Exercise is Regenerative Medicine: Impact on Chronic Disease

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Core Muscle Research Laboratory, GRECC, Birmingham VA Medical Center
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.
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.

**Exercise prescription dose**
- Mode, Intensity, Frequency, Volume

**Adherence / compliance**

**Other environmental & behavioral factors**

**Physiologic and Disease-Modifying Outcomes**
- Neuromotor function
- Musculoskeletal integrity
- Cognition & memory
- Cardiorespiratory function
- Vascular function
- Metabolic homeostasis
- Body composition
- Inflammatory burden
- Mobility and activity participation
- Quality of life
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**: ?
<table>
<thead>
<tr>
<th>Functional</th>
<th>ET</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength performance</td>
<td>↔️</td>
<td>↑️</td>
</tr>
<tr>
<td>Specific strength (per unit muscle)</td>
<td>↔️</td>
<td>↑️</td>
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<tr>
<td>Endurance capacity</td>
<td>↑️️️️️</td>
<td>↑️</td>
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<tr>
<td>Steady state exercise HR</td>
<td>↓️</td>
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<tr>
<td>Steady state exercise Ve</td>
<td>↓️</td>
<td>↓️</td>
</tr>
<tr>
<td>Steady state exercise RER</td>
<td>↓️</td>
<td>↓️</td>
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</tbody>
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**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. VO₂ max)
- Hallmark measure of fitness
- Major predictor of disease risk and mortality
- Assessed via maximal graded exercise test with a ramp protocol (typically on a treadmill)
- Total test time correlates well
- Highly responsive to exercise training and deconditioning
IMPACT OF PHYSICAL INACTIVITY ON MORBIDITY AND MORTALITY
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

Physical inactivity by county
Heart disease mortality by county

Heart Disease Death Rates, 2008-2010
Adults, Ages 35+, by County

Rates are spatially smoothed to enhance the stability of rates in counties with small populations.

Data Source:
National Vital Statistics System
National Center for Health Statistics

CDC Logo
Diabetes by county

County-level Estimates of Diagnosed Diabetes among Adults aged ≥ 20 years: United States 2009

www.cdc.gov/diabetes
Obesity by county

County-level Estimates of Obesity among Adults aged ≥ 20 years:
United States 2009

Age-adjusted percent
0 - 19.4
19.5 - 23.8
23.9 - 27.0
27.1 - 30.7
≥ 30.8


www.cdc.gov/diabetes
Lung cancer by county
Colo-rectal cancer by county

Colo-Rectal Cancer Mortality Rates* By County
2000-2009

Legend
Age Adjusted Rates
- 7.10 - 16.10
- 16.11 - 18.00
- 18.01 - 19.80
- 19.81 - 22.30
- 22.31 - 45.30
- Insufficient Data

*Rates are per 100,000 Age Adjusted to the 2000 US Census
Source: CDC Wonder, http://wonder.cdc.gov/

Health Disparities Research Center of Excellence at Meharry Medical College
IMPACT OF FITNESS ON MORTALITY
New Findings:
Longitudinal study with 11 yr follow-up

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
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

Over 71,000 participants
Reduced Disability and Mortality Among Aging Runners

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

A 21-Year Longitudinal Study

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

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).
“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

Ischemic Heart Failure Etiology

Mean KCCQ Summary Score

No. of participants
Exercise training
Usual care

Baseline 3 6 9 12 24 36
598 547 511 472 470
599 514 481 471 431
277 285
131 151

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

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**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

The Look AHEAD Trial

Adjustment Change in HbA1c

DSE and ILI Combined

DSE

ILI

-10% decline in fitness
-0% to 10% decline in fitness
0% to 10% increase in fitness
>10% increase in fitness
Missing Fitness at Year 4

Diabetes Care 36:1297–1303, 2013
The New England Journal of Medicine

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NUMBER 6

REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN

DIABETES PREVENTION PROGRAM RESEARCH GROUP*
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

- **Major mobility disability**
  - Proportion of Event-Free Participants
  - Follow-up Time, y
  - HR, 0.82 (95% CI, 0.69-0.98); P = .03

- **Persistent mobility disability**
  - Proportion of Event-Free Participants
  - Follow-up Time, y
  - HR, 0.72 (95% CI, 0.57-0.91); P = .006

Physical activity
Health education
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.

