

# Cardiometabolic Benefits of Low Intensity Physical Activity

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# Financial Acknowledgements/Disclosures

## Research Funding:

National Institutes of Health

United States Department of Agriculture

National Space Biomedical Research Institute

American Heart Association

Schlieder Educational Foundation (to Pennington Foundation)

The Coca-Cola Company (to Pennington Foundation)

## Employment:

University of Texas School of Medicine

University of Missouri College of Veterinary Medicine

Pennington Biomedical Research Center

# My Goal For Inactivity Physiology

*To discover a potent solution for millions of people who can't (or won't) exercise.*



Well beyond expectations

# How Can This Be Achieved?

That is the holy grail of healthy lifestyles!



## *Inactivity Physiology Explained Simply*

Some of the most potent mechanisms at the root cause of chronic disease are caused by inactivity (generally sitting) because the body needs frequent muscular activity.

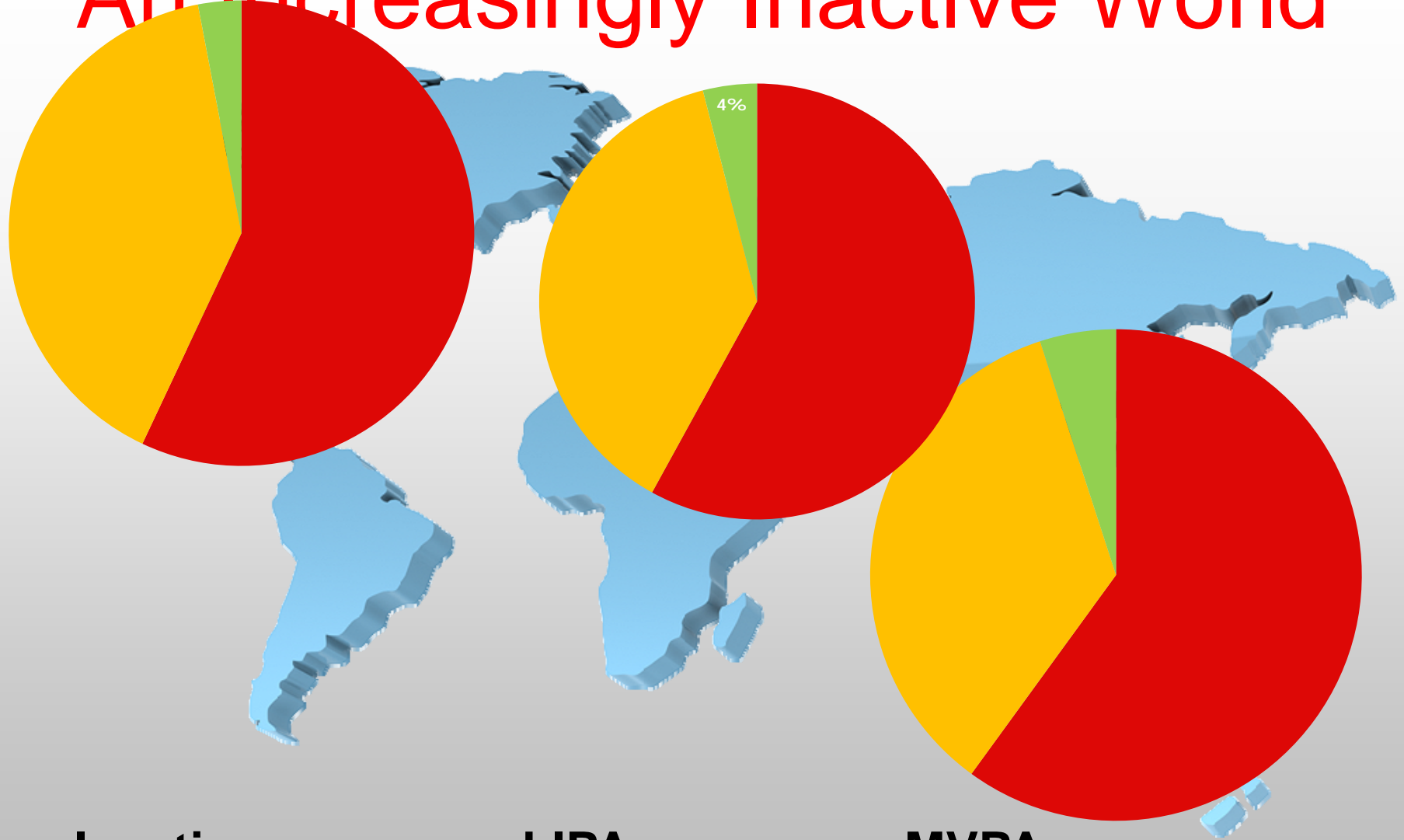
See - ESSR, 2004 & Diabetes, 2007



**Simple But Profound Rationale-**  
**Cells receive input from their environment**  
**every minute of every day.**



# An Increasingly Inactive World



**Inactive**



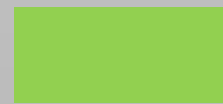
muscular inactivity

**LIPA**



Low Intensity

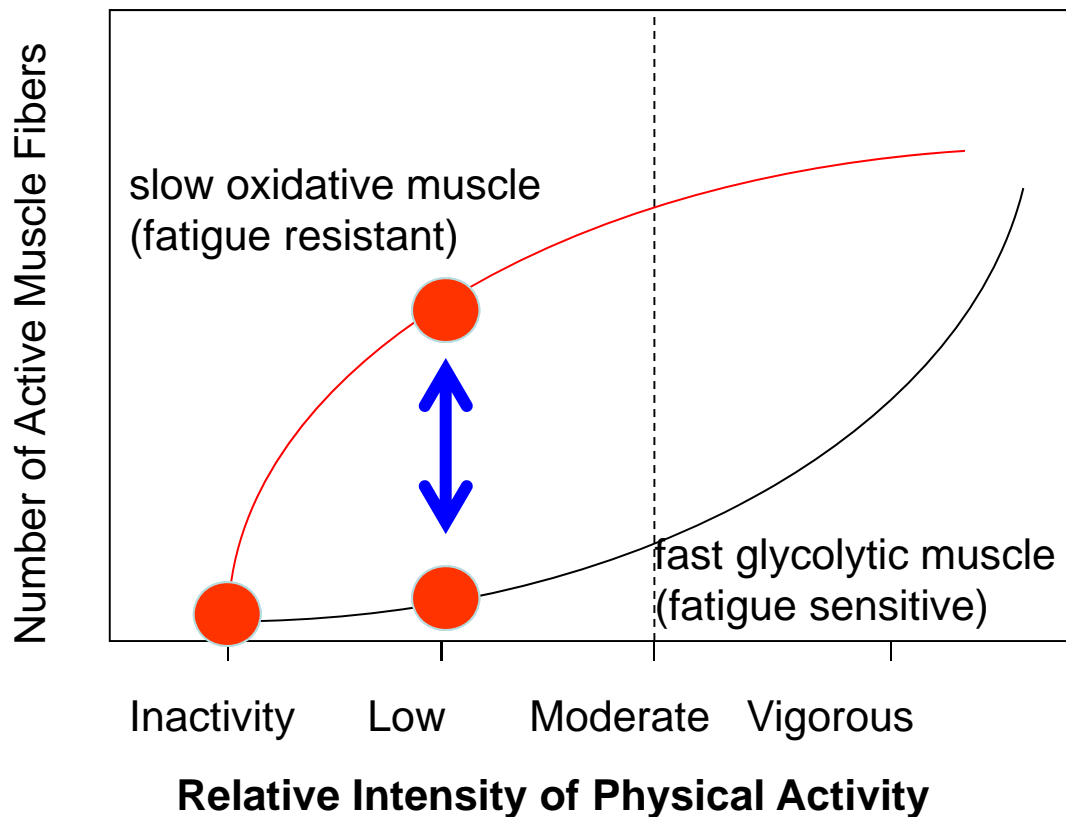
**MVPA**



Moderate + vigorous

# Understanding Why LIPA is Non-Fatiguing & Abundant

## Skeletal Muscle Fiber Type Recruitment



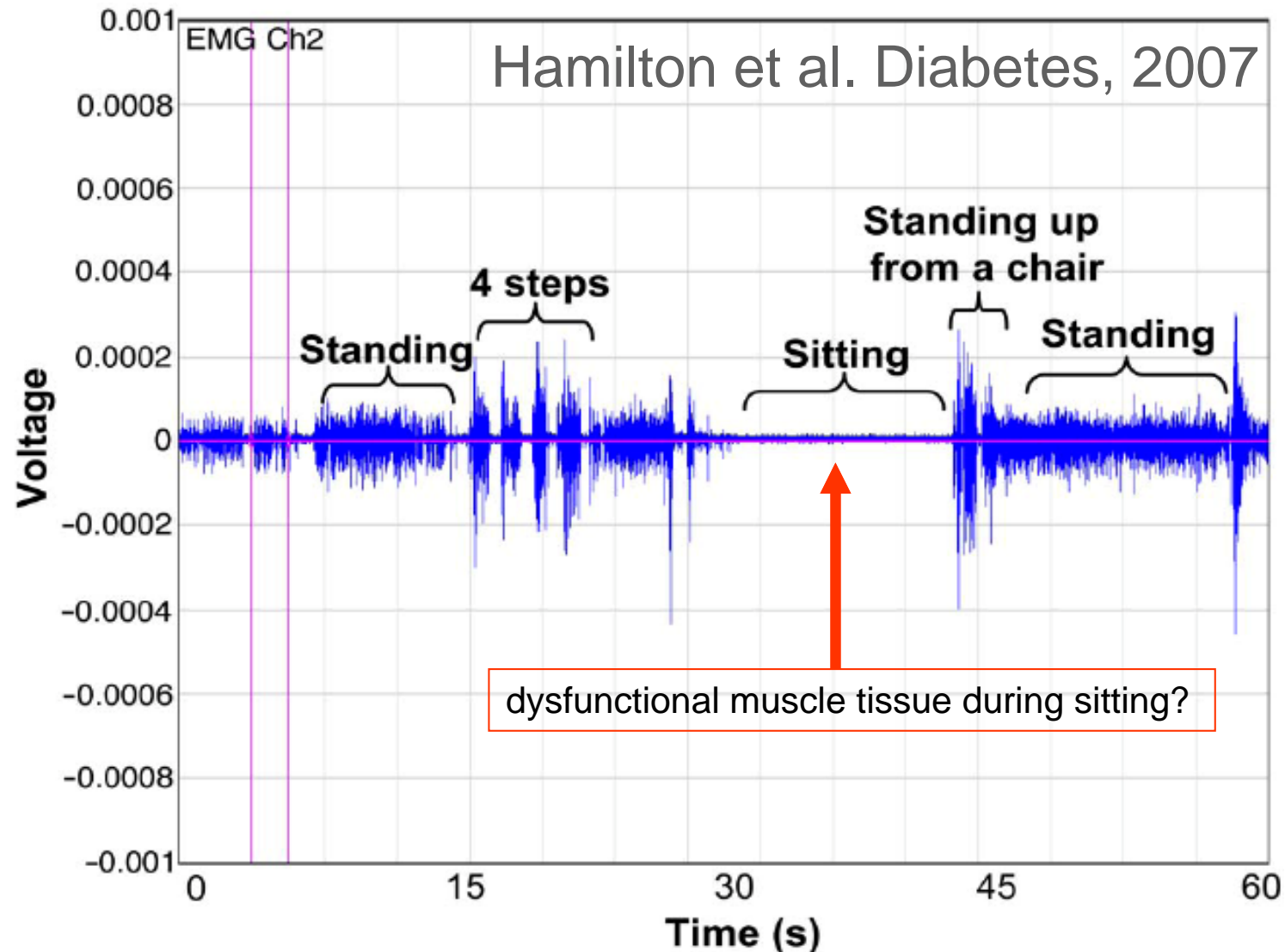
Hamilton and Owen, **Sedentary Behavior and Inactivity Physiology (2012)**. In *Physical Activity and Health*, 2<sup>nd</sup> edition.



