Exercise Medicine for Cancer Management

Rob Newton PhD, AEP, CSCS*D
PHYSICAL ACTIVITY AND EXERCISE

- World Health Organisation defines physical activity as “any bodily movement produced by skeletal muscles that requires energy expenditure”.

- WHO is explicit that the term “physical activity” should not be used interchangeably with “exercise”.
EXERCISE MEDICINE

“Exercise medicine” is the physical assessment and prescription of exercise specifically for the prevention or treatment of injury or illness.

- Specific exercise drives endogenous “medicine”
  - Hormones and cytokines
- Direct structural adaptation and repair
- Blood perfusion and vascular adaptations
- Facilitates other therapies, ameliorates side-effects
EXERCISE MEDICINE & THE CANCER CONTROL FRAMEWORK

Specific phases along the cancer continuum

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>CANCER CONTROL CATEGORIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>prevention/detection</td>
<td>treatment preparation</td>
</tr>
<tr>
<td>prescreening screening</td>
<td>treatment effectiveness</td>
</tr>
<tr>
<td>prediagnosis</td>
<td>recovery</td>
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<tr>
<td></td>
<td>disease prevention</td>
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<td></td>
<td>palliation</td>
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<tr>
<td></td>
<td>survival</td>
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<td>postdiagnosis</td>
<td>pretreatment</td>
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<tr>
<td></td>
<td>treatment</td>
</tr>
<tr>
<td></td>
<td>survivorship</td>
</tr>
<tr>
<td></td>
<td>end of life</td>
</tr>
<tr>
<td>cancer-related time periods</td>
<td></td>
</tr>
</tbody>
</table>

Courneya and Friedenreich Sem Onco Nurs 2007;23:242-52
Survival!

Cancer Survival: Time to Get Moving? Data Accumulate Suggesting a Link Between Physical Activity and Cancer Survival

Across 26 studies of breast, colorectal and prostate cancer patients, there is a 37% reduction in risk of cancer-specific mortality, comparing the most versus the least active patients (pooled relative risk=0.63, 95% confidence interval: 0.54-0.73)

Risks of recurrence or recurrence/cancer-specific death (combined outcome) also reduced (pooled relative risk=0.65, 95% confidence interval: 0.56-0.75)
Compared to Chemotherapy

• Data from these studies suggest a reduced risk of recurrence or death of 50% to 60%.

Exercise is NOT an alternative to chemotherapy but a critical synergistic medicine.

Definitive Trials in Exercise and Cancer Survival

American College of Sports Medicine
Roundtable on Exercise Guidelines for Cancer Survivors

SPECIAL COMMUNICATIONS
Roundtable Consensus Statement

EXPERT PANEL
Kathryn H. Schmitz, PhD, MPH, FACSM
Kerry S. Courneya, PhD
Charles Matthews, PhD, FACSM
Wendy Demark-Wahnefried, PhD
Daniel A. Galvão, PhD
Bernardine M. Pinto, PhD
Melinda L. Irwin, PhD, FACSM
Kathleen Y. Wolin, ScD, FACSM
Roanne J. Segal, MD, FRCP
Alejandro Lucia, MD, PhD
Carole M. Schneider, PhD, FACSM
Vivian E. von Gruenigen, MD
Anna L. Schwartz, PhD, FAAN

A - overwhelming data from RCTs
B - few RCTs exist
C - uncontrolled, nonrandomized and/or observational studies
D - insufficient for categories A-C

Focus on adult cancers and sites with the most evidence
Evaluation of Evidence A-D*
Breast, Prostate, Colon, Hematological, Gynecological

*National Heart Lung and Blood Institute

Evidence for Prostate Cancer

During and after treatment - Effects of exercise on key endpoints

Results from 12 trials

During or following ADT/Radiation

- Evidence category A – Safety
- Evidence category A – Aerobic Fitness
- Evidence category A – Muscle Strength
- Evidence category A – Fatigue
- Evidence category B – Body Size/Composition
- Evidence category B – Quality of Life
- Evidence category B – Physical Function

