CCNA webinar in partnership with BrainXchange
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"Can we prevent some dementias now? Lifestyle Interventions and results from the SYNERGIC trial"

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Disclosures

I have no financial conflicts of interest relevant to this activity.

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Objectives

1- To appraise the role of the multiple neuropathology that is associated with dementia

2- To understand population level estimates of risk factors and its potential reversibility

3- To peruse current evidence for dementia prevention from RTCs

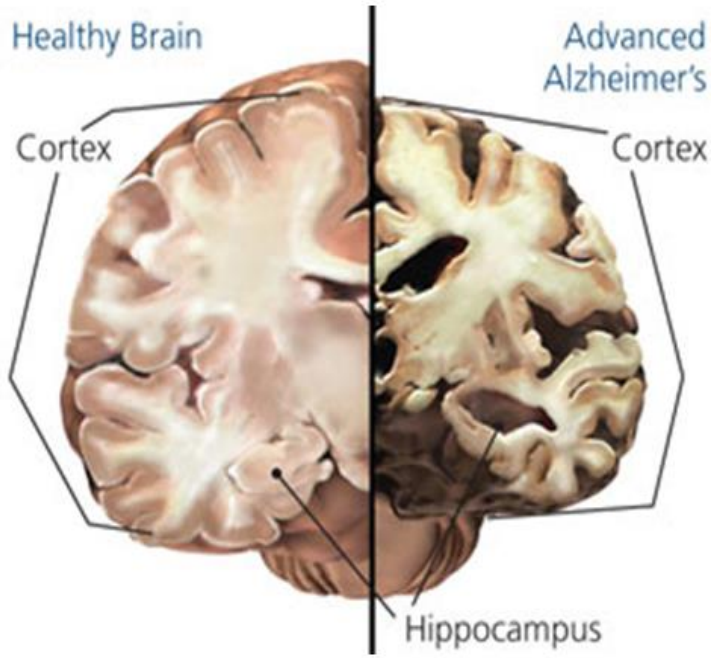
4- To present results from the national SYNERGIC trial

Dementia

Dementia is a syndrome characterized by cognitive impairment affecting activities of the daily living

Most frequent of Dementias is Alzheimer's disease (AD) that encompasses neurodegenerative and cerebrovascular diseases, often presenting in combination

Mechanism of neurodegeneration is protein misfolding and aggregation (beta amyloid, hyper-phosphorylated tau) followed by neurotoxicity



Disease modifying therapies aimed to prevent or delay the onset or progression of cognitive impairment are still under development.

https://www.alzint.org/about/dementia-facts-figures/dementia-statistics/

Why are we discussing whether 30% to 40% of dementia cases can be prevented?

1- Drug treatments for Dementia have not delivered results we hoped

(Last approved drug by Health Canada was memantine in 2004!)

2- Amyloid hypothesis for Alzheimer's Disease does not explain the clinical variability we see in our patients

3- Studies support that lifestyle modifications may reduce dementia incidence

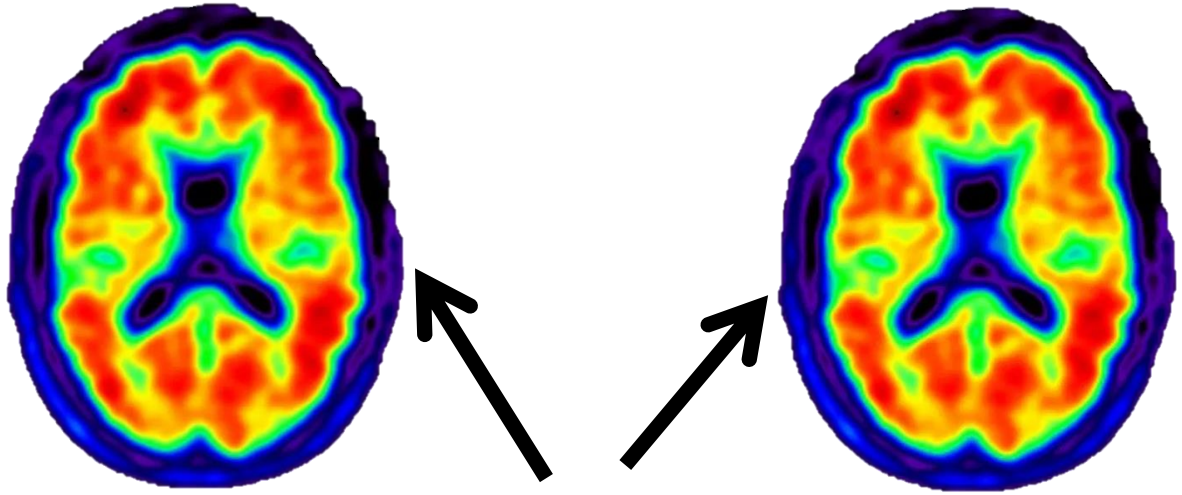
Shift for dementia management.
Today, treatment is prevention

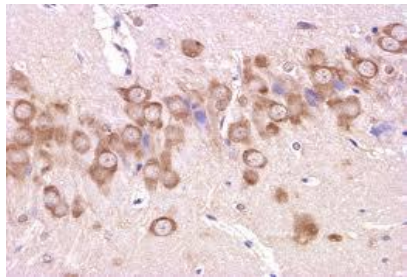
But, do we really know that we can prevent dementia?
Are there any problems in the "encouraging" data?

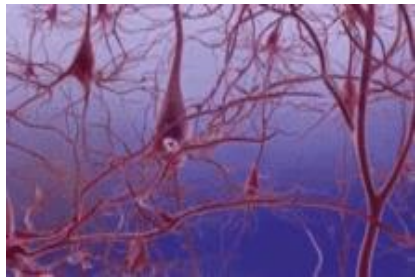
Alzheimer's Disease (AD) = The most common form of dementia

Association with beta amyloid brain load and cognitive impairment **lessens with age**

85 y/o F, severe Dementia and wheelchair bound



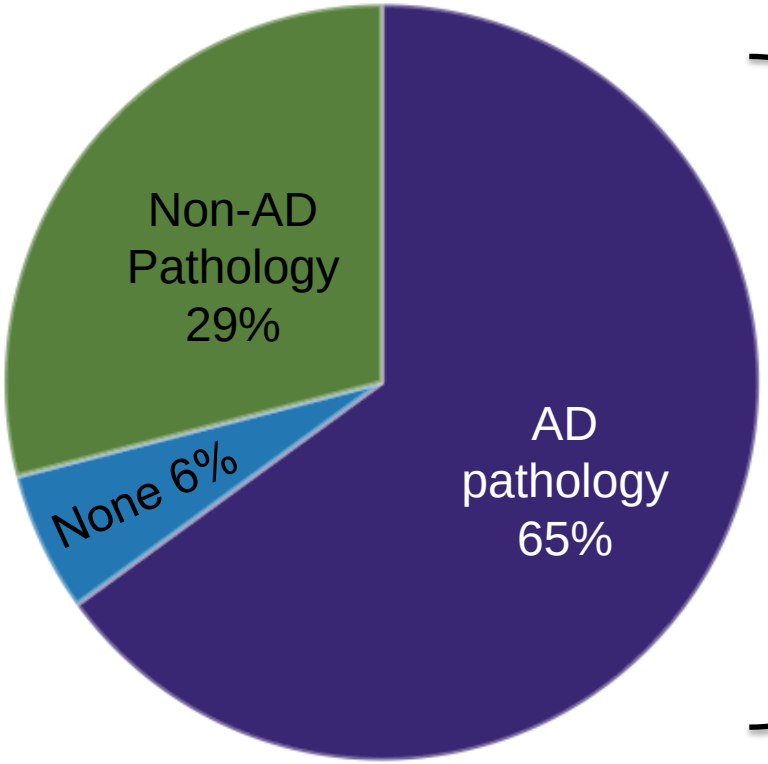


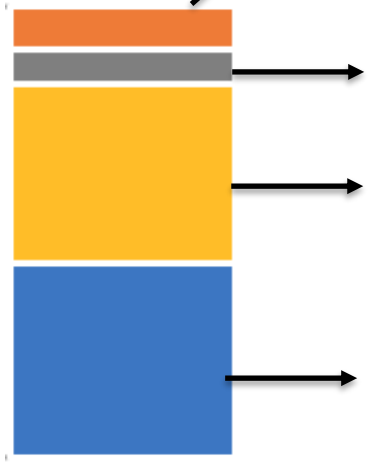


85 y/o M, Cognitive healthy and highly functional

80% of dementias are in people aged >75 years
Dementia is multifactorial, even for clinical AD