Flat-line signals alert to dysfunctional tissue



***Inactivity Physiology*** focuses on the benefits of *large durations of intermittent muscular contractile activity* during **Low-Intensity Physical Activity (LIPA)** instead of sitting inactive

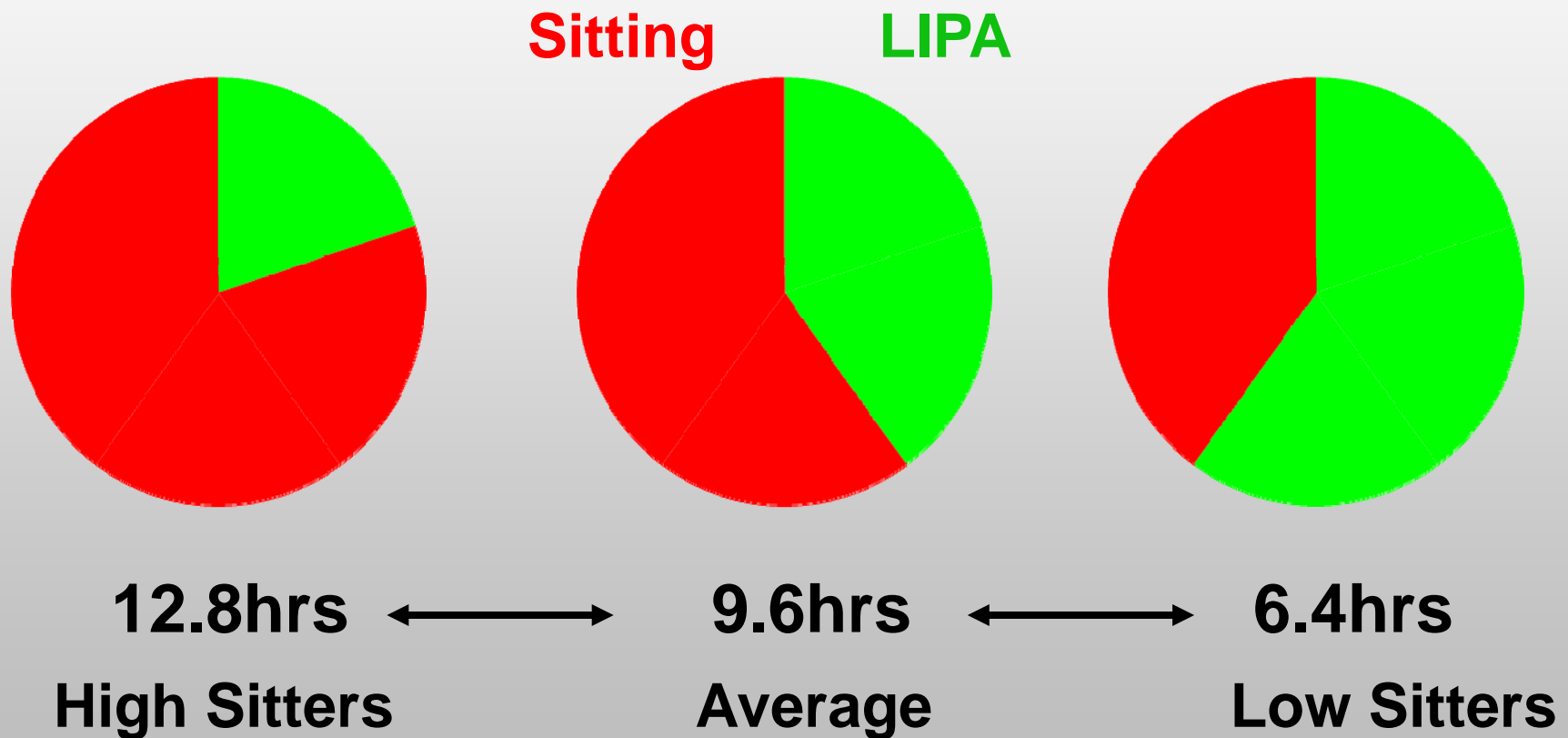


Human physiology is naturally well geared for a large daily duration of muscular activity

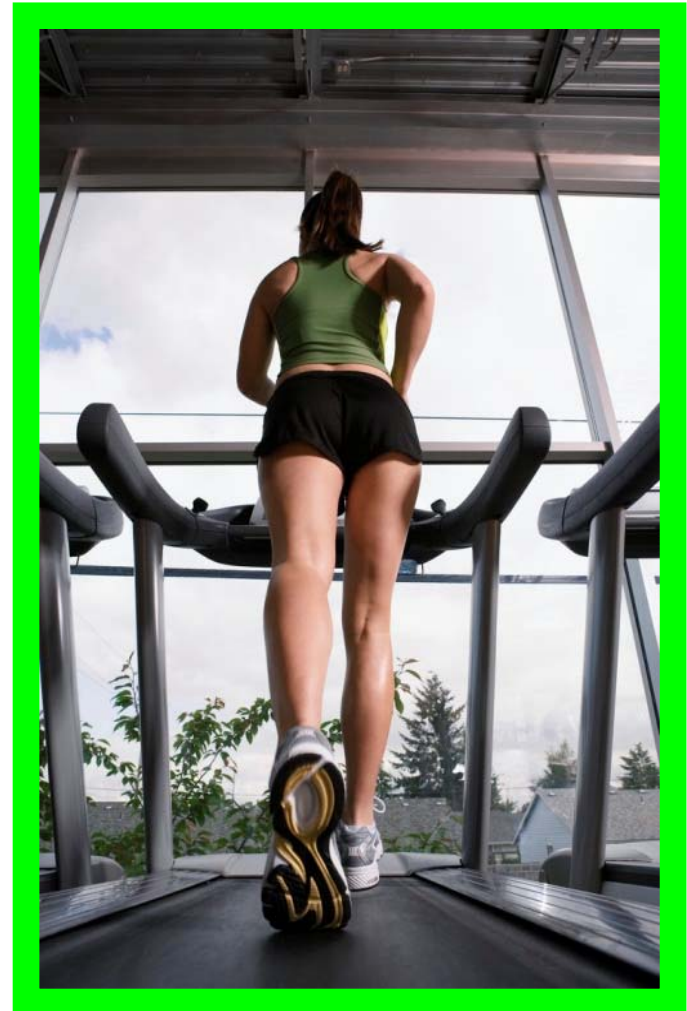
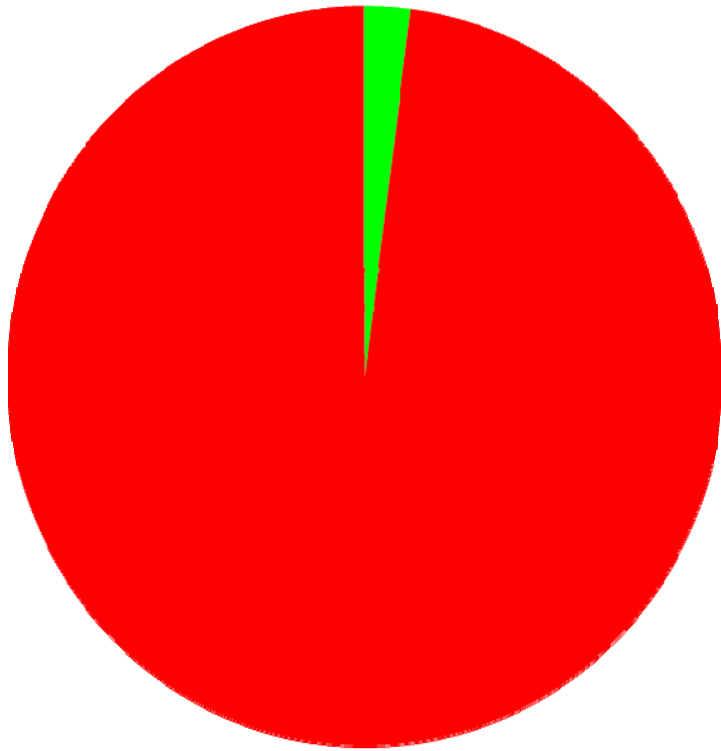


Hamilton et al. Diabetes, 2007

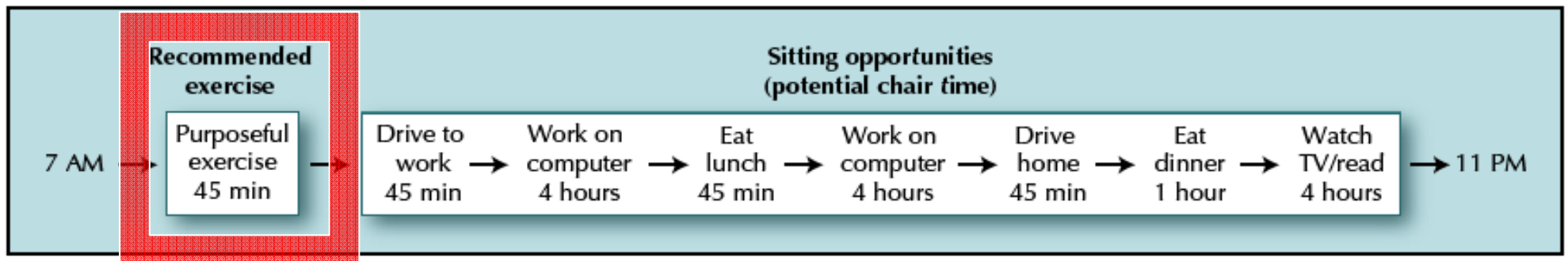
Saying that *people spend too many hours each day being sedentary (mostly sitting)* is actually the same as saying **people don't spend enough hours each day being active.**



**30 min is  $1/48^{\text{th}}$  of one day**



# Are you an “exercising couch potato”?

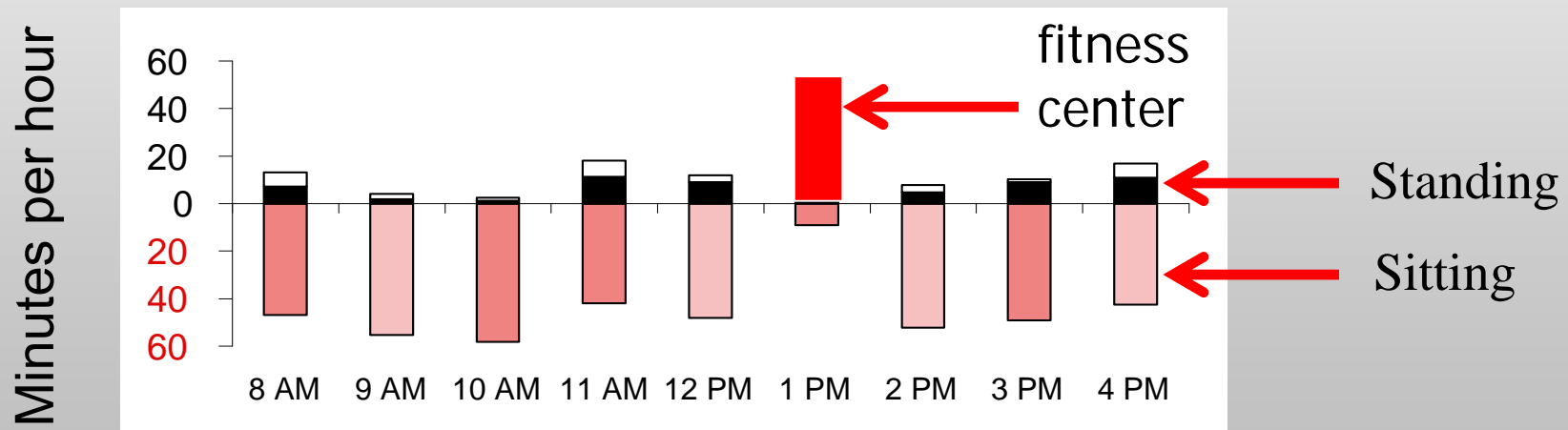


Hamilton et al. *Too Little Exercise and Too Much Sitting: Inactivity Physiology and the Need for New Recommendations on Sedentary Behavior*

Current Cardiovascular Risk Reports, 2008

Even in the minority of people who achieve the recommended 150 min/week of moderate activity...

...this still leaves ~16 hrs, ~**1400 minutes** of each waking day with physical inactivity!!!



Hamilton, Diabetes, 2007

# INACTIVITY PHYSIOLOGY STUDIES

The Early Years 1998-2003



# Exercise Physiology versus Inactivity Physiology: An Essential Concept for Understanding Lipoprotein Lipase Regulation

Marc T. Hamilton,<sup>1,2</sup> Deborah G. Hamilton,<sup>1</sup> and Theodore W. Zderic<sup>1</sup>

<sup>1</sup>Department of Biomedical Sciences and <sup>2</sup>Dalton Cardiovascular Research Center, University of Missouri-Columbia, Columbia, MO

HAMILTON, M.T., D.G. HAMILTON, and T.W. ZDERIC. Exercise physiology versus inactivity physiology: An essential concept for understanding lipoprotein lipase regulation. *Exerc. Sport Sci. Rev.*, Vol. 32, No. 4, pp. 161–166, 2004. Some health-related proteins such as lipoprotein lipase may be regulated by qualitatively different processes over the physical activity continuum, sometimes with very high sensitivity to inactivity. The most powerful process known to regulate lipoprotein lipase protein and activity in muscle capillaries may be initiated by inhibitory signals during physical inactivity, independent of changes in lipoprotein lipase messenger RNA. Key Words: dose response, coronary heart disease (CHD), transcription, posttranslational, signaling, sedentary, aging

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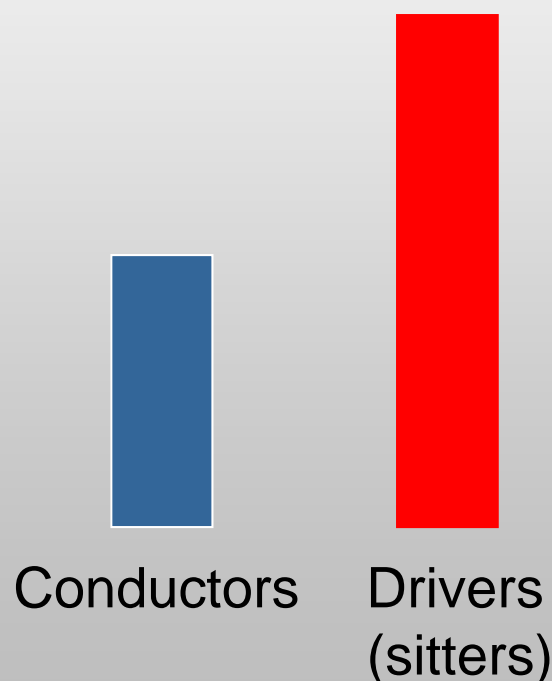
Why does sitting inactive have potent and hazardous effects on the body?

And are these processes independent of traditional exercise ("leisure time physical activity"), diet, and weight?

