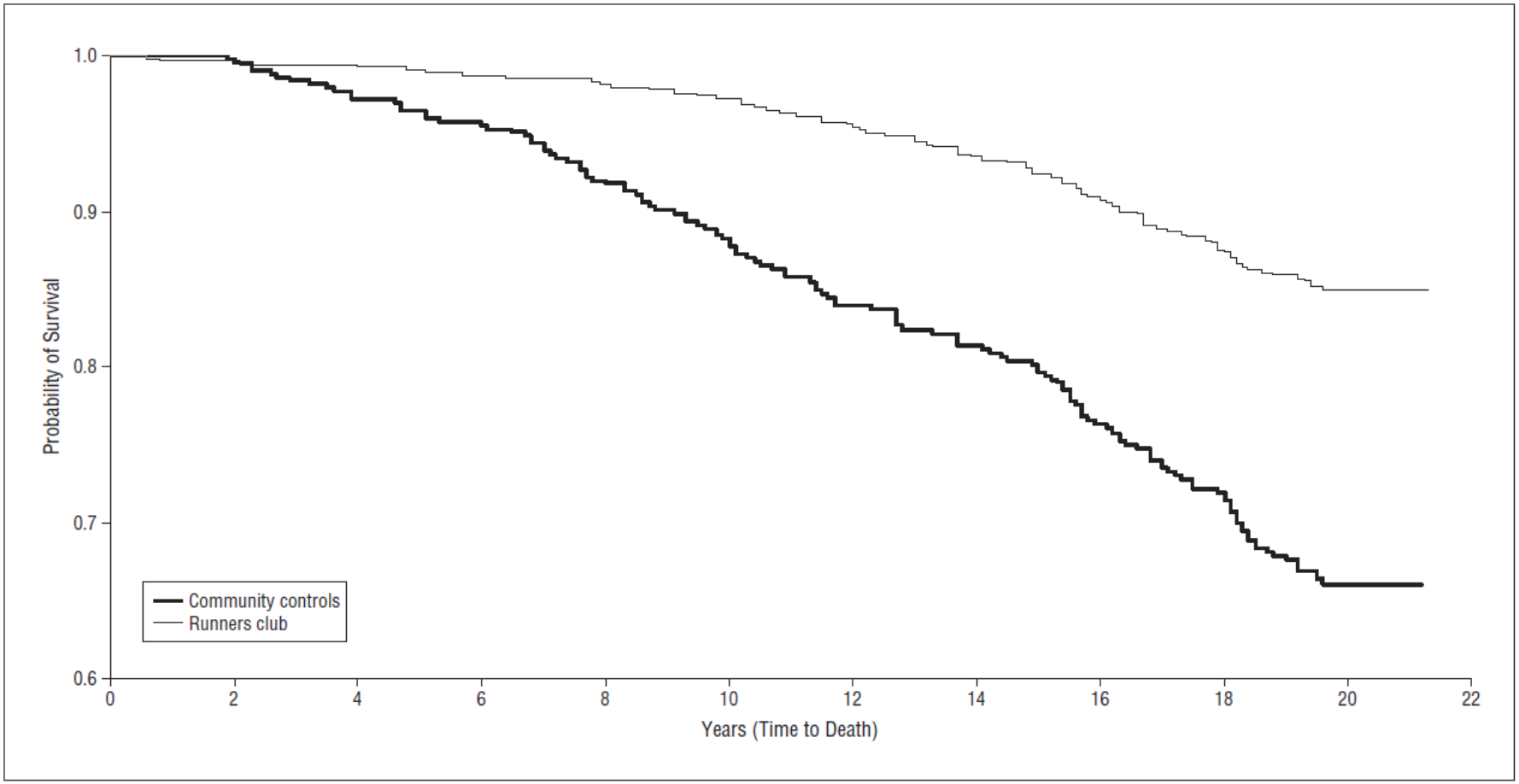
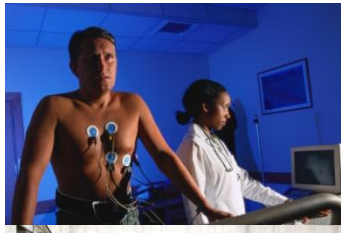
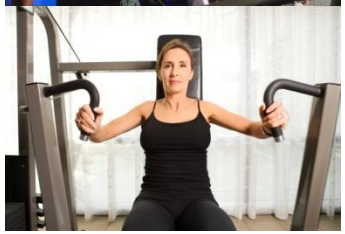


Figure 4. Kaplan-Meier unadjusted survival curves for all cause mortality in runners club members and community controls from study onset through 19 years of follow-up. All 941 subjects at study inception are included. The difference between groups remained significant ($P < .001$ by log rank test).



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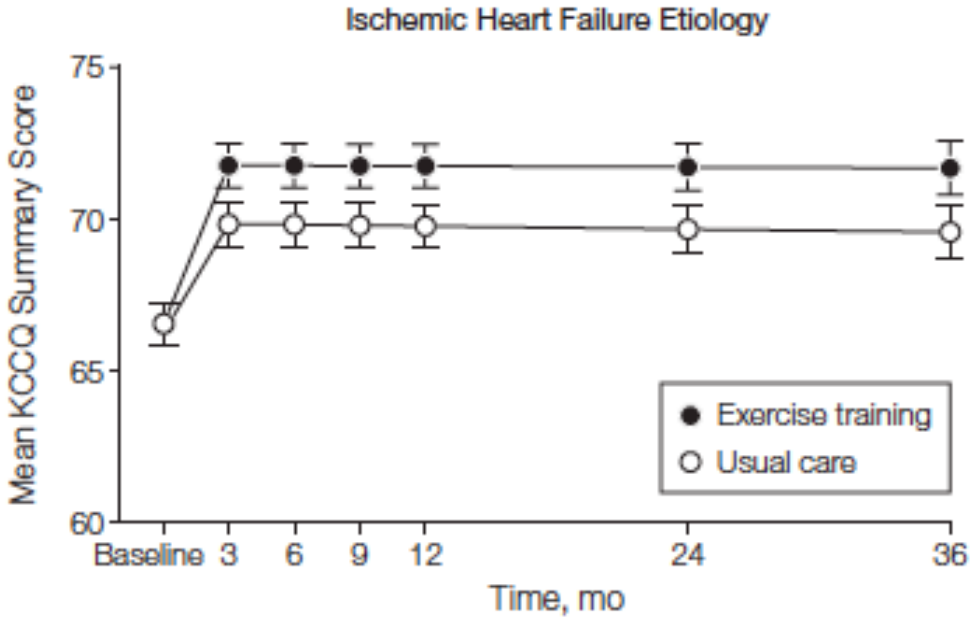
www.glasbergen.com
GLASBERGEN
"What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?"

MULTI-CENTER TRIALS OF MODERATE EXERCISE/PHYSICAL ACTIVITY (+/- DIETARY MODIFICATION) IN CHRONIC DISEASE

Effects of Exercise Training on Health Status in Patients With Chronic Heart Failure

