

Exercise in Psychiatry

Karen Wooten, MD

PGY2 Psychiatry

MS Exercise Physiology

Outline

- What is exercise?
- Physical activity and psychiatry
- Possible mechanisms of exercise interventions
- How is exercise measured?
- Negative findings in depression studies
- Exercise promotion



WHAT IS EXERCISE?

Physical Activity vs. Exercise

Physical Activity

- Any bodily movement produced by skeletal muscles that results in energy expenditure
 - Exercise
 - Sports
 - ADL's
 - Occupational activity
 - Leisure activity
 - Transportation activity
- Epidemiological Studies

Exercise

- Physical activity that is planned, structured, and repetitive done to improve or maintain one or more components of physical fitness
- Controlled Trials

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
- Components of Fitness
 - Cardiorespiratory
 - Muscular strength
 - Muscular endurance
 - Body composition
 - Flexibility
 - Balance, Agility, Reaction time
 - Power

Epidemiological Studies

PHYSICAL ACTIVITY IN PSYCHIATRY

Physical Activity and Psychiatry

Epidemiologic Studies: Cross Sectional

- National Comorbidity Survey
 - based on a national probability sample ($n = 5877$)
 - individuals of ages 15 to 54
 - Non-institutionalized
 - random sample
- WHO Composite International Diagnostic Interview
 - administered by trained lay interviewers
- “How often do you get physical exercise—either on your job or in a recreational activity?”
- Negative association between regular physical activity and lower prevalence
 - MDD
 - Panic attacks
 - Social phobia
 - Specific phobia
 - Agoraphobia
- Persisted after adjusting for
 - Sociodemographic characteristics
 - Self-reported physical disorders
 - Comorbid mental disorders.

Physical Activity and Psychiatry

Epidemiologic Studies: Cross Sectional

	Regularly n=3703 (%)	Occasional N=1417 (%)	Rarely N=596 (%)	Never N=157 (%)	P value
MDD	8.24	11.55	15.58	16.80	<0.0001
GAD	2.26	2.97	5.93	6.49	=0.0001
Panic attacks	3.32	4.85	7.33	8.52	=0.0003
Specific Phobia	7.35	9.59	13.52	17.13	<0.0001
Social Phobia	6.63	9.49	12.29	12.95	<0.0001
Agoraphobia	2.73	3.33	8.26	10.28	<0.0001
Substance Depen.	2.60	2.41	3.20	9.30	=0.0004

- PA level also showed a dose-response relation with current mental disorders
- Negative association between PA and depression in Norwegian study
- Lower rates of any affective, anxiety or substance use disorder in subjects who exercised at least 1 h/week in Dutch Study

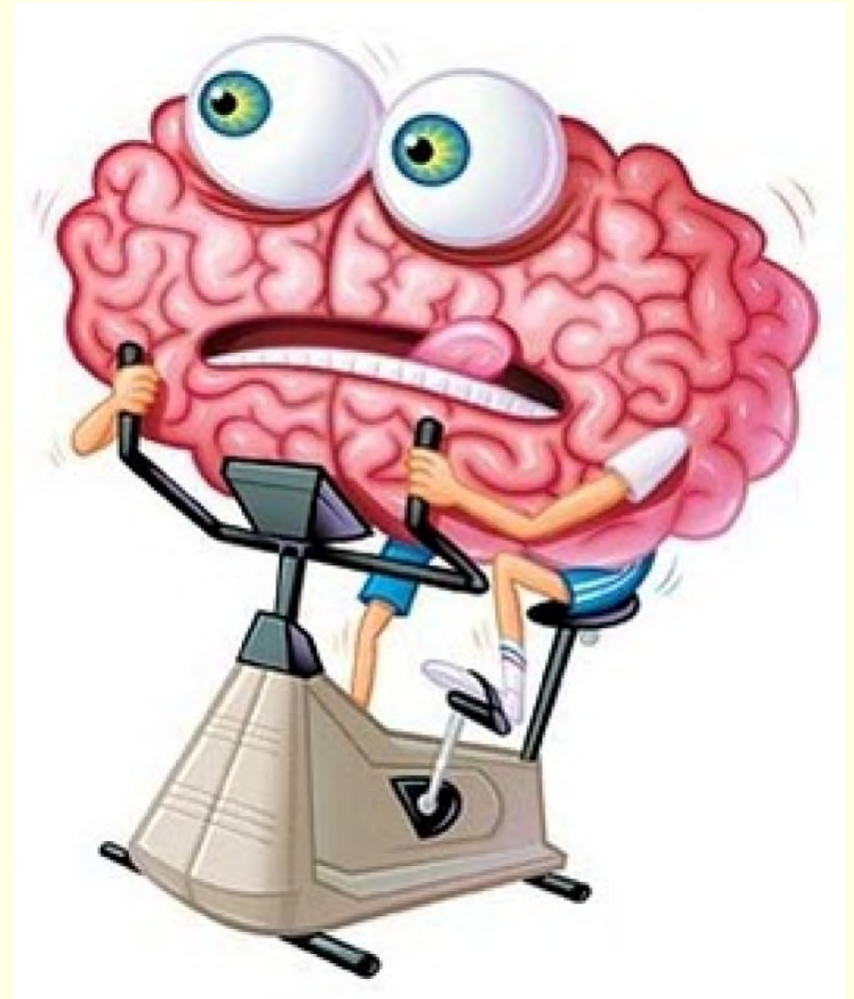
Physical Activity and Psychiatry

Epidemiologic Studies: Prospective Studies

- ↑ Physical activity ↓ *incidence* of
 - Mental disorders
 - Co-morbid mental disorders
 - Anxiety
 - Somatoform
 - Dysthymic disorder
- Patients engaging in regular PA were more likely to recover from their mental illness at a three-year follow-up

Psychological
Social
Cognitive
Biological

MECHANISMS



Psychological Mechanisms



- Mastery hypothesis
 - Control of challenging pursuit instills a sense of independence and success
- Distraction hypothesis
 - Diversion from unpleasant stimuli or somatic pain
- Self-efficacy theory
 - Exercising increases belief in one's ability to reach other goals
- Learning and extinction
 - Improved coping strategies
- Control-orientation
 - Shift of external to more internal locus of control

Social Mechanisms

- Social integrating
 - Especially chronic disorders
 - Schizophrenia
 - Dementia
 - Improved well-being
 - Greater ability to cope with stress
- Exercising in a group
 - Can train social skills and deficits
 - Might boost the self-confidence
 - Structures the patient's day

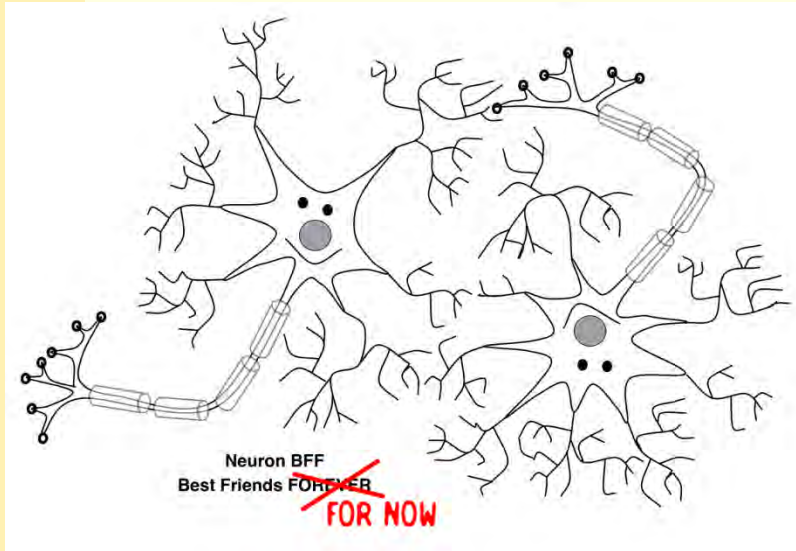


Social relationships and mutual support provided by other exercisers may account for beneficial effects of exercise on mental health

Zschucke, Exercise and Physical Activity in Mental Disorders: Clinical and Experimental Evidence. *J Prev Med Public Health* 2013;46: S12-S21

Knöchel C. Cognitive and behavioural effects of physical exercise in psychiatric patients. *Prog Neurobiol.* 2012 Jan;96(1):46-68.