# In 2004 and 2007, **We Reinterpreted** the Classical Vocational Studies by Morris (c 1953)



Death From CHD  
middle age men



Hamilton, Hamilton, Zderic ESSR, 2004  
Hamilton, Hamilton, Zderic Diabetes, 2007

# Meta-analysis for Sedentary Time

## Type 2 Diabetes

## Metabolic Syndrome

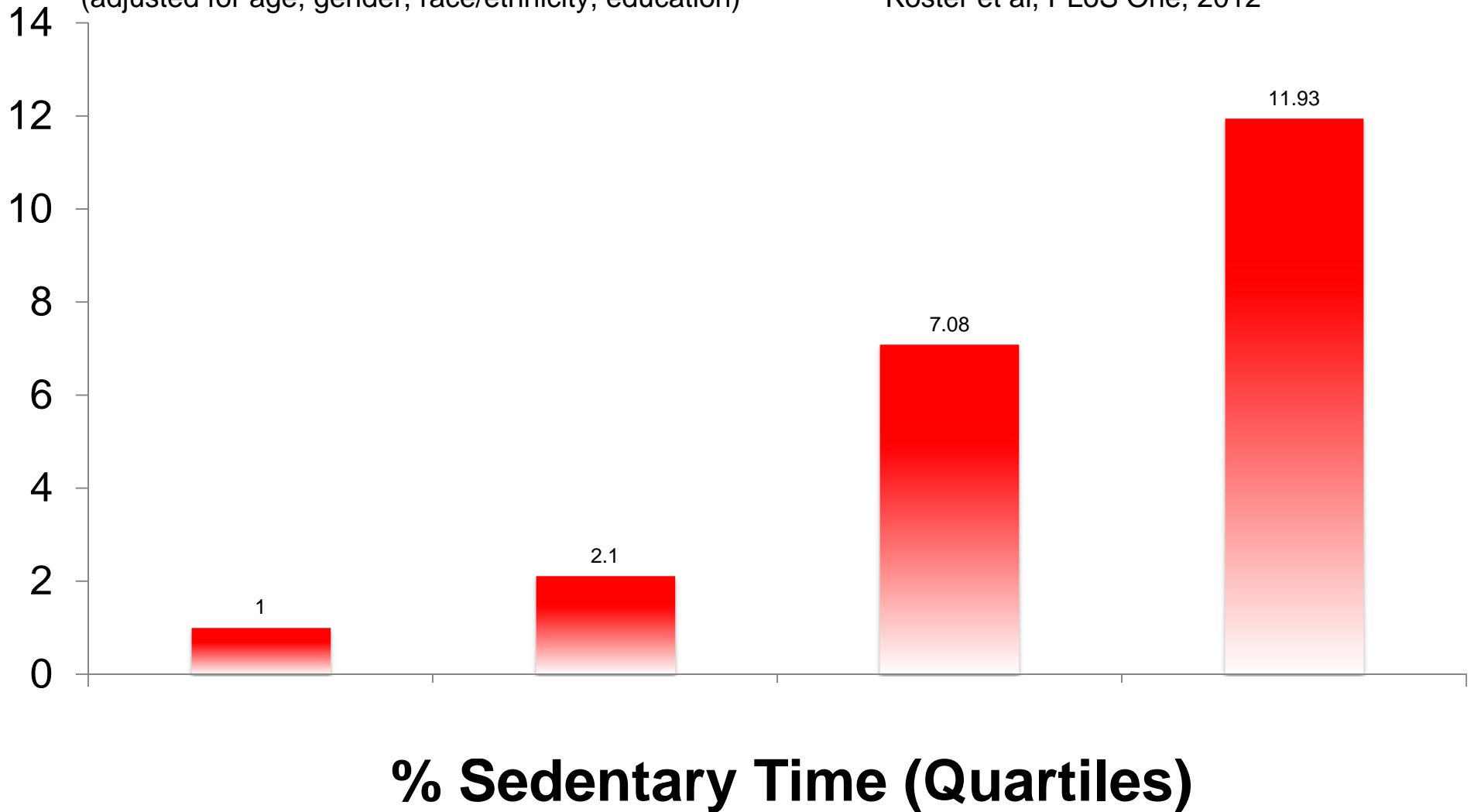
Relative Risk (95% CI/CrI)	Reference	Odd Ratio (95% CI)	Reference
2.87 (1.46, 5.65)	Hu et al	1.89 (1.42, 2.53)	Bertrais et al
1.70 (1.19, 2.42)	Hu et al	1.84 (1.41, 2.39)	Dunstan et al
2.34 (1.41, 3.90)	Dunstan et al	2.07 (1.23, 3.46)	Ford et al
1.86 (1.54, 2.24)	Krishnan et al	2.20 (1.10, 4.20)	Gao et al
2.18 (1.95, 2.43)	Tonstad et al	2.99 (0.83, 10.84)	Li et al
1.63 (1.17, 2.27)	Ford et al	1.68 (1.34, 2.11)	Chang et al
2.75 (1.83, 4.13)	Stamatakis et al	1.52 (1.01, 2.29)	Chen et al
1.85 (1.41, 2.43)	Wijndaele et al	1.72 (1.26, 2.35)	Sisson et al
1.22 (0.87, 1.72)	Hawkes et al	1.87 (1.17, 2.99)	Trinh et al
4.00 (3.62, 4.42)	Matthews et al	1.16 (0.77, 1.74)	Bankoski et al
<b>2.12 (1.61, 2.78)</b>	<b>Refs Pooled</b>	<b>1.73 (1.55, 1.94)</b>	<b>Refs Pooled</b>

Wilmot et al 2012

Edwardson et al 2012

# Mortality From Recent Studies

■ Mortality Hazard Ratio in 1,906 persons >50 yrs of age (averaging 63.8±10.5 yrs) from accelerometry (adjusted for age, gender, race/ethnicity, education) Koster et al, PLoS One, 2012

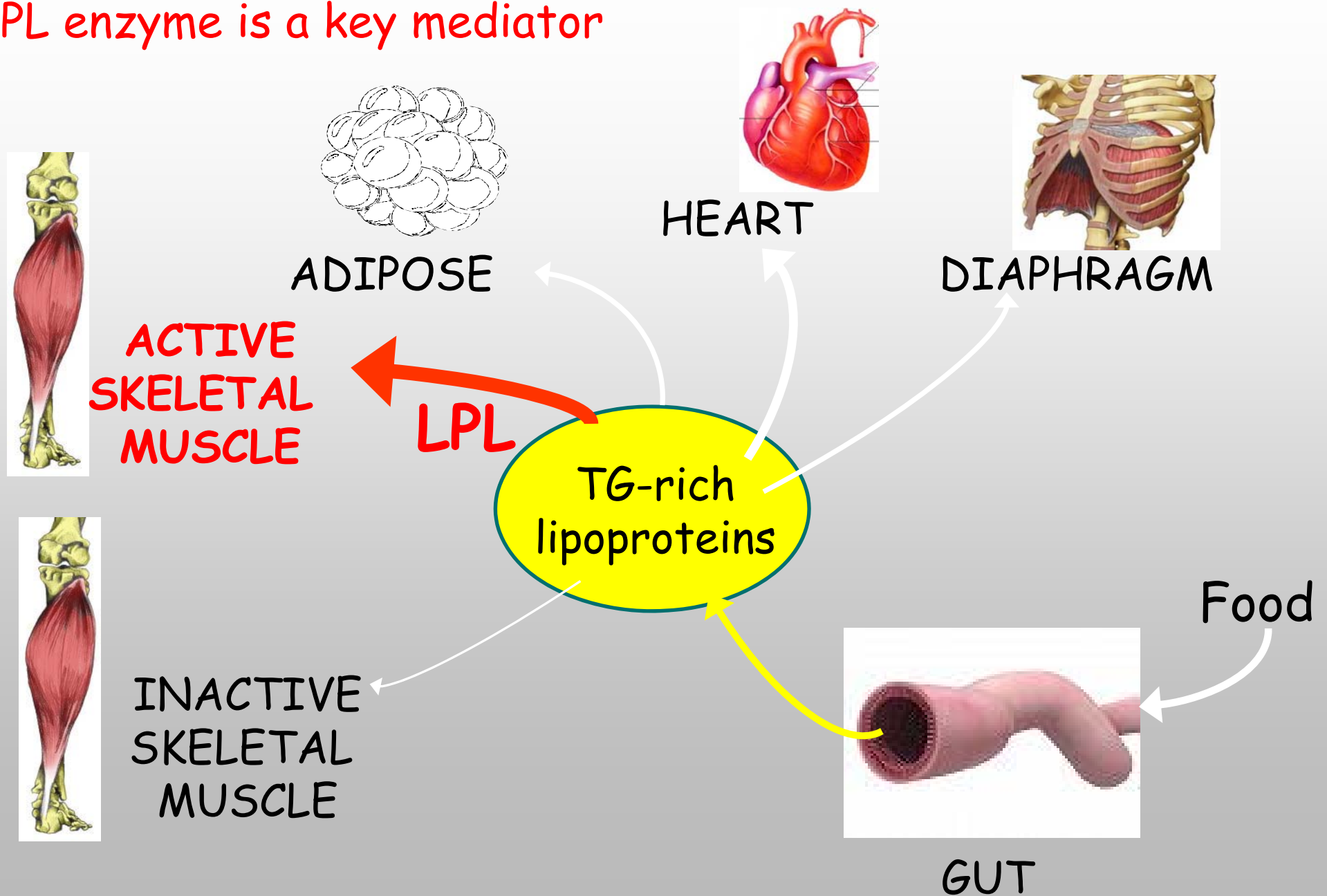


# Distinct Effects of Inactivity Physiology Independent from Exercise

- A focus on the research discovery that is focused on the *root causes* to explain why a lifestyle of sitting all day is hazardous for cardiovascular disease, diabetes, metabolic syndrome, inflammation, and blood clotting.

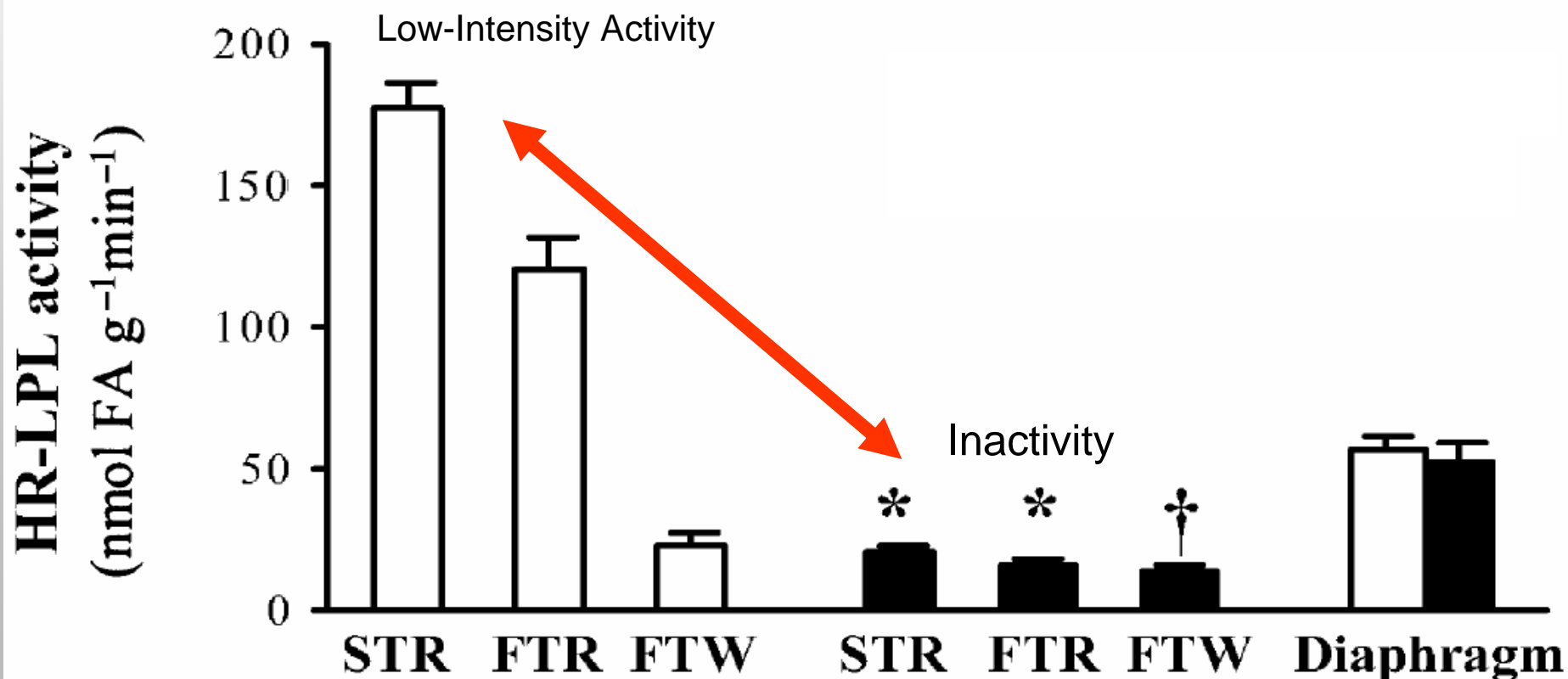
# Plasma Lipid Traffic

LPL enzyme is a key mediator



## Suppression of skeletal muscle lipoprotein lipase activity during physical inactivity: a molecular reason to maintain daily low-intensity activity