HF-ACTION Randomized Controlled Trial

Figure 2. Predicted Mean Health Status Trajectories by Treatment Group

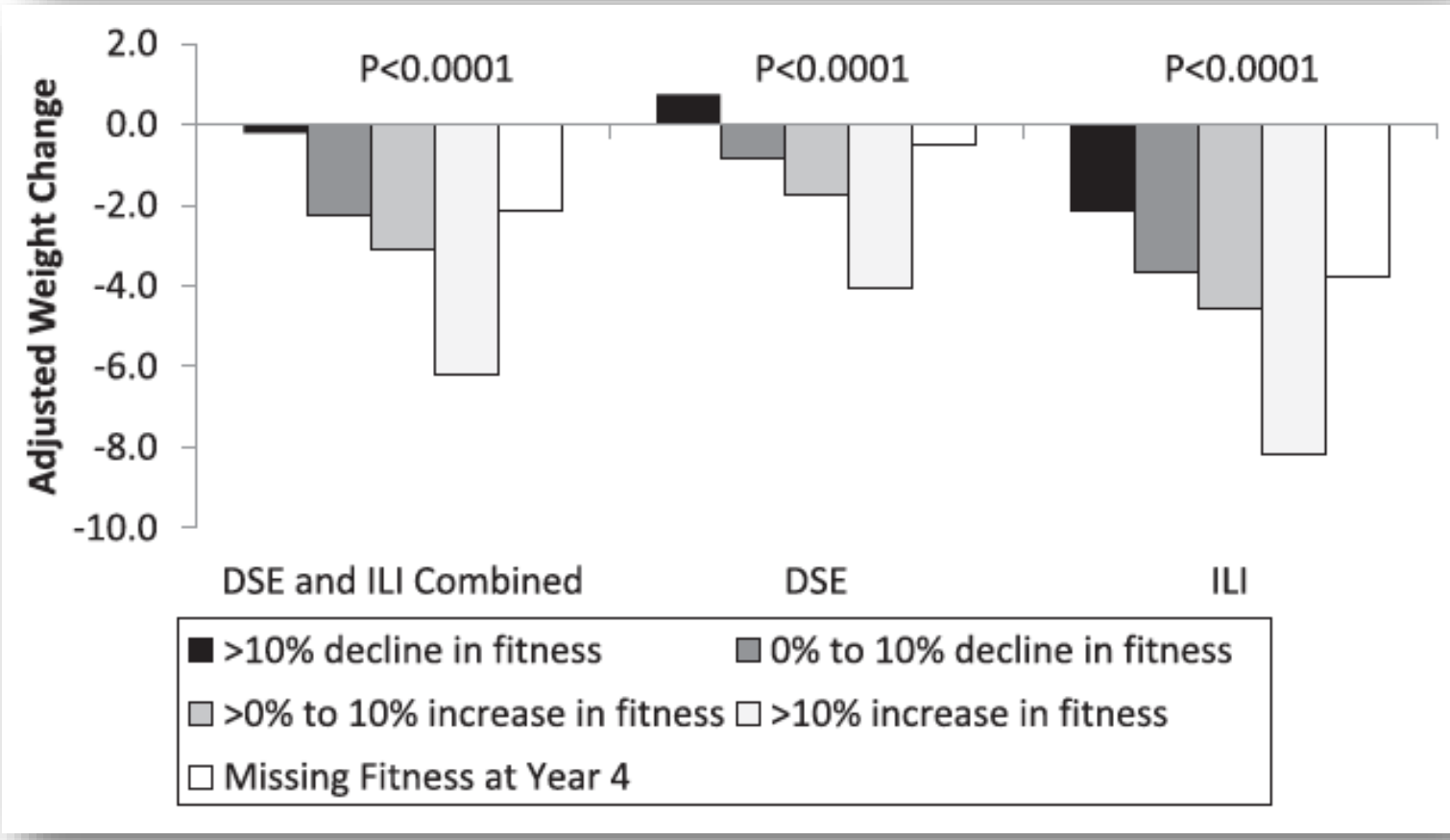


No. of participants							
Exercise training	598	547	511	472	470	277	131
Usual care	599	514	481	471	431	285	151

JAMA. 2009;301(14):1451-1459

Four-Year Change in Cardiorespiratory Fitness and Influence on Glycemic Control in Adults With Type 2 Diabetes in a Randomized Trial

The Look AHEAD Trial



Diabetes Care 36:1297–1303, 2013

Four-Year Change in Cardiorespiratory Fitness and Influence on Glycemic Control in Adults With Type 2 Diabetes in a Randomized Trial

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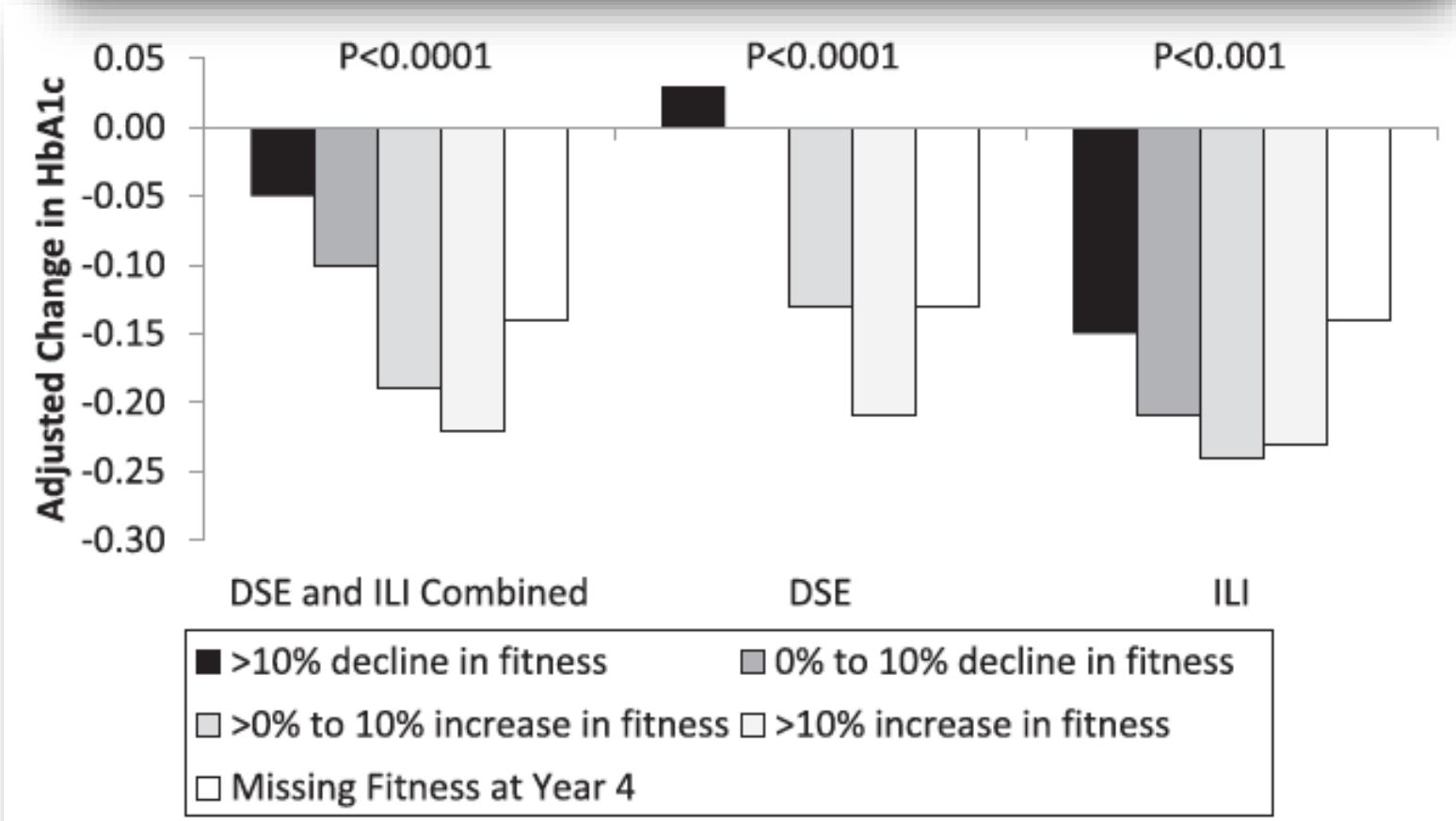


