Exercise for primary prevention among patients receiving Lung Cancer Screening

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Overview

- What do we know about exercise and prevention of CVD, Pulmonary Disease, Cancer…. Including lung cancer?
  - Mechanisms
- What would happen if we exercised patients screened for lung cancer?
- Muscle matters to these patients in overcoming COPD problems.
  - Review musculature in COPD as seen on Thoracic CT
    - Can exercise change this?
- Implementation issues
  - How do we mobilize exercise as a drug of presymptomatic COPD, Heart Disease, Lung Cancer?
  - CT scans happen annually, could this be an opportunity to prescribe exercise?
  - We know exercise works, how do we make it happen?

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Source for this section…

2018 Physical Activity Guidelines Advisory Committee Scientific Report

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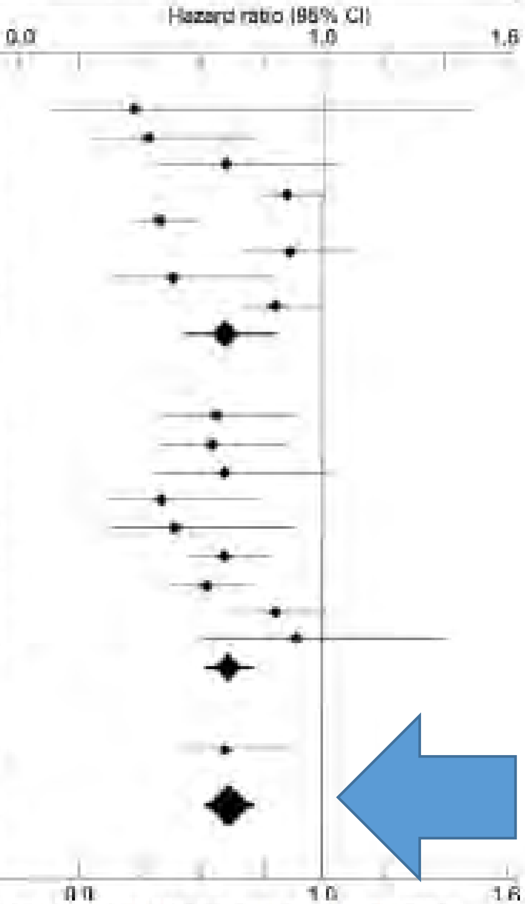
Exercise and Prevention of CVD Mortality

Figure F6-4. The Association Between Walking and Cardiovascular Mortality Risk in Men and Women

	Authors (year)	Exposure	Sample size	Hazard ratio (95% CI)	
Male					
1	Hakim et al (1998)[12]	Walking > 3.2 km/day	707	0.39	0.10 to 1.49
2	Hakim et al (1999)[16]	Walking > 2.5 km/day	2678	0.43	0.24 to 0.77
3	Bijnen et al (1998)[13]	Walking > 1 hour/week	802	0.69	0.45 to 1.05
4	Sesso et al (2000)[17]	Walking > 10 km/week	12 516	0.88	0.78 to 1.00
5	Davey Smith et al (2000)[18]	Brisk walking	6702	0.47	0.37 to 0.59
6a	Tanasescu et al (2002)[22]	Walking > 3.5 hours/week	44 452	0.90	0.73 to 1.10
6b	Tanasescu et al (2002)[22]	Brisk walking	44 452	0.51	0.31 to 0.84
7	Noda et al (2005)[25]	Walking > 1 hour/day	31 023	0.85	0.72 to 1.00
	Subtotal		143 332	0.68	0.55 to 0.85
Female					
1a	Manson et al (1999)[15]	Walking > 3 hours/week	72 488	0.65	0.47 to 0.91
1b	Manson et al (1999)[15]	Brisk walking	72 488	0.64	0.47 to 0.88
2	Sesso et al (1999)[14]	Walking > 10 km/week	1564	0.67	0.45 to 1.01
3a	Lee et al (2001)[20]	Walking > 2 hours/week	39 372	0.48	0.29 to 0.78
3b	Lee et al (2001)[20]	Brisk walking	39 372	0.52	0.30 to 0.90
4	Manson et al (2002)[21]	Walking > 3 hours/week	73 743	0.68	0.56 to 0.82
5	Gregg et al (2003)[23]	Walking > 898 kcal/week	9518	0.62	0.49 to 0.78
6	Noda et al (2005)[25]	Walking > 1 hour/day	42 242	0.84	0.70 to 1.02
7	Matthews et al (2007)[27]	Walking > 10 MET-hour/day	67 143	0.82	0.60 to 1.40
	Subtotal		417 930	0.69	0.61 to 0.77
Male and female					
1	LaCroix et al (1996)[19]	Walking > 4 hours/week	1645	0.68	0.52 to 0.90
	Total		562 907	0.69	0.61 to 0.77
	Test for heterogeneity			$\chi^2(17) = 42.91, p < 0.001$	
	Test for overall effect			$\chi^2(1) = 47.88, p < 0.001$	



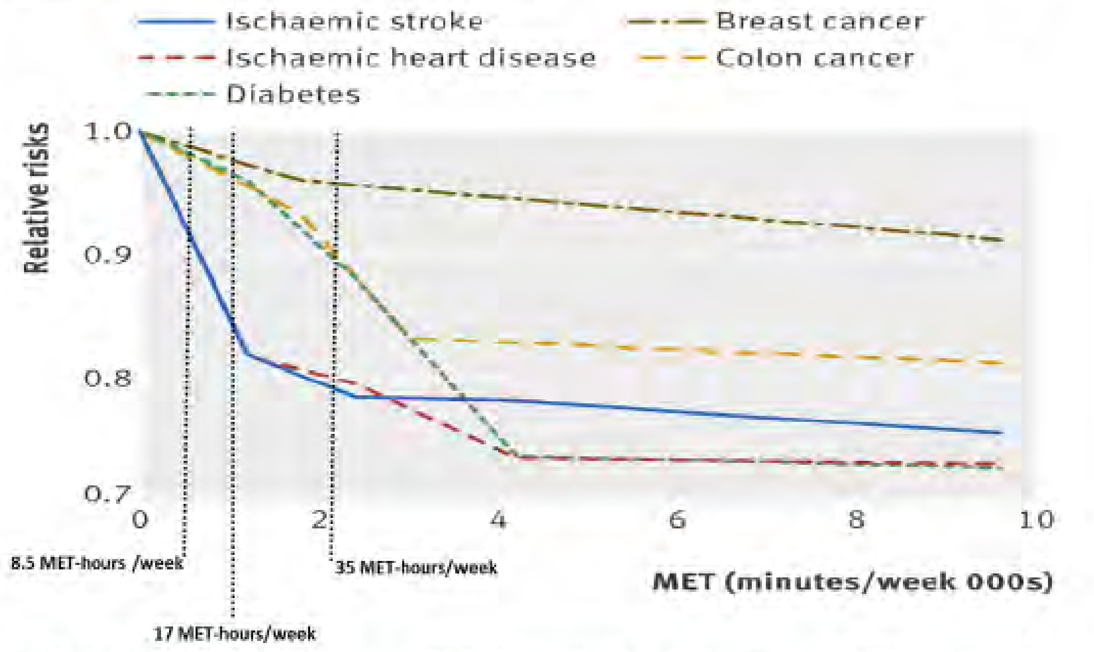
Note: Walking is favored, with a shift of the estimate to the left. Notice the similarity of these estimates to the effects on all-cause mortality in Question 1, Figure F6-1.