American College of Sports Medicine
Roundtable on Exercise Guidelines for Cancer Survivors

Evidence for Breast Cancer

During chemotherapy or radiation

Results from 22 RCTs

- Evidence category A – Safety
- Evidence category A – Aerobic Fitness
- Evidence category A – Muscle Strength
- Evidence category B – Body Size/Composition
- Evidence category B – Quality of Life
- Evidence category B – Fatigue
- Evidence category B – Anxiety

Evidence for Breast Cancer

- Evidence category A - Safety
- Evidence category A - Aerobic Fitness
- Evidence category A - Muscle Strength
- Evidence category A - Flexibility
- Evidence category A - Physical Function
- Evidence category A - Safety Lymphedema Onset or Worsening
- Evidence category B - Body Size/Composition
- Evidence category B - Quality of Life
- Evidence category B - Fatigue/Energy/Vitality
- Evidence category B - Depression/Anxiety
- Evidence category B - Body Image
- Evidence category C - Symptoms/Adverse Effects and Pain

Following treatment
Results from 32 RCTs

EXERCISE MECHANISMS: SURVIVAL AND TUMOUR BIOLOGY

Effect of Low-Intensity Physical Activity and Moderate- to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy Completion Rates: Results of the PACES Randomized Clinical Trial

### Table 6. Rates of and Reasons for Chemotherapy Dose Reduction

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 230)</th>
<th>OnTrack (n = 76)</th>
<th>Onco-Move (n = 77)</th>
<th>Usual Care (n = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients requiring dose adjustments, No. (%)</td>
<td>61 (26)</td>
<td>9 (12)</td>
<td>26 (34)</td>
<td>26 (34)</td>
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<tr>
<td>Mean prescribed length of chemotherapy, days</td>
<td>118.6</td>
<td>119.2</td>
<td>119.9</td>
<td>116.7</td>
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<tr>
<td>Neuropathy</td>
<td>19 (31)</td>
<td>3</td>
<td>10</td>
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<tr>
<td>Myelosuppression</td>
<td>7 (11)</td>
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<td>2</td>
<td>3</td>
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<tr>
<td>Febrile neutropenia</td>
<td>7 (11)</td>
<td>0</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>7 (11)</td>
<td>2</td>
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<td>3</td>
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<tr>
<td>Pain</td>
<td>6 (10)</td>
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<td>2</td>
<td>3</td>
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<td>Infection</td>
<td>4 (7)</td>
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<td>3</td>
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<tr>
<td>Dyspnea</td>
<td>4 (7)</td>
<td>0</td>
<td>2</td>
<td>2</td>
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<td>Edema</td>
<td>3 (5)</td>
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<td>3</td>
<td>0</td>
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<tr>
<td>Cardiac signs or symptoms</td>
<td>2 (3)</td>
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<td>0</td>
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<tr>
<td>Obstipation/diarrhea</td>
<td>2 (3)</td>
<td>1</td>
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<td>0</td>
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<tr>
<td><strong>Average % dose reduction</strong></td>
<td><strong>9.8</strong></td>
<td><strong>9.7</strong></td>
<td><strong>25.2</strong></td>
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</tr>
</tbody>
</table>

*Average dose reductions per group among participants needing a dose adjustment.
EXERCISE SUPPRESSION OF CANCER CELL GROWTH

- 10 male individuals - 60 minutes cycling
- Serum pre+post
- Prostate cancer cell line LNCaP exposed
- 9 out of 10 individuals growth inhibition
- Pooled exercise serum 31% inhibition

July 5, 2013
EXERCISE INDUCED IMMUNOTHERAPY

- Improved immune function through increased cell surveillance, activation, and infiltration by the innate system.

Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution

Line Pedersen, Martin Joormann, Gitte H. Olofsson, Britt Laumborg, Intawat Nookaew, Rasmus Huse Hansen, Helge Hjorth JohanneSEN, Jürgen Becker, Katrine S. Pedersen, Christine Drotthelsofen, Jens Nielsen,Julie Gahl, Bente K. Pedersen, Per Thor Straten, and Perrnille Hejman

Cell Metabolism (2016), http://dx.doi.org/10.1016/j.cmet.2016.01.011
**EXERCISE INDUCED IMMUNOTHERAPY**

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<thead>
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<th>CON</th>
<th>EX</th>
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<tr>
<td><img src="image1.png" alt="Control Images" /></td>
<td><img src="image2.png" alt="Exercise Images" /></td>
</tr>
</tbody>
</table>

*Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution*

Lin Peterson, Maria Ivanova, Gilli M. Olofsson, Britt Laenborg, Henrik Röckner, Marcus Hovas Pinto, Helge Erikth Johansson, Jorge C. Becker, Karina S. Peterson, Christina Grill, Anna Jerne, Jonas Kent, Bernt K. Pihl, Per Harth, Stenius, Timo, and Per soleman.  

*Cell Metabolism (2016), http://dx.doi.org/10.1016/j.cmet.2016.01.011*
Exercise-Dependent Regulation of NK Cells in Cancer Protection

Manja Idorn\(^1\) and Pernille Hojman\(^2,\,*\)

Mobilization of NK cells are affected by:
- muscle derived myokines
- exercise-dependent hyperthermia
- intratumoral vascularization and perfusion

subsequently inducing the regulation, redistribution, and activation of mobilized NK cells
Increased tumour blood perfusion enhancing immune system effectiveness as well as chemotherapy delivery.
The oxygen enhancement effect in radiotherapy:

1) Irradiation induces water ionization and destabilization, leading to the formation of reactive radical species.
2) React with neighboring molecules to yield reactive oxygen species (ROS).
3) Hydroxyl radical most cytotoxic and with other less energetic species attack DNA.
4) However, formation of a DNA radical is readily reversible.
5) In the presence of oxygen, DNA damage can be stabilized - “oxygen enhancing effect” of radiotherapy.

Jordan and Sonveaux, Frontiers in Pharmacology, 2012
Hypoxia in tumors results from a mismatch between the oxygen supply by poorly efficient blood vessels and oxygen consumption by metabolically overactive tumor cells.

Jordan and Sonveaux, Frontiers in Pharmacology, 2012
EXERCISE SYNERGY WITH RADIATION THERAPY

• Acute exercise increases blood perfusion of tumors
  – Tumor arterioles lack exercise induced vasoconstriction
  – Plus increased blood pressure

• Chronic exercise normalises blood vessel structure in tumors

• Cancer patients must exercise chronically at all stages of cancer treatment.

• Cancer patients recommended to exercise immediately prior to Radiation Therapy
## Effects of Varying Exercise Modes: A 12 Month RCT

### Study protocol

**A phase III clinical trial of exercise modalities on treatment side-effects in men receiving therapy for prostate cancer**

Robert U Newton*¹, Dennis R Taaffe², Nigel Spry³,⁴, Robert A Gardiner⁵, Gregory Levin¹, Bradley Wall¹, David Joseph³,⁴, Suzanne K Chambers⁶ and Daniel A Calvão¹

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>RCT</td>
</tr>
<tr>
<td>Sample</td>
<td>163</td>
</tr>
</tbody>
</table>
| Intervention | 12-month (2x week)  
(i) impact & resistance  
(ii) resistance & aerobic  
(iii) delayed & aerobic |
| Primary endpoint | lean mass, BMD, VO2 |

Weight and muscle mass change over 12 months.

A - Muscle Strength (1-RM) kg

B - Whole Body Lean Mass kg

Muscle strength and total lean mass change over 12 months.