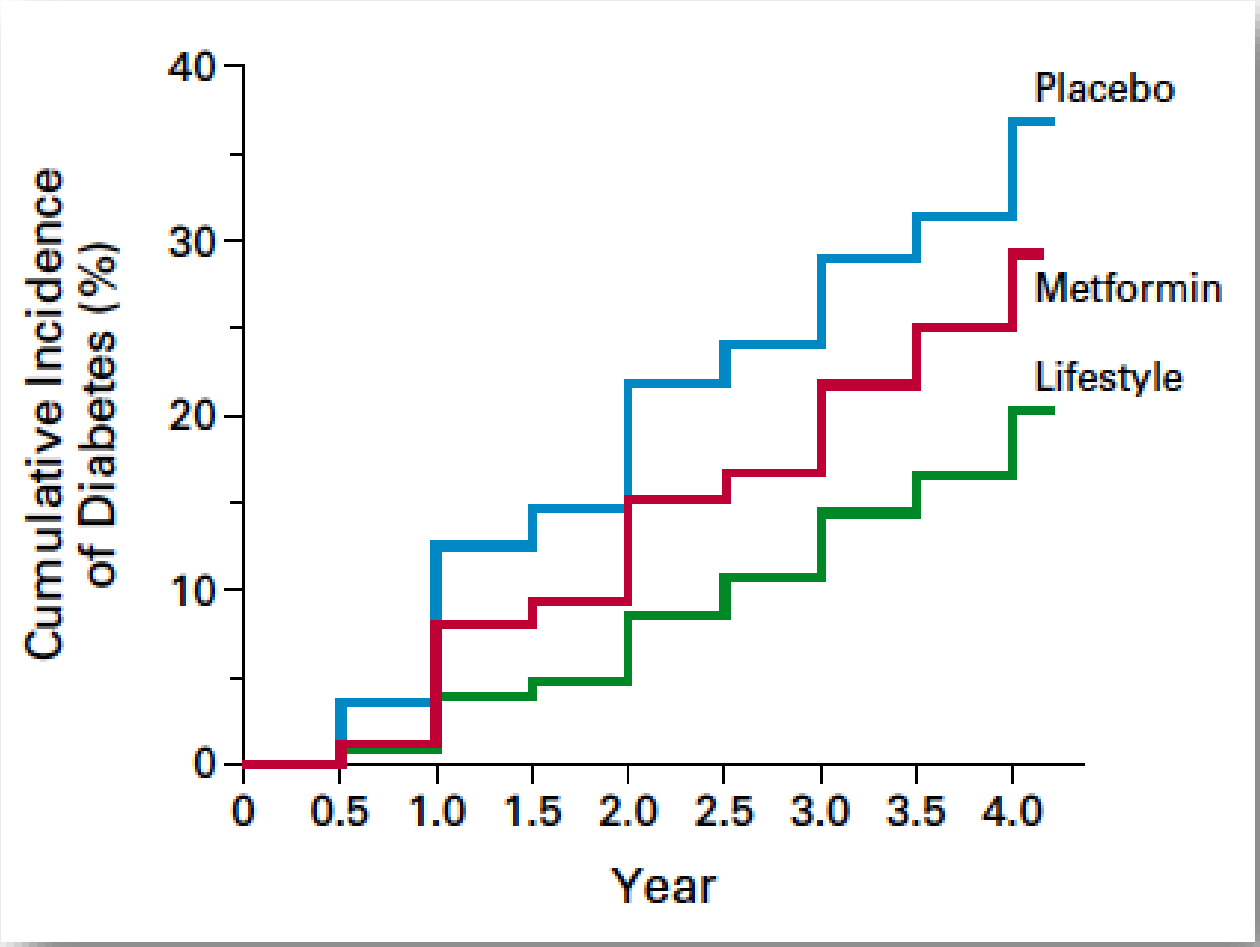
Diabetes Care 36:1297–1303, 2013

The New England Journal of Medicine

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*

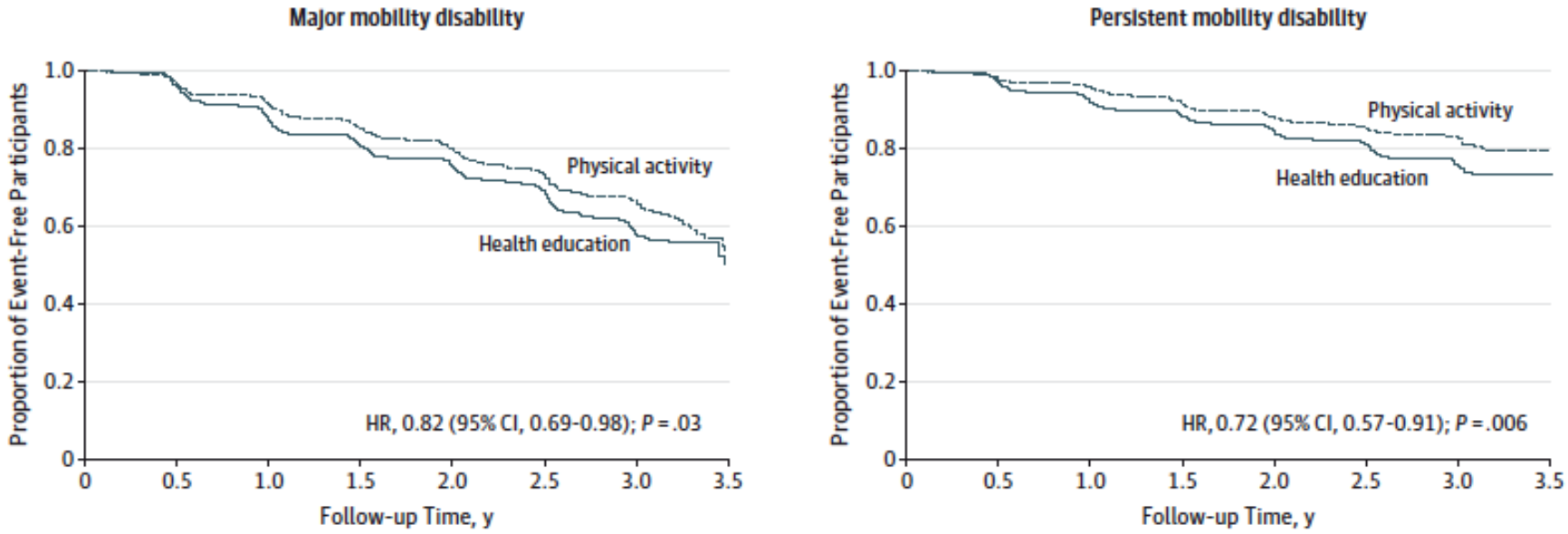

Cumulative Incidence of Diabetes (%)
40
30
20
10
0
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Year
Placebo
Metformin
Lifestyle

Original Investigation

Effect of Structured Physical Activity on Prevention of Major Mobility Disability in Older Adults

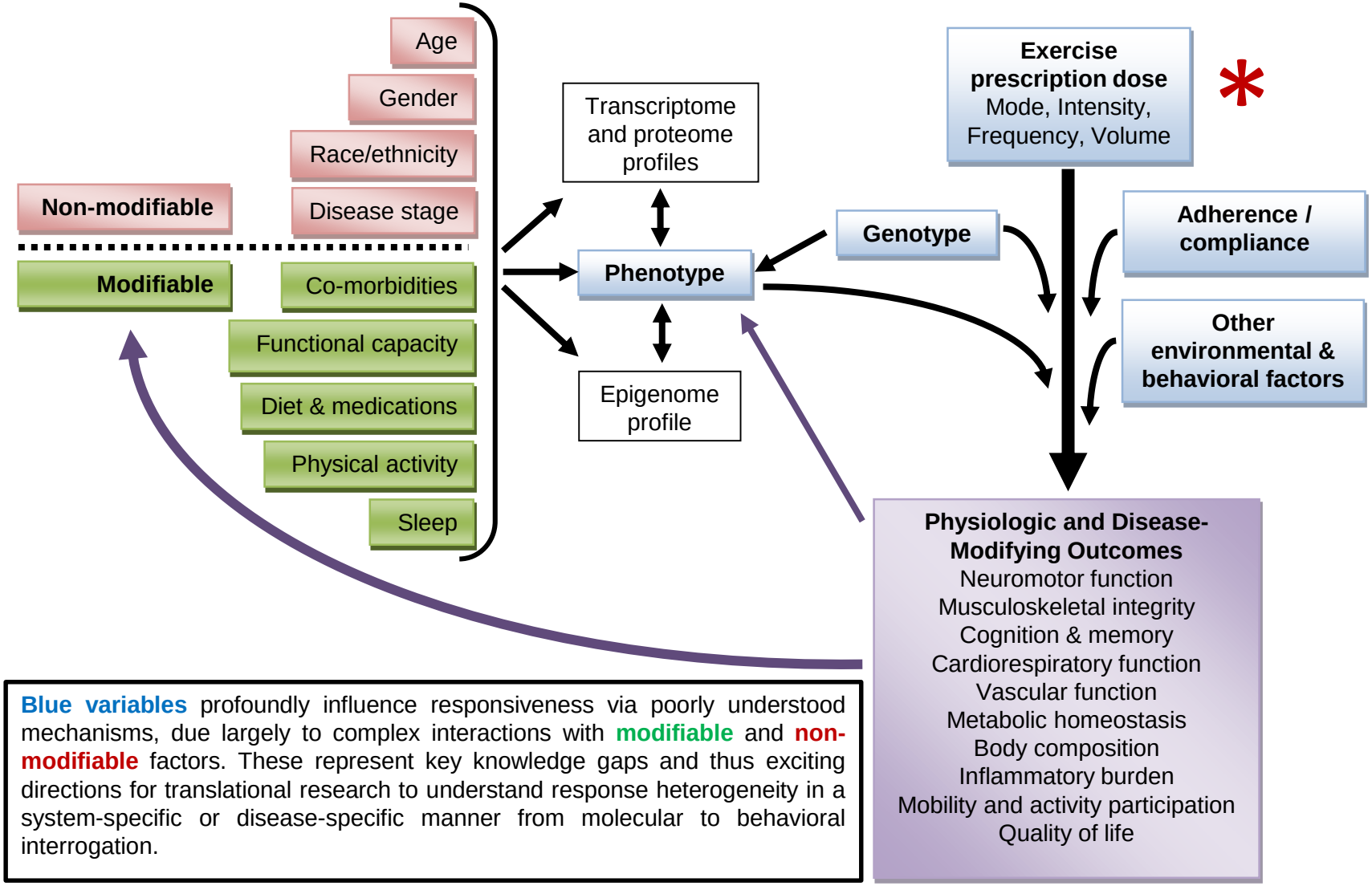
The LIFE Study Randomized Clinical Trial

Figure 3. Effect of a Moderate Physical Activity Intervention on the Onset of Major Mobility Disability and Persistent Mobility Disability



FACTORS INFLUENCING EXERCISE ADAPTATION

Factors influencing exercise adaptation: key research priorities



Blue variables profoundly influence responsiveness via poorly understood mechanisms, due largely to complex interactions with **modifiable** and **non-modifiable** factors. These represent key knowledge gaps and thus exciting directions for translational research to understand response heterogeneity in a system-specific or disease-specific manner from molecular to behavioral interrogation.