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.

Exercise prescription dose
- Mode, Intensity, Frequency, Volume

Adherence / compliance
- Other environmental & behavioral factors

Phenotype
- Transcriptome and proteome profiles
- Epigenome profile

Genotype

Exercise
- Prescriptions dose
- Mode, Intensity, Frequency, Volume

Adherence / compliance
- Other environmental & behavioral factors

Physiologic and Disease-Modifying Outcomes
- Neuromotor function
- Musculoskeletal integrity
- Cognition & memory
- Cardiorespiratory function
- Vascular function
- Metabolic homeostasis
- Body composition
- Inflammatory burden
- Mobility and activity participation
- Quality of life

Non-modifiable factors
- Age
- Gender
- Race/ethnicity
- Disease stage

Modifiable factors
- Co-morbidities
- Functional capacity
- Diet & medications
- Physical activity
- Sleep

Environmental & behavioral factors
- Other environmental & behavioral factors

*
Optimal prescription/dose?

- Mode
- Intensity
- Frequency
- Volume

UAB Magazine
Fall/Winter Issue 2011
Molecular Transducers of Physical Activity Consortium (MoTrPAC)
Molecular Transducers of Physical Activity Consortium (MoTrPAC)
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*, Andrea Mattera*, Laura Micheli*, Manuela Ceccarelli*, Luca Leonardo*, Daniele Saraulli*, Marco Costanzi*,b, Vincenzo Cestari*,c, Jean-Pierre Rouault*, and Felice Tirone*

Dentate gyrus region of hippocampus

Only 12 days of free wheel running

Long-term effect of running

Sedentary

Exercise
Exercise increases delivery of chemotherapeutic drugs to tumors

Exercise + chemo decreases tumor growth more than chemo alone

**Tumor vessel normalization after aerobic exercise enhances chemotherapeutic efficacy**

Keri L. Schadler¹, Nicholas J. Thomas¹, Peter A. Galie², Dong Ha Bhang¹, Kerry C. Roby¹, Prince Addai¹, Jacob E. Till¹, Kathleen Sturgeon¹, Alexander Zaslavsky¹, Christopher S. Chen³, Sandra Ryeom¹
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. Mikołowska 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

Muscle Aging

- ↓Physical activity
- ↑Disability
- ↑Fatigability
- ↓Muscular Endurance
- ↑Risk of falls and fracture
- ↓Power
- ↓Strength

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

Top: 25y male
Bottom: 63y male
Ht & wt matched
Restoration of muscle mass and myofiber size

Unilateral thigh muscle mass (kg) normalized to height (m\(^2\))

- Pre-training
- After 16 wk PRT

Type II myofiber CSA (um\(^2\))

- Pre-training
- After 16 wk PRT

Healthy Standard 95% CI

* indicates significance.
Restoration of neuromuscular function

Unilateral knee extension strength (kg) (isometric maximum voluntary contraction)

- Pre-training
- 8-wk PRT
- 16-wk PRT

Leg power (W)

- Pre-training
- 8-wk PRT
- 16-wk PRT

Healthy Standard 95% CI
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.
Funded by the U.S. National Institutes of Health:
National Center for Medical Rehabilitation Research
National Institute of Neurological Disorders and Stroke
National Institute of Biomedical Imaging and Bioengineering
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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REACTCenter@uab.edu
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Funded by National Institutes of Health grant P2CHD086851 (NICHD/NCMRR, NINDS, and NIBIB)
Quick Facts:
• Est. 2012; grown to 70 Member Institutions
• Partners: UAB CTSA (CCTS), CTSA Consortium, ACSM