Lionel Bey and Marc T. Hamilton

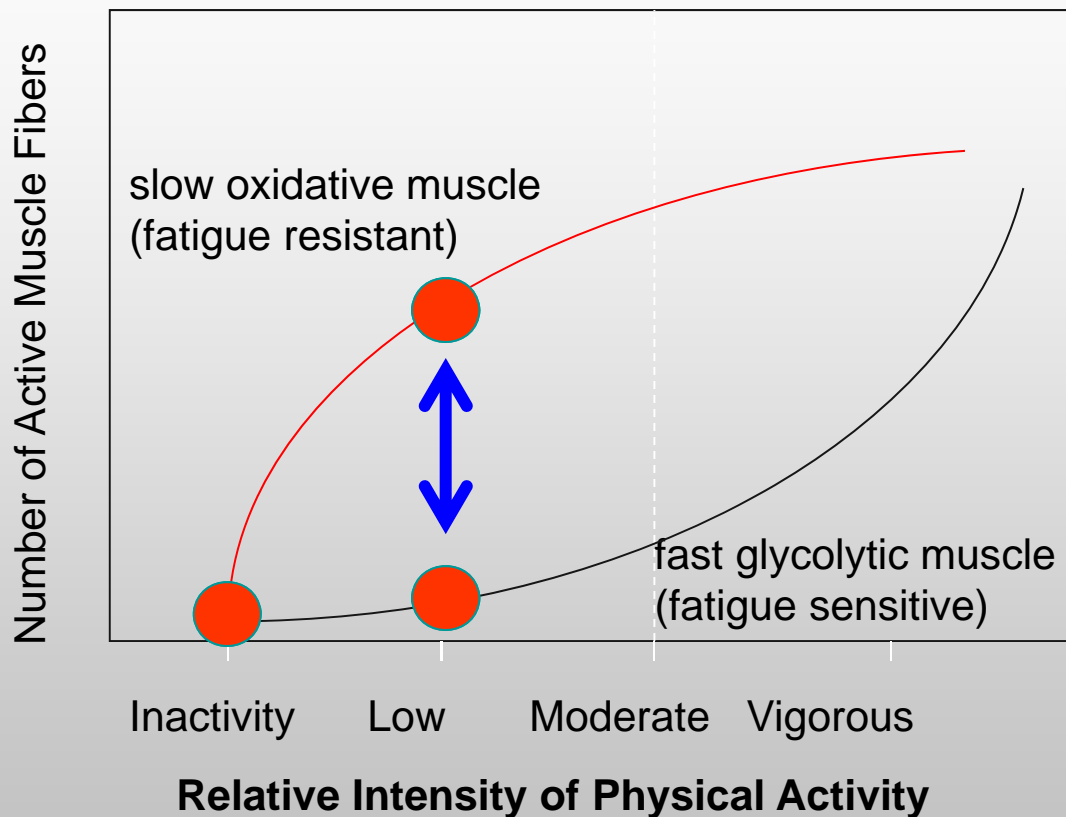


Bey and Hamilton, *J Physiology*, 2003



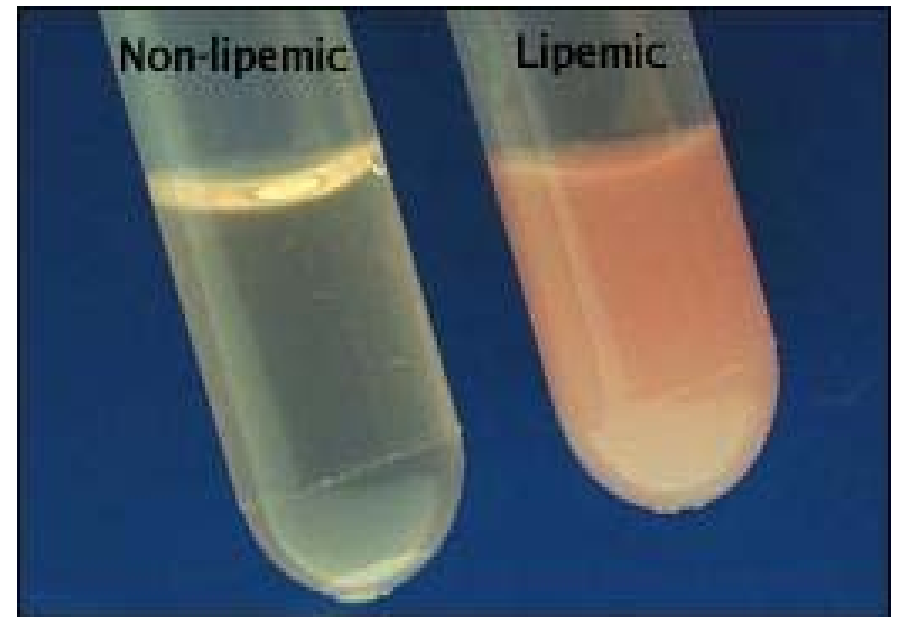
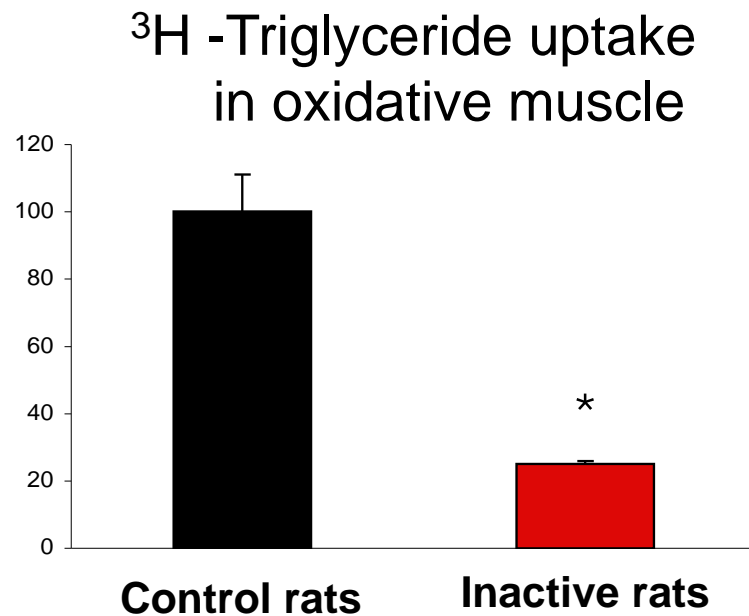
# Understanding Why LIPA is Non-Fatiguing & Abundant

## Skeletal Muscle Fiber Type Differences



Hamilton and Owen, **Sedentary Behavior and Inactivity Physiology (2012)**. In Physical Activity and Health, 2<sup>nd</sup> edition.

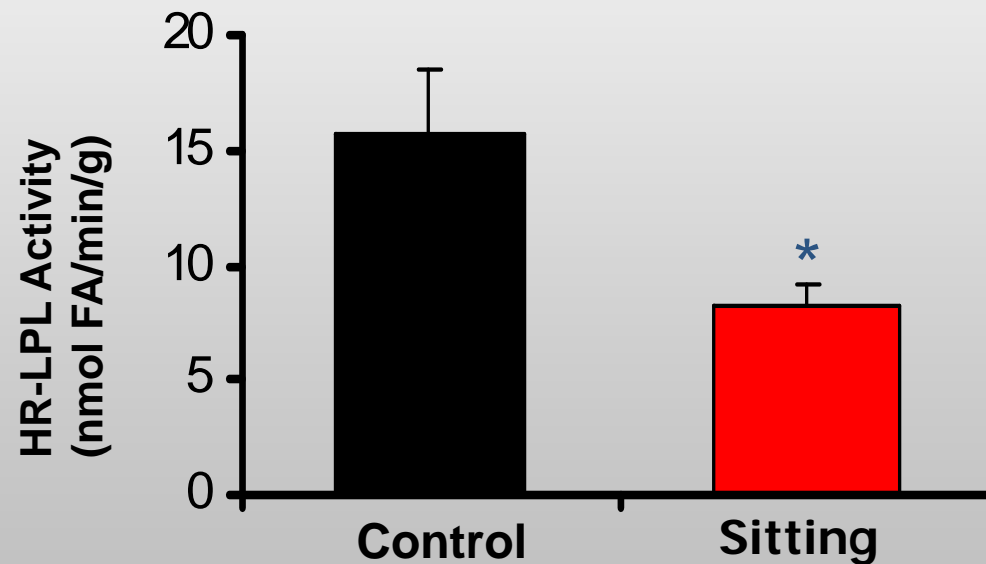
# Lipoprotein metabolism is stalled during inactivity



Bey & Hamilton. J.Physiol. 2003

# One day of physical inactivity suppresses LPL activity in human skeletal muscle

## HUMAN SKELETAL MUSCLE (N=10)



Zderic and Hamilton, unpublished observations

# **Inactivity Powerfully Shuts Off Lipoprotein Lipase**

“The muscular vacuum for TG-rich lipoproteins becomes unplugged.”

**Hamilton et al. *American Journal of Physiol (Endoc Metab)* 1998**

**Bey and Hamilton, *J Appl Physiol* 2001**

**Bey and Hamilton, *J Physiol (Lond)* 2003**

**Zderic and Hamilton, *J Appl Physiol* 2007**

# **Sitting Time Is Associated With Atherogenic Lipoproteins And Hyperinsulinemia Independent Of BMI, VO2max, And MVPA**

Individuals in the top quartile of sitting ( $11 \pm 1$  h/day) compared to the lowest quartile ( $7 \pm 1$  h/day), had...

- 106% greater mean insulin concentrations,
- 48% more total VLDL particles,
- 45% more small VLDL particles,
- 0.3 nm smaller mean LDL diameter

In Review

## Sex Specific Associations Between Screen Time and Lipoprotein Subfractions

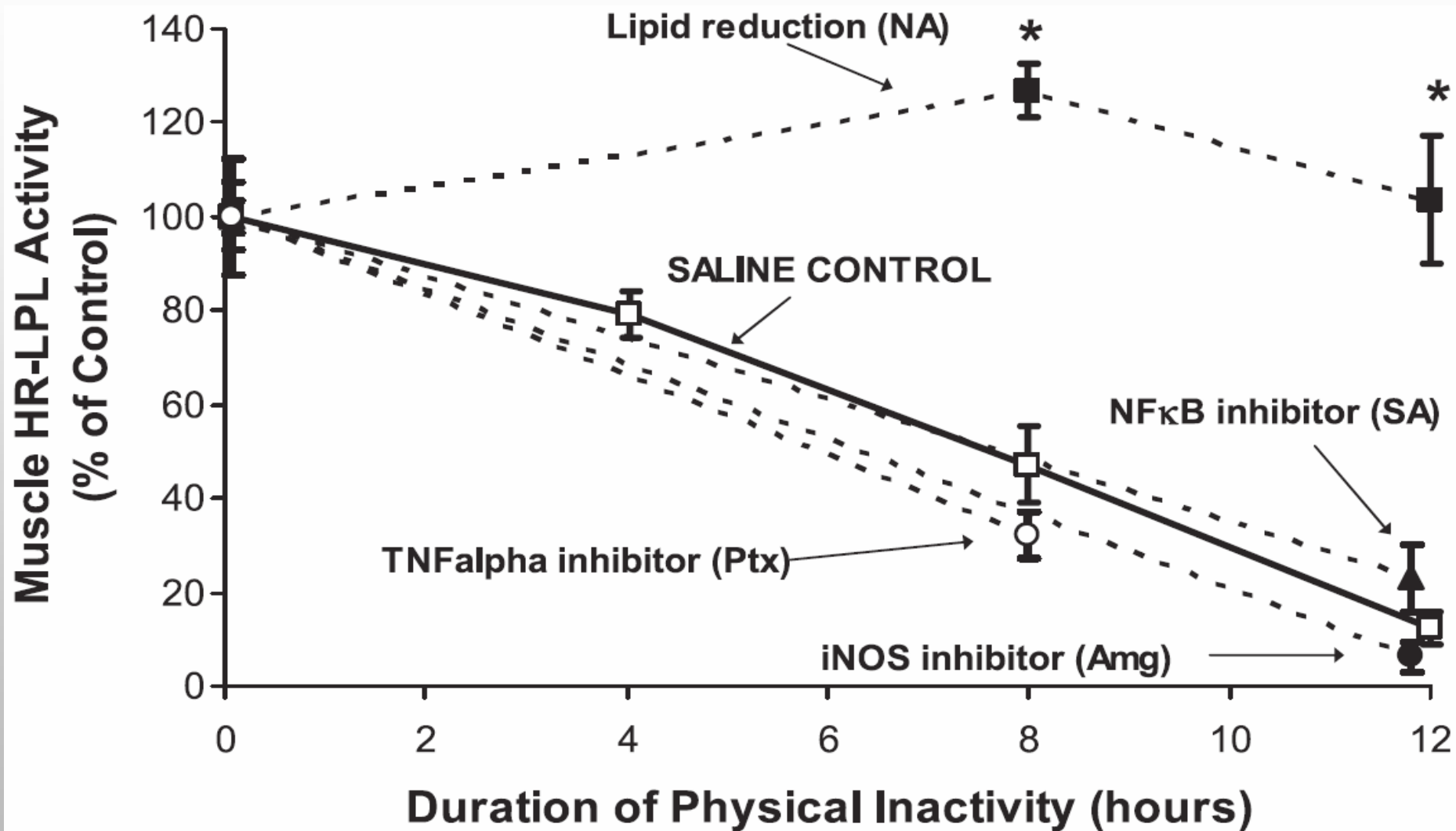
Frazier-Wood et al 2013

## Physical Activity versus Sedentary Behavior: Associations with Lipoprotein Particle Subclass Concentrations in Healthy Adults