Source: Reproduced from [Walking and primary prevention: A meta-analysis of prospective cohort studies, Hamer and Chida[6], 42, 2008] with permission from BMJ Publishing Group Ltd.

30% reduced CVD mortality for walkers

Dose Response Relationships PA and Breast Cancer, Colon Cancer, Diabetes, Ischemic Heart Disease, and Ischemic Stroke

Figure F6-6. Dose-Response Relationships Between Total Physical Activity and Risk of Breast Cancer, Colon Cancer, Diabetes, Ischemic Heart Disease, and Ischemic Stroke Events Using 174 Studies (43 For Ischemic Heart Disease, and 26 For Ischemic Stroke)



Note: For reference, shown are the lower end (8.5 MET-hours/week) and upper bounds (17 MET-hours/week) of the 2008 Guidelines for moderate-to-vigorous physical activity. Also indicated is the moderate-to-vigorous physical activity amount associated with normalization of the risk from greater than 8 hours per day of sedentary activity from Ekelund, 2016 (35 MET-hours/week).

Source: Reproduced from [Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: Systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013, Kyu et al[44], 354, 2016] with permission from BMJ Publishing Group Ltd. and Ekelund et al., 2016.[5]

MET-hours/week = time walking

- 8.5 MET-hrs/week = 2 hrs, 15 min
- 17 MET-hrs/week = 4 hrs, 30 min
- 35 MET-hrs/week = 9 hrs, 15 min

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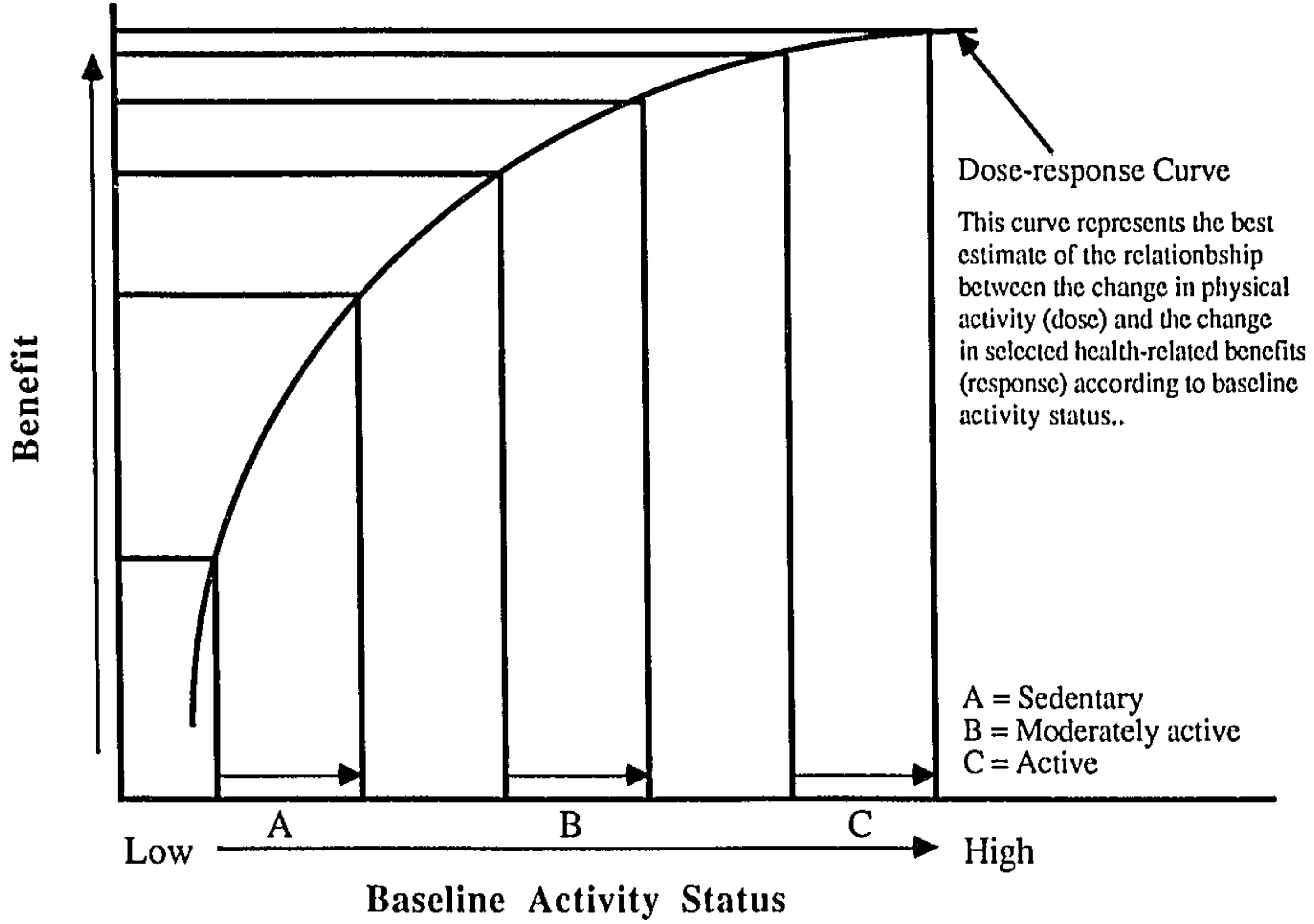
Haskell MSSE 1994

Figure 3—This is theoretical dose-response curve demonstrating that the magnitude of the benefit for any given increase in activity is greater for less active persons.