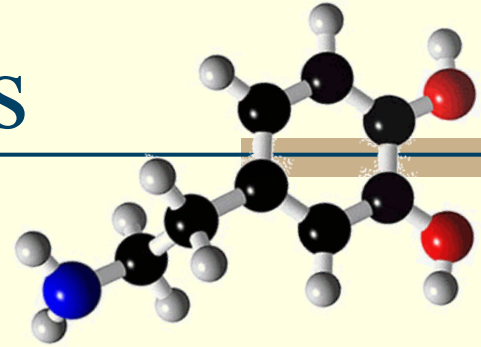
Cognitive Mechanisms



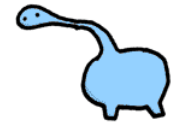
- Induction of epigenetic and neurophysiological adaptations
 - cortical capillary blood supply
 - number of synaptic connections
 - development of new neurons
- Improves cognitive functioning
 - Executive control
 - Cognitive flexibility
 - Information processing
 - Selective/ sustained attention
 - Working memory
- Prevents deterioration
 - Reduced dementia risk (humans)
 - Reduced amyloid- and tau pathology (animal models)

Biologic Mechanisms: Neurotransmitters

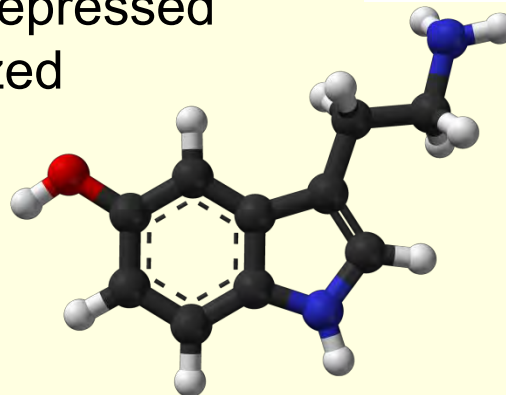
- Common neurotransmitters increase or decrease activity during stress
 - Serotonin
 - Dopamine
 - Norepinephrine
- Exercise changes the activity of these neurotransmitters
- Example: Serotonin reuptake deregulation in depressed patients normalized



SEROTONIN & DOPAMINE

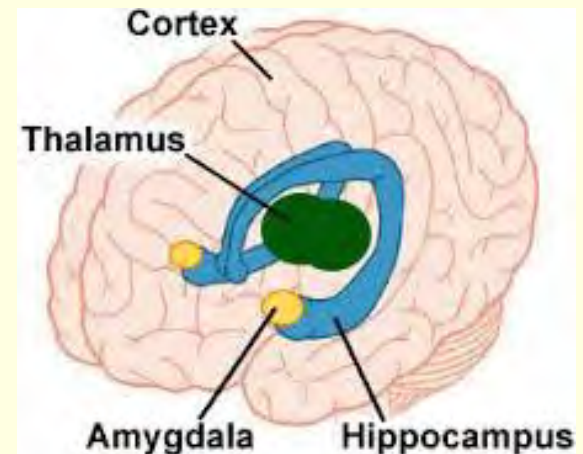


Technically, the only two things
you enjoy



Biologic Mechanisms: Inflammation

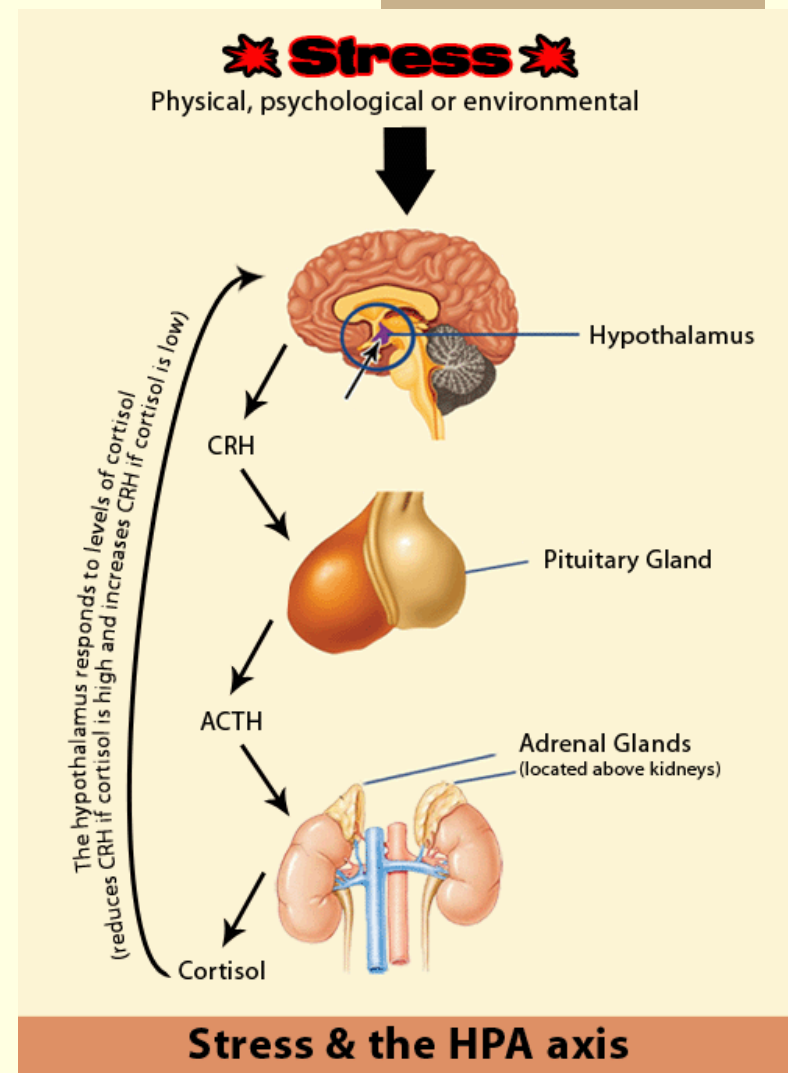
- Chronic inflammation increases Cytokines
 - Target the amygdala, other brain regions
 - “Sickness behavior”
 - Negative symptoms
 - Neuro-vegetative behavior
 - CSF cytokine level correlates to magnitude of anxiety, depression, and cognitive impairment
- Exercise decreases inflammation
 - Increased ROS scavenging
 - Decreased metabolic syndrome



Biologic Mechanisms:

Hypothalamic-pituitary-adrenal axis

- HPA hyperactive in depression
 - Higher basal cortisol levels
 - Non-suppression of endogenous cortisol with dexamethasone
- Exercise delays HPA axis response to stress (animals)
- Exercise-trained subjects exhibit hyposensitive HPA axis response to exercise challenge (humans)
- Improved cardiovascular functioning
 - Decreases serum cortisol level



Biologic Mechanisms: Molecular Mechanisms

- Brain Derived Neurotrophic Factor (BDNF)
 - ↓ in stress/ depression
 - ↑ in exercise (acutely)
 - Neurogenesis,
 - Especially in amygdala
- Insulin Like Growth Factor 1 (IGF-1)
 - ↑ blood flow ↑ neuronal uptake
 - Involved in neuroprotective signaling pathway
- Endogenous opoid peptides
 - Bind opoid receptors in brain
 - Feeling of well being after exercise



Biologic Mechanisms: Molecular Mechanisms

- Anti-apoptotic signaling pathways
 - Mitogen activated protein kinase (MAPK)
 - Extracellular signal related kinase (ERK)
 - Conserve neural stem cells
- Atrial Natriuretic Peptide (ANP)
 - Inhibits stress hormones
 - Anxiolytic effects



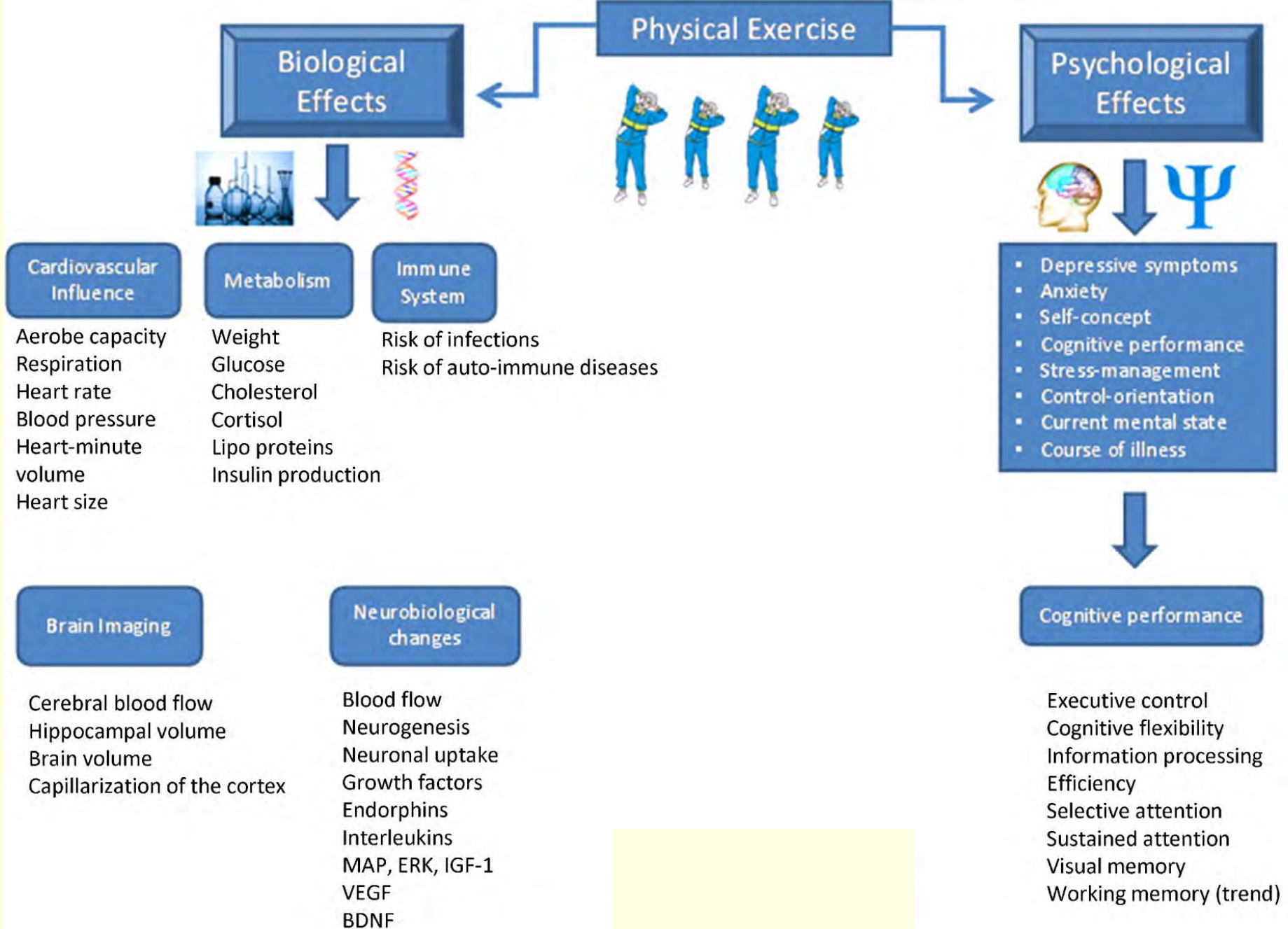
ANP and BNP promote local
anti-hypertrophic actions