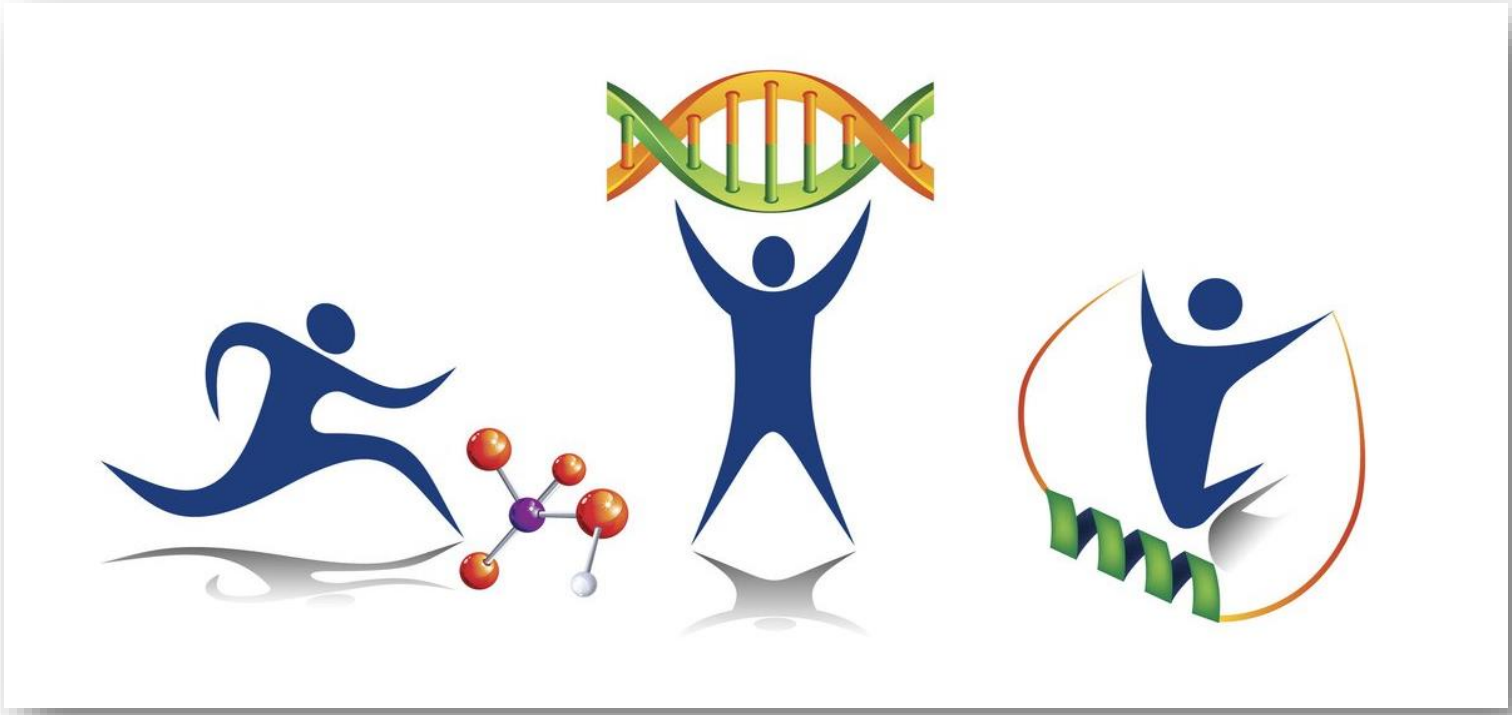
Optimal prescription/dose?

- **Mode**
- **Intensity**
- **Frequency**
- **Volume**

UAB Magazine
Fall/Winter Issue 2011

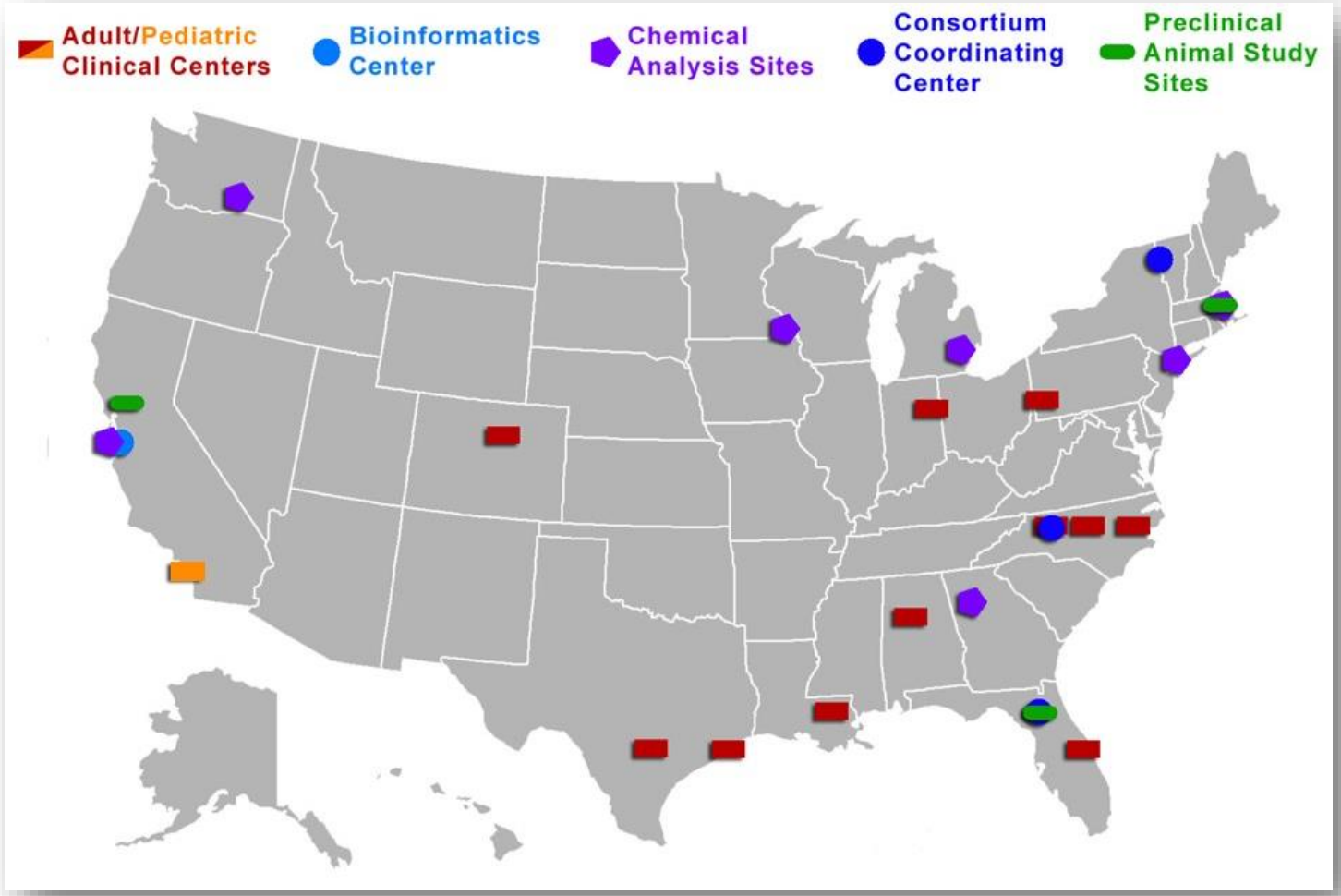
UAB CENTER FOR EXERCISE MEDICINE

Molecular Transducers of Physical Activity Consortium (MoTrPAC)



NIH National Institutes of Health
Office of Strategic Coordination - The Common Fund

Molecular Transducers of Physical Activity Consortium (MoTrPAC)