Journal of Physical Activity and Health, 2010, 7, 622-626

Life-Long Physical Activity Involvement Reduces the Risk of Chronic Obstructive Pulmonary Disease: A Case-Control Study in Japan

Fumi Hirayama, Andy H. Lee, and Tetsuo Hiramatsu

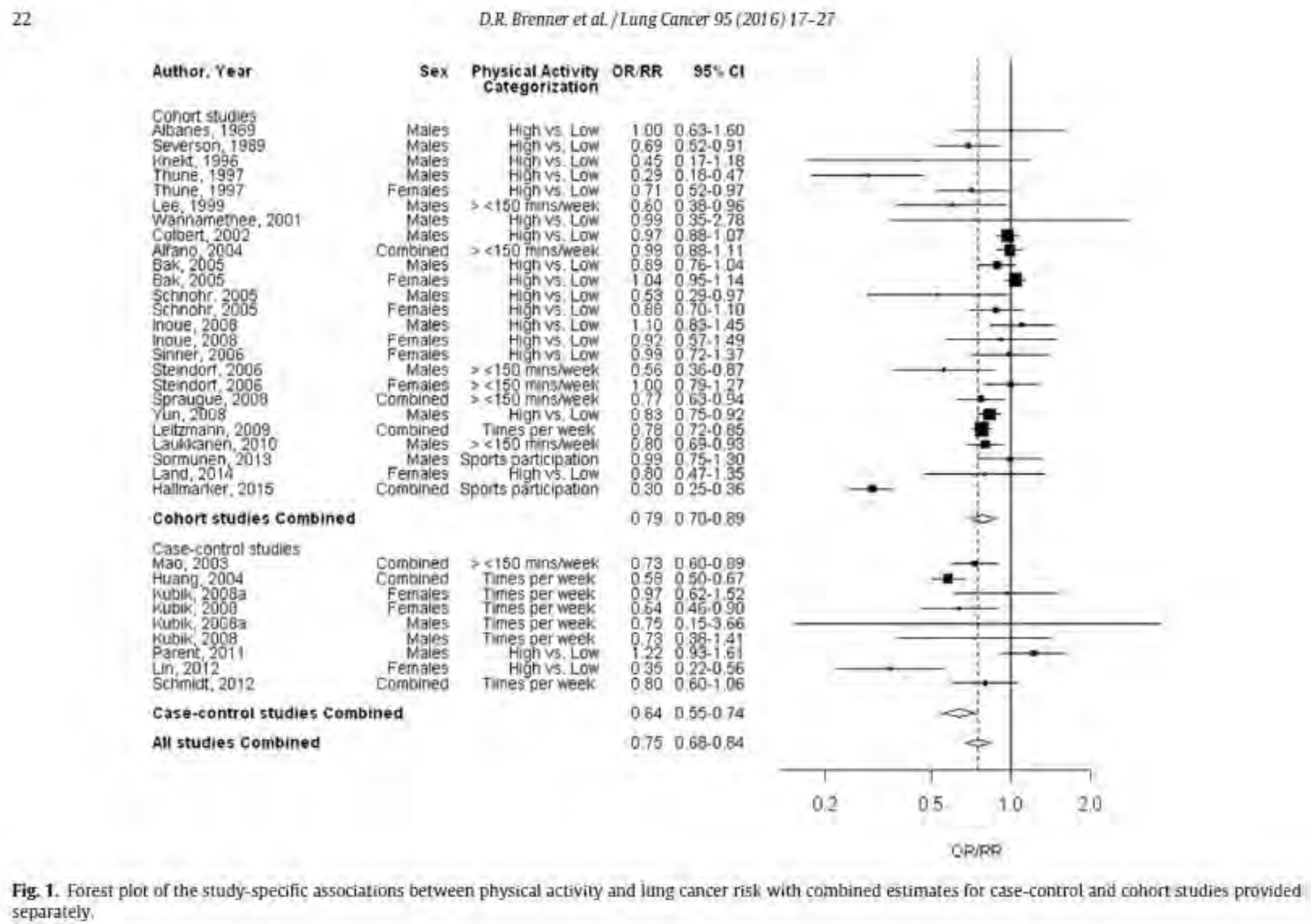
- Case-Control Study
- 278 patients
- 335 controls
- Spirometry

Table 3 Life-Long Physical Activity and Risk of COPD and Breathlessness

Outcome	Life-long physical activity	Crude OR	95% CI	Adjusted OR*	95% CI
COPD				*P* = .036	
	inactive	1		1	
	active	0.73	(0.51, 1.06)	0.59	(0.36, 0.97)
Breathlessness				*P* = .012	
	inactive	1		1	
	active	0.65	(0.44, 0.97)	0.56	(0.36, 0.88)

* Logistic regression models adjusting for age, gender, BMI (5 years ago), education level, marital status, residential location, alcohol drinking, cigarette smoking, smoking pack-years, daily intake of red meat, chicken, fish, vegetables, and fruits (in grams).