AD pathology rarely occurs in isolation





Up to 9 different pathologies were found

AD Only 6%

AD + neurodegenerative 6%

AD + Vascular 26%

AD + Vascular + other neurodegenerative (PD-LB) 28%

May, 2001

Religious Orders Study and the Memory and Aging Project

- N = 1,079 (92.9%) free of dementia at baseline
- Mean Age = 75.7 years
- Mean Education = 18.1 years
- Up to 22 years of follow up

Lei Yu et al (Neuropathologic Correlates of Human Cortical Proteins in Alzheimer Disease and Related Dementias) Neurology 2022;98:e1031-e1039

Bennett DA et al. Religious orders study and rush memory and aging project. *Journal of Alzheimer's disease.* 2018; *64*(s1): S161-S189

Rush Study of Aging:
Treating Pathology vs. Enhancing Resilience

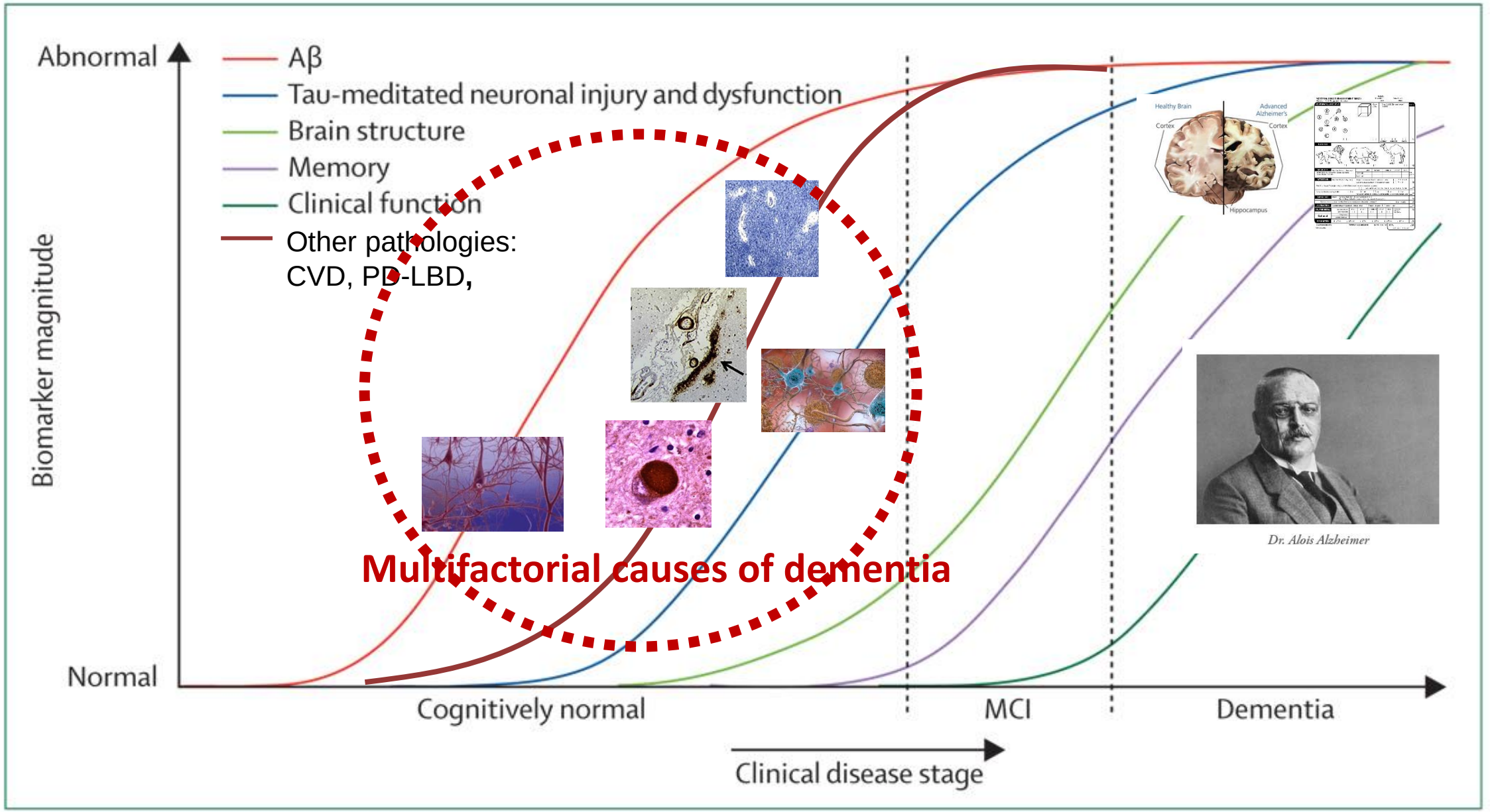
Treating Pathology

- Amyloid does *not* predict cognitive decline after controlling for tangles.
- **Amyloid and tangles together only account for about 25% of the variance in cognitive decline.**
- "*The impact of 9 common pathologies varies widely depending on the presence of other pathologies. Is developing a biomarker for each pathology and a cocktail to treat each pathology scalable? This could result in multiple cocktails over a long period of time in older persons with aged livers and kidneys, at a cost that is likely beyond what can be paid.*"

An alternative therapy would be to target resilience (organ reserve)

Bennett D A et al. Religious orders study and rush memory and aging project. *Journal of Alzheimer's disease.* 2018; *64*(s1): S161-S189.

The road to Dementia. Changes before clinical manifestations



*Adapted from Jack et al. model. *Lancet Neurology* 2010

Research context for prevention of dementia Lancet Commission reports 2017 and 2020

The Lancet Commissions

Dementia prevention, intervention, and care

Gill Livingston, Andrew Sommerlad, Vasiliki Orgeta, Sergi G Costafreda, Jonathan Huntley, David Ames, Clive Ballard, Sube Banerjee, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Eric B Larson, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam

Executive summary

Acting now on dementia prevention, intervention, and care will vastly improve living and dying for individuals with dementia and their families, and in doing so, will transform the future for society.

Dementia is the greatest global challenge for health and social care in the 21st century. It occurs mainly in people older than 65 years, so increases in numbers and costs are driven, worldwide, by increased longevity resulting from the welcome reduction in people dying prematurely. The *Lancet* Commission on Dementia Prevention, Intervention, and Care met to consolidate the huge strides that have been made and the emerging knowledge as to what we should do to prevent and manage dementia.

Globally, about 47 million people were living with dementia in 2015, and this number is projected to triple by 2050. Dementia affects the individuals with the condition, who gradually lose their abilities, as well as their relatives and other supporters, who have to cope with seeing a family member or friend become ill and decline, while responding to their needs, such as increasing dependency and changes in behaviour. Additionally, it affects the wider society because people with dementia also require health and social care. The 2015 global cost of dementia was estimated to be US$818 billion, and this figure will continue to increase as the number of people with dementia rises. Nearly 85% of costs are related to family and social, rather than medical, care. It might be that new medical care in the future, including public health measures, could replace and possibly reduce some of this cost.

Dementia is by no means an inevitable consequence of reaching retirement age, or even of entering the ninth

Key messages

1 The number of people with dementia is increasing globally
Although incidence in some countries has decreased.

2 Be ambitious about prevention
We recommend active treatment of hypertension in middle aged (45–65 years) and older people (aged older than 65 years) without dementia to reduce dementia incidence. Interventions for other risk factors including more childhood education, exercise, maintaining social engagement, reducing smoking, and management of hearing loss, depression, diabetes, and obesity might have the potential to delay or prevent a third of dementia cases.

3 Treat cognitive symptoms
To maximise cognition, people with Alzheimer's disease or dementia with Lewy bodies should be offered cholinesterase inhibitors at all stages, or memantine for severe dementia. Cholinesterase inhibitors are not effective in mild cognitive impairment.

4 Individualise dementia care
Good dementia care spans medical, social, and supportive care; it should be tailored to unique individual and cultural needs, preferences, and priorities and should incorporate support for family carers.

5 Care for family carers
Family carers are at high risk of depression. Effective interventions, including STrAtegies for RelaTives (START) or Resources for Enhancing Alzheimer's Caregiver Health intervention (REACH), reduce the risk of depression, treat the symptoms, and should be made available.

6 Plan for the future
People with dementia and their families value discussions about the future and decisions about possible attorneys to make decisions. Clinicians should consider capacity to make different types of decisions at diagnosis.