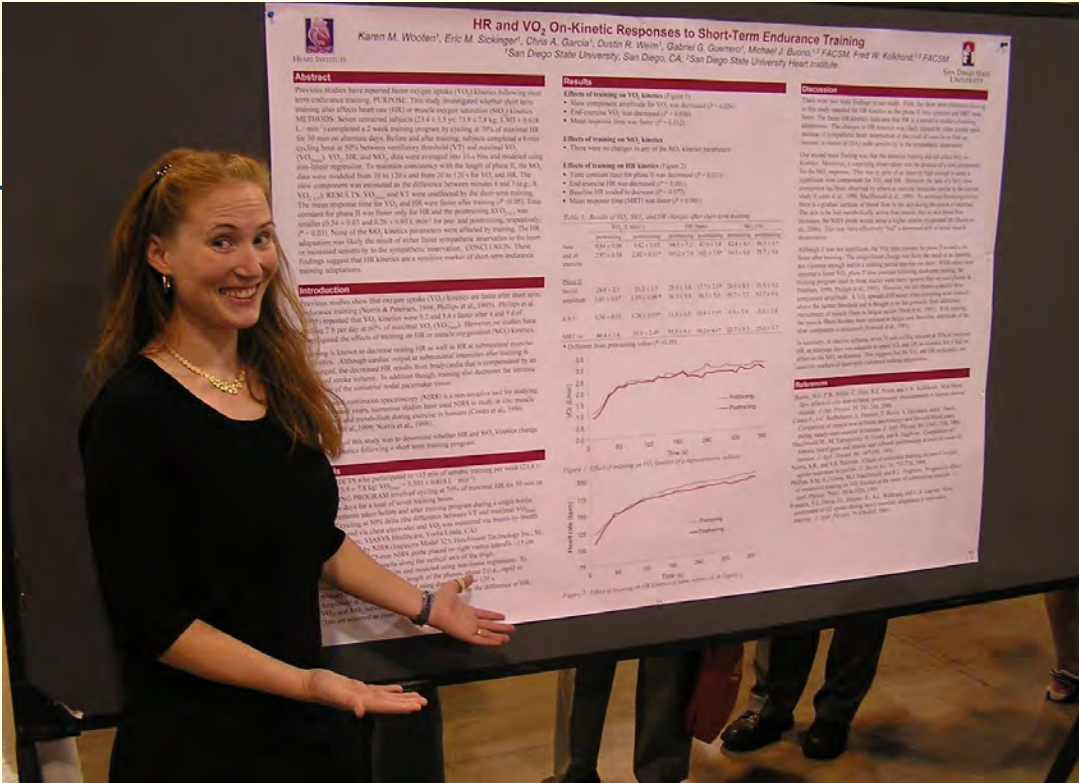


Vasodilation
Endothelial Permeability

Aldosterone Inhibition
Natriuresis, Diuresis,
Renin Inhibition







HOW IS EXERCISE MEASURED?

Variables in Exercise Interventions

Components of Fitness

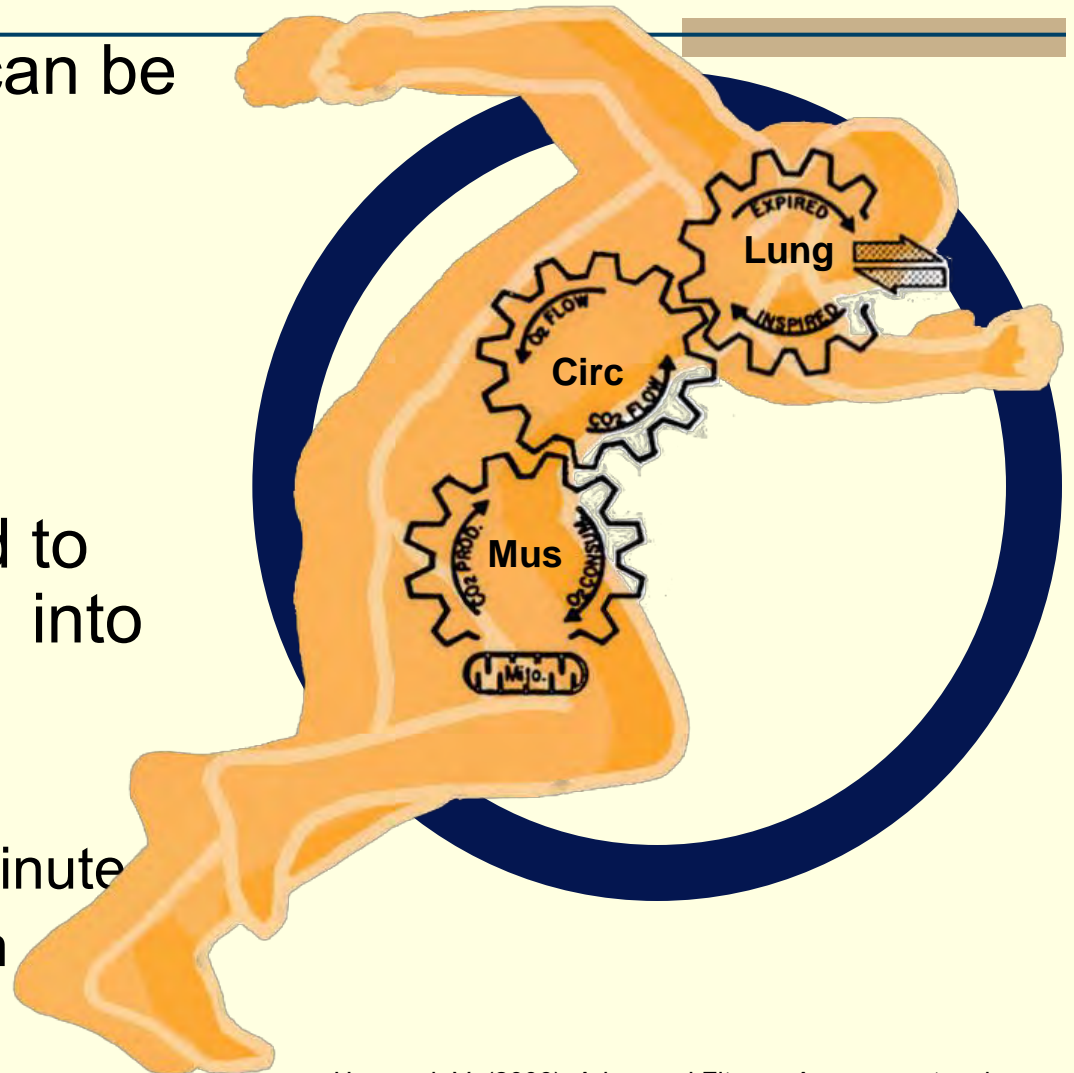
- Cardiorespiratory fitness
- Muscular strength/endurance
- Body composition
- Flexibility
- Balance
- Agility
- Reaction time
- Power

Training Parameters

- Mode
- Frequency
- Duration
- Intensity
- Progression
- (Sets, Repetitions, Rest)

Oxygen Consumption (VO_2)

- Rate at which O_2 can be consumed during exercise
 - taken in
 - distributed
 - used by the body
- Oxygen is required to turn stored energy into ATP
- Units
 - Absolute: Liters/ minute
 - Relative: ml/kg/min
 - METs: \div by 3.5