Brenner et al. Lung Cancer 2016



22 D.R. Brenner et al. / Lung Cancer 95 (2016) 17–27

Author, Year	Sex	Physical Activity Categorization	OR/RR	95% CI
Cohort studies				
Albanes, 1989	Males	High vs. Low	1.00	0.63-1.60
Severson, 1989	Males	High vs. Low	0.69	0.52-0.91
Knekt, 1996	Males	High vs. Low	0.45	0.17-1.18
Thune, 1997	Males	High vs. Low	0.29	0.18-0.47
Thune, 1997	Females	High vs. Low	0.71	0.52-0.97
Lee, 1999	Males	> <150 mins/week	0.60	0.38-0.96
Wannamethee, 2001	Males	High vs. Low	0.99	0.35-2.78
Colbert, 2002	Males	High vs. Low	0.97	0.88-1.07
Alfano, 2004	Combined	> <150 mins/week	0.99	0.88-1.11
Bak, 2005	Males	High vs. Low	0.89	0.76-1.04
Bak, 2005	Females	High vs. Low	1.04	0.95-1.14
Schnohr, 2005	Males	High vs. Low	0.53	0.29-0.97
Schnohr, 2005	Females	High vs. Low	0.88	0.70-1.10
Inoue, 2008	Males	High vs. Low	1.10	0.83-1.45
Inoue, 2008	Females	High vs. Low	0.92	0.57-1.49
Sinner, 2006	Females	High vs. Low	0.99	0.72-1.37
Steindorf, 2006	Males	> <150 mins/week	0.56	0.36-0.87
Steindorf, 2006	Females	> <150 mins/week	1.00	0.79-1.27
Spraugue, 2008	Combined	> <150 mins/week	0.77	0.63-0.94
Yun, 2008	Males	High vs. Low	0.83	0.75-0.92
Leitzmann, 2009	Combined	Times per week	0.78	0.72-0.85
Laukkanen, 2010	Males	> <150 mins/week	0.80	0.69-0.93
Sormunen, 2013	Males	Sports participation	0.99	0.75-1.30
Land, 2014	Females	High vs. Low	0.80	0.47-1.35
Hallmarker, 2015	Combined	Sports participation	0.30	0.25-0.36
Cohort studies Combined			0.79	0.70-0.89
Case-control studies				
Mao, 2003	Combined	> <150 mins/week	0.73	0.60-0.89
Huang, 2004	Combined	Times per week	0.58	0.50-0.67
Kubik, 2008a	Females	Times per week	0.97	0.62-1.52
Kubik, 2008	Females	Times per week	0.64	0.46-0.90
Kubik, 2008a	Males	Times per week	0.75	0.15-3.66
Kubik, 2008	Males	Times per week	0.73	0.38-1.41
Parent, 2011	Males	High vs. Low	1.22	0.93-1.61
Lin, 2012	Females	High vs. Low	0.35	0.22-0.56
Schmidt, 2012	Combined	Times per week	0.80	0.60-1.06
Case-control studies Combined			0.64	0.55-0.74
All studies Combined			0.75	0.68-0.84

Fig. 1. Forest plot of the study-specific associations between physical activity and lung cancer risk with combined estimates for case-control and cohort studies provided separately.

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Among the mechanisms: Exercise Reduces Chronic Inflammation

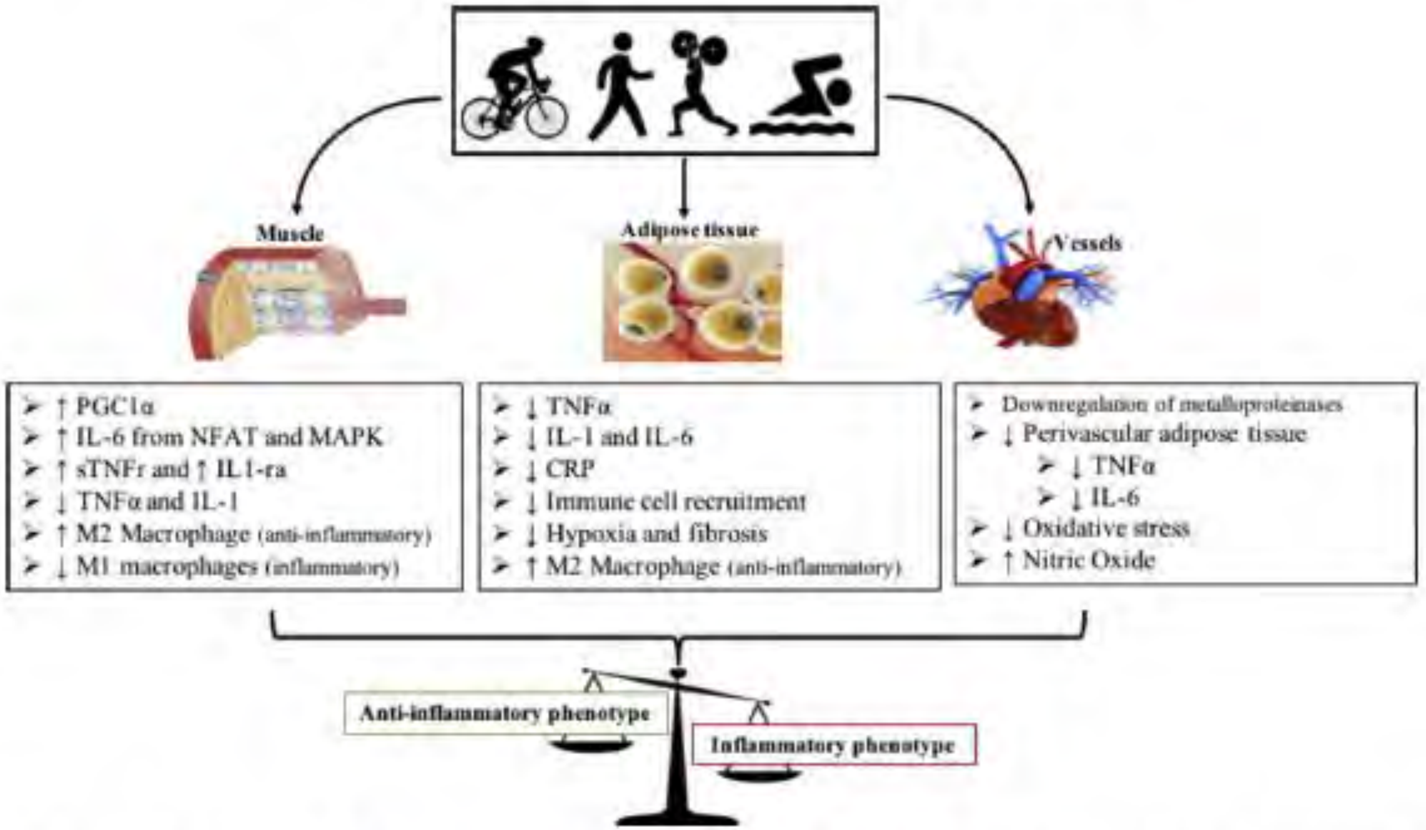

Fig. 1. Exercise may promote an anti-inflammatory phenotype in different tissues. PGC1α: peroxisome proliferator-activated receptor γ co-activator 1α, IL-6: interleukin 6, NFAT: nuclear factor of activated T-cells, MAPK: mitogen-activated protein kinase, sTNFr: soluble tumour necrosis factor receptors, IL-1ra: interleukin 1 receptor antagonist, TNFα: tumour necrosis factor alpha, IL-1: interleukin 1, CRP: C-reactive protein.