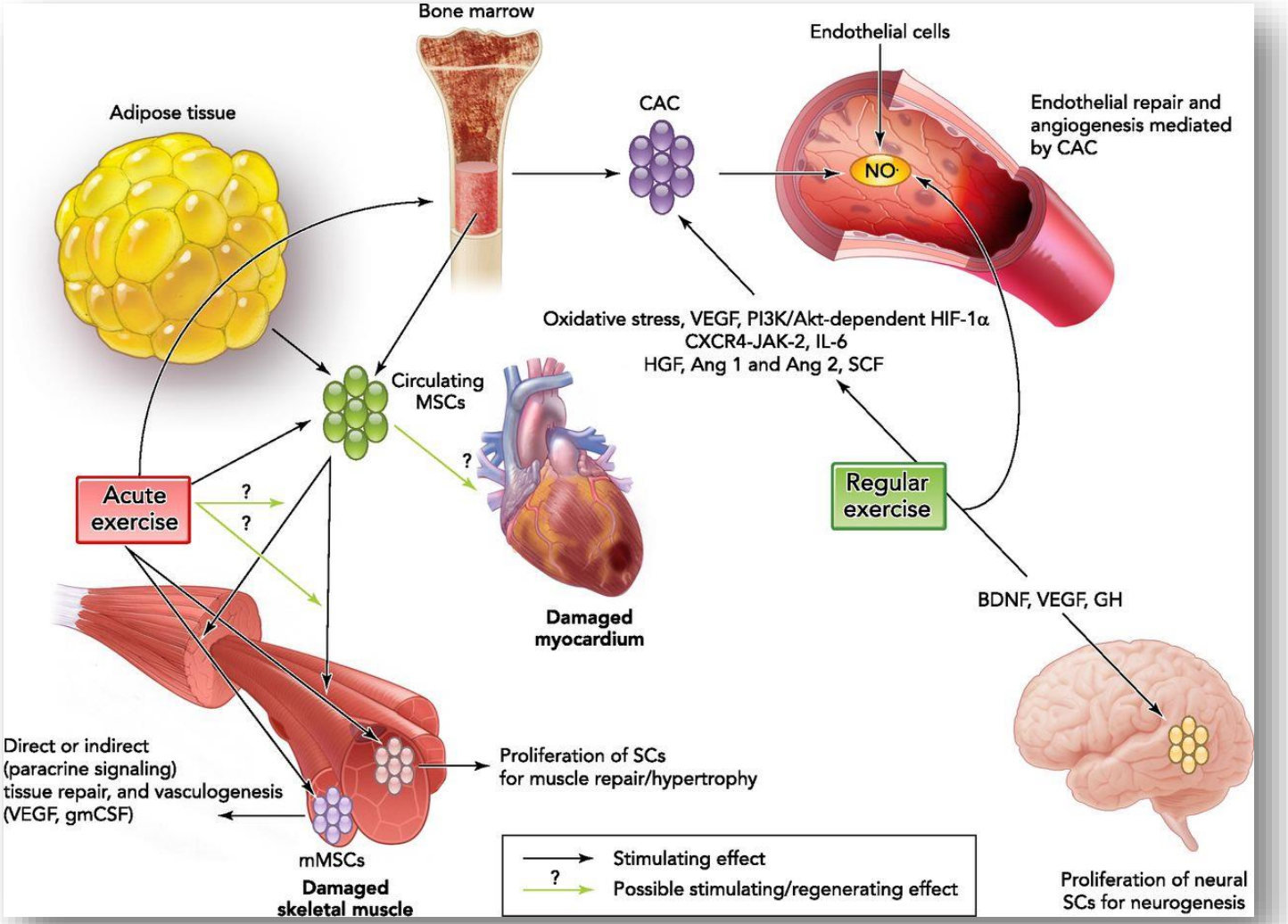
NIH National Institutes of Health
Office of Strategic Coordination - The Common Fund

EXERCISE IS REGENERATIVE MEDICINE

Regenerative medicine defined

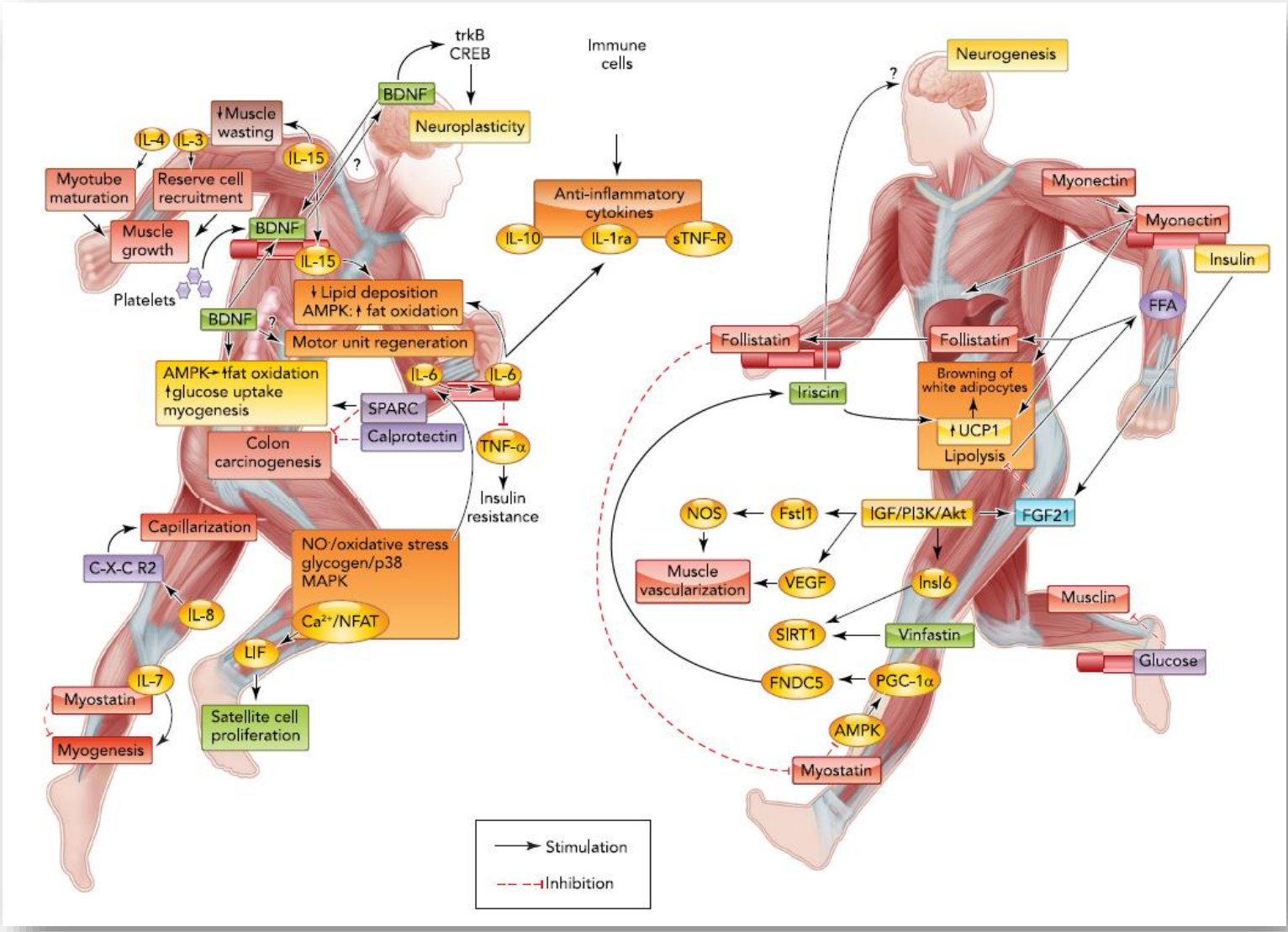
- A nascent field of (cutting edge) medicine described as **the creation of tissues that provide, repair, replace or restore structures and functions** absent or lost due to congenital defects, ageing, disease, or damage (Segen's Medical Dictionary 2012)

Exercise is Regenerative Medicine



Physiology. 28:330-58, 2013

Exercise is Regenerative Medicine



Physiology. 28:330-58, 2013

Exercise is Regenerative Medicine

- Endogenous stem cell activation
- Neurogenesis
- Myogenesis
- Angiogenesis
- Osteogenesis
- Mitochondrial biogenesis
- Lipolysis
- **Reduced tumorigenesis?** (very encouraging data in animal models)

Leveraging animal models

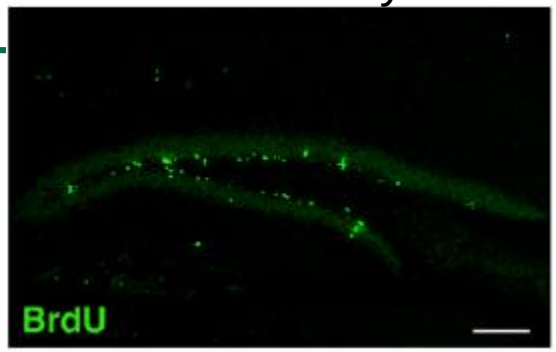
EXERCISE IS REGENERATIVE MEDICINE

Running Rescues Defective Adult Neurogenesis by Shortening the Length of the Cell Cycle of Neural Stem and Progenitor Cells

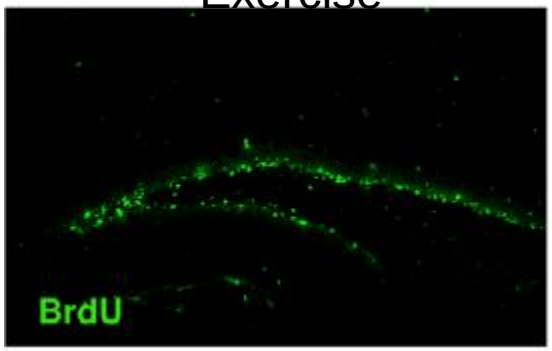
STEFANO FARIOLI-VECCHIOLI[a*], ANDREA MATTERA[a*], LAURA MICHELI[a], MANUELA CECCARELLI[a], LUCA LEONARDI[a], DANIELE SARAULLI[a], MARCO COSTANZI[ab], VINCENZO CESTARI[ac], JEAN-PIERRE ROUAULT[d], AND FELICE TIRONE[a]