7 Protect people with dementia
People with dementia and society require protection from possible risks of the condition, including self-neglect, vulnerability (including to exploitation), managing money, driving, or using weapons. Risk assessment and management at all stages of the disease is essential, but it should be balanced against the person's right to autonomy.

8 Manage neuropsychiatric symptoms
Management of the neuropsychiatric symptoms of dementia including agitation, low mood, or psychosis is usually psychological, social, and environmental, with pharmacological management reserved for individuals with more severe symptoms.

9 Consider end of life
A third of older people die with dementia, so it is essential that professionals working in end-of-life care consider whether a patient has dementia, because they might be unable to make decisions about their care and treatment or express their needs and wishes.

10 Technology
Technological interventions have the potential to improve care delivery but should not replace social contact.

Lancet 2017; 390: 2673–734
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http://dx.doi.org/10.1016/S0140-6736(17)31363-6
See Comment pages 2614 and e51

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The Lancet Commission 2020

1- Up to 40% of Dementia cases worldwide can be attributed to 12 modifiable risk factors (diabetes, hypertension, obesity, physical inactivity, smoking, low education, hearing/vision deficits, air pollution, alcohol, TBI, and depression)

2- Recommend treatment and management of these conditions to prevent up to 40% of dementias

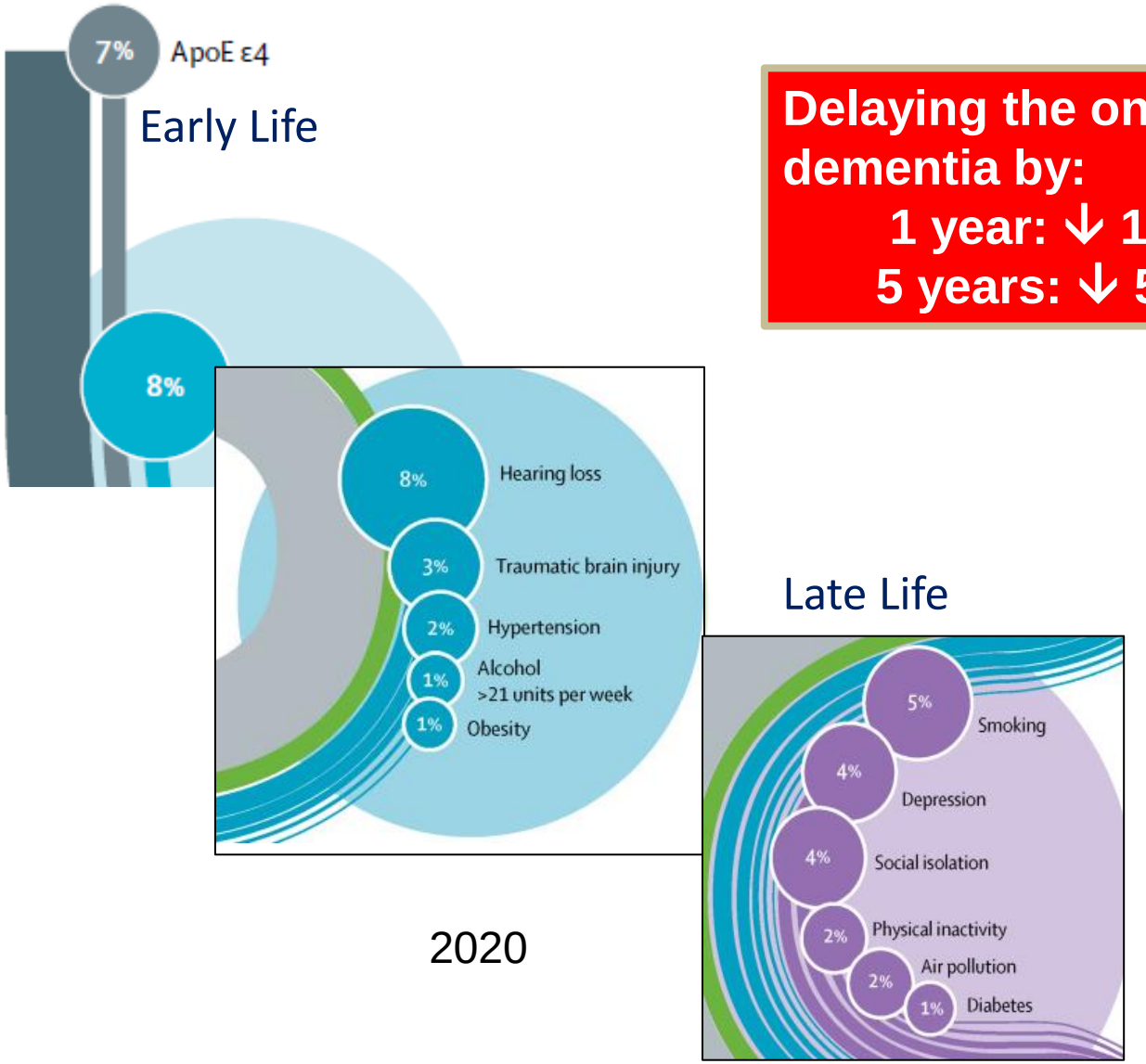
3- Similar studies have been conducted in Brazil, India, China, New Zealand, US, but it hasn't been done yet in Canada

Livingston et al. Lancet. 2020; 396: 413-46.

Risk Factors Along the Life Course: Preventing Dementia

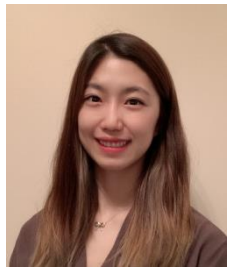
Risk factor	PAR
Diabetes mellitus	2.9%
Midlife hypertension	5.1%
Midlife obesity	2.0%
Physical inactivity	12.7%
Depression	7.9%
Smoking	13.9%
Low education	19.1%
Combined PAR*	40%

PAR=population-attributable risk.
*Adjusting for non-independence of the risk factors.



Delaying the onset of dementia by:
1 year: ↓ 10%
5 years: ↓ 50%

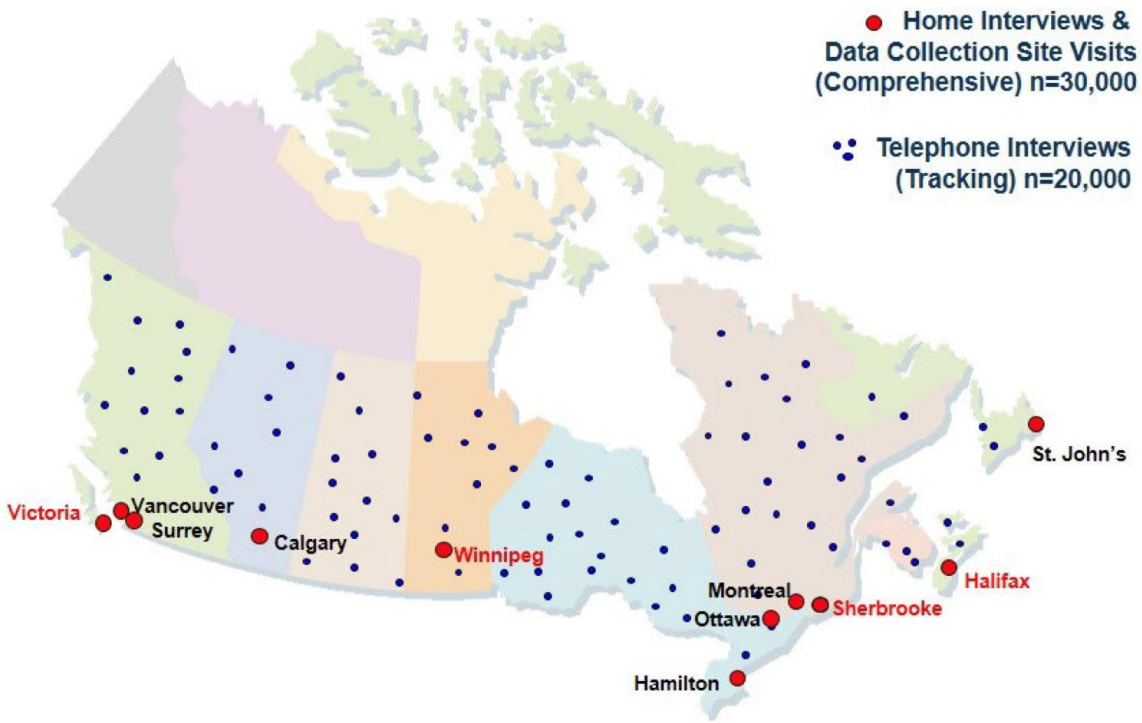
Brookmeyer R et al., 1988; Norton et al., 2014, *Lancet Neurol, 2014;* Livingstone et al., 2017 & 2020, *Lancet Neurol.*