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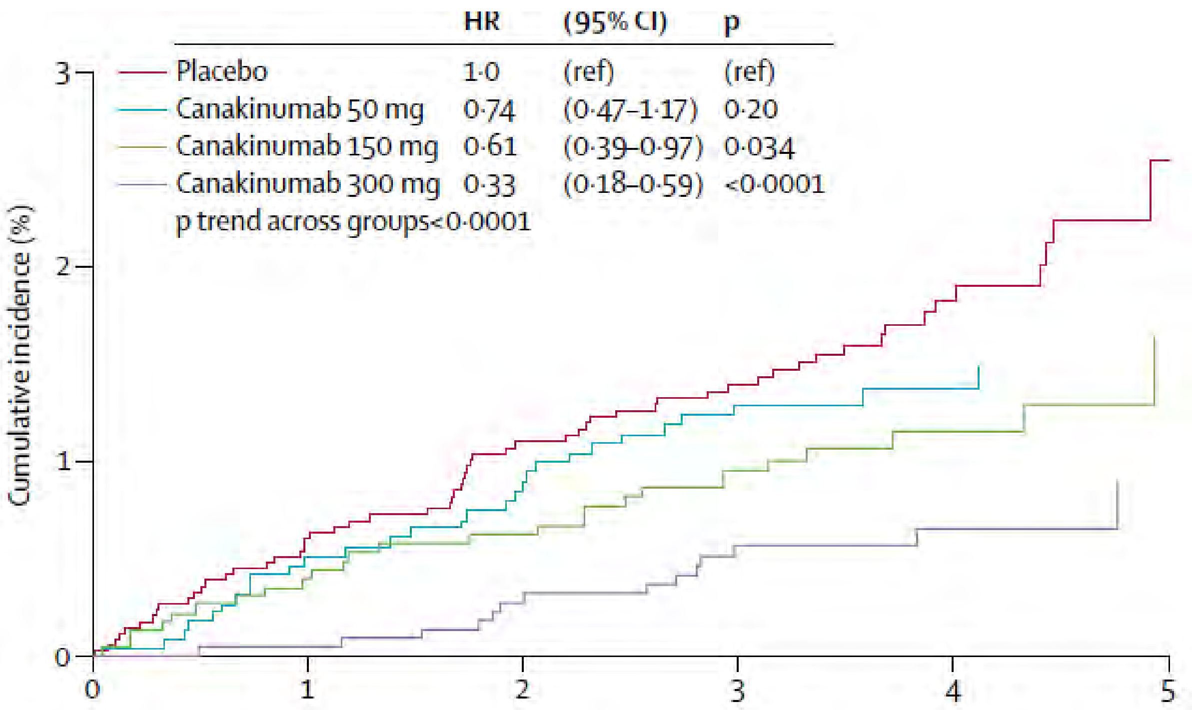
Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial

Paul M Ridker, Jean G MacFadyen, Tom Thuren, Brendan M Everett, Peter Libby*, Robert J Glynn*, on behalf of the CANTOS Trial Group†

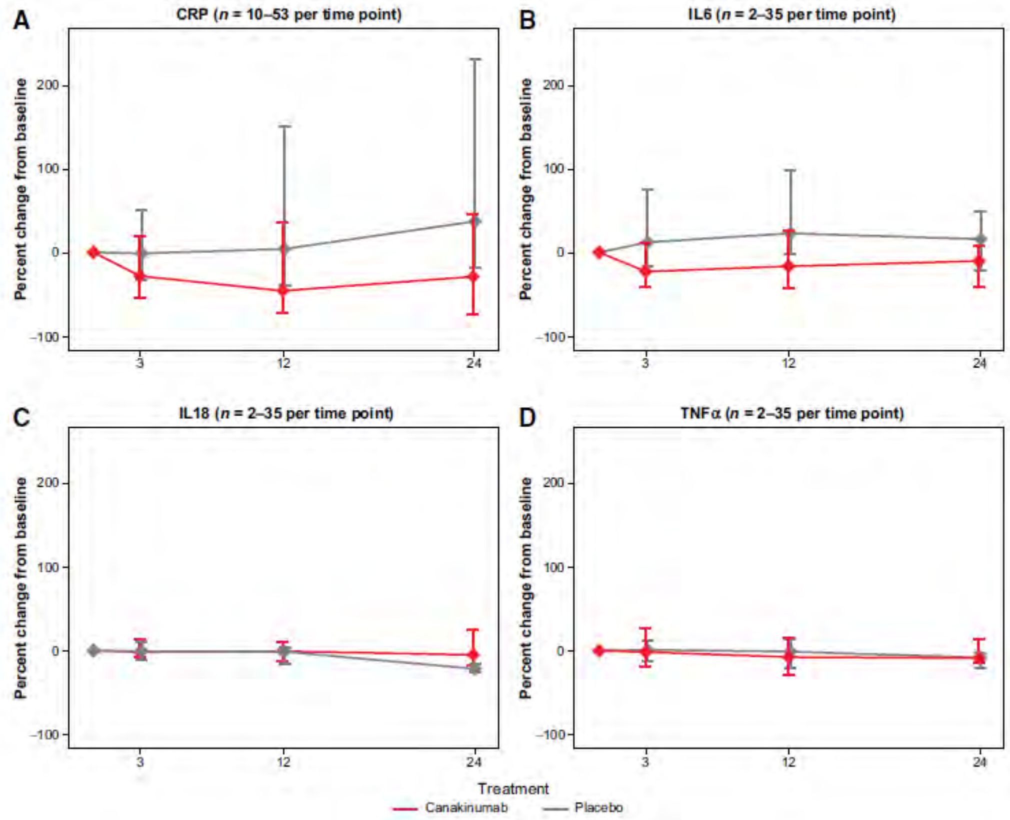
Summary

Background Inflammation in the tumour microenvironment mediated by interleukin 1β is hypothesised to have a

Lancet 2017; 390: 1833–42



Number at risk	0	1	2	3	4	5
Placebo	3344	3241	3142	2835	1401	251
Canakinumab 50 mg	2170	2110	2047	1825	827	53
Canakinumab 150 mg	2284	2207	2148	1950	982	233
Canakinumab 300 mg	2263	2201	2128	1928	1002	222



Wong et al. Cancer Research 2020

What would happen if we started to exercise patients screened for lung cancer?