Stem Cells, 2014

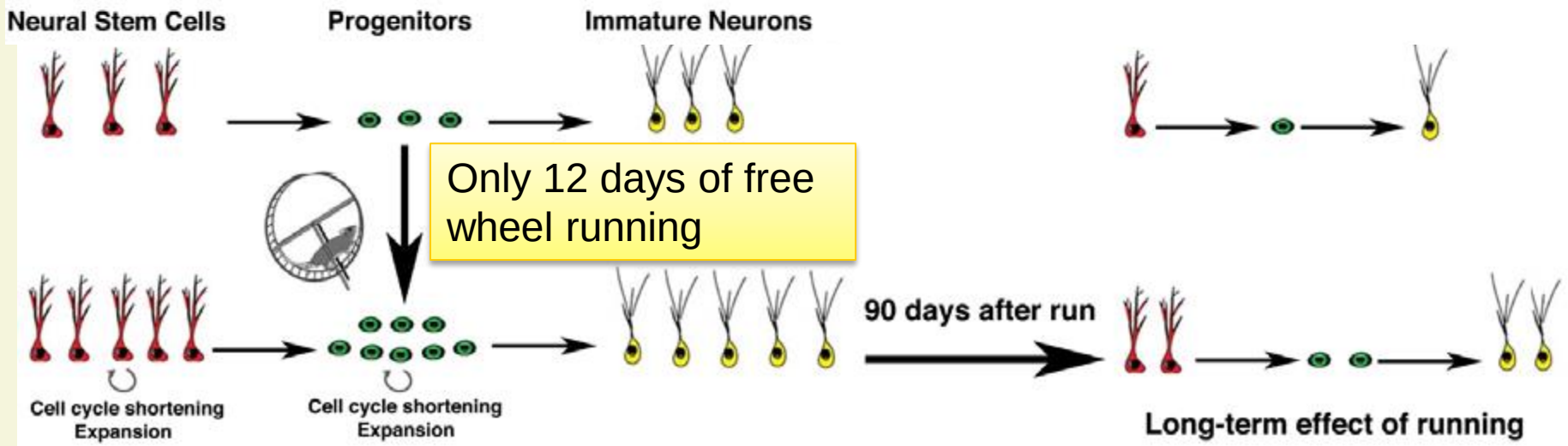
Sedentary



Exercise



Dentate gyrus region of hippocampus



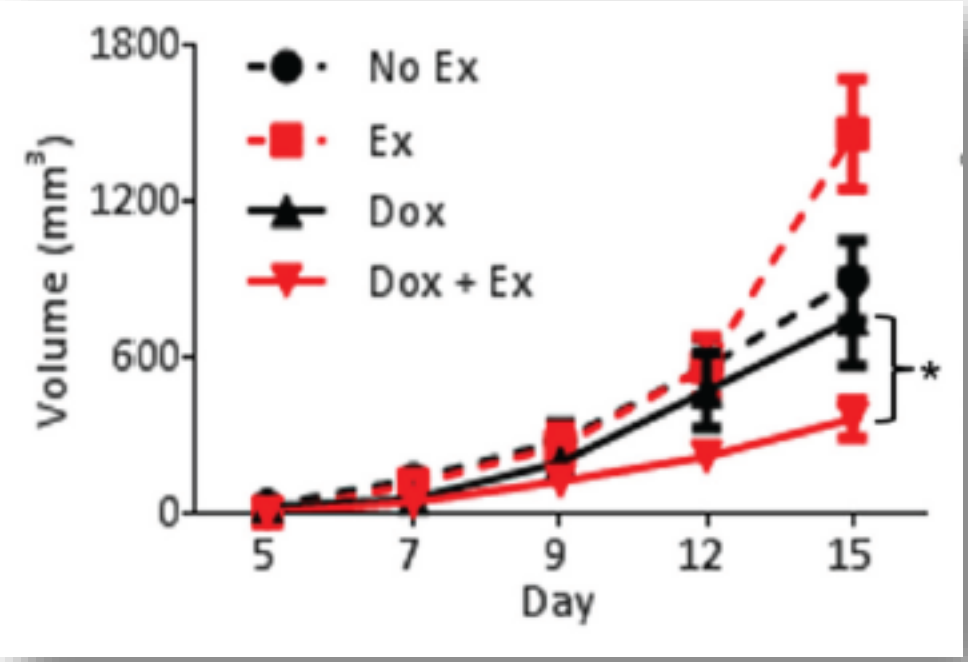
www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 40

Research Paper

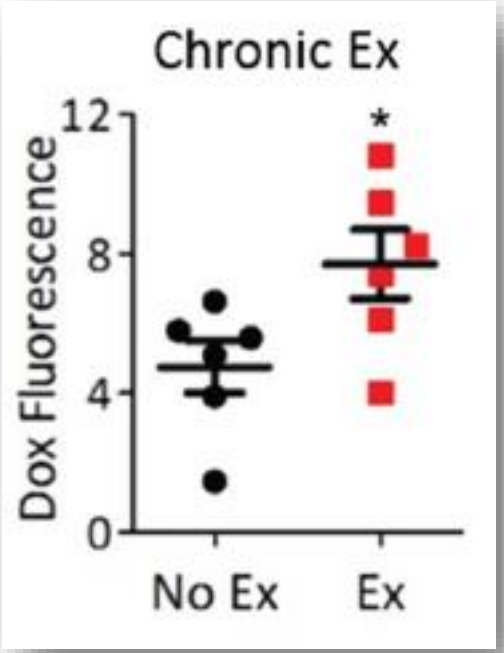
Tumor vessel normalization after aerobic exercise enhances chemotherapeutic efficacy

Keri L. Schadler[1], Nicholas J. Thomas[1], Peter A. Galie[2], Dong Ha Bhang[1], Kerry C. Roby[1], Prince Addai[1], Jacob E. Till[1], Kathleen Sturgeon[1], Alexander Zaslavsky[1], Christopher S. Chen[3], Sandra Ryeom[1]

Exercise + chemo decreases tumor growth more than chemo alone



Exercise increases delivery of chemotherapeutic drugs to tumors



Biochemical and Biophysical Research Communications 463 (2015) 811–817

Contents lists available at ScienceDirect

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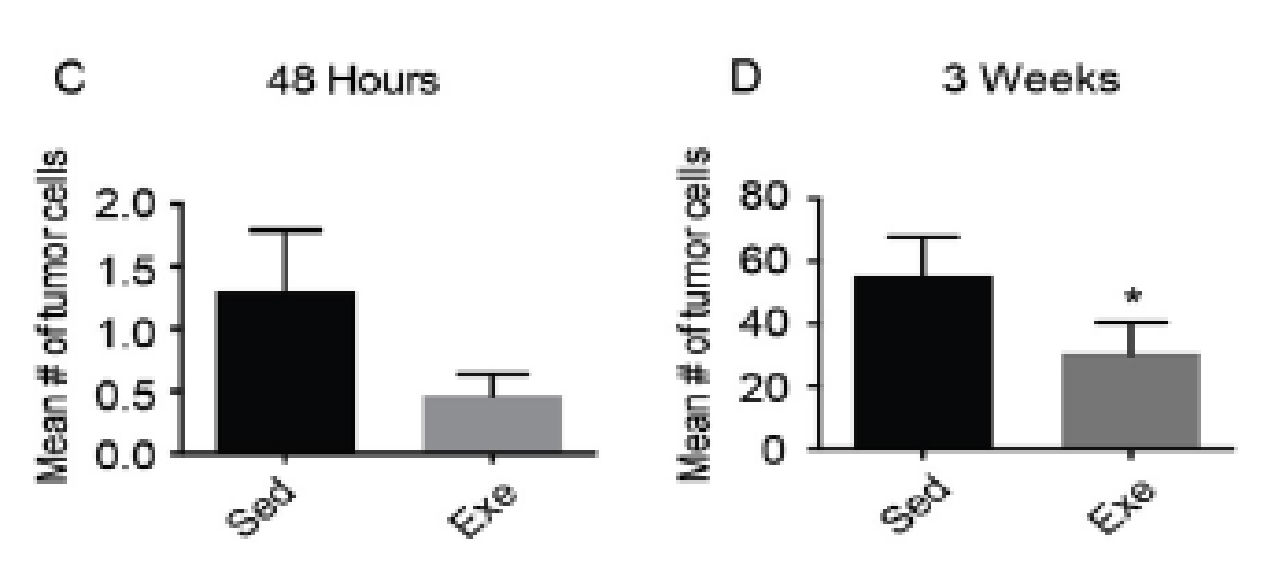
journal homepage: www.elsevier.com/locate/ybbrc

Exercise maintains blood–brain barrier integrity during early stages of brain metastasis formation

Gretchen Wolff [a], Sarah J. Davidson [a], Jagoda K. Wrobel [a], Michal Toborek [a, b, *]

[a] Department of Biochemistry and Molecular Biology, University of Miami, Miller School of Medicine, 1011 NW 15th, St., Miami, FL 33136, USA
[b] Jerzy Kukuczka Academy of Physical Education, ul. Mikolowska 72a, Katowice 40-065, Poland