IMPACT EXERCISE FOR BONE HEALTH
LUMBAR SPINE BMD (% CHANGE OVER 6 MONTHS)

Change in Lumbar BMD over 6 months of AST
Comparision of two exercise programs
to usual care

- resistance/impact loading: p = 0.839
- resistance/cardiovascular: p = 0.019
- usual care: p < 0.001

Newton et al 2013 World Prostate Cancer Congress
Efficacy and safety of a modular multi-modal exercise program in prostate cancer patients with bone metastases: a randomized controlled trial

Daniel A Galvão¹, Dennis R Taaffe¹, Prue Cormie¹, Nigel Spry³, Suzanne K Chambers², Carolyn Peddle-McIntyre¹, Michael Baker¹, James Denham¹,², David Joseph¹,², Geoff Groom² and Robert U Newton¹

Abstract

Background: The presence of bone metastases has excluded participation of prostate cancer patients in exercise intervention studies to date and is also a relative contraindication to supervised exercise in the community setting because of concerns of fragility fracture. However, this group of patients often have developed significant muscle atrophy and functional impairments from prior and continuing androgen deprivation that is exacerbated by subsequent and more intensive interventions such as chemotherapy. The aim of this study is to determine the efficacy and safety of a modular multi-modal exercise program in prostate cancer patients with bone metastases.

Methods/Design: Multi-site randomized controlled trial in Western Australia and New South Wales to examine the efficacy and safety of a modular multi-modal physical exercise program in 90 prostate cancer survivors with bone metastases. Participants will be randomized to (1) modular multi-modal exercise intervention group or (2) usual medical care group. The modular multi-modal exercise group will receive a 3-month supervised exercise program based on bone lesion location/extent. Measurements for primary and secondary endpoints will take place at baseline, 3 months (end of the intervention) and 6 months follow-up.

Discussion: Delaying or preventing skeletal complication and improving physical function for men with bone metastases would provide clinically meaningful benefits to patients. However, exercise programs must be designed and executed with careful consideration of the skeletal complications associated with bone metastatic disease and cumulative toxicities from androgen deprivation such as osteoporosis and increased risk of fractures. The results from this study will form the basis for the development of a specific exercise prescription in this patient group in order to alleviate disease burden, counteract the adverse treatment related side-effects and enhance quality of life.

Trial Registration: ACTRN: ACTRN1261001158954

Background

Metastasis to bone occurs in approximately 80% of men with advanced prostate cancer [1] and the majority of these patients are at risk of developing pathological fractures, hypercalcemia, bone marrow suppression and nerve compression or spinal cord compressions that result in significant morbidity, limited function and decreased quality of life [2-4]. The clinical course of metastatic bone disease in prostate cancer survivors is relatively long, with a 5-year survival rate of approximately 30% [5]. Prostate cancer causes predominately sclerotic lesions and commonly metastasize to the pelvis and axial skeleton [6]. Therefore, patients with bone metastases experience considerable morbidity resulting from skeletal complications and fatigue secondary to chemotherapy for those with castrate-resistance prostate cancer [3,7]. Delaying or preventing skeletal complication, improving physical function and increasing levels of physical activity in prostate cancer patients with bone metastases can provide clinically meaningful benefits to patients.
ORIGINAL ARTICLE

Safety and efficacy of resistance exercise in prostate cancer patients with bone metastases

P Cormie¹, RU Newton¹, N Spry¹,²,³, D Joseph¹,²,³, DR Taaffe¹,⁴ and DA Galvão¹
# SAFETY

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events during the exercise sessions</td>
<td>0</td>
</tr>
<tr>
<td>Attendance (out of 24 sessions)</td>
<td>20.2 ± 7.6</td>
</tr>
<tr>
<td>Compliance (% of successfully completed sessions)</td>
<td>93.2 ± 6.3</td>
</tr>
<tr>
<td>Perceived tolerance of the exercise sessions</td>
<td>6.1 ± 0.7</td>
</tr>
<tr>
<td>(0 = intolerable; 7 = highly tolerable)</td>
<td></td>
</tr>
<tr>
<td>Perceived exercise intensity (session RPE)</td>
<td>13.8 ± 1.5</td>
</tr>
<tr>
<td>Severity of bone pain at the start of each session (average of all sessions; 0 = no pain; 10 = very severe pain)</td>
<td>0.6 ± 0.7</td>
</tr>
<tr>
<td>Incidence of bone pain negatively affecting the ability to undertake ADL between exercise sessions</td>
<td>0</td>
</tr>
</tbody>
</table>