- Improved use of oxygen
- Energy levels
- Anxiety, depression
- Sleep
- Self-esteem
- Cardiovascular Fitness
- Muscular Strength
- Improved shortness of breath

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Muscle Matters

- Altered body composition is predictive of increasing mortality among COPD patients
- Thoracic CT scans allow for measurement of
  - Pectoralis Muscle Area
  - Erector Spinae muscles
  - Intercostal muscles
  - Subcutaneous Adipose Tissue

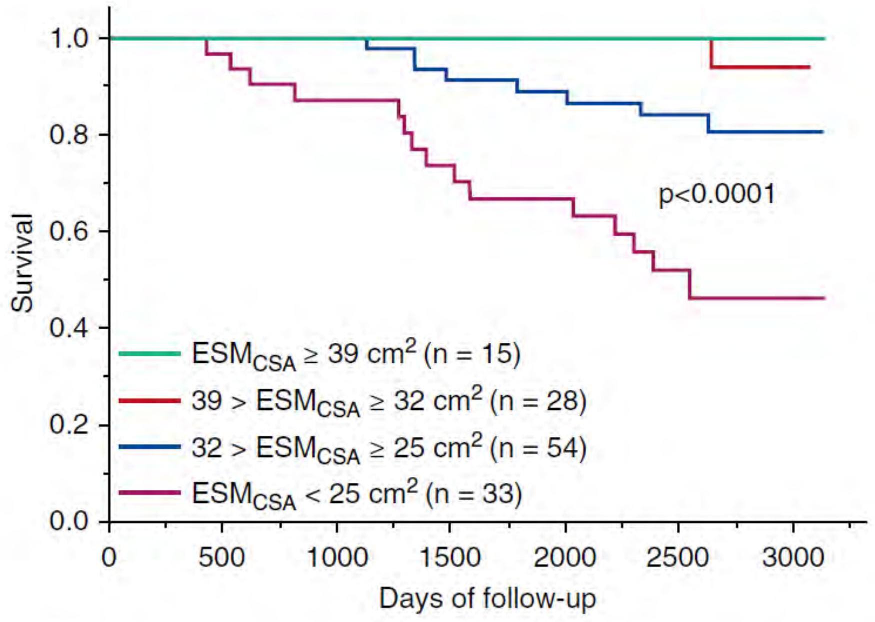

Figure 3. Kaplan–Meier survival curves stratified by the cross-sectional area of the erector spinae muscles (ESM_{CSA}) (n = 130). The cutoff values correspond to the mean, mean −1 SD, and mean −2 SD determined in the smoking control subjects (39, 32, and 25 cm^2, respectively). The patients with COPD with lower ESM_{CSA} values exhibited significantly worse survival rates ($P < 0.0001$ by log-rank test).

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Tanimura Ann Am Thorac Soc 2016

Intercostal Muscles, Pectoral Muscles

Intercostal muscles and breathlessness

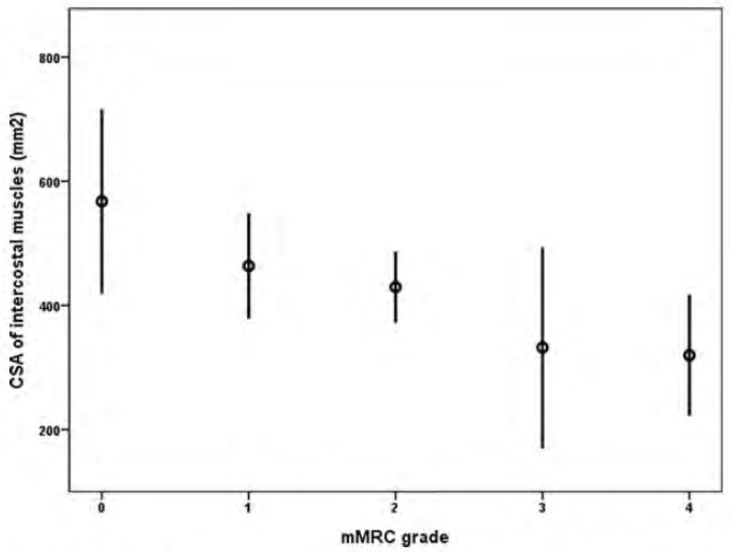
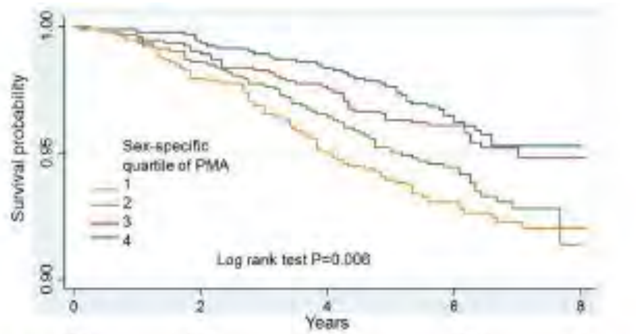


FIGURE 6 Cross-sectional area (CSA) of the intercostal muscles by extent of breathlessness (mMRC grade) in patients with COPD

Ju Clin Respir J 2018

Pectoral Muscle Quartiles and Mortality



PMA quartile	0	2	4	6	8
1	926	907	880	706	11
2	926	913	894	678	9
3	926	917	904	676	8
4	927	922	912	757	4

Number of subjects at risk

Fig. 2 Kaplan-Meier curves for all-cause mortality by sex-specific quartiles of pectoralis muscle area (PMA) in at-risk smokers. The survival probabilities decrease with decreasing PMA quartiles