Aadland et al 2013

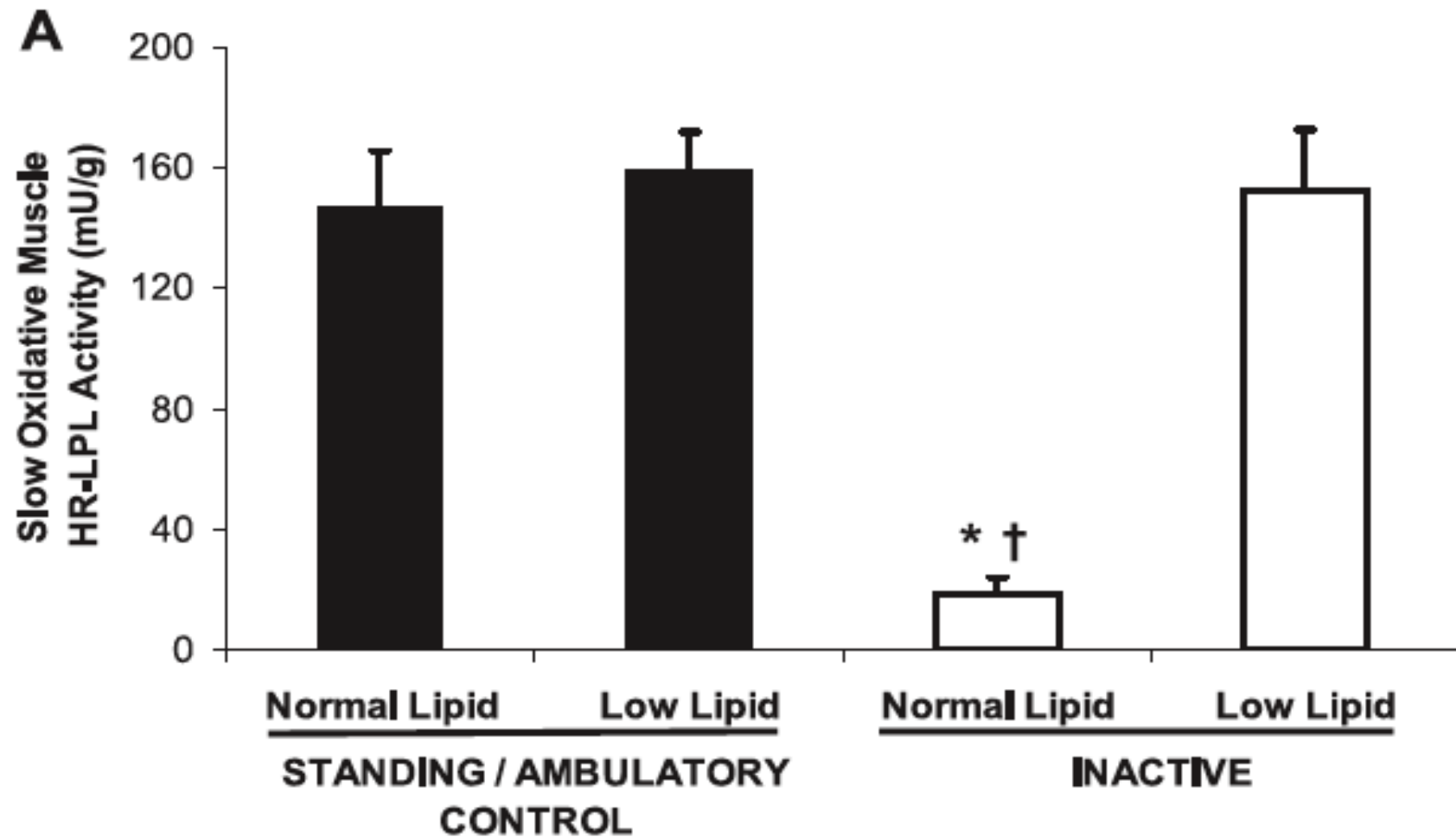
What is underlying signal for decreased LPL activity during inactivity?

High dose niacin prevented fall in LPL activity caused by acute inactivity





## Physical inactivity amplifies the sensitivity of skeletal muscle to the lipid-induced downregulation of lipoprotein lipase activity



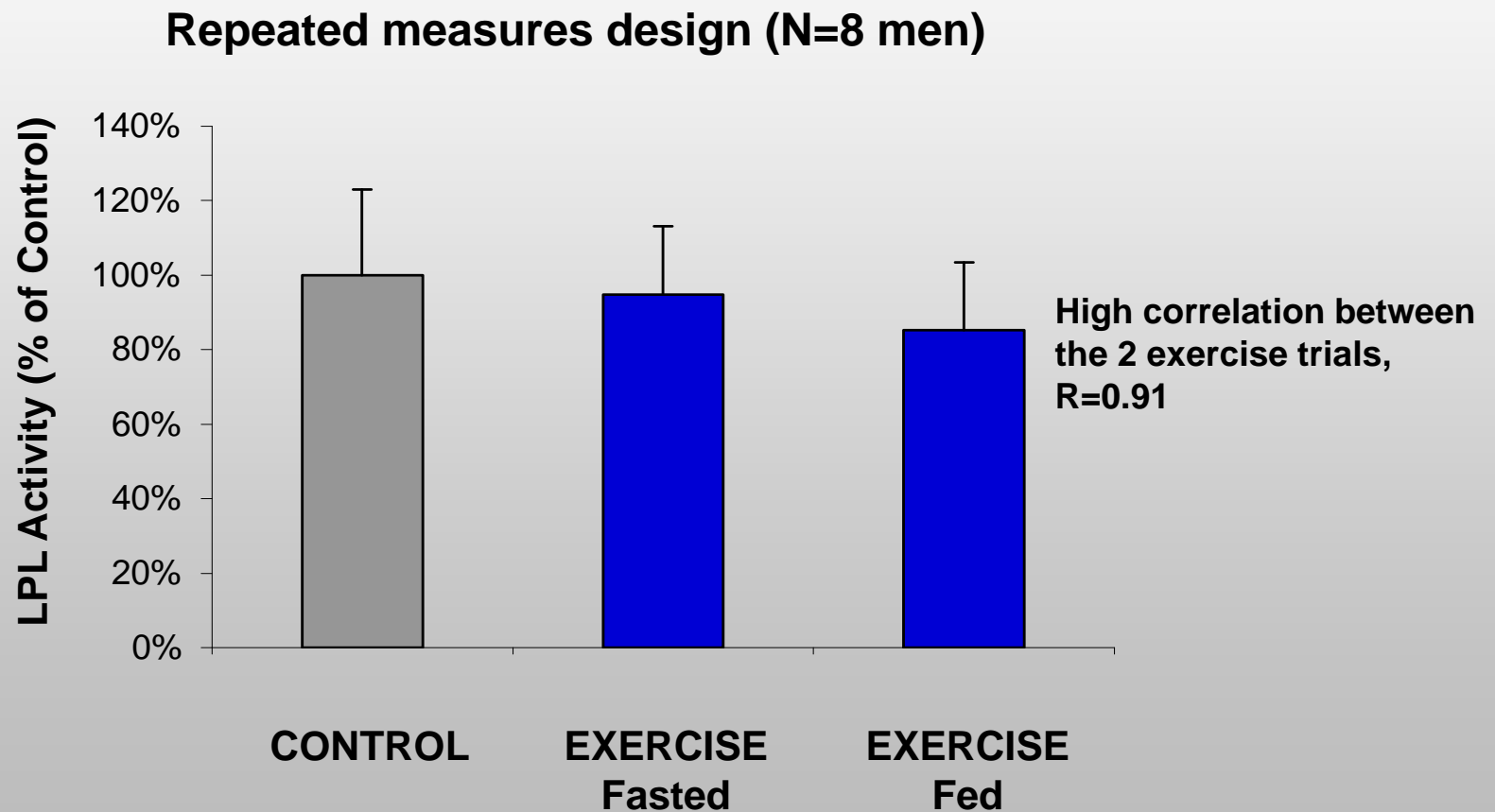
# The Specificity Principle

The signals harming the body during physical inactivity are specific and distinct from exercise.

(one reason why “too much sitting is not the same as too little MVPA”)