Components of $\dot{V}O_2$

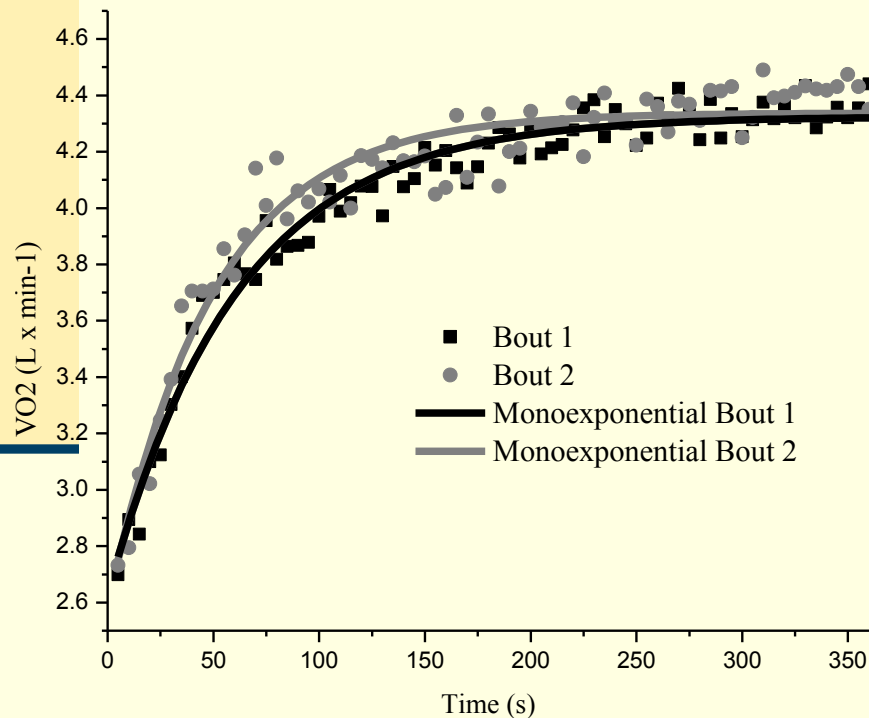
$$\dot{V}O_2 = 1.39 \times [\text{Hb}] \times \text{HR} \times \text{SV} \times (\text{S}_a\text{O}_2 - \text{S}_v\text{O}_2)$$

Diagram illustrating the components of $\dot{V}O_2$ (Oxygen Consumption) with labels and groupings:

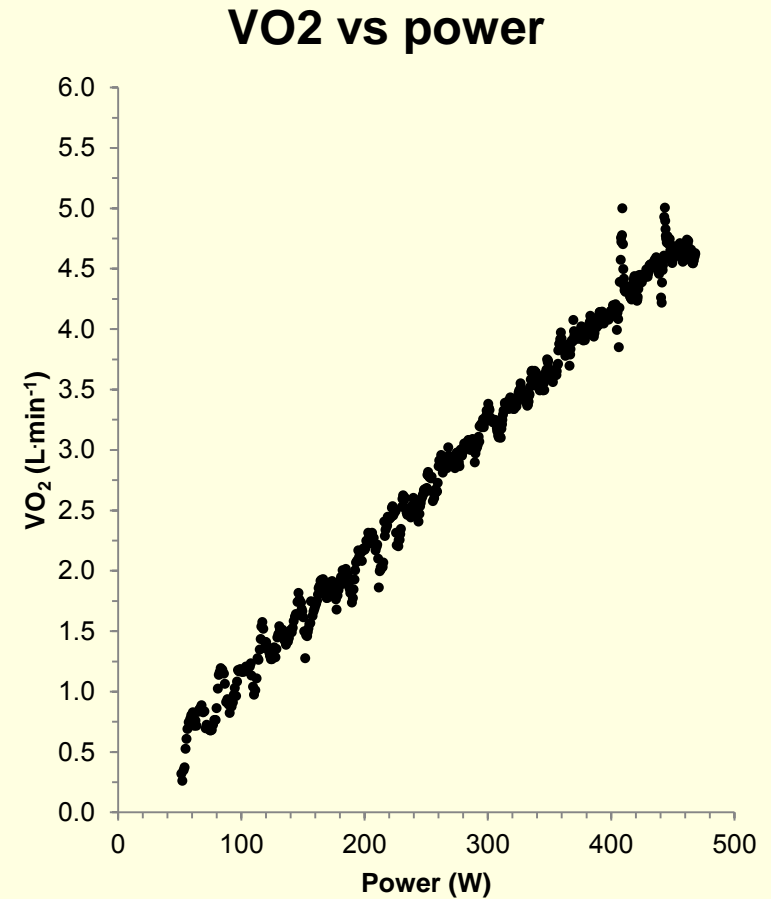
- 1.39 : O_2 binding capacity of 1g of Hb
- $[\text{Hb}]$: haemoglobin concentration
- HR : heart rate
- SV : stroke volume
- $(\text{S}_a\text{O}_2 - \text{S}_v\text{O}_2)$: arterio-venous O_2 saturation difference
- $\text{HR} \times \text{SV}$: cardiac output

$$\dot{V}O_2 = \text{HR} \times \text{SV} \times (a-v \text{ O}_2)$$

VO₂ Measurement At Constant Power



VO₂ Measurement With Increasing Power

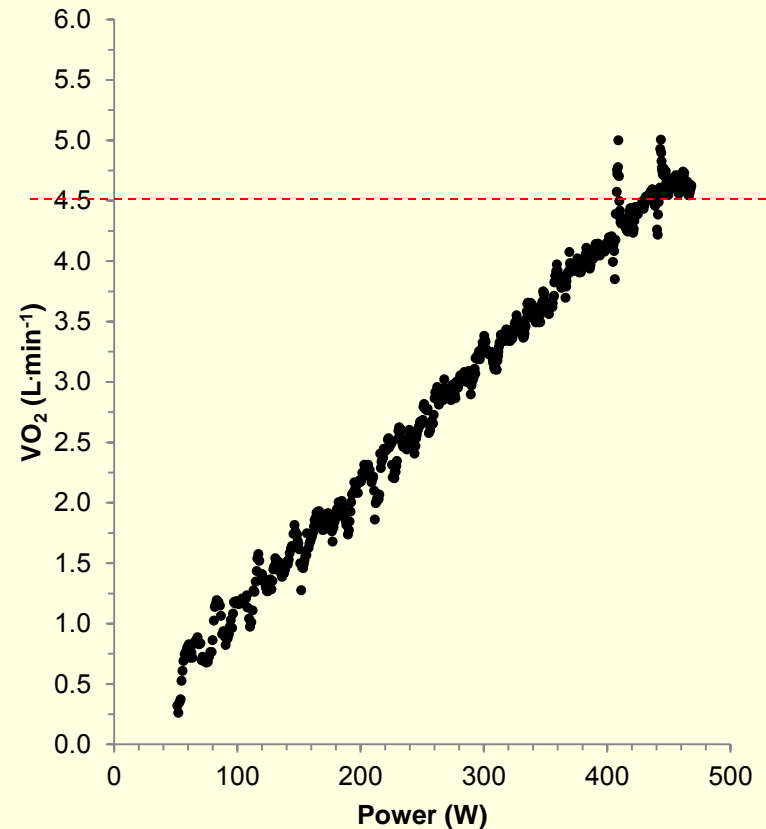


Images courtesy of Dr. Dan Cannon, PhD and Coach Sean Burke, MS

What is VO_2 Max ?

- VO_2 at maximal exertion
 - Plateau with power
- Also called
 - Max VO_2
 - Peak aerobic power
 - Maximal aerobic power
 - Maximum voluntary oxygen consumption
 - Cardio-respiratory aerobic capacity
 - Maximal cardio-respiratory fitness
 - Maximal functional aerobic capacity

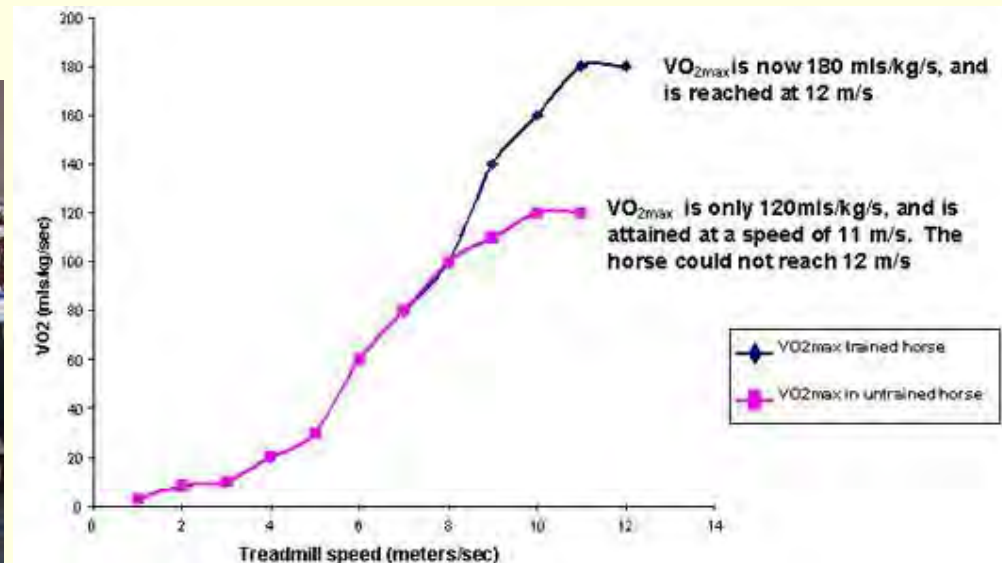
VO_2 vs power



Why is VO_2 Max Important?