Diaz Respiratory Research 2018

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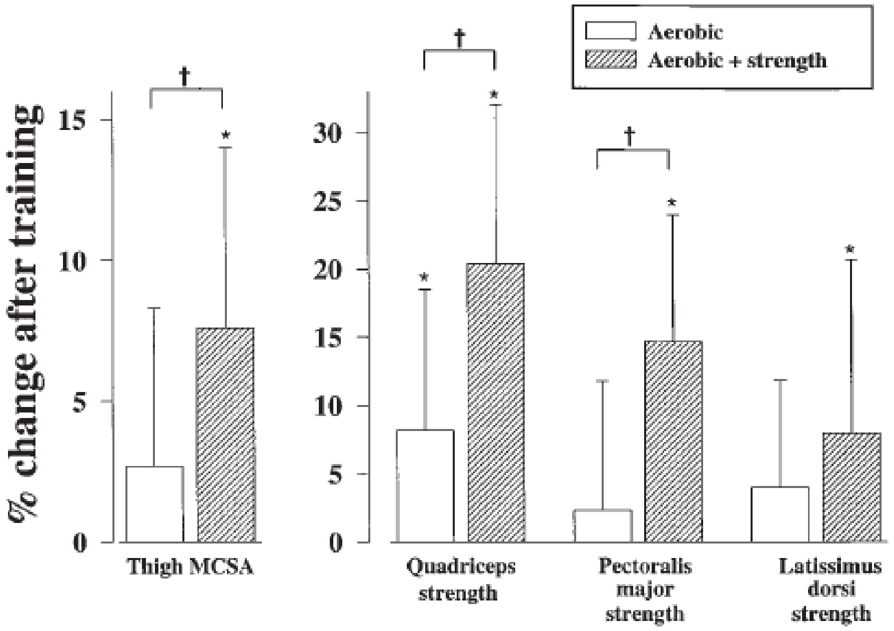
Exercise improves musculature relevant to COPD

Pectoralis Major Muscles



Bernard Am J Respir Crit Care Med 1999

Intercostal muscles

TABLE 4. HISTOMORPHOMETRY OF THE EXTERNAL INTERCOSTAL MUSCLES BEFORE AND AFTER SPECIFIC INSPIRATORY MUSCLE TRAINING

	Sham Training Group		Inspiratory Training Group	
	Pre	Post	Pre	Post
Global fiber size				
Least diameter, μm	47 ± 9	51 ± 10	47 ± 8	55 ± 6 $^{p=0.09}$
CSA, μm^2	3.08 ± 1.25	3.27 ± 1.28	2.73 ± 0.81	3.88 ± 0.48*
Type I fibers				
Proportion, %	50 ± 14	47 ± 16	42 ± 20	58 ± 14*
CSA, $\mu m^2 \times 10^3$	2.60 ± 0.94	2.94 ± 1.24	2.92 ± 1.39	3.72 ± 0.68 $^{p=0.06}$
Least diameter, μm	44 ± 7	49 ± 9	49 ± 10	55 ± 10
SD, μm	6 ± 1	7 ± 1	8 ± 1	10 ± 3
Type II fibers				
Proportion, %	50 ± 14	53 ± 16	57 ± 20	42 ± 14*
CSA, $\mu m^2 \times 10^3$	3.67 ± 1.47	3.58 ± 1.32	2.82 ± 0.91	4.06 ± 0.86*
Least diameter, μm	50 ± 12	53 ± 11	47 ± 10	57 ± 8*
SD, μm	7 ± 2	8 ± 1	9 ± 2	11 ± 2

Definition of abbreviations: CSA = cross sectional area; SD = standard deviation of mean least fiber diameters.
* p Value < 0.05 when compared with pretraining evaluation.

Ramirez-Sarmiento Am J Respir Crit Care Med 2002

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So we know exercise helps…

How do we make it happen as standard of care?

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Current State of Implementation

- Exercise is not standard of care in the setting of pulmonary screening for lung cancer
- A minority of patients are adequately active
- Multifactorial causes include:
  - Lack of awareness by patients and providers
  - Lack of programming
  - Lack of referral from clinicians
  - Lack of a well trained exercise workforce
  - Lack of payment for programming

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Themes toward the goal of broad implementation of exercise in the lung cancer screening population

- Policy, funding
  - Federal
  - Organizational
  - Institutional
- Research
- Workforce development
- Program development
- Stakeholder engagement: changing culture

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Policy, Funding: Federal Government level

- Exercise interventions require funding. Options:
  - Delivery by health care professionals (e.g.; PTs)
  - Change policy so that exercise professionals become HCP
  - Demonstrate that programs are effective in community settings, change policy to 'cover' costs of programs (e.g.; DPP model)
- Issues in determining how best to proceed
  - Workforce preparedness
  - Referrals to programs remain low

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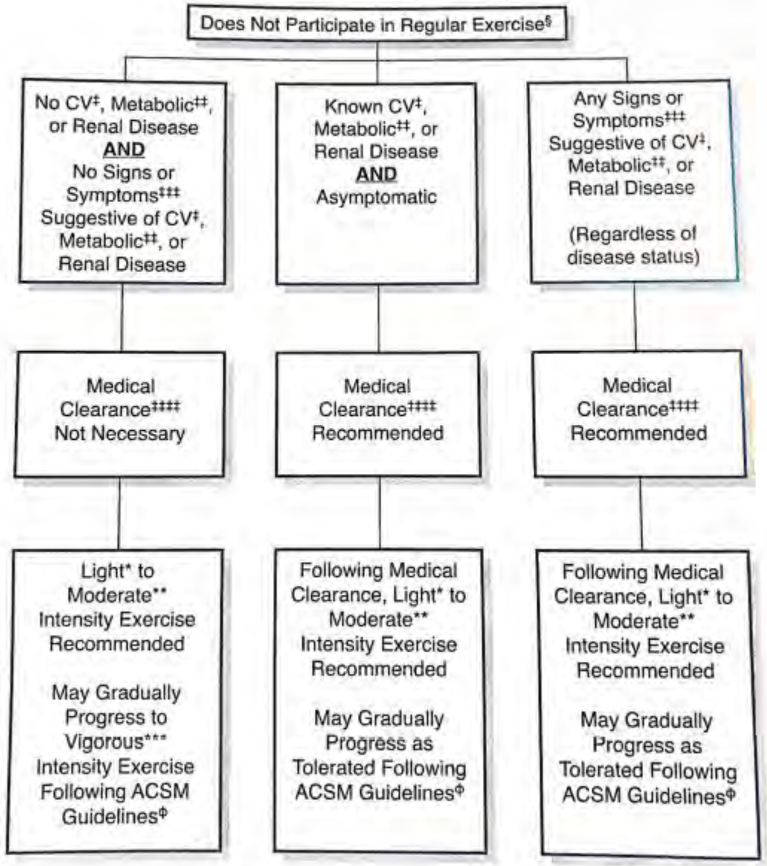
Policy relevant to exercise in lung cancer screening populations: Organizational level examples