Surim Son *et al. (under review)*

Prevalence of Modifiable Risk Factors for Low Cognition and Dementia in Canada: an analysis of Canadian Longitudinal Study of Aging

Canadian Longitudinal Study on Aging



- A large national, longitudinal study of **50,000 Canadian men and women who** were between the ages of 45 and 85 when recruited.
- This study analyzed Comprehensive cohort (N=28,588)
- After applying sampling weight, this data represents N=3,599,967.

clsa élcv

12 Modifiable risk factors

- using the operational definitions used in the Lancet 2020

Less Education	Less than secondary school graduation
Hearing loss	>25 dB at 500, 1000, 2000 and 4000 Hz in the better ear
Traumatic brain injury	A head injury resulted in losing consciousness
High blood pressure	>140 mmHg (average of 5 measurements)
Excessive Alcohol	>21 unit of alcohol per week
Obesity	BMI of ≥30 kg/m^2
Smoking	Current cigarette smoker (in past 30 days)
Depression	Self-report diagnosis
Social isolation	Less than monthly social contact
Physical inactivity	<150 mins of moderate-to-vigorous physical activity or <75 mins of vigorous activity
Diabetes	Self-report diagnosis
Sleep disturbance	poor sleep quality, insomnia, sleep apnea, daytime sleepiness, restless leg syndrome

Lancet. 2020; 396: 413-46.

Population Attributable Fractions

- The population attributable fractions (PAF) for a risk factor indicates the proportion of the low cognition and dementia in the population that would be removed it the exposure (ie. physical inactivity) was eliminated.

$$PAF = \frac{P_{exp}\left(RR_{exp-1}\right)}{\left[1 - P_{\exp}(RR_{exp} - 1)\right]}$$

P_{exp}: prevalence of the exposure

RR_{exp}: risk ratio of exposure

Lancet Commission vs. CLSA

Table 1. Prevalence and PAF in Early and Mid-Life

	Lancet Commission (2020)			CLSA (2022)	
	RR	Prevalence	Unweighted PAF	Prevalence	Unweighted PAF
Early life (age <18 years)					
Education (≤ primary school)	1.6	40%	19.4%	17%	9.3%
Midlife (age 45-65 years)					
Hearing loss	1.9	32%	22.2%	34%	23.4%
Hypertension	1.6	9%	5.1%	13%	7.24%
Excessive alcohol consumption (>21 units/wk)	1.2	12%	2.1%	11%	2.15%
Obesity	1.6	3.4%	2.0%	31%	15.7%

Lancet Commission vs. CLSA

Table 2. Prevalence and PAF in Later Life

	Lancet Commission (2020)			CLSA	
	RR	Prevalence	Unweighted PAF	Prevalence	Unweighted PAF
Later life (age >65 years)					
Smoking	1.6	27%	14.1%	11%	6.19%
Depression	1.9	13%	10.6%	17%	13.3%
Social isolation	1.6	11%	4.2%	20%	10.7%
Physical inactivity	1.4	18%	9.6%	67%	21.1%
Diabetes	1.5	6%	3.1%	9%	4.1%
Sleep disturbance	1.2‡	NA	NA	43%	7.9%

‡RR extracted from Shi et al. (2018). Sleep disturbances increase the risk of dementia: a systematic review and meta-analysis. Sleep Med Rev. 40:4-16.

Canadian Findings

- Highest prevalence of RFs in **Canada** were **Physical Inactivity (67%), Sleep disturbance (43%),** and **Obesity (31%)**.

- Highest prevalence of RFs in **World** were **Education (40%), Hearing loss (32%), and Smoking (27%)**.

- The prevalence of RFs in Canada differ from Worldwide prevalence (reported in Lancet Commission 2020).

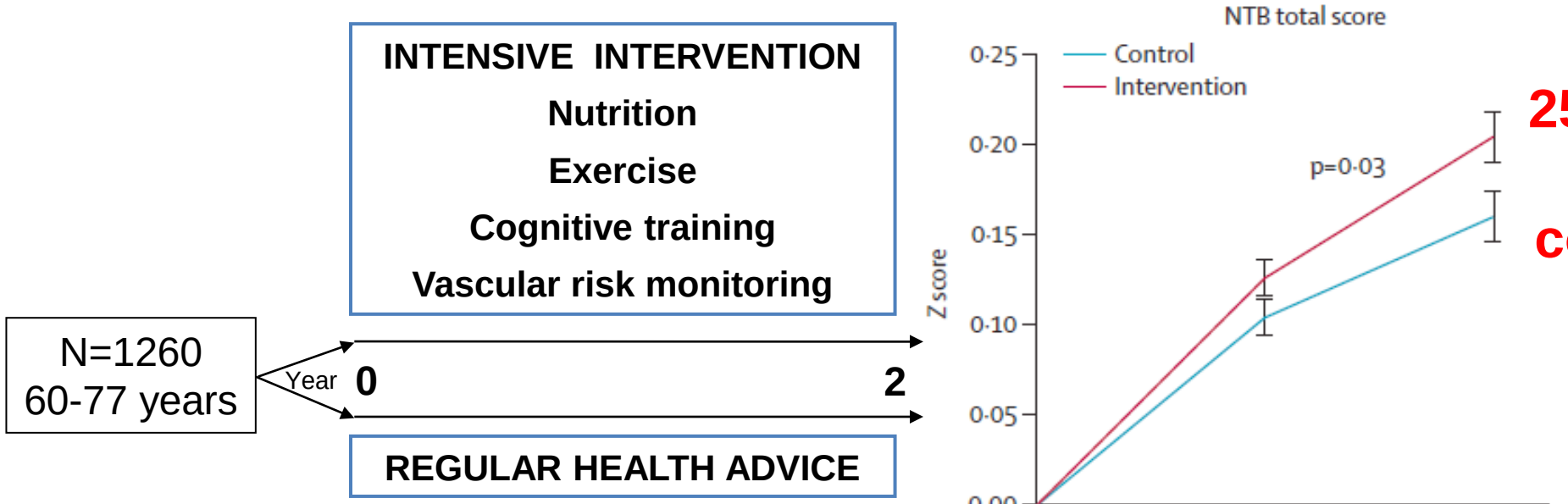
What about RCTs using lifestyle interventions to improve cognition and prevent dementia?

Lancet 2015; 385: 2255–63

FINGER TRIAL

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

Tiia Ngandu, Jenni Lehtisalo, Alina Solomon, Esko Levälahti, Satu Ahtiluoto, Riitta Antikainen, Lars Bäckman, Tuomo Hänninen, Antti Jula, Tiina Laatikainen, Jaana Lindström, Francesca Mangialasche, Teemu Paajanen, Satu Pajala, Markku Peltonen, Rainer Rauramaa, Anna Stigsdotter-Neely, Timo Strandberg, Jaakko Tuomilehto, Hilkka Soininen, Miia Kivipelto



25% improvement in Composite cognitive score!!!

Interpretation Findings from this large, long-term, randomised controlled trial suggest that a multidomain intervention could improve or maintain cognitive functioning in at-risk elderly people from the general population.