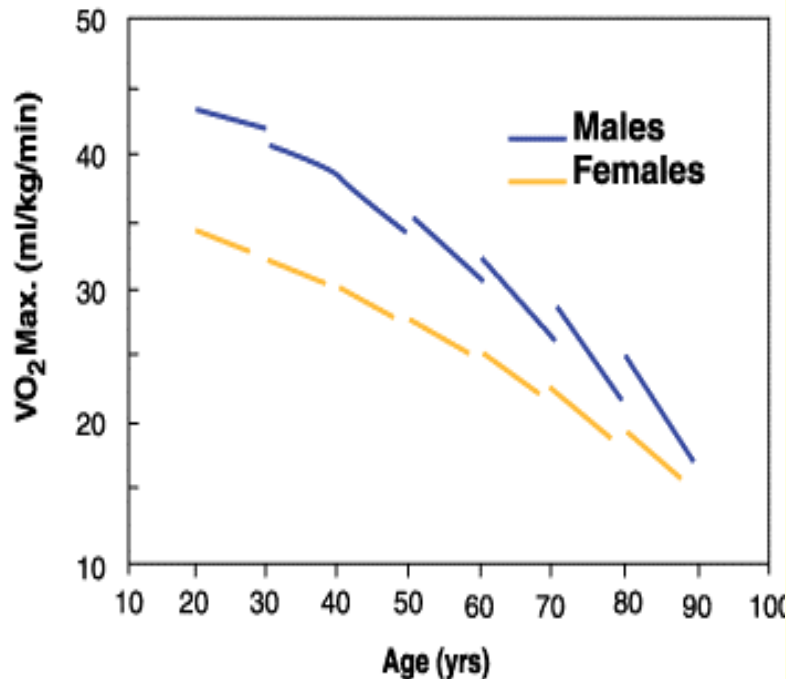
Indicator of fitness

- Criterion measure of cardiorespiratory endurance
 - Used in epidemiological research
 - Monitor changes in aerobic fitness
 - Bragging rights!



Why is VO_2 Max Important?

Functional Capacity



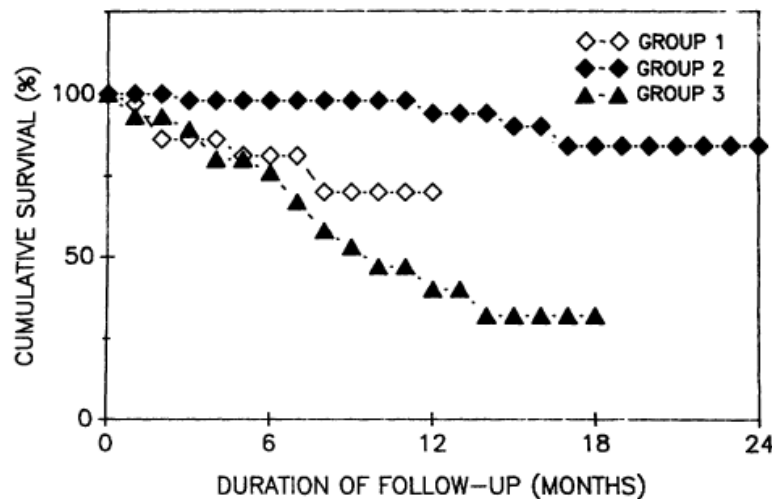
VO ₂ (ml/kg/min)	Activity level
3	Sleeping
3.5	Sitting, watching TV
7	Slow walking
11.5	Vacuuming
14	Climb one flight of stairs
20	Push mowing the lawn

- Older adults whose maximal aerobic power has dropped to approximately 12-15 ml/kg/min often become very challenged to autonomously complete activities of daily living.
- Independent living seniors tend to have VO_2 max values of at least 18 ml/kg/min (in men) and 15 ml/kg/min (in women)

Why is VO_2 Max Important?

Predictor of mortality in health and disease

Transplant Listing and $\text{HFSS}/\text{VO}_{2\text{peak}}$

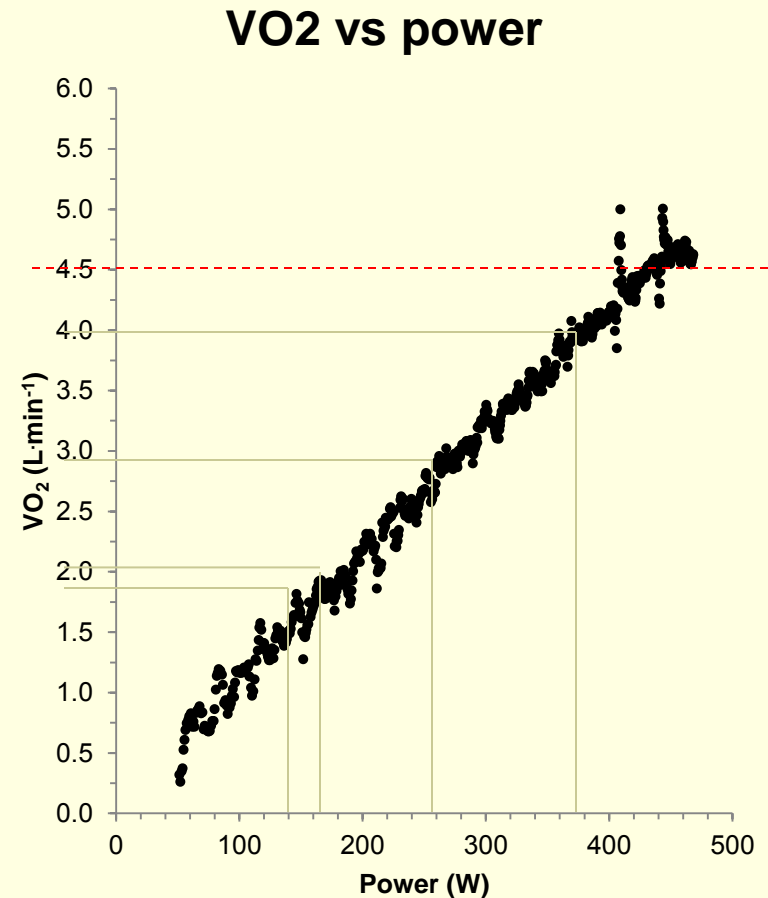


- ◇ Accepted for Transplant;
 $\text{VO}_{2\text{peak}} < 14 \text{ ml.kg}^{-1}.\text{min}^{-1}$
- ◆ Rejected for Transplant;
 $\text{VO}_{2\text{peak}} > 14 \text{ ml.kg}^{-1}.\text{min}^{-1}$
- ▲ Ineligible for Transplant;
 $\text{VO}_{2\text{peak}} < 14 \text{ ml.kg}^{-1}.\text{min}^{-1}$

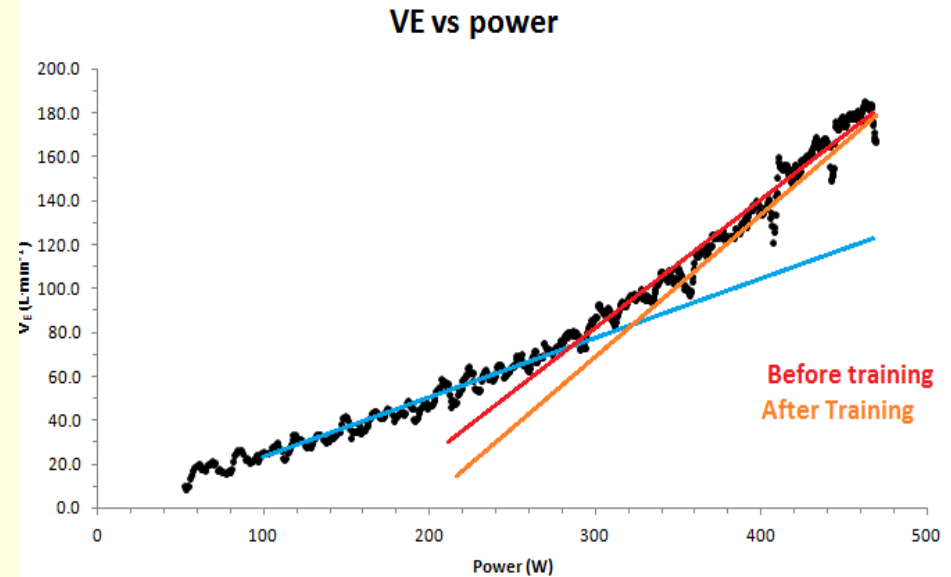
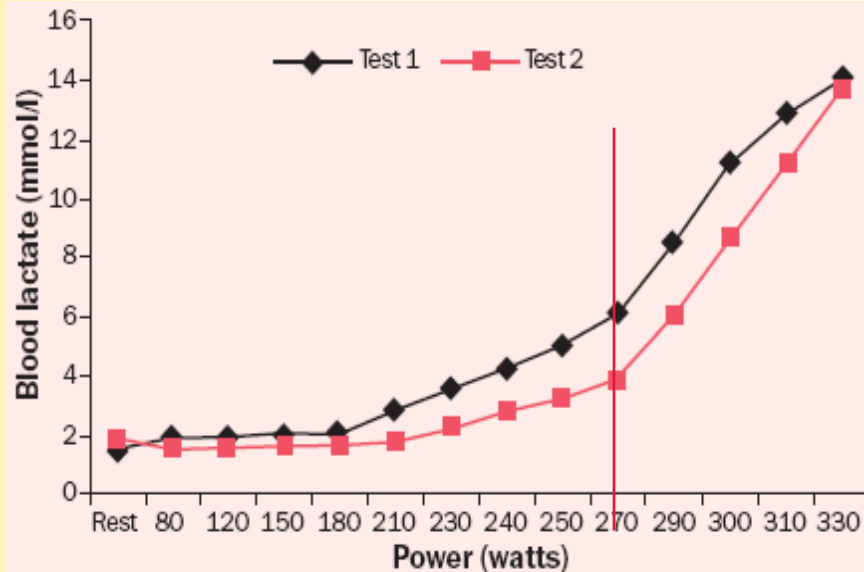
Why is VO_2 Max Important?