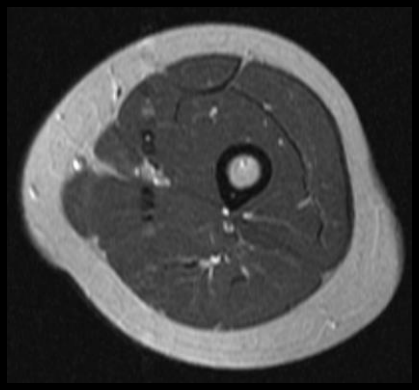
Exercise reduces brain metastasis



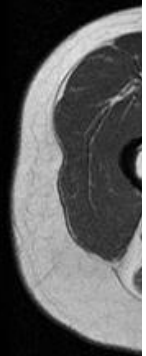
Essential role for resistance training in cancer rehabilitation

EXERCISE IS REGENERATIVE MEDICINE

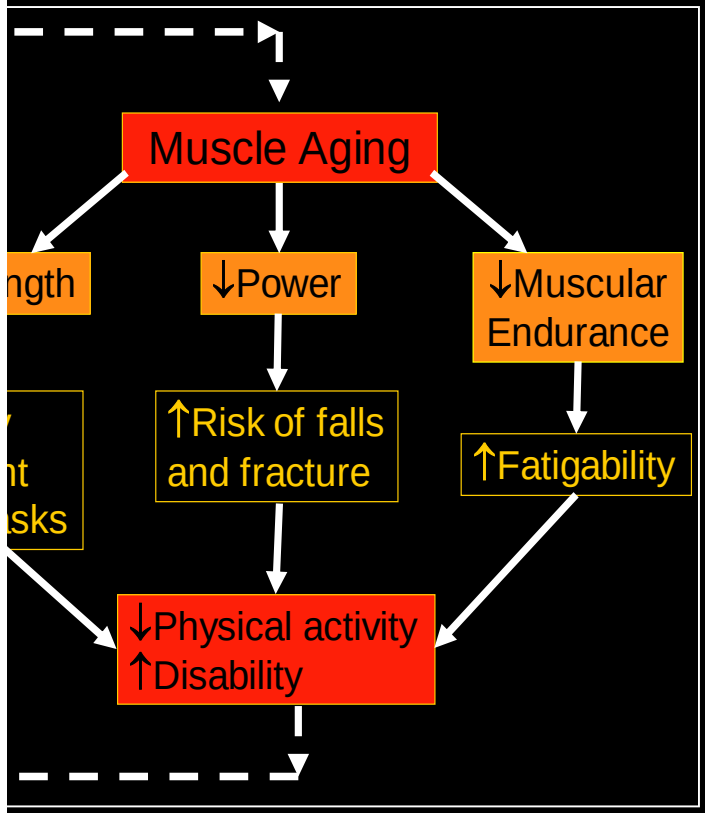
Aging muscle atrophy and functional consequences



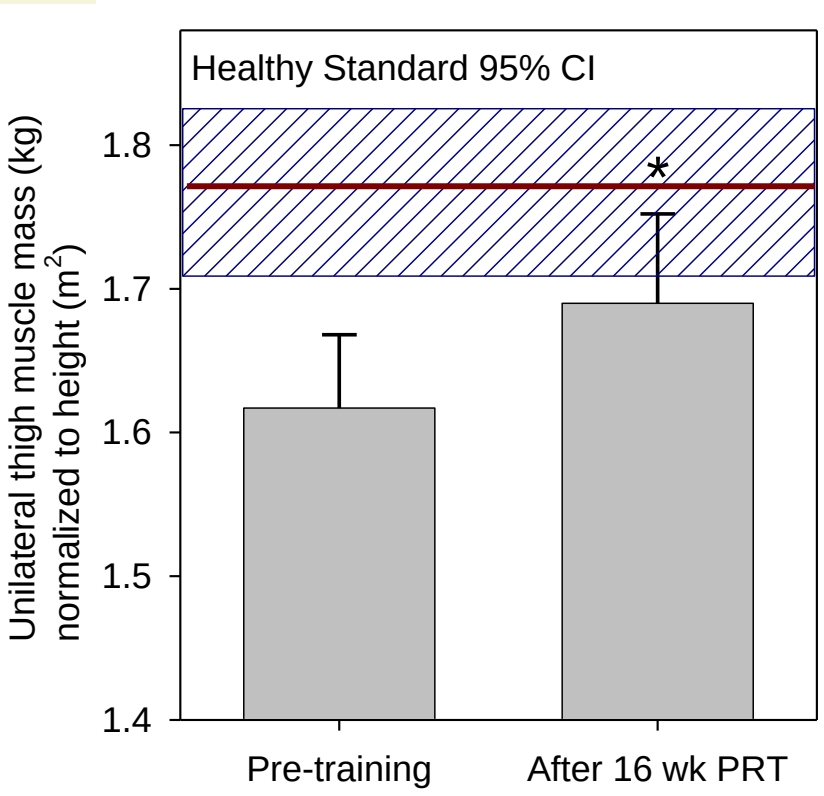
Top: 27y female
Bottom: 65y female
Ht & wt matched