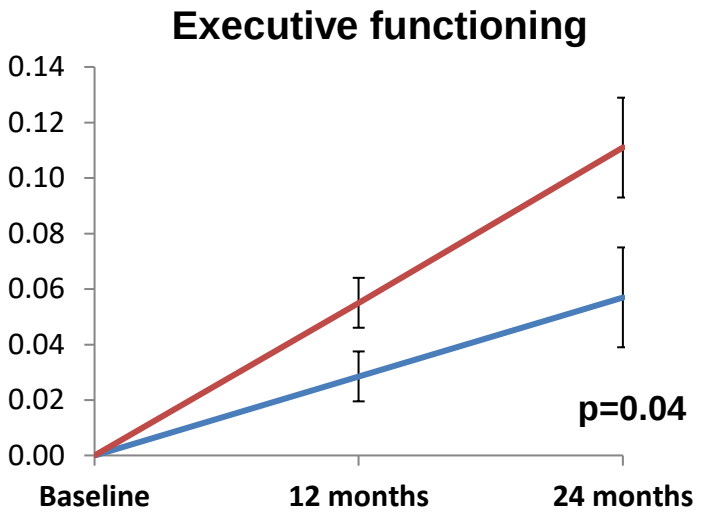
Ngandu, Kivipelto et al. Lancet 2015

FINGER Trial: summary of primary findings

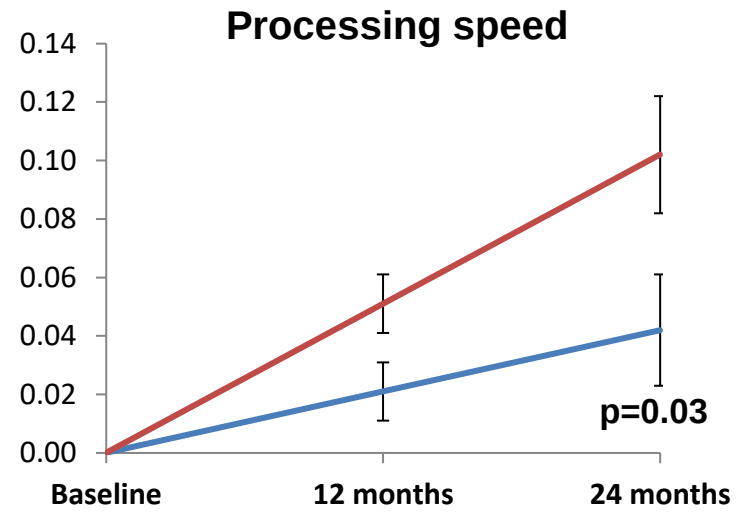
Primary: NTB total score
(Composite z-score)

p=0.03

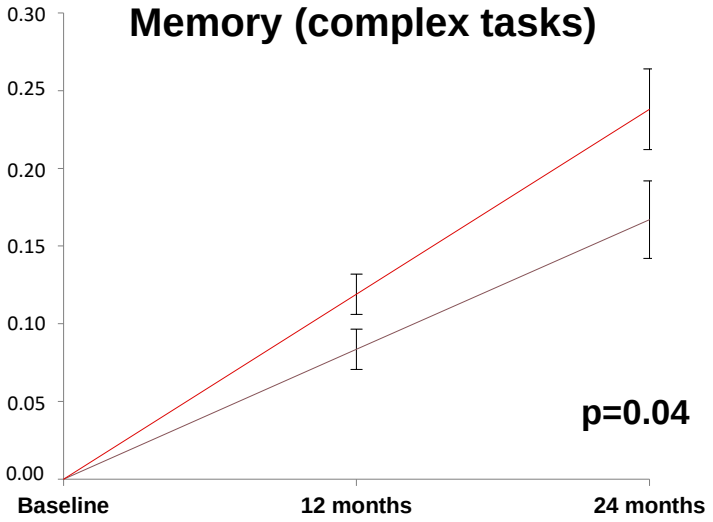
25% higher improvement



83% higher improvement



150% higher improvement



40% higher improvement

Intervention
Control

Lines *= estimates for change from baseline to 1 & 2 years*
Error bars *= standard errors*
P-values *= difference in trajectories over time between groups*

Ngandu, Kivipelto et al. Lancet 2015

The SYNERGIC Trials
Part of CAN Thumbs-UP

CCNA Canadian Consortium on Neurodegeneration in Aging

CCNV Consortium canadien en neurodégénérescence associée au vieillissement

ccna-ccnv.ca

Gait & Brain Lab, Lawson Health Research Institute
Western
McGill
Ontario Shores Centre for Mental Health Sciences
Laurier Inspiring Lives.
University of Alberta
UBC The University of British Columbia
Concordia University
University of Waterloo
Université de Montréal

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The SYNERGIC Trials
Part of CAN Thumbs-UP

- SYNERGIC Trial
- SYNERGIC @Home
- SYNERGIC 2.0 Trial

on Neurodegeneration in Aging

neurodégénérescence associée au vieillissement

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SYNERGIC Trial

Successfully completed

Published Main Results in *JAMA Open* - July 20, 2023

SYNchronizing, **E**xercises, **R**emedies in **G**a**I**t and **C**ognition
A randomized controlled double blind trial
NCT02808676 HC6-24-c195918

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Canadian Therapeutic Platform Trial for Multidomain Interventions to Prevent Dementia (CAN-Thumbs UP)

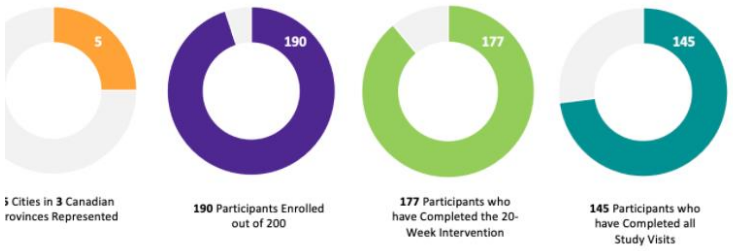
CCNV CCNA

SYNERGIC TRIAL

Cutting-edge interventions to improve cognition, mobility and falls.

Western University · Université de Montréal · The University of British Columbia · Laurier · University of Waterloo

Home | About Our Study | In the Media | Site Leaders | Funding | Photo Gallery | Contact Us



Join Us!

Are you feeling forgetful?

Have you had changes in you memory?

Are you 60 years old or older?

Contact one of our sites for more information about how you can join us!

SYNchronizing, Exercises, Remedies in Galt and Cognition

www.synergictrial.com

200 older adults with Mild Cognitive Impairment

Goal: Efficacy of bi-modal personlized exercise (aerobic+ resistance) + potential synergistic effects of adding cognitive training + vitamin D to improve cognition

CAN Thumbs Up

Montero-Odasso et al. BMC Geriatrics (2018) 18:93
https://doi.org/10.1186/s12877-018-0782-7

BMC Geriatrics

STUDY PROTOCOL Open Access

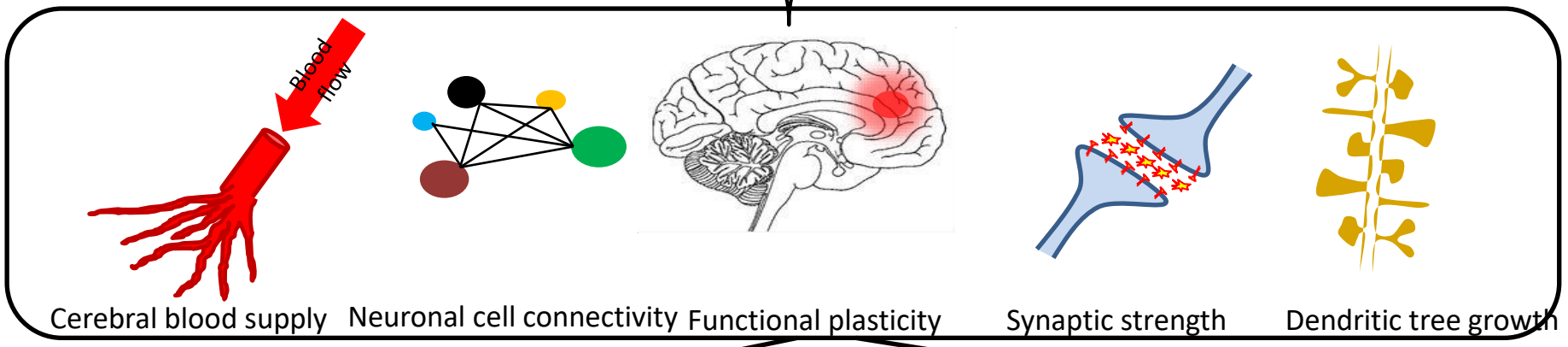
SYNERGIC TRIAL (SYNchronizing Exercises, Remedies in Gait and Cognition) a multi-Centre randomized controlled double blind trial to improve gait and cognition in mild cognitive impairment

Manuel Montero-Odasso[1,2,3*], Quincy J. Almeida[4], Amer M. Burhan[5], Richard Camicioli[6], Julien Doyon[7], Sarah Fraser[8], Karen Li[9], Teresa Liu-Ambrose[10], Laura Middleton[11], Susan Muir-Hunter[12], William McIlroy[13], José A. Morais[14], Frederico Pieruccini-Faria[1,3], Kevin Shoemaker[15], Mark Speechley[2], Akshya Vasudev[16], G. Y. Zou[2,17], Nicolas Berryman[18,19], Maxime Lussier[18,20], Leanne Vanderhaeghe[21] and Louis Bherer[9,18,20,22]