- No between-group difference in bone pain (p = 0.602)
- No change in use of pain medication throughout 12 weeks
**EFFICACY IN ADVANCED PROSTATE CANCER**

**Adjusted Group Difference in Mean Change Over 12 weeks***

- **Muscle Strength**: $p = 0.016$
- **Aerobic Fitness**: $p = 0.010$
- **Ambulation**: $p < 0.001$
- **Lean Mass**: $p = 0.026$
- **Physical Activity Level**: $p = 0.003$

*Between group change by ANCOVA adjusted for baseline values

*aIncludes adjustment for use of pain medication
“mechanical loading dramatically reduced osteolysis and tumor formation and increased tibial cancellous mass due to trabecular thickening”

Basis of a new Exercise Trial in Breast and Prostate Cancer led by Dr Nicolas Hart
No established recommendations exist for delaying (or preventing) the progression of low-risk PCa cancer.

**Preliminary** evidence suggests that lifestyle and/or exercise interventions might have therapeutic potential:

- **Delay disease progression**
- **Transition to active therapy**
Accumulating Evidence for Physical Activity and Prostate Cancer Survival: Time for a Definitive Trial of Exercise Medicine?

Robert U. Newton *, Daniel A. Galvão
Exercise Medicine Research Institute, Edith Cowan University, Joondalup, WA, Australia

INTense Exercise for surVivAL among men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL – mCRPC)

Multicentre, randomised, controlled phase III trial evaluating highly specific anabolic and aerobic exercise prescription tailored for men with metastatic castrate-resistant prostate cancer with the primary outcome being overall survival

866 men with mCRPC, 24 month intervention

Elucidate mechanisms by which exercise delays cancer progression

Jointly led by ECU and UCSF

Protocol presented at ASCO 2016 Saad et al.
Primary Outcome?
- Exercise and Overall Survival.
- [https://clinicaltrials.gov/ct2/show/NCT02730338](https://clinicaltrials.gov/ct2/show/NCT02730338)

Global trial
- Funded by Movember Foundation - $9million AUD.
- ~23 sites worldwide, across AU, NZ, UK, EU, USA, Canada.

~ 866 patients worldwide
- 3 year recruitment period.
- 2 year intervention (with OS follow-up).
- 5 year ‘on-trial’ completion goal.
Two year involvement:

- **Arm A: Intervention Arm.**
  - Individualised / tailored exercise program.
    - Involves ‘vigorous and moderate aerobic exercise’
    - Involves ‘structured and periodised resistance exercise’
    - Auto-regulated
    - Modified to each patients unique clinical presentation.
  - Behavioural and Psychosocial Support
    - Involves ‘text messaging’ and ‘newsletters’

- **Arm B: Control Arm**
  - Psychosocial Support only: (educational).
  - 6 monthly exercise/physical assessments.
  - 3 monthly questionnaire completions.
## GENERIC EXERCISE PRESCRIPTION

<table>
<thead>
<tr>
<th>Mode</th>
<th>Dosage</th>
</tr>
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<tbody>
<tr>
<td><strong>Aerobic</strong></td>
<td>150min per week moderate intensity (RPE 5-6 out of 10) or</td>
</tr>
<tr>
<td></td>
<td>75min per week vigorous intensity (RPE 7-8 out of 10)</td>
</tr>
<tr>
<td><strong>Anabolic (Resistance)</strong></td>
<td>6-10 exercises, 6-12RM, 2-3x per week, 3-4 sets per exercise</td>
</tr>
</tbody>
</table>
• Tailored exercise prescription for patients during radiation and/or chemotherapy
• Assessment and prescription by our Accredited Exercise Physiologists – trained and experienced in exercise oncology
• Implementing latest research from our clinical trials into best practice patient support
• World first in terms of proximity to therapy
• Convenience, stress reduction, acute exercise effects
• Efficacy, tolerance, effectiveness pilot trial
EXERCISE IS NOT A SINGLE MEDICINE

- **Mode, dosage, recovery, periodization, nutrition**
- **Create large contrasts in acute responses and chronic adaptations of the body systems**
- **Are we prescribing antibiotics for contraception!**
- **Expand and utilize the endogenous pharmacy**
- **Is MICT detrimental to fatigue?**