Intensity Ranges for Training

- $\text{VO}_2 = 4.5 \text{ L/min}$
- High Intensity
 - 64-90% VO_2 max
 - 2.9-4 L/min
 - 270- 380 W
- Moderate Intensity
 - 46-64% VO_2 max
 - 2-2.8 L/min
 - 190- 269 W
- Low Intensity
 - 37-45% VO_2 max
 - 1.85- 2 L/min
 - 160-190 W



Anaerobic Threshold

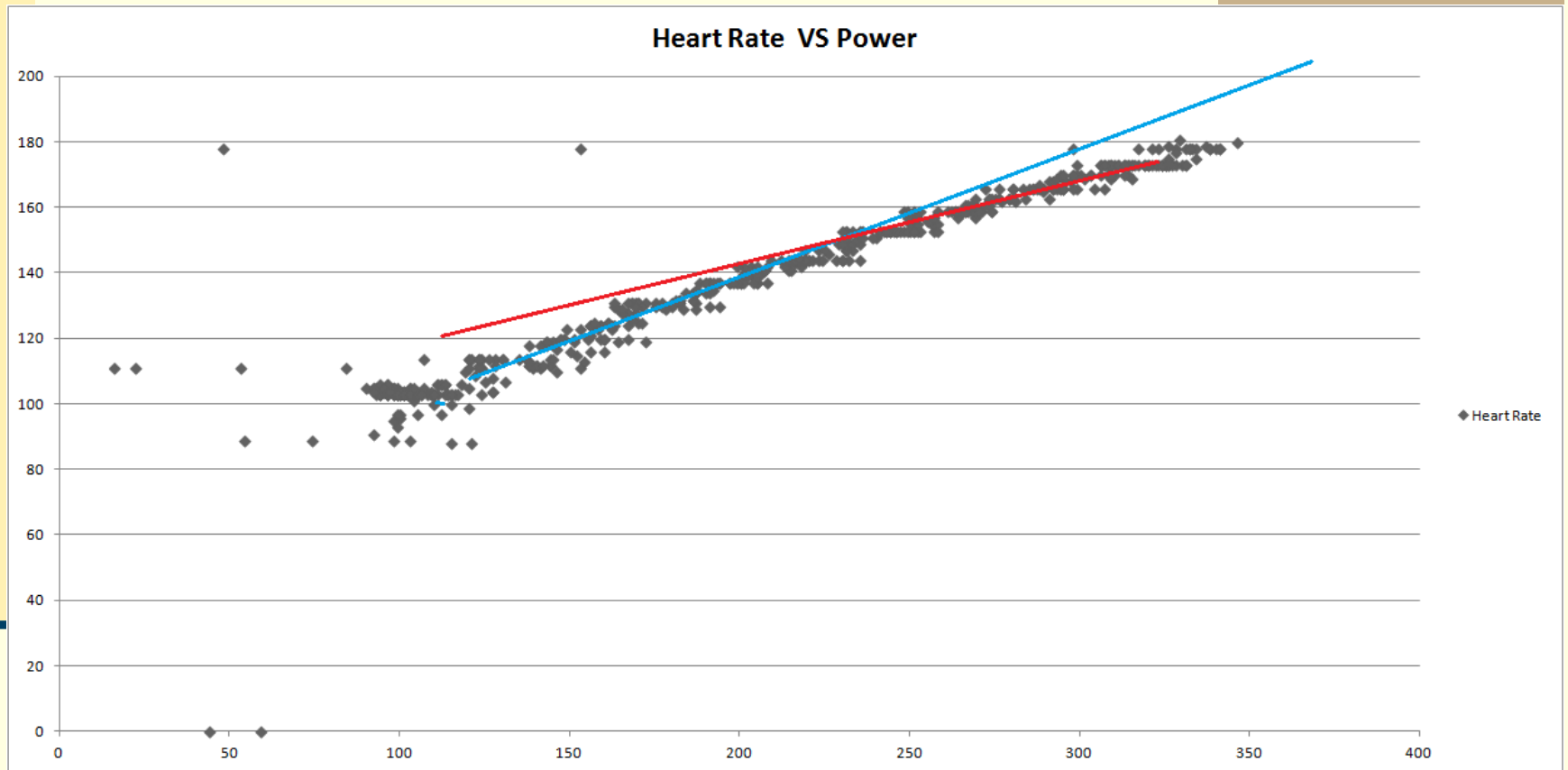


■ Lactate Threshold (LT)

- Lactate is present even at low levels of work
- At some point it can't be removed quickly enough
 - Levels begin to build
 - This is when it starts to hurt!
- Lactate threshold trainable even in athletes (VO2 max is not)

■ Ventilatory Threshold (VT): increase in rate of breathing \cong LT

Heart Rate



Classifications of Relative Exercise Intensity

Intensity	%HRR	%HR _{max}	%VO _{2 max}	RPE
Very Light	<30	<57	<37	<9
Light	30-39	57-63	37-45	9-11
Moderate	40-59	64-76	46-63	12-13
Vigorous	60-89	77-95	64-90	14-17
Maximal	≥90	≥96	≥91	≥18

HRR: Heart Rate Reserve= $HR_{\max} - HR_{\text{rest}}$

RPE: Rate of Perceived Exertion

Remember: Intensity levels must be adjusted with training!!!



Negative Findings in

STUDIES OF DEPRESSION

Cochrane Meta-Analysis



- 39 Randomized Control Trials
- Subjects
 - Defined as having depression
 - By any method
 - Any severity
 - Clinical populations
 - Non-clinical
 - Both
 - No age cap (age 18+)
- Control Groups
 - No intervention
 - Waiting list control
 - Placebo
 - Other active treatments
 - Sertraline
 - CBT
 - Other alternative treatments
 - Exercise as adjunct
 - Excluded
 - 2 types of exercise
 - No control group

Cochrane Meta-Analysis

Exercise: (*n.*) “planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness.”

■ Components of fitness:

- Cardiorespiratory (33 trials)
- Muscular strength
- Muscular endurance
- Body composition
- Flexibility
- Balance, Agility, Reaction time
- Power

Cochrane Meta-Analysis



- Exercise is **moderately** more effective than **no therapy** for reducing symptoms of depression.
- Exercise is **no more effective** than
 - Antidepressants
 - Psychological therapies
 - These conclusions are based on small number of studies

High Quality Studies?

- “when only high-quality studies were included, the difference between exercise and no therapy is less conclusive.”
 - Allocation concealment
 - Use of intention-to-treat analysis
 - Blinded outcome assessment
- “There was a small clinical effect in favor of exercise, which *did not reach statistical significance.*”

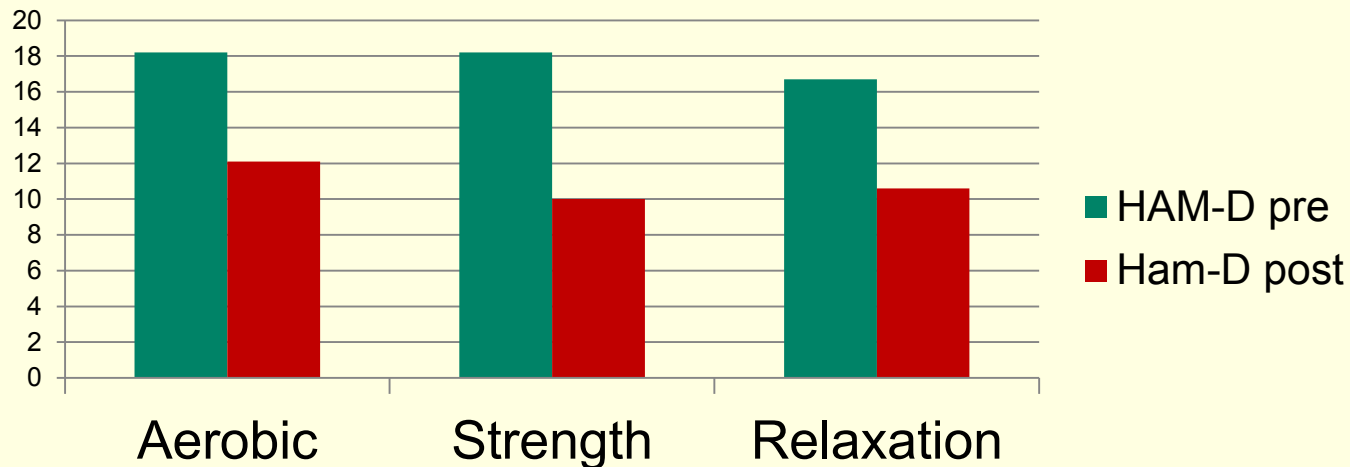
High Quality Studies?