Potential changes induced by multimodal interventions in MCI

Levels	Aerobic exercise	Resistance exercise	Cognitive training	Vitamin D
Physiological	1.Blood supply 2.Anti-inflammatory 3.Immunologic factors 4.Growth factors Colcombe et al 2004; 2006; Cotman, Berchtold & Christie, 2007	1.Blood supply 2.Growth factors 3.Functional plasticity Cotman, Bertchtold & Christie, 2007 Liu-Ambrose et al 2012; Nagamatsu et al 2012	1.Functional plasticity 2.Connectivity Erickson et al 2007a,b; Chapman et al 2015	1.Anti-inflammatory 2.Calcium metabolism 3.Anti-oxidant Montero-Odasso and Duque, 2005 Annweiler et al 2013 Morley, 2014 Morley & Farr, 2014

Enhancement of neural networks connectivity



Behavioural

Cognitive

- Executive functions
- Attention
- Visuospatial function
- Speed processing
- Memory

Colcombe & Kramer 2003;
Nagamatsu et al . 2012;
Ballestros et al. 2014;
Bherer et al 2005, 2006,2013;
Liu-Ambrose et al 2010, 2012;
Langlois et al .2013;

Cognitive-motor interactions

Montero-Odasso et al., 2012; 2015

Mobility

- Walking
- Multi-tasking
- Balance
- Falls
- Activities of daily living

Sage & Almeida, 2009;
Li et al. 2010;
Muir & Montero-Odasso, 2011;

Annweiler et al. 2013;
Suzuki et al .2013;
Langlois et al .2013

Montero-Odasso et al. 2017 *BMC Neurol*

Exercise is Medicine

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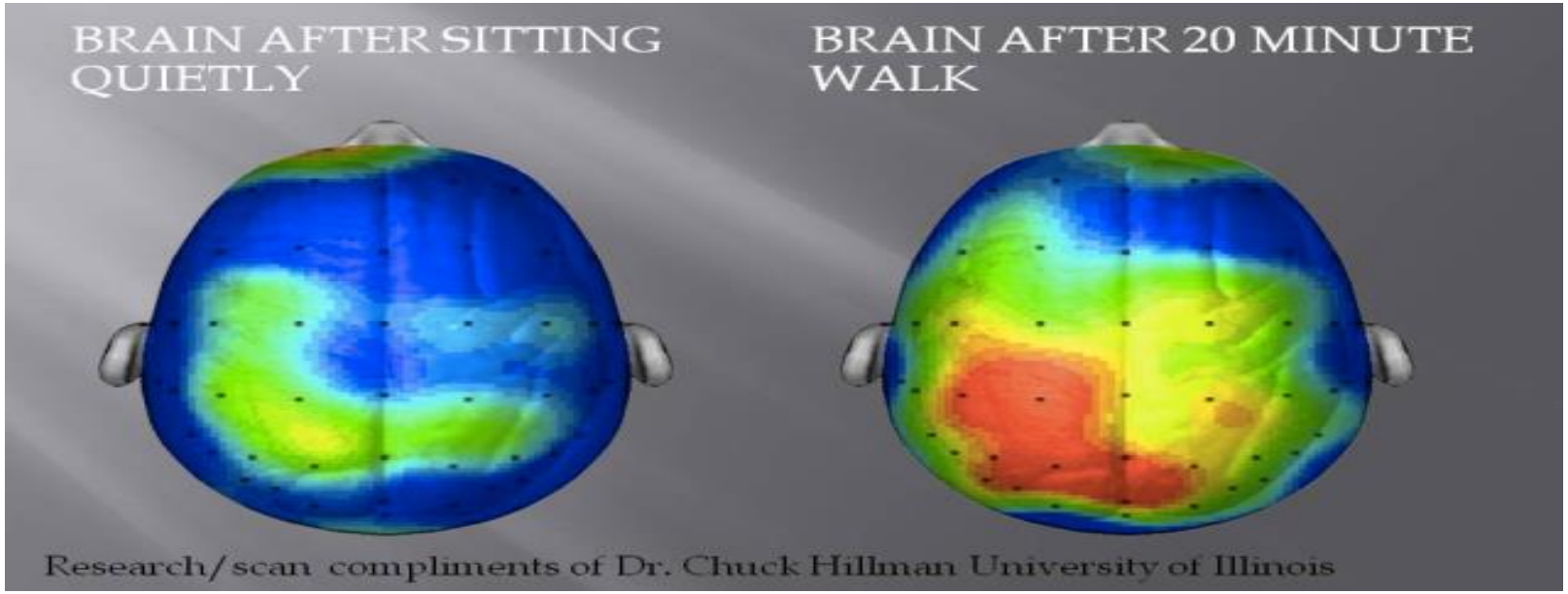

What is good for your heart, is good for your brain!

CCNA Canadian Consortium on Neurodegeneration in Aging

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- Types of Exercise
  - Aerobic Training
    - Running, walking, swimming
  - Resistance Training
    - Lifting weights
  - Anaerobic Training
  - Balance/Agility Training
  - Others: Yoga, Tai Chi, dance

Photo courtesy of SYNERGIC participants, London site

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"I have been working out for six months, but all my gains have been in cognitive function"

Kaamran Hafeez in the The New Yorker, October 2015

Domains of Cognition affected by physical exercises and cognitive training

- Executive Functions
  - Planning, decision making, multi-tasking
  - Sensitive to aging effects
  - Impairment common in AD and VCI/VaD

- Hippocampal-Dependent Memory
  - Impairment common in AD and VCI
  - Impairment associated with conversion from MCI to AD

Canadian Consortium
on Neurodegeneration in Aging.
The Canadian Component of CIHR's International
Collaborative Research Strategy for Alzheimer's Disease.

CCNA Motor, Exercise & Cognition (MEC) Team 12

CIHR IRSC
Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

Distinctive expertise in, **motor/cognitive interaction, interventions exercise, gait/physical activity, cognition**

Including 2 Canada Research Chairs

Bill McIlroy
(U of Waterloo/Toronto)
Quincy Almeida
(Laurier U)
Laura Middleton
(U of Waterloo)
Manuel Montero-Odasso
(Western)
Susan Muir-Hunter
Akshya Vasudev
Amer Burham
Mark Speechley
Kevin [illegible]
Chris [illegible]
of Ne[illegible]

Teresa Liu-Ambrose
(UBC)

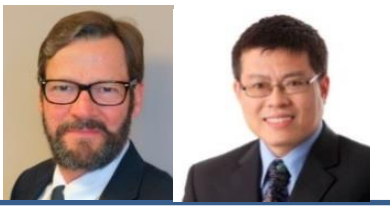
Richard Camicioli
(U of Alberta)

Louis Bherer
(U Montreal)
Julien Doyon
(U de Montreal)
Karen Li
(Conc[illegible]
Jose [illegible]
Sarah [illegible]
(U of [illegible]

International advisory board
Stephanie Studenski
Caterina Rosano
Joseph Verghese
Jeffrey Hausdorff
Olivier Beauchet