- Accreditation bodies for lung cancer screening centers
  - Standards drive behavior (example: distress screening in cancer)
- American College of Sports Medicine
  - Preparticipation guidelines do not currently include pulmonary disease



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Research

- Efficacy trials
  - Outcomes need to fit the policy needs
    - Treatment efficacy
    - Health services outcomes
- Evaluative trials
  - Comparison of the common implementation models
    - Counseling, individual training, group training
  - Cost evaluation
  - Health care utilization
- Implementation science trials

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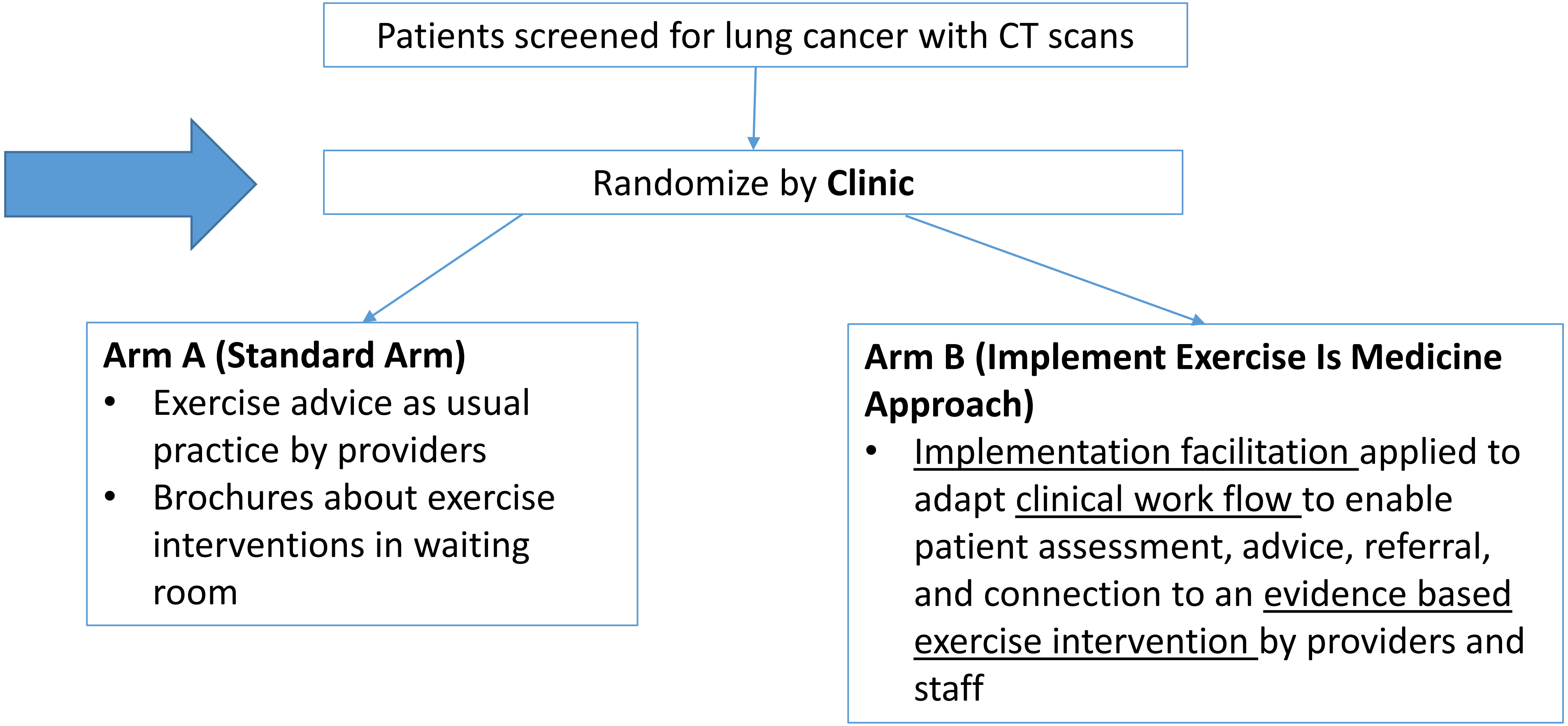
Example Study Schema



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Design: Cluster Randomized Trial

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Implementing exercise interventions in community CT screening clinics

- Existing gap in testing effective implementation strategies for improving physician referrals and utilization of evidence-based exercise interventions *in the setting of lung cancer screening clinics*
  - Evidence base exists for SBIRT in primary care

- Community clinics are important in studying the real-world factors that influence implementation

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Multilevel intervention

- Patient
  - Evidence based Exercise Intervention
- Treating Clinician
  - Clinical work flow: The Ask Advise Refer Connect Process
- Care Delivery Team / Level of the Practice
  - Implementation Facilitation

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Specific Aims

- Aim 1: To assess whether implementation facilitation of the Ask, Advise, Refer, Connect (AARC) process results in increased proportion of patients with a completed referral to exercise. (IMPLEMENTATION OUTCOME)

- Aim 2: To examine mechanisms by which implementation facilitation of the AARC process results in increased proportion of patients with a completed referral. (IMPLEMENTATION AIM)

- Aim 3: To assess the effectiveness on patient level outcomes regarding symptom burden (breathlessness). (CLINICAL EFFECTIVENESS OUTCOME)

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Workforce Development

- Exercise professionals are, in general, not currently being prepared to work with lung cancer screening patients
  - This needs to change
- Need to identify KSAs needed in exercise professionals to work with lung cancer screening patients
  - Credential re-tool at ACSM
- Creation of 101 module

Program Development

- Identify where programs already exist
- Map them
- Enlist national fitness chains to start pulmonary specific programs
- Help existing programs to spread

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Implementation of exercise for patients receiving screening for lung cancer

- Policy
- Stakeholder awareness
- Program development
- Workforce development
- Research

Thank you!

@fitaftercancer on twitter