Trial	n	Subjects	Outcome	Controls
Blumenthal 1999	156	≥ 55 yo	HAM-D BDI	Sertraline, Ex + Sertraline combo
Blumenthal 2007	202		HAM-D	Home Ex, Sertraline, Placebo
Blumenthal 2012a	101	CHD	HAM-D	Sertraline, Placebo
Krogh 2009	165	18-55 yo	HAM-D	Strength, Relaxation
Dunn 2005	80	20-45 yo	HRSD	4 Ex groups, Flexibility group
Mather 2002	86	≥ 53 yo, >6wk Rx Tx	HRSD	Health education

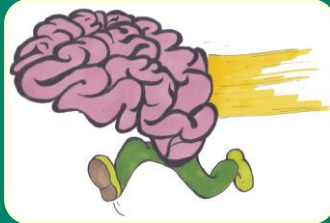
HAM-D= Hamilton Rating Scale for Depression,
BDI= Beck Depression Inventory,
HRSD= 17 item Hamilton Rating Scale for Depression

DEMO Trial: Krogh 2009

- Randomized pragmatic trial
 - Exercise adjunct to other treatments
- Patients with unipolar depression (ICD-10)
- Primary outcome HAM-D

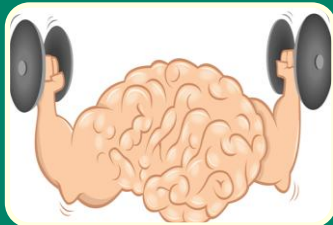


DEMO: Intervention Design



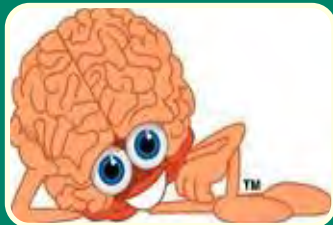
Aerobic Exercise Group

- 10 exercises (running, stepping, rowing, etc.)
- Interval circuit aerobic training 40-60 min



Strength Training Group

- 12 machine exercises (leg/ chest press, etc.)
- 12 reps, 2-3 sets, @50% to 75% 1 rep max



Relaxation Group

- Avoid muscular contraction, CV stimulation
- Rate of perceived exertion <12 out of 20

1.5 Hours each session total
2 Sessions per week/ 4 months

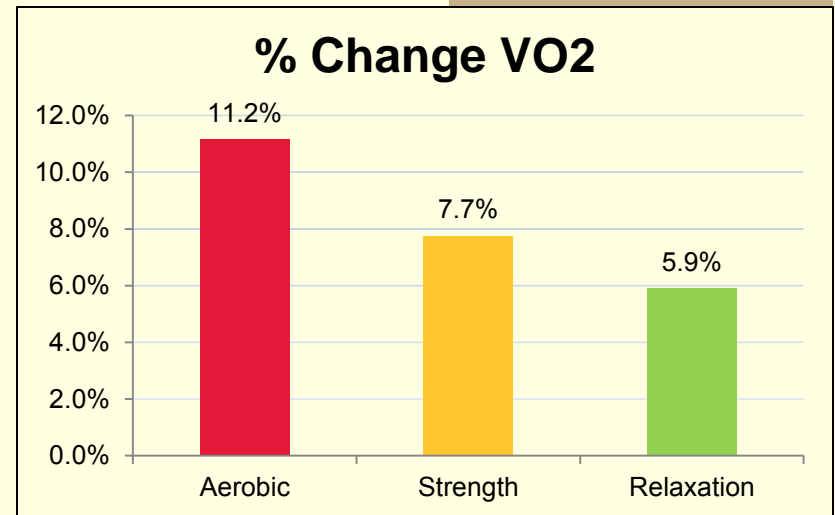
DEMO: Inadequate Control

- 20 minute low intensity warm up
- 20-30 minutes
 - **exercises** on mattress or ball
 - -OR- back massage
- 10-20 minutes light balance **exercises**
- 20-30 minutes relaxation exercises
 - alternating **muscle contraction** and relaxation in different muscle groups
 - while laying down



DEMO: Inadequate Dose

- Frequency: 2 x per wk
 - Less than minimum recommendations
 - ACSM
 - US dept health
 - Average participation only 16.2 sessions
 - Only 1 session/ wk!
- Intensity
 - 70-89% Max Heart Rate
 - Not HRR or VO₂ or LT
- Duration
 - 2/2 -3/1 exercise/rest ratio
 - Total 30-60 min exercising



- Relaxation “control” group increased VO₂
- No statistical difference between Aerobic and Strength groups



"All I want to do is lie around all day. This isn't helping"

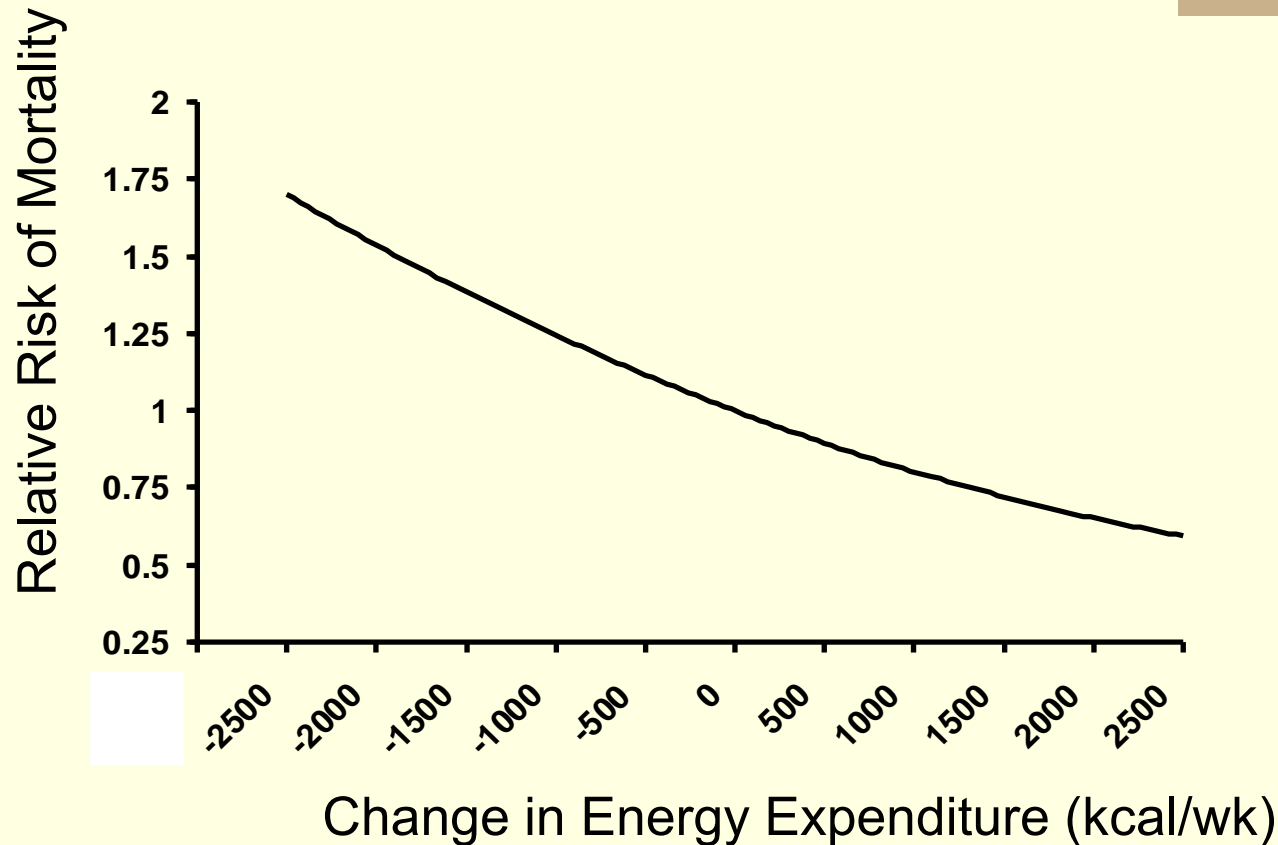
EXERCISE PROMOTION IN PSYCHIATRY

Exercise is Healthy

- Tremendous health benefits with even low levels of exercise.
- Amount of exercise needed to benefit health is much lower than amount needed for fitness.
- Regular physical activity at the correct intensity:
 - Reduces the risk of heart disease by 40%.
 - Lowers the risk of stroke by 27%.
 - Reduces the incidence of diabetes by almost 50%.
 - Reduces the incidence of HTN, by almost 50%.
 - Can reduce mortality & risk of recurrent breast cancer by almost 50%.
 - Can lower the risk of colon cancer by over 60%.
 - Can reduce the risk of developing Alzheimer's disease by one-third.