Site leaders

Methodologists



Imaging

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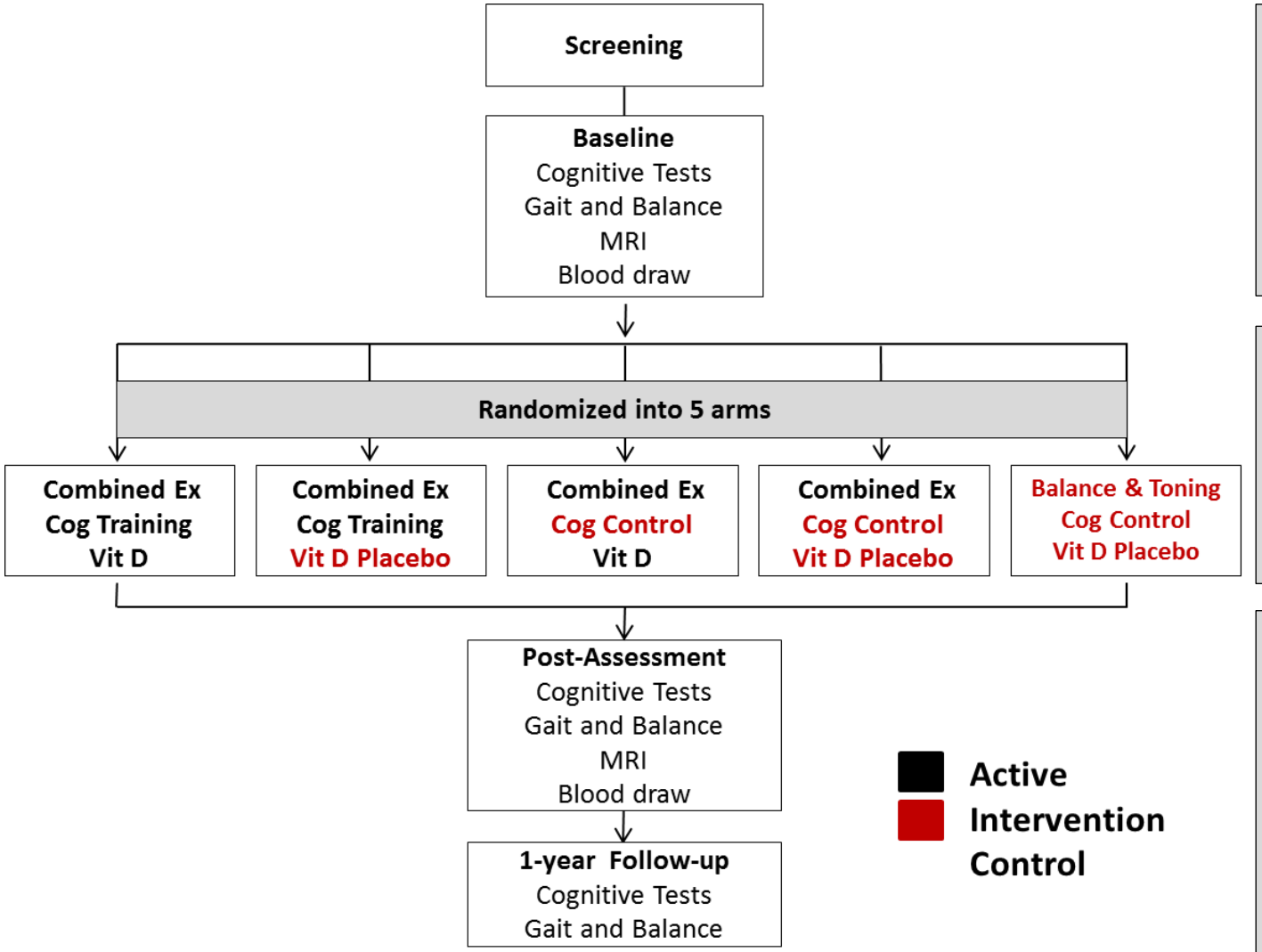
SYNERGIC Trial Design and sample

- 20-week multicenter phase II double-blind RCT + 6 months of follow-up
- Sample size n=200 with Mild Cognitive Impairment (MCI), age 60-85 years
- Assessments points: Baseline, week 22 (6 m), and week 52 (12 m)
- Investigating **efficacy** of multimodal aerobic and resistance training, with potential synergistic effects of cognitive training and vitamin D
- **Primary Outcome:** ADAS Cog 13 and plus
- **Secondary Outcomes**: Other cognitive domains, brain MRI, gait and mobility, falls, and blood biomarkers

SYNERGIC Trial - CONSORT Flow chart



Enrollment

Interventions
6 months

Follow-up
6 months

Goal:

To test **efficacy** of **multimodal** (aerobic + resistance) **exercise** with potential synergistic effects of adding **cognitive training and vitamin D**

SYNERGIC Trial Interventions

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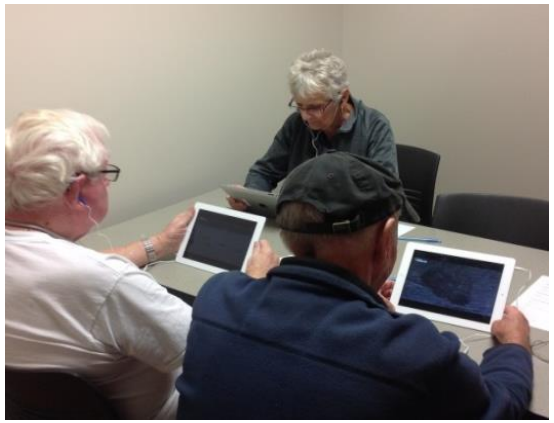
3 interventions… in individuals with MCI

Cognitive training + Physical exercises + Vitamin D



<u>Cognitive Training</u> (Neuropeak®)

- Cognitive Training (CT) is a tablet-based multimodal and multi-domain dual-task training with memory load imbibed
- CT happens before each of the fitness-training sessions for a duration of 30 min

Attentional training method

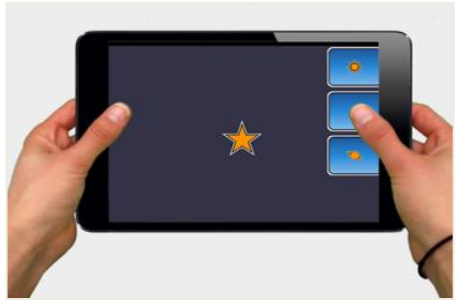
(Bherer, Kramer, et al., 2005; Erickson et al., 2008)

Cognitive Training
(Neuropeak®)

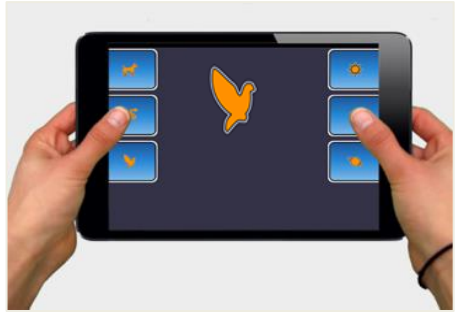
- 30 minutes of single and dual-task blocks
- Task A: celestial bodies
- Task B: Animals
- Adaptive increase in difficulty over sessions
- Memory load imbibed