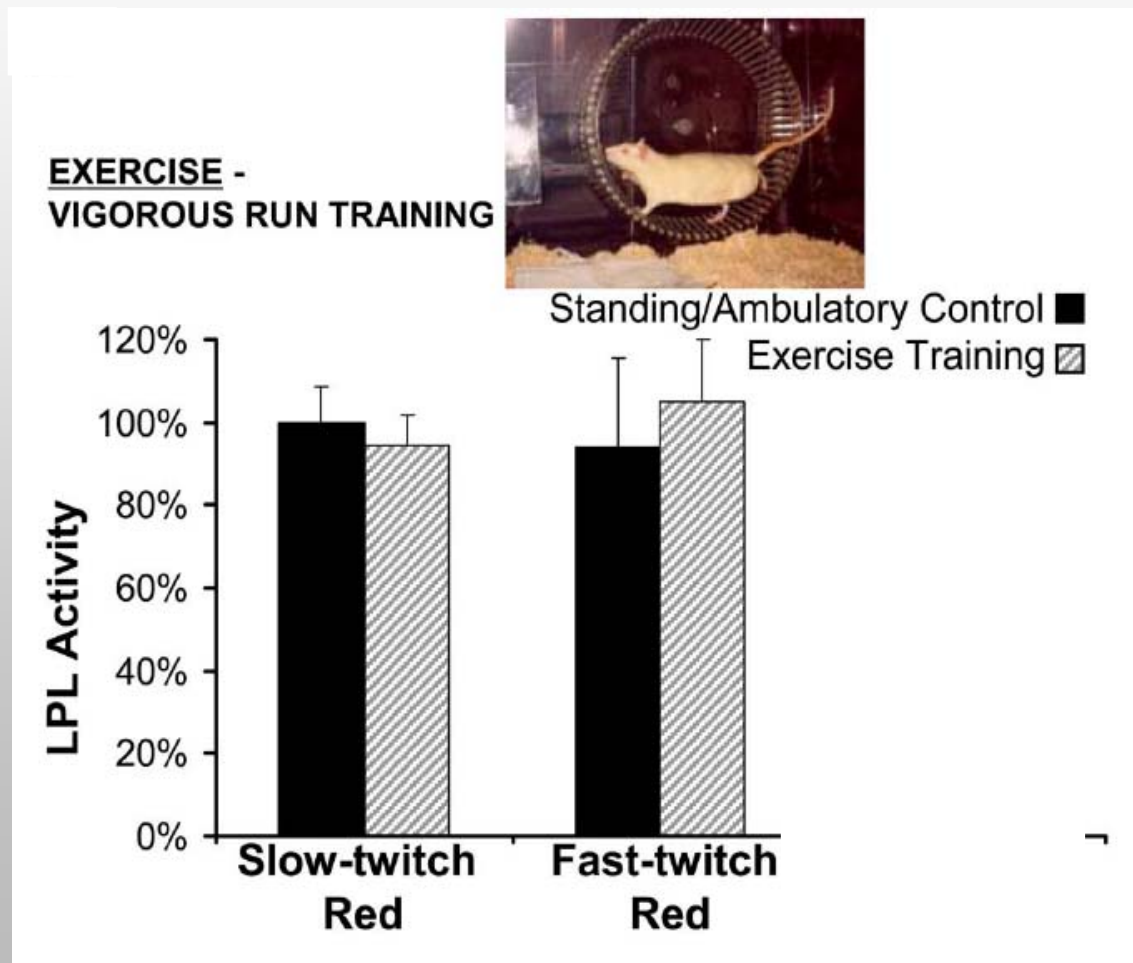
Hamilton Diabetes 2007

# A vigorous bout of exercise on skeletal muscle LPL activity in humans



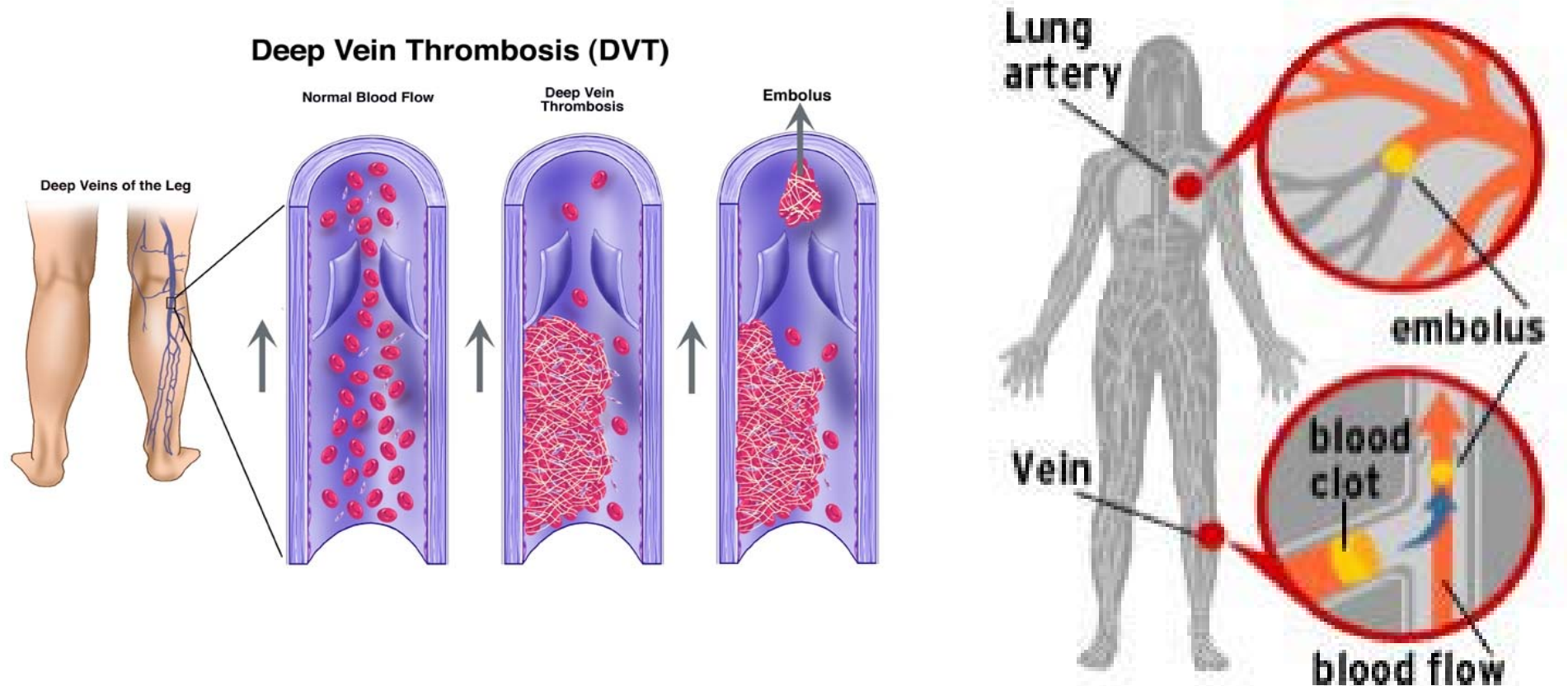
Harrison, Zderic et al. 2012

Run training does NOT have the same potency



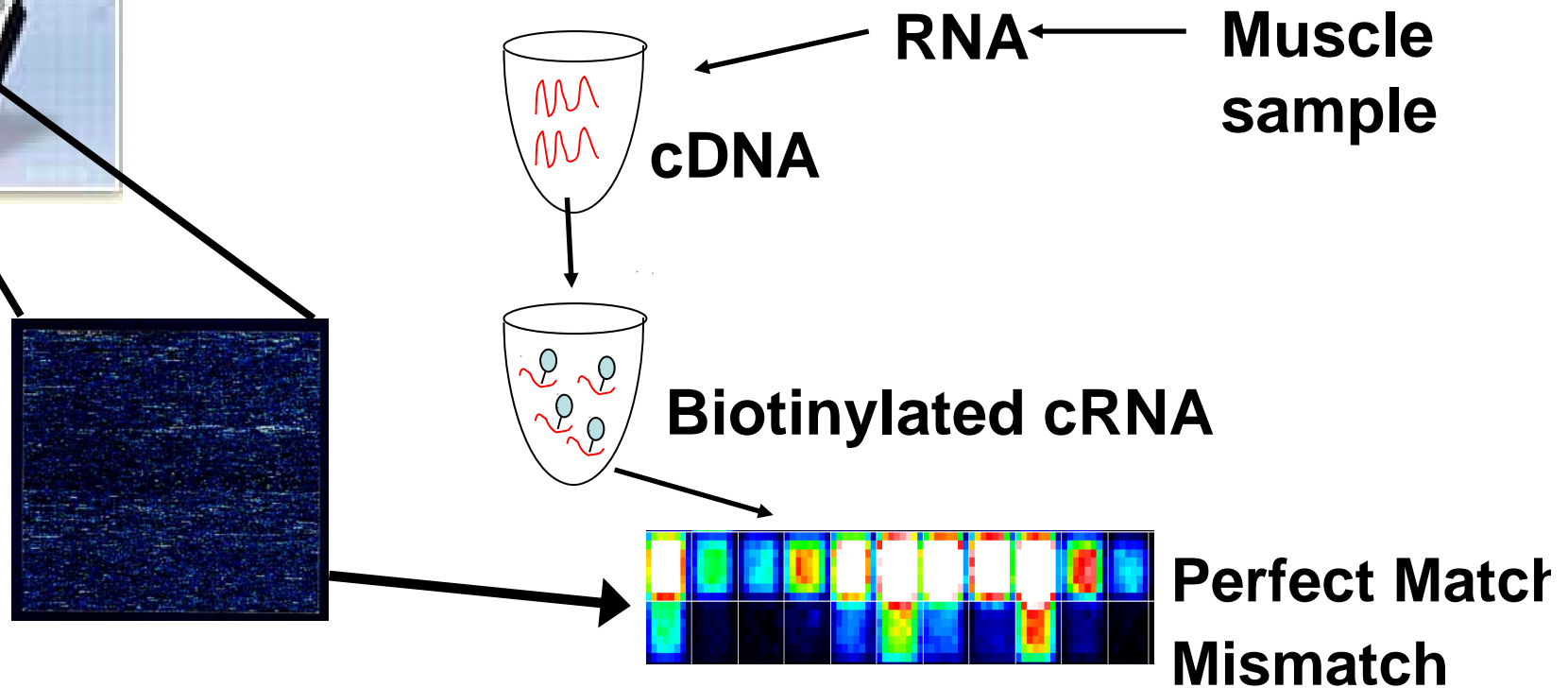
Hamilton et al. *Am. J. Physiol*, 1998

# Inactivity Physiology is opening doors for a novel solution to the elusive and dangerous condition of deep venous thrombosis (DVT)



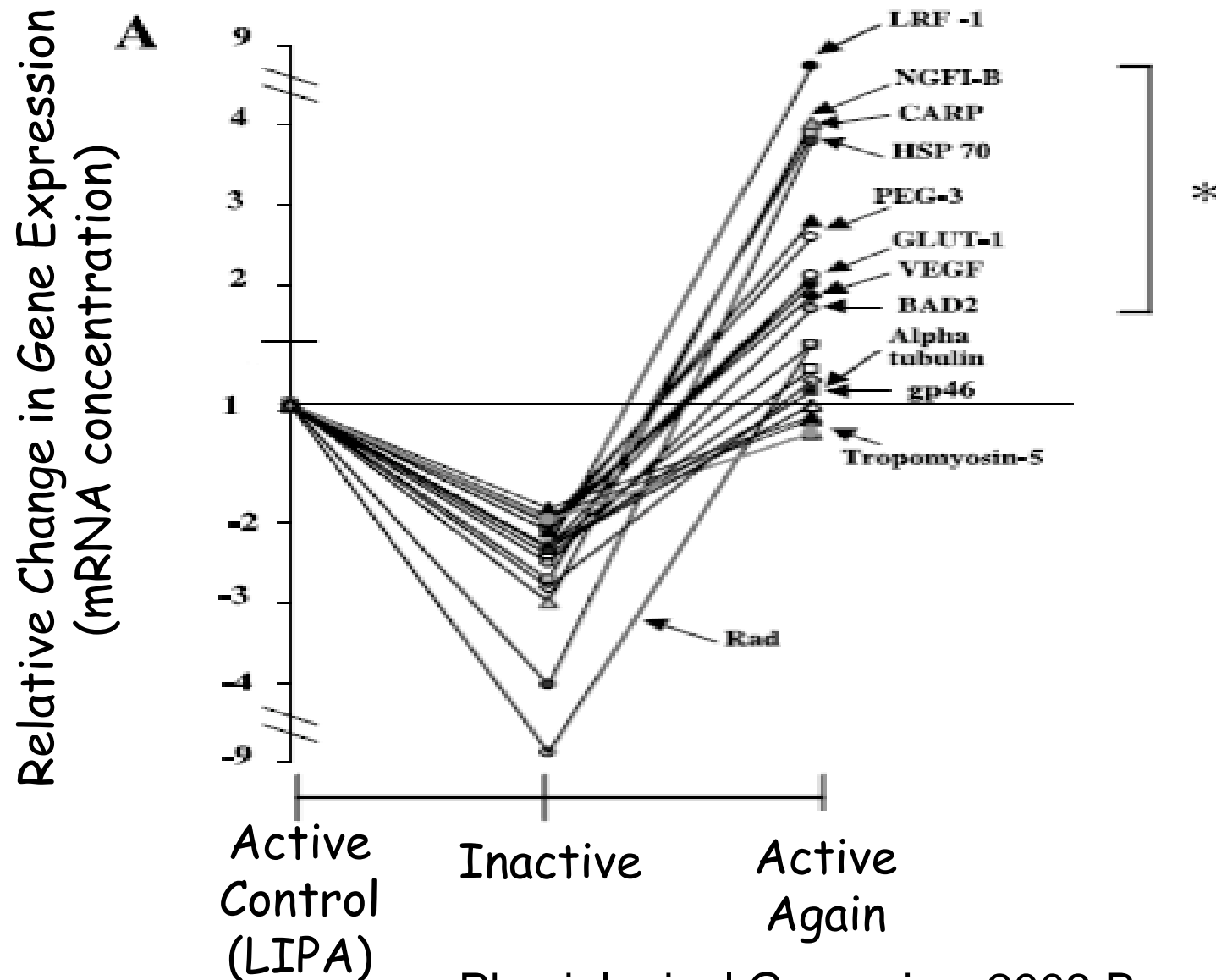
*Too much sitting can cause DVT – not too little exercise*

# Inactivity-Responsive Genes



**~980,000 oligonucleotide probes for ~33,000 genes**

## The Homeostasis for Expression of Hundreds of Genes is Rapidly Disturbed By Contractile Inactivity



Physiological Genomics, 2003 Bey and Hamilton

# Identification of hemostatic genes expressed in human and rat leg muscles and a novel gene (LPP1/PAP2A) suppressed during prolonged physical inactivity (sitting)

Theodore W Zderic<sup>\*</sup> and Marc T Hamilton<sup>\*</sup>

Zderic and Hamilton, 2012



# HEMOSTATIC GENE EXPRESSION IN SKELETAL MUSCLE

## COAGULANT FUNCTIONS

Coagulation factor VIII

Coagulation factor VII

Vitamin K epoxide reductase complex

von Willebrand factor (vWF)