Change in Activity and Adjusted* Risk of Death



- *Adjusted for baseline activity, age, sex, race, smoking, alcohol, adiposity, comorbidities

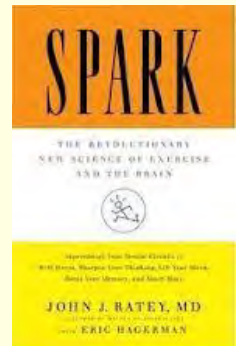
Ask not what exercise can do for psychiatry. . .

The
groundwork
of all happiness
is health.

James Leigh Hunt

- “It’s time to put Childish Things Aside. Time to get serious about Play and Exercise”

— John Ratey, MD, author of *Spark: the Revolutionary New Science of Exercise and the Brain*, <http://sparkinglife.org/page/home>



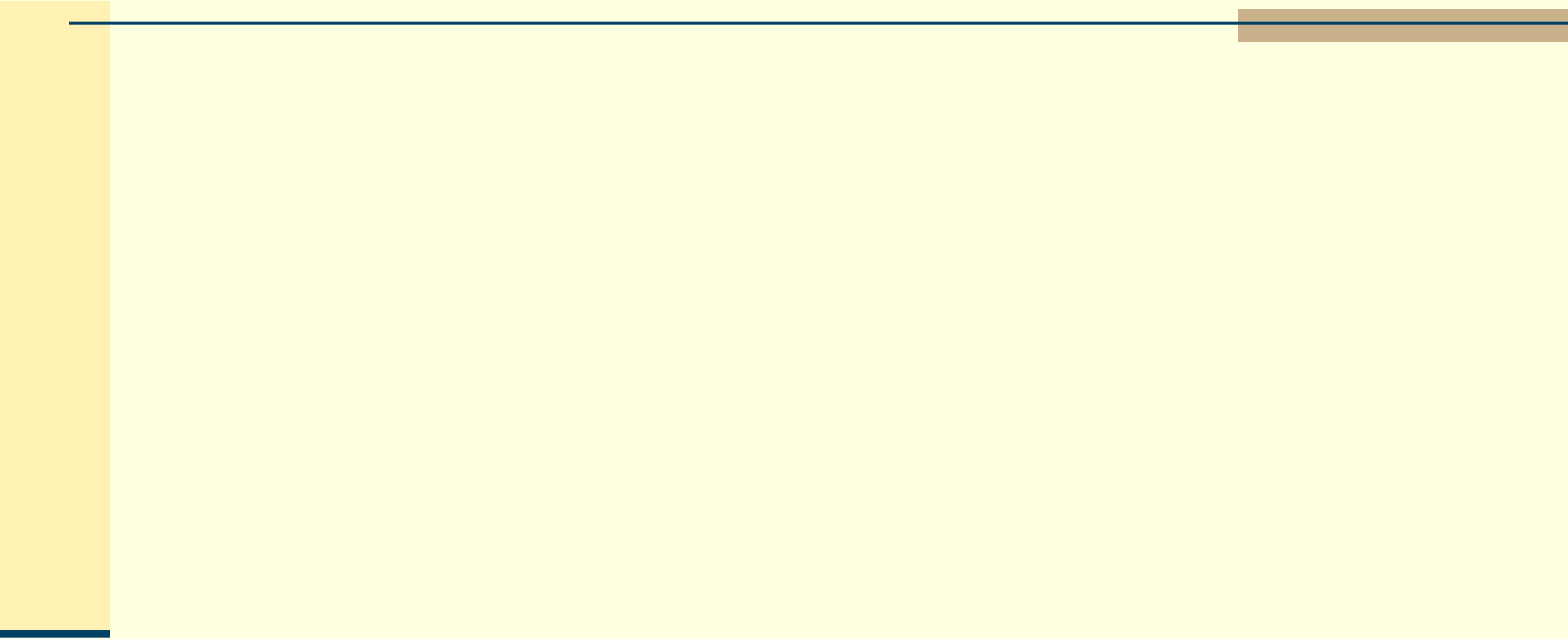
Acknowledgments



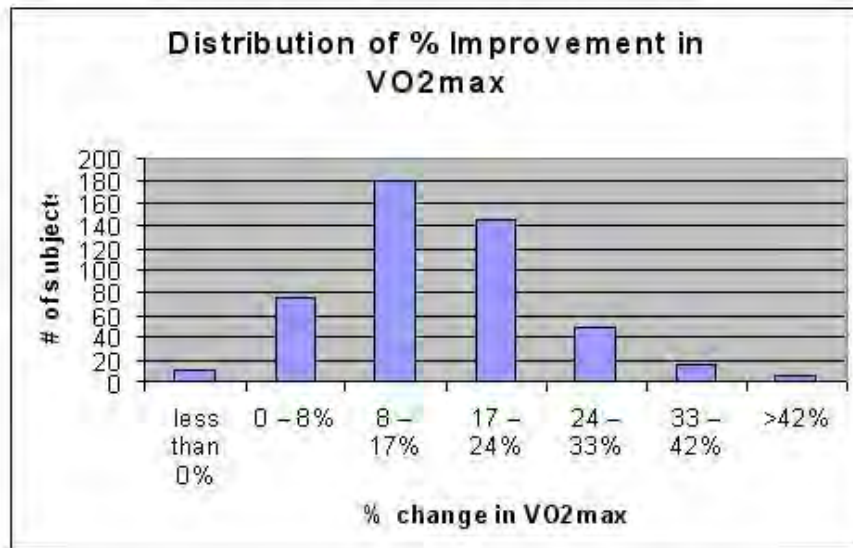
- Derek Brehm
- Sean Burke, MS
- Dan Cannon, PhD
- Nicole Nguyen, MD
- Lynn Ringenberg, PhD
- Robert Sallis, MD, FACSM

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Training Effect



Bouchard C, An P, Rice T, Skinner J, et al Familial aggregation of VO₂max response to exercise training: results from the HERITAGE family study J. Appl. Physiol. 87(3): 1003-1008, 1999

- **HERITAGE family study**
 - 5 research universities
 - research the role genotype in response to training.
 - 481 healthy, sedentary subjects
- **3 days per week exercise program for 20 weeks.**
 - 30 minutes of cycling on a cycle ergometer at 55% of VO₂max 3 days per week
 - gradually increased to 50 minutes of cycling at 75% of VO₂max 3 days per week.
 - This range of exercise intensity (55% – 75%) is considered to be an easy work load.
- **Results**
 - average increase in VO₂max was 400 ml/min, a 17% improvement.
 - range of response was -5% to 56%.

Randomized Controlled Trial

Blumenthal JA et al, *Arch Intern Med*, 1999

- 156 depressed older patients randomly assigned to 1 of 3 groups
 - Supervised aerobic exercise at 70%-85% of heart rate reserve for 30 minutes on 3 days per week
 - Zoloft Rx at 50 mg to 200 mg daily
 - Both aerobic exercise and Zoloft Rx
- Primary outcomes = scores on Hamilton Rating Scale for Depression (HAM-D) and Beck Depression Inventory (BDI)

Blumenthal JA et al (Cont'd)

- Findings at 4 months...
 - All 3 groups achieved comparable & significant remission of MDD based on DSM-IV criteria
 - 60.4% in exercise group
 - 68.8% in Zoloft group

Bottom line:

- Exercise – walking or jogging – at 70%-85% of maximum aerobic intensity is as effective as Zoloft therapy in treating mild MDD
- Zoloft therapy had a faster initial response than exercise in improvement of MDD symptoms

Systematic Review

Lawlor et al, *BMJ*, 2001

- Outcomes = mean differences in effect size in BDI score between exercise & no treatment and between exercise & cognitive therapy
- 72 potentially relevant studies; 56 were excluded from analysis

Lawlor et al (Cont'd)

■ Findings...

- Exercise c/w placebo intervention or as adjunct to standard treatment
 - Effect size was significant at -1.1 (-1.5 to -0.6)
- Exercise c/w standard treatments

Limitations

Bottom line:

- Effectiveness of exercise in reducing sx's of depression cannot be determined because of a lack of good quality research

Best Evidence (so far) – DOSE trial

Dunn et al, *Am J Prev Med*, 2005

- 80 adults w/ mild-moderate depression randomly assigned to 1 of 5 treatment groups
 - 7 kcal/kg/week (low dose) performed on 3 or 5 days/week
 - 17.5 kcal/kg/week (high dose) performed on 3 or 5 days/week
 - flexibility exercise control performed on 3 days/week
- Subjects exercised individually in rooms under supervision by laboratory staff
- Primary outcome = score on 17-item Hamilton rating scale for depression (HRSD₁₇)

Dunn et al (Cont'd)

■ Findings...

- Adjusted mean HRSD₁₇ scores at 12 weeks
 - Reduced 47% for high dose exercisers
 - Reduced 30% for low dose exercisers
 - Reduced 29% for controls
 - No main effect of exercise frequency

Bottom line(s):

- Both high & low-dose aerobic exercise are effective as monotherapy in the treatment of mild to moderate MDD
- Exercising 3 times per week is at least as effective as 5 times per week