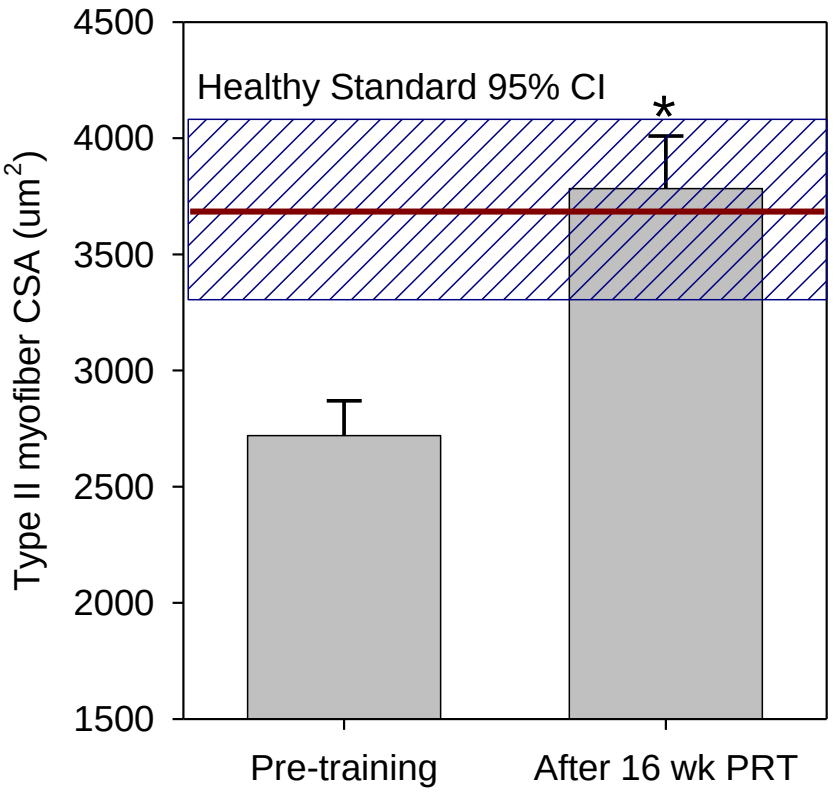


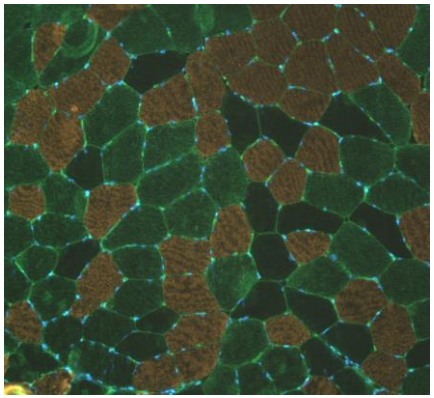
Top: 25y
Bottom: 6
Ht & wt m

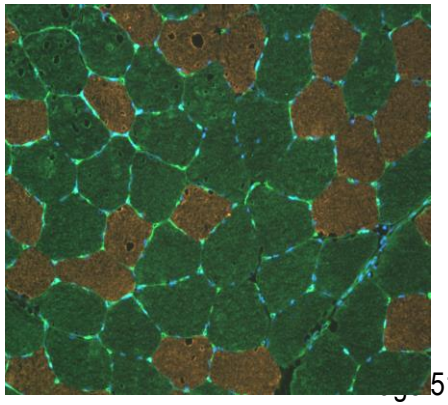


Restoration of muscle mass and myofiber size



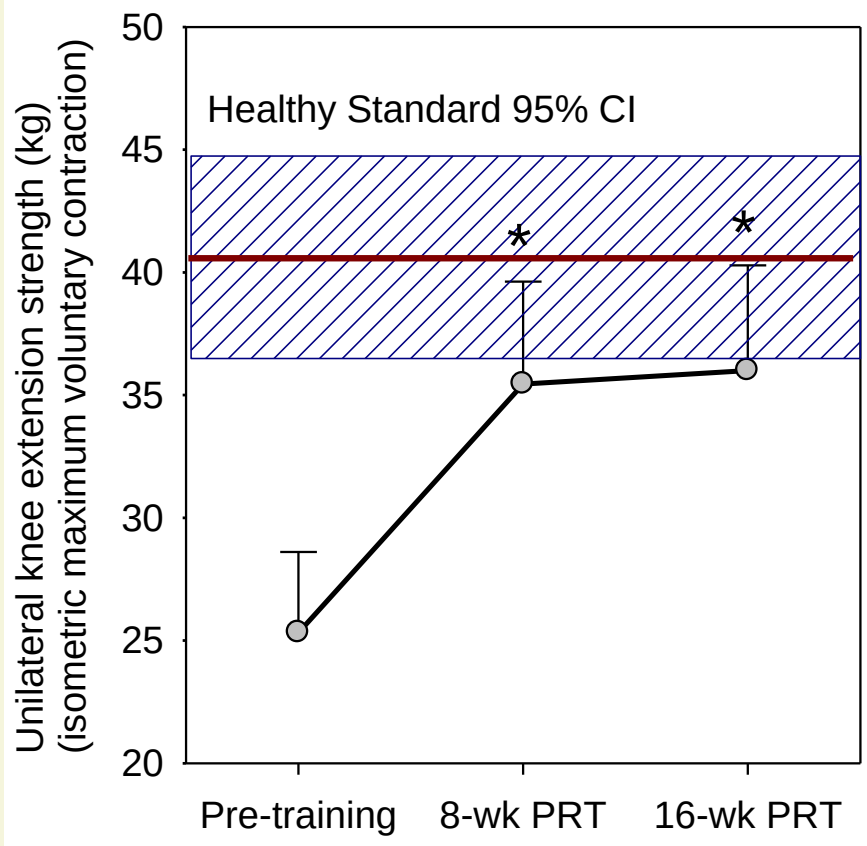


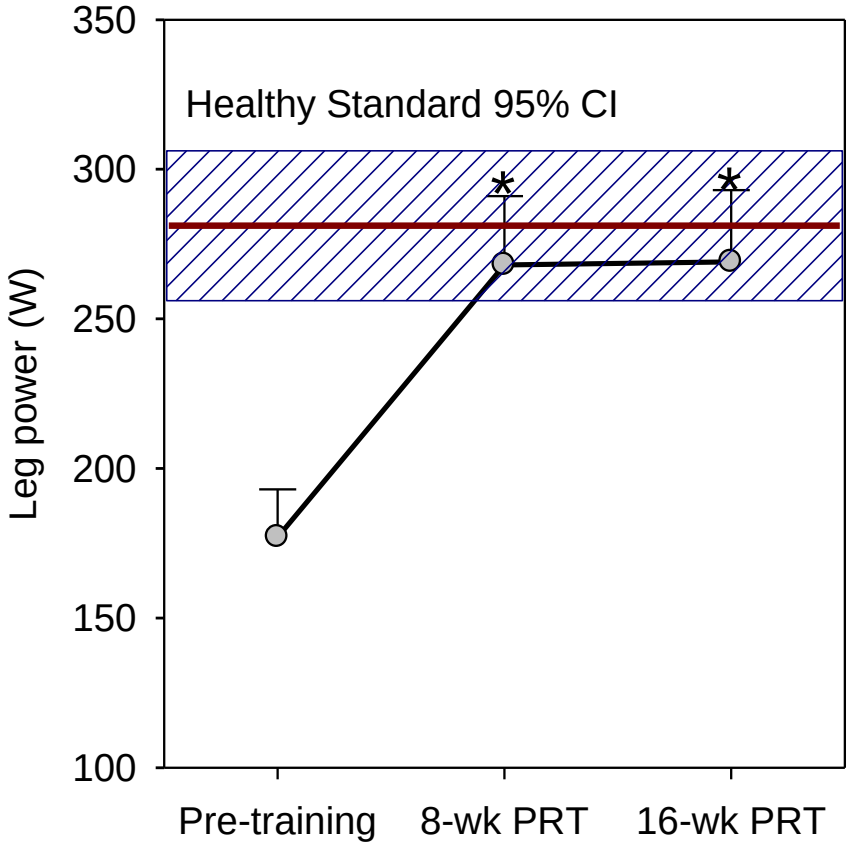




UAB MEDICINE
Knowledge that will change your world

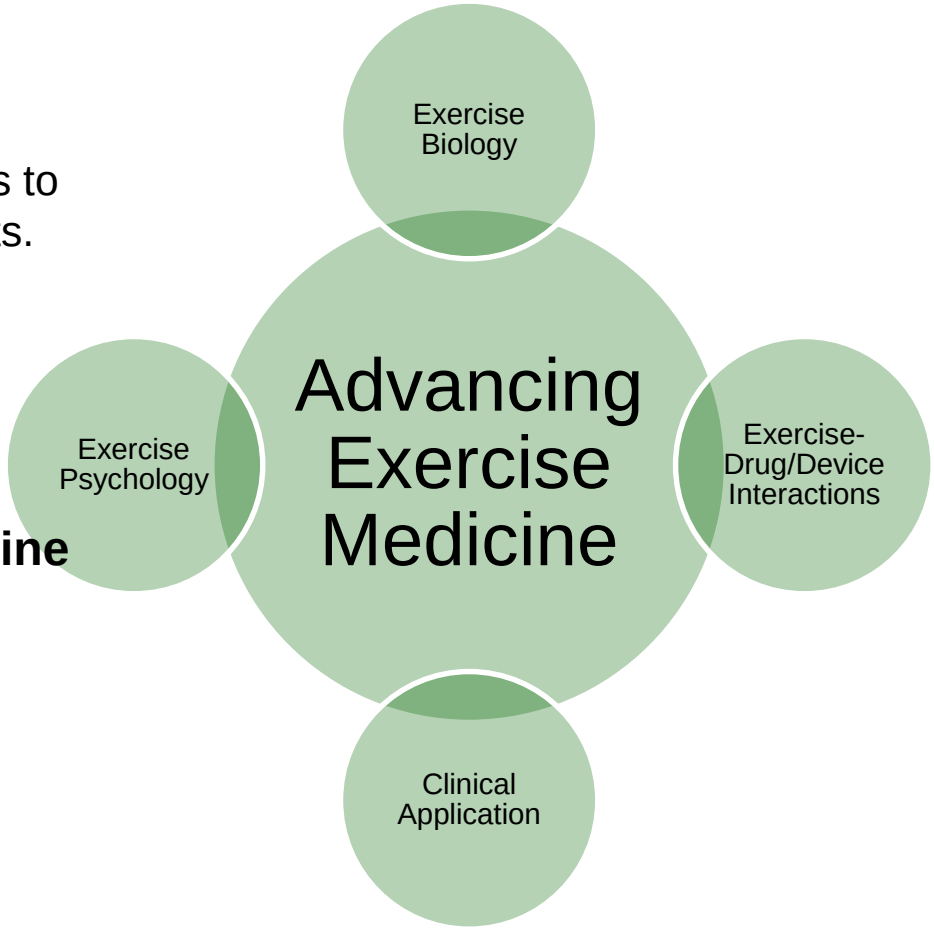
Restoration of neuromuscular function





Major Knowledge Gaps: *Interdisciplinary research priorities*

- **Exercise Biology**
  - Dose-response mechanisms.
  - Genetic and phenotypic variations.
  - Mechanisms by which **inactivity** fosters development and progression of CNCDs.
  - Taking advantage of potent exercise stimulus to discover new pathways and molecular targets.
- **Exercise-Drug/Device Interactions**
  - Differences in drug/device efficacy between active and inactive individuals.
  - Synergism, antagonism, drug metabolism.
  - Drug re-purposing via exercise responses.
- **Exercise Psychology/Behavioral Medicine**
  - Genetic and non-genetic determinants of exercise adherence and lasting lifestyle modification.
- **Clinical Application**
  - Optimizing disease-specific and population-specific exercise dosing/prescription to streamline clinical care.



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National Institute of Biomedical Imaging and Bioengineering

MR3 Medical Rehabilitation Research Resource NETWORK

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R&ACT

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Rehabilitation Research Resource to Enhance Clinical Trials

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

BCM Baylor College of Medicine

Our mission is to promote, support, and enhance medical rehabilitation clinical research to optimize patient care and quality of life.

Resources:

- Education & training for clinical trials
- Clinical databases
- Consultative & collaborative services:
  - Clinical trials design assistance
  - Access to core laboratories & clinical resources
- Pilot studies program
- Visiting scientist opportunities
- Mobile Technology Laboratory
  - Wearables, biosensors, mHealth apps
- Scholar awards to support research and training

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NExTNet

National Exercise Clinical Trials Network

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Quick Facts:

- Est. 2012; grown to 70 Member Institutions
- Partners: UAB CTSA (CCTS), CTSA Consortium, ACSM