Tissue factor

Gamma-glutamyl carboxylase

⋮

## ANTI-COAGULANT FUNCTIONS

### **LPP1**

Platelet-activating factor acetylhydrolase

Annexin A5

Tissue factor pathway inhibitor

Protein C receptor

⋮

## FIBRINOLYTIC FUNCTIONS

Annexin A2

Tetranectin

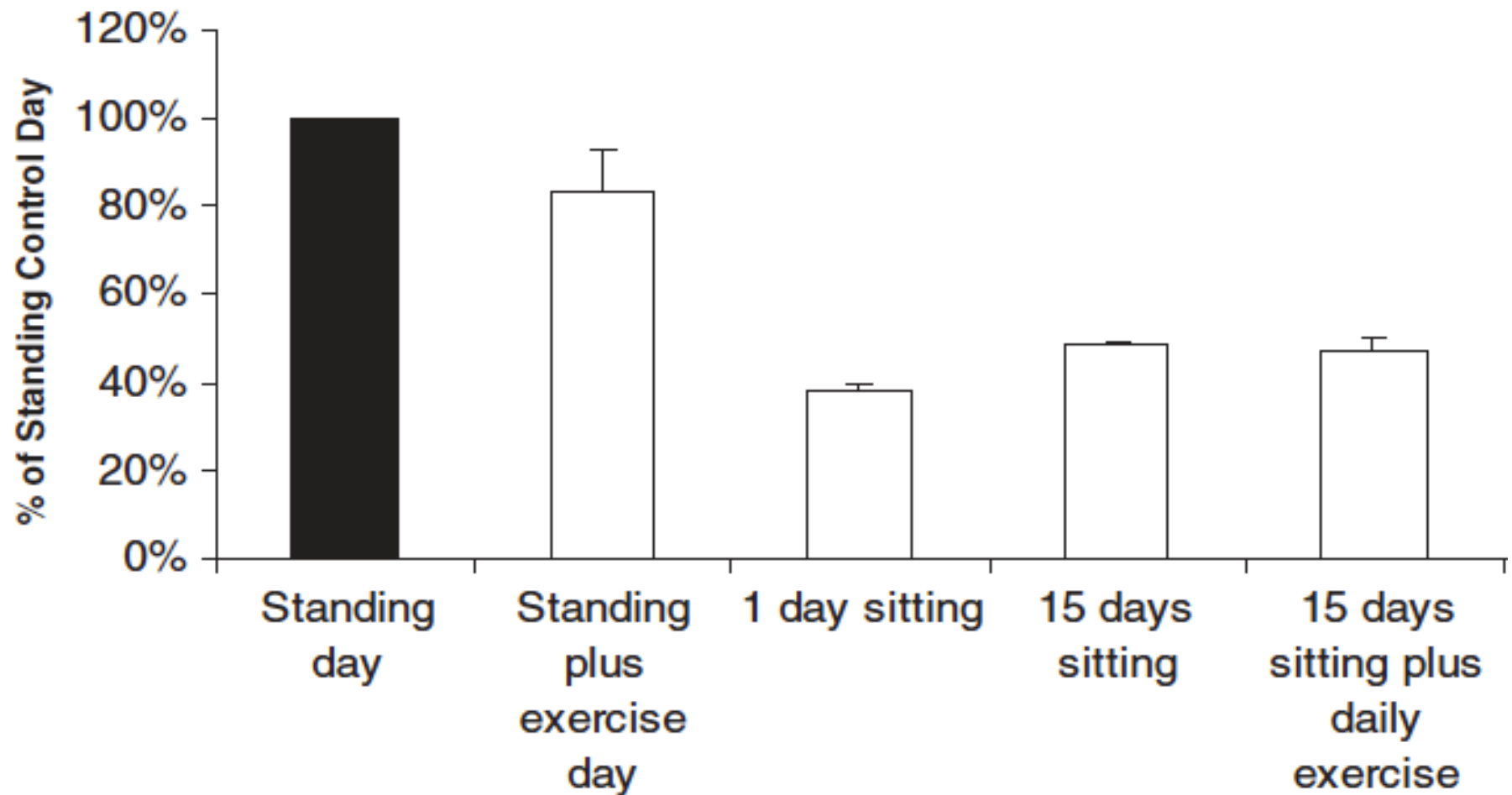
Tissue plasminogen activator

Urokinase plasminogen activator

⋮

***LPP1 was robustly sensitive to contractile inactivity and LIPA in both rats and humans***

# LPP1 is Suppressed During Sitting & Resistant to Exercise



# A Reminder of the Public Health Guidelines

## Physical Activity Guidelines for Americans

<http://www.health.gov/paguidelines>



JAMA, 1995 – ACSM

Circulation and MSSE, 2007 - AHA/ACSM

**How much time do people in modern societies sit, or alternatively do upright activities?**



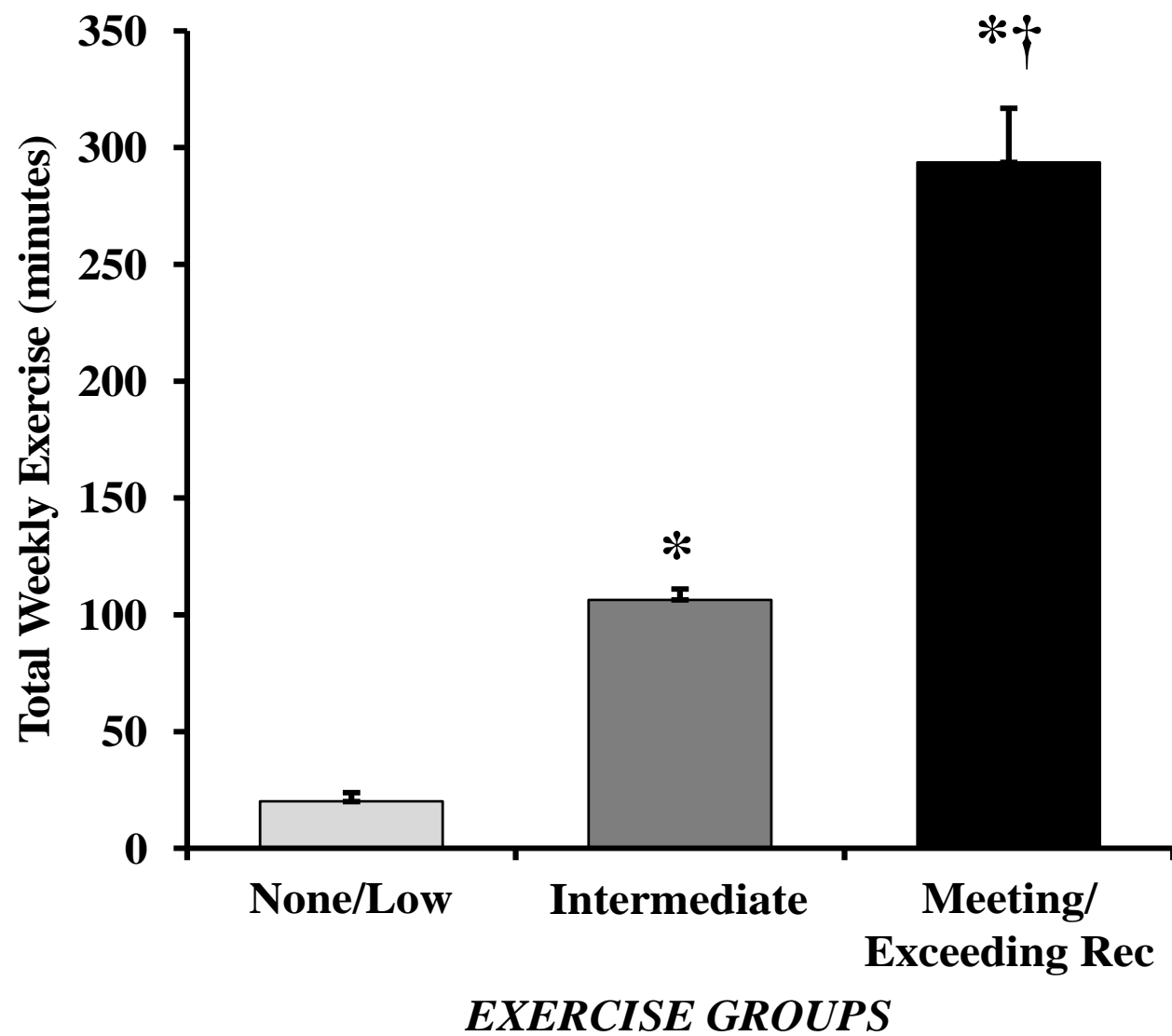
A sobering thought about the historical focus on *Moderate-Vigorous Physical Activity* in public health recommendations:

3.5-10% of the people do them!



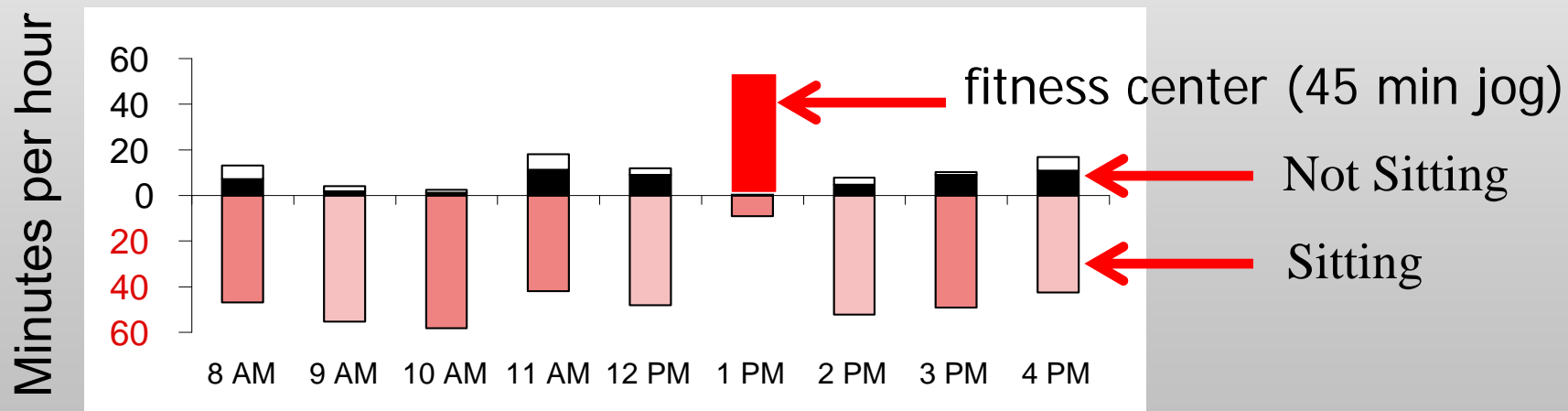
# Are exercisers less sedentary?





# A POP QUIZ

Is it odd to you that this person is categorized by experts as “very *physically active*”?



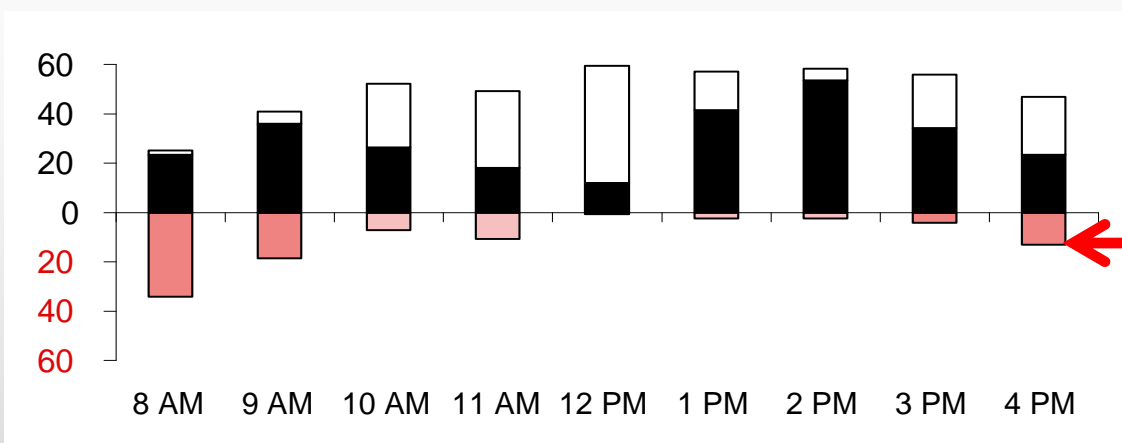
Hamilton, Diabetes, 2007



## Who ACTUALLY spends more time in physical activity?

Minutes per hour  
in each activity

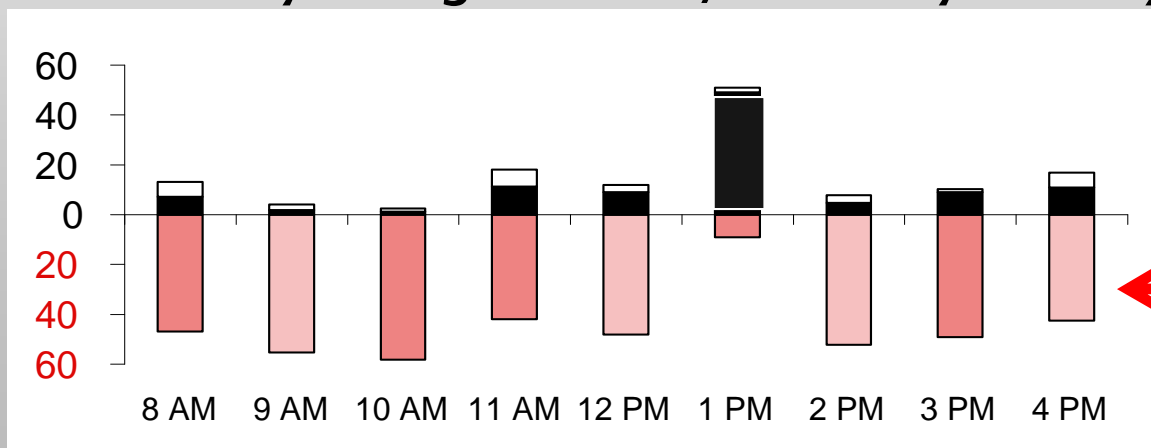
Generally doing ~45 min/hr doing LIPA



Sitting

Minutes per hour  
in each activity

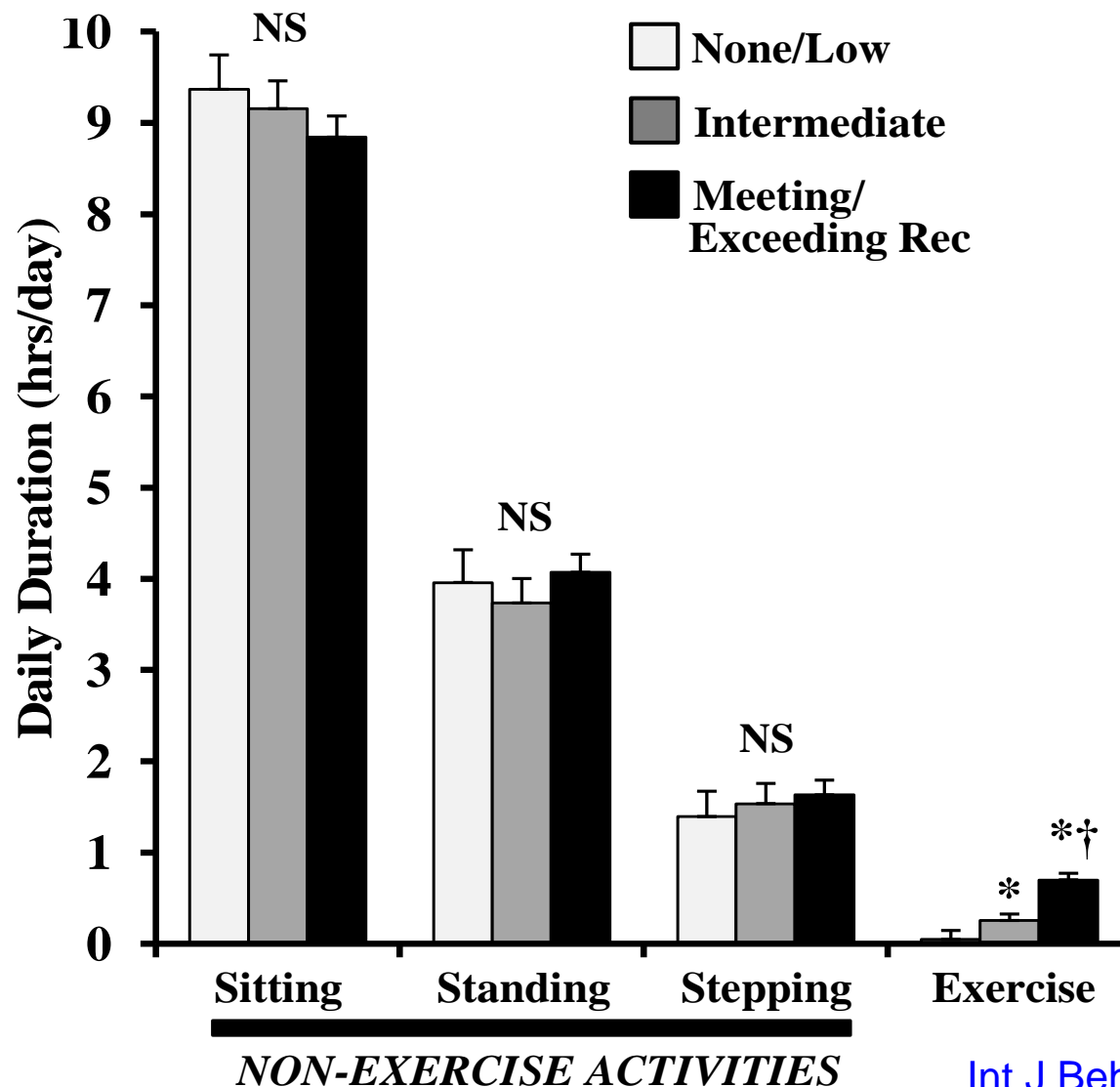
Generally doing <20 min/hr of any activity