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Pedersen, B. K. & Febbraio, M. A.  
*Nature Reviews Endocrinology, 8, 457-465 (Aug2012)*
PRACTICAL RECOMMENDATIONS
EXERCISE MEDICINE DIAGNOSIS AND PRESCRIPTION

• Commence exercise ASAP after diagnosis
• Maintain exercise regardless of cancer type, stage or when undergoing difficult treatments
• Tailored exercise medicine prescription to address specific needs
  – Prehabilitation for surgery, chemotherapy, radiation therapy, immunotherapy
  – Enhance primary treatments
  – Ameliorate treatment side effects
  – Optimize recovery
  – Reduce co-morbidities and recurrence
  – Palliative support
• Best practice protocols for key types, stages, treatments, side-effects and co-morbidities
• Complemented by tailoring to specific patient needs, financial situation, location, resources
“Exercise is medicine” is a program originating in USA and now in Australia.

Physical assessment and prescription of exercise specifically for the treatment of diagnosed illness.
Exercise is Medicine Australia has developed factsheets on exercising with chronic diseases or disorders. These have been developed for health and medical professionals as well as the general public.

November in Focus
October’s focus is breast cancer, the most common cancer found in women. Exercise can play a beneficial role during treatment and recovery. Read more.

Public
What is your current level of health? Find out more in this section and start talking to your doctor about ways to improve.

Health Care Providers
Every patient, every visit, every time. Resources to assist health care providers improve public health through exercise prescription.

Active Workplaces
Active employees are productive employees. Tools and resources to encourage physical activity in the workplace.

Industry Partners
Working together with Australia’s leading organisations. Exercise is Medicine.

Policy, Advocacy & Media
Prevention is the key. Exercise is Medicine. Media contacts and press release history.
### FACT SHEETS

#### New in 2014
- Chronic Obstructive Pulmonary Disease (COPD)
- Postnatal rehabilitation
- Pregnancy and exercise
- Multiple sclerosis
- Spinal Cord Injury
- Stroke

#### Available Factsheets

<table>
<thead>
<tr>
<th>Factsheet</th>
<th>Full version</th>
<th>Brief version</th>
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<tbody>
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<td>Alzheimer’s Disease</td>
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</tbody>
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Sign up today for the FREE monthly EIM newsletter

* indicates required

**First Name**

**Last Name**

**Email Address** *

[Subscribe]
• Referral to appropriate allied health professional is critical
• Accredited Exercise Physiologists are minimum 4 year university educated including extensive clinical experience
• Accredited by: Exercise and Sport Science Australia (ESSA)

www.essa.org.au
Accredited Exercise Physiologist

- AEP’s are recognized by the “Australian General Practice Network” and “Royal Australian College of General Practitioners” as the most appropriate allied health professionals for:
  - Exercise Prescription and Management
  - Prevention and Wellness
  - Secondary Management of Chronic Disease including cancer
Rebates for Exercise Physiology Services

- MBS Chronic Disease Management – GP Services includes referral to AEPs
- Up to 5 consults per calendar year
- Many private health insurers now cover AEP services
FIND AN ACCREDITED EXERCISE PHYSIOLOGIST

www.essa.org.au/find-aep

AEP SEARCH

FIND AN ACCREDITED EXERCISE PHYSIOLOGIST (AEP), ACCREDITED EXERCISE SCIENTIST (AES) OR ACCREDITED SPORTS SCIENTIST (ASP)

ESSA > Find AEP, AES, ASP

NAME OF AEP, AES OR ASP

POSTCODE

SEARCH RADIUS

20 km

DESIGNATION

All

SPECIALTY

All rounder
Cancer
Cardiac
Disability service
Ergonomics
HEAL facilitator
Mental health
Metabolic
Musculoskeletal
Neurologic

LANGUAGE

AUSTRALIAN
Arabic
Cantonese
Croatian
English
French
German
Greek
Hindi
Italian

CLAIMING

Department of V
Hicaps
Macis
MDS
Private Health F