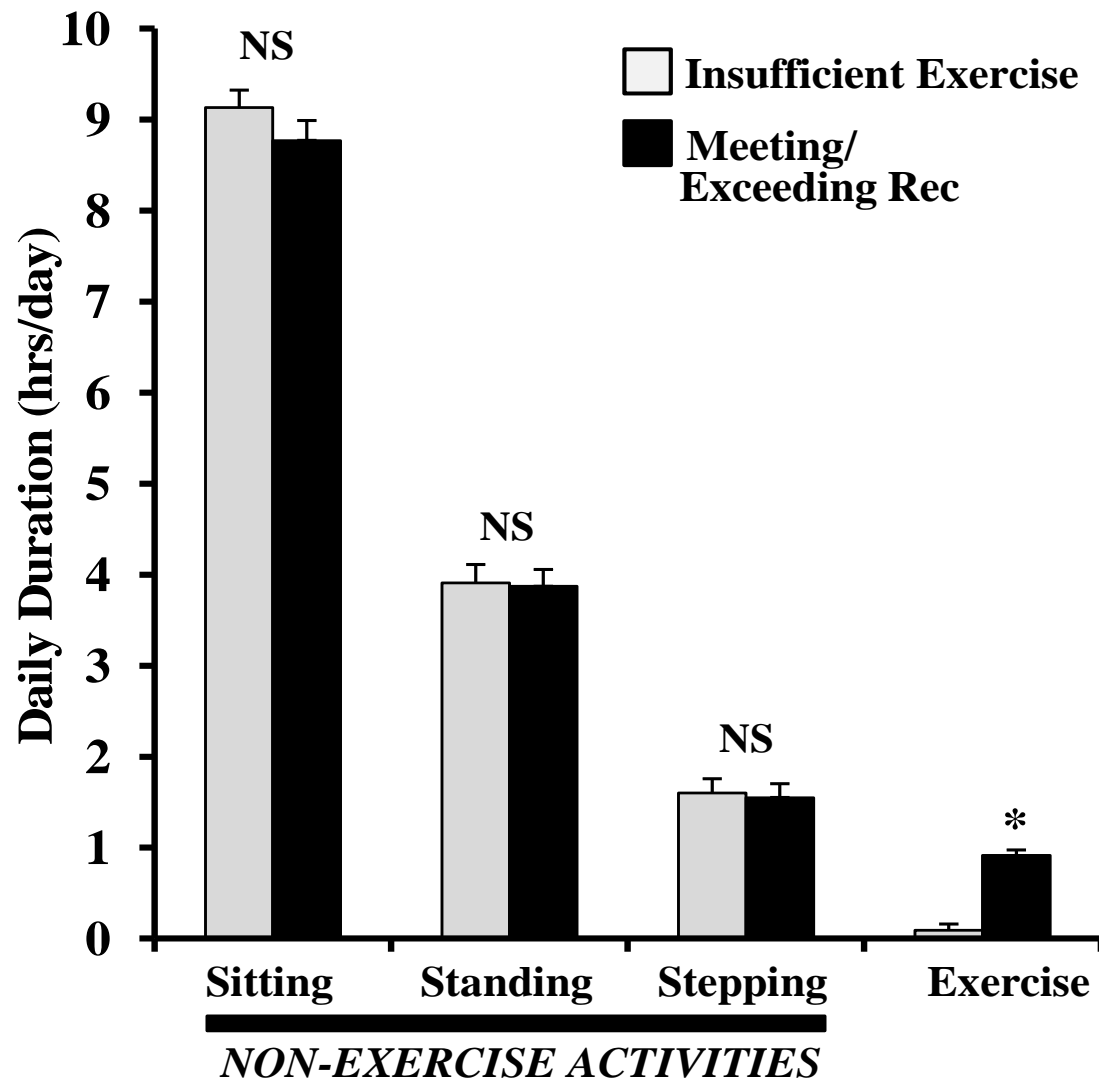
Sitting

**Exercisers are not less sedentary (sit less) than people who do not exercise**

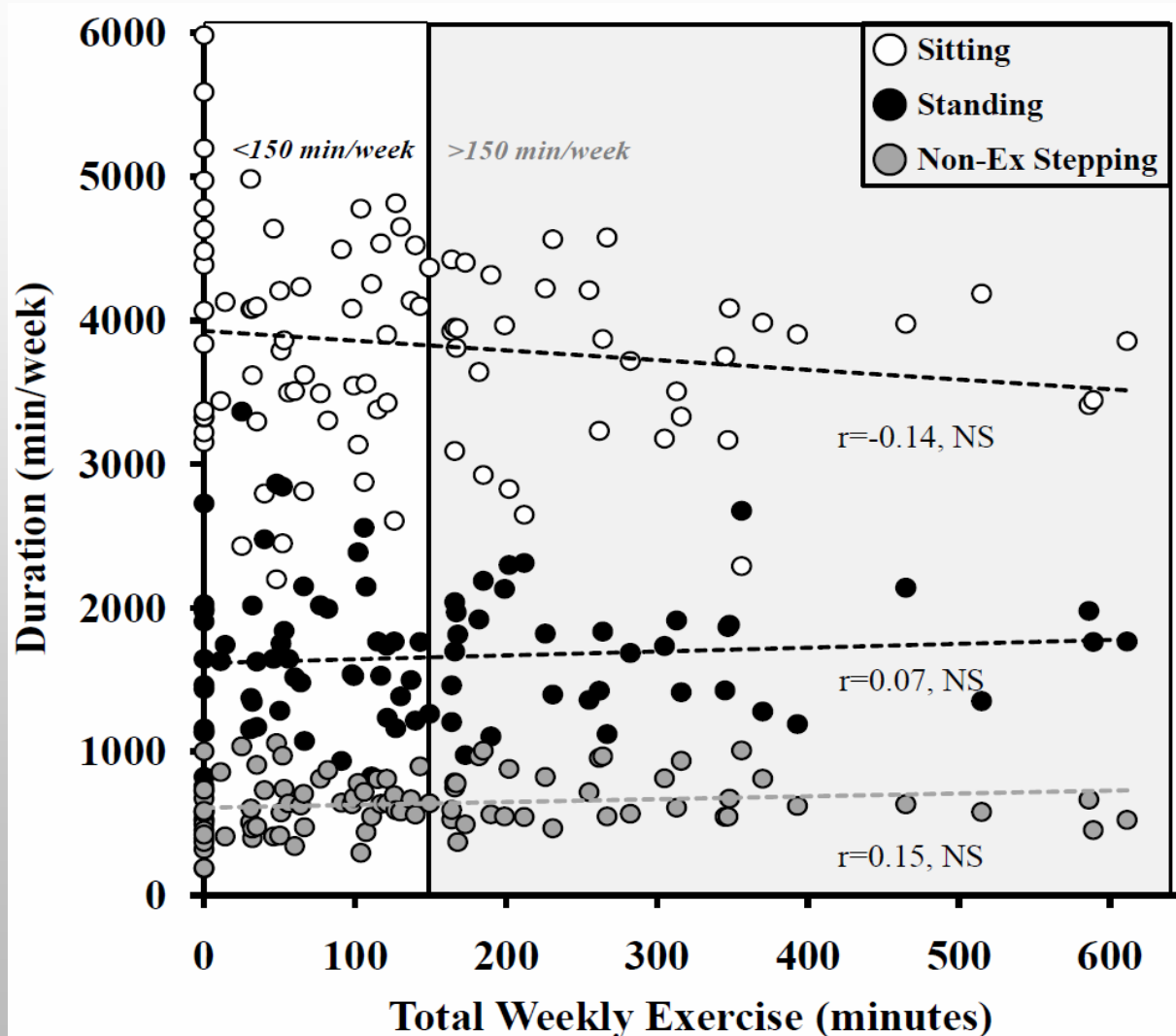
**Exercisers sit just as much as people who don't exercise**



## Exercisers are not less sedentary (sit less) even on the days they exercise



Regardless how much time was spent doing moderate activity there was the same sedentary time and total physical activity.



Total weekly sedentary time and LIPA is NOT less in women who do a large amount of moderate intensity walking



Evidence that women meeting physical activity guidelines do not sit less: An observational inclinometry study.

Craft and Hamilton Int J Behav Nutr Phys Act. 2012

# Inactivity Physiology

*To discover a potent solution for millions of people who can't (or won't) exercise.*



Well beyond expectations

*“The dire concern for the future may rest with growing numbers of people unaware of potentially insidious dangers of sitting too much.”*

Hamilton Diabetes 2007

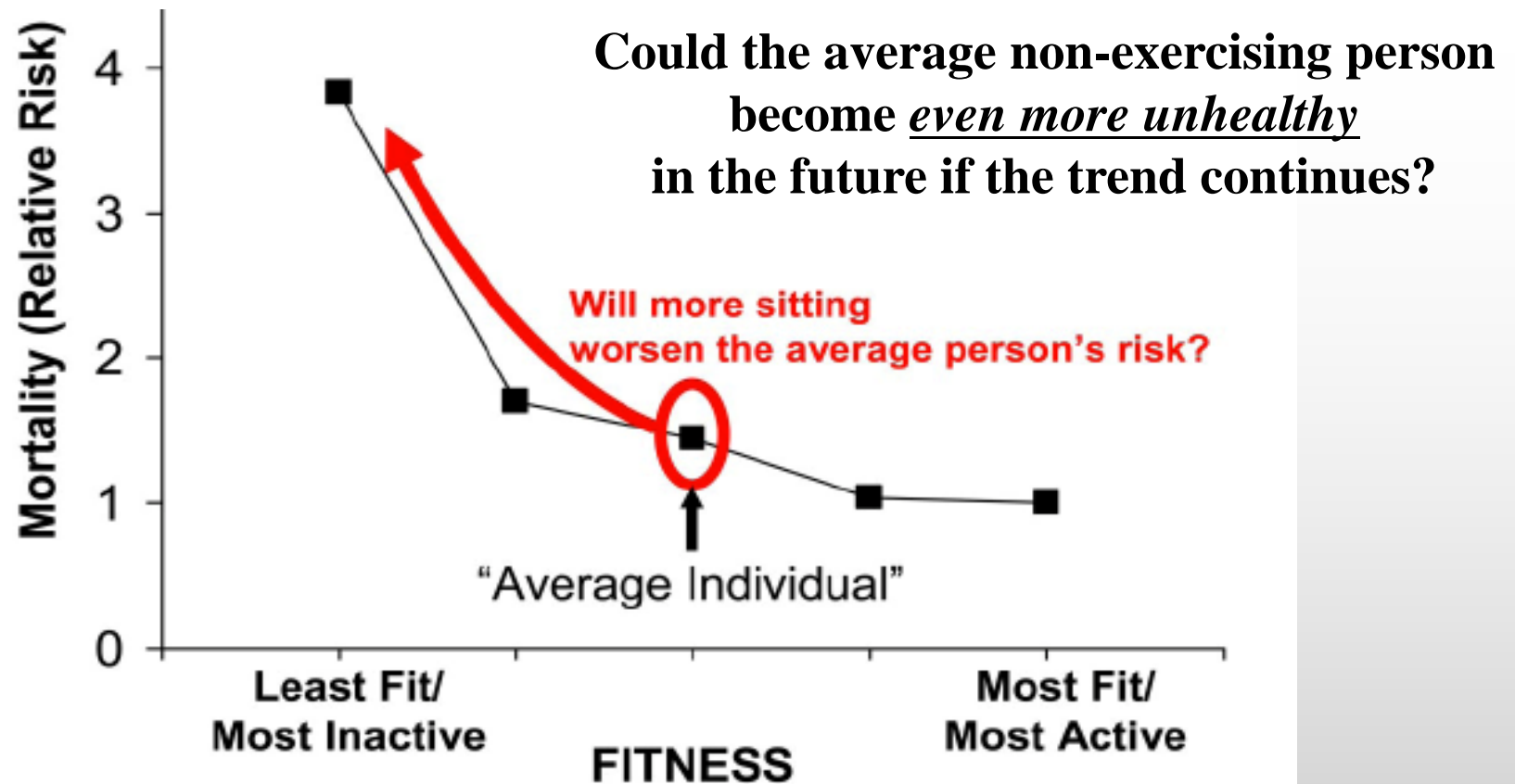


FIG. 1. A major question raised by the inactivity physiology paradigm is whether the typical person who already does not perform structured exercise regularly will have increased risks of metabolic diseases in the coming years as a result of too much sitting. The red circle shadows the median of 13,344 middle-aged men and women (adapted from ref. 86). As described in the text, the majority of people in the general population already do not follow the prescription for enough moderate-vigorous exercise. It logically follows that in people who already do not exercise, it is impossible for higher rates of age-adjusted metabolic syndrome, type 2 diabetes, obesity, and CVD over the coming years to be caused by further exercise deficiency. Inactivity physiology is a discipline concerned with the future of people who may be sitting too much. (Please see <http://dx.doi.org/10.2337/db07-0882> for a high-quality



# Concluding Points

**Inactivity physiology is a new field seeking solutions in ways never studied before.**

**Total daily sedentary time (predominantly sitting) is abundant, and independent of how much time someone exercises.**

**There are some very potent metabolic mechanisms in skeletal muscle responding to low-intensity activity. These mechanisms are qualitatively distinct from exercise.**