Single tasks

A

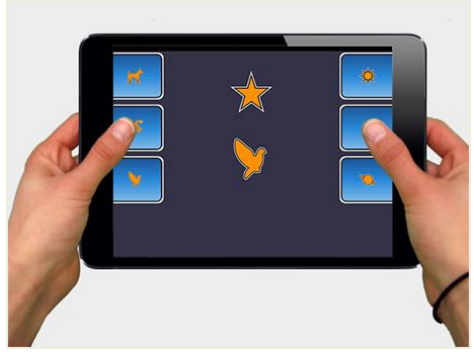


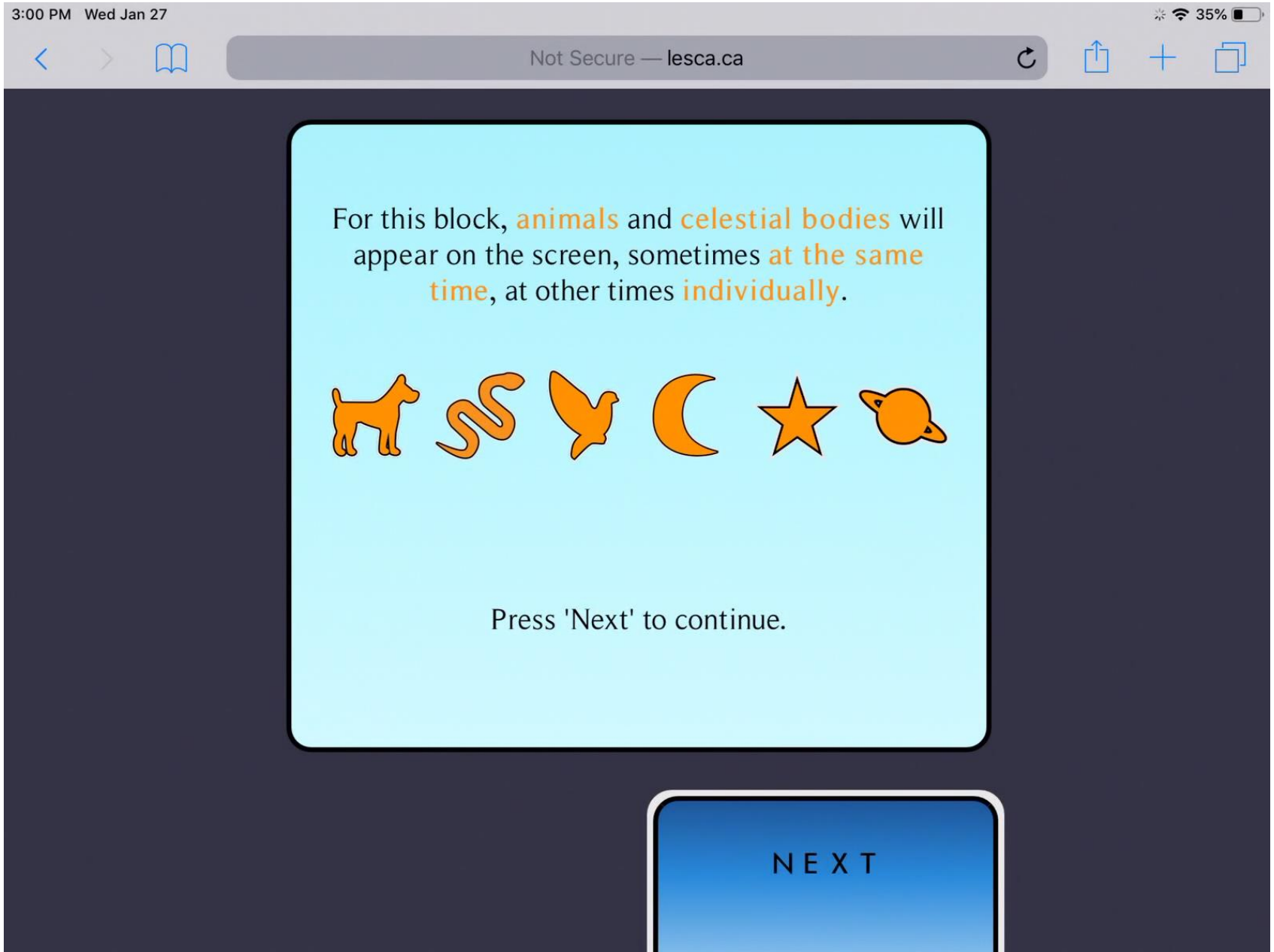
B



Dual task

A+B




3:00 PM Wed Jan 27
35%
Not Secure — lesca.ca
For this block, animals and celestial bodies will appear on the screen, sometimes at the same time, at other times individually.
Press 'Next' to continue.
NEXT

SYNERGIC Trial Interventions

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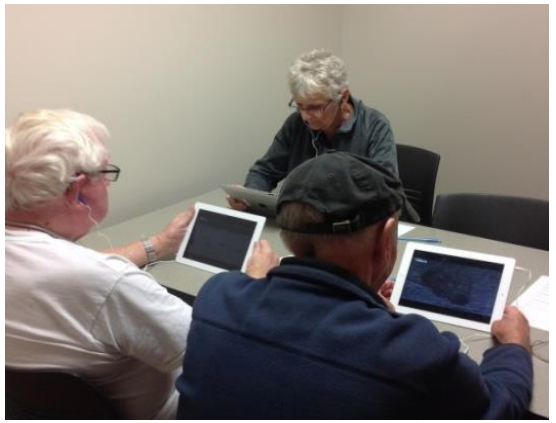
3 interventions… in individuals with MCI

Cognitive training + Physical exercises + Vitamin D



<u>Multimodal Exercise</u> (SYNEXCog®)

- 3 weekly sessions, 60 min each
- Includes 40 min **progressive** resistance training (lower and upper body exercises) + 20 min **aerobic exercise**

SYNERGIC Trial Interventions

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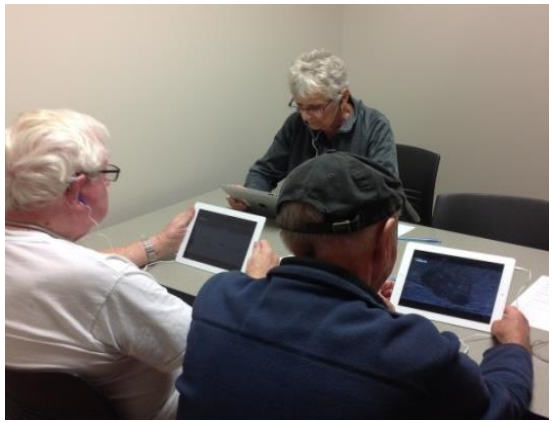
CCNV Consortium canadien en neurodégénérescence associée au vieillissement

3 interventions… in individuals with MCI

Cognitive training + Physical exercises + Vitamin D



<u>Vitamin D</u>

- 10,000 IU of Vitamin D3 or matching placebo 3 x/week (daily dose: 4,258 IU)
- Maximum daily dose approved by Health Canada as a supplementation is 10,000 IU

SYNERGIC Trial
CONSORT Flow chart

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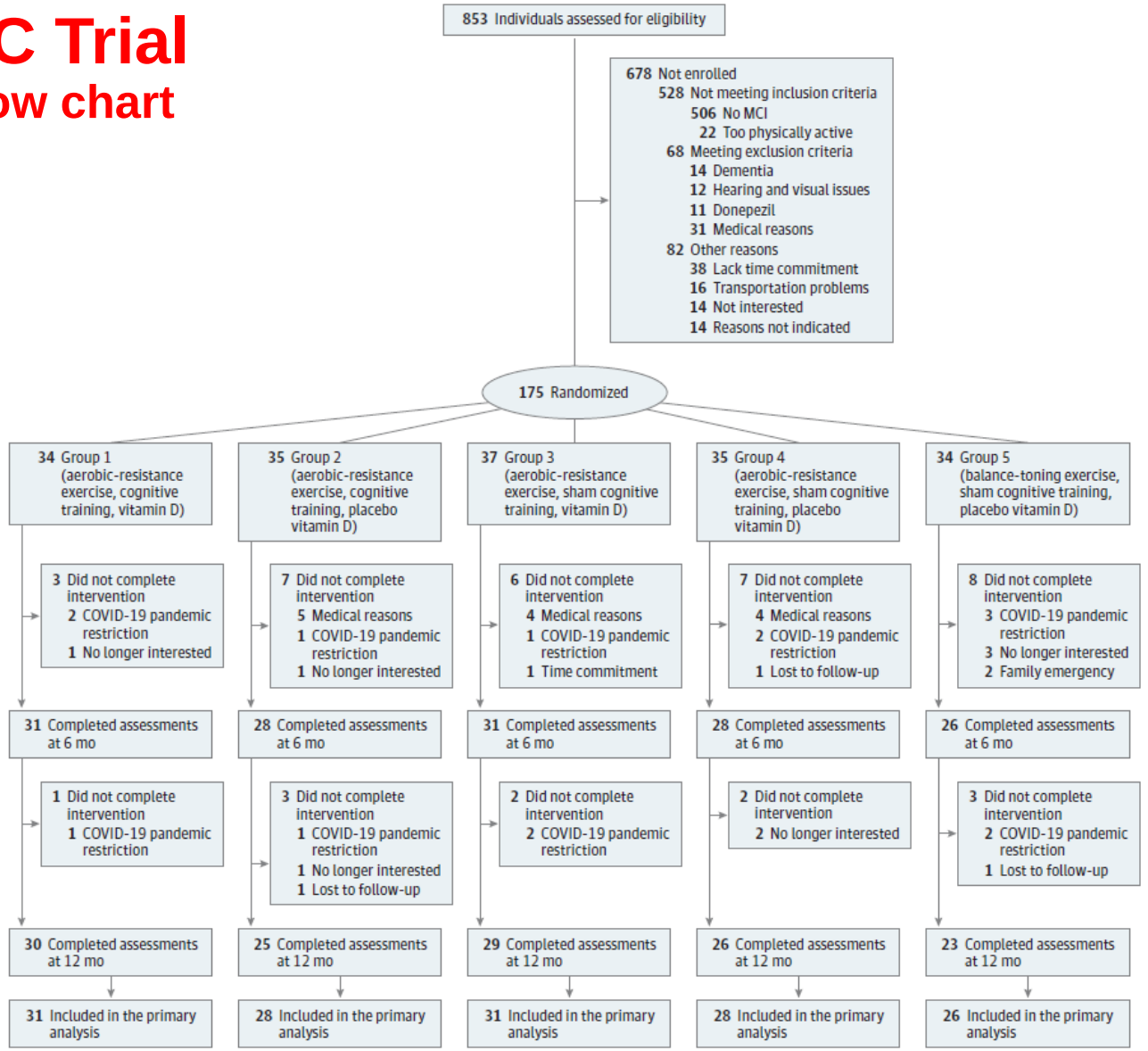
CCNV Consortium canadien en neurodégénérescence associée au vieillissement



T0 (Baseline)

T6 (Post-intervention)

T12 (Follow-up)

Figure 1. SYNERGIC Trial consortium flowchart. MCI, mild cognitive impairment.

JAMA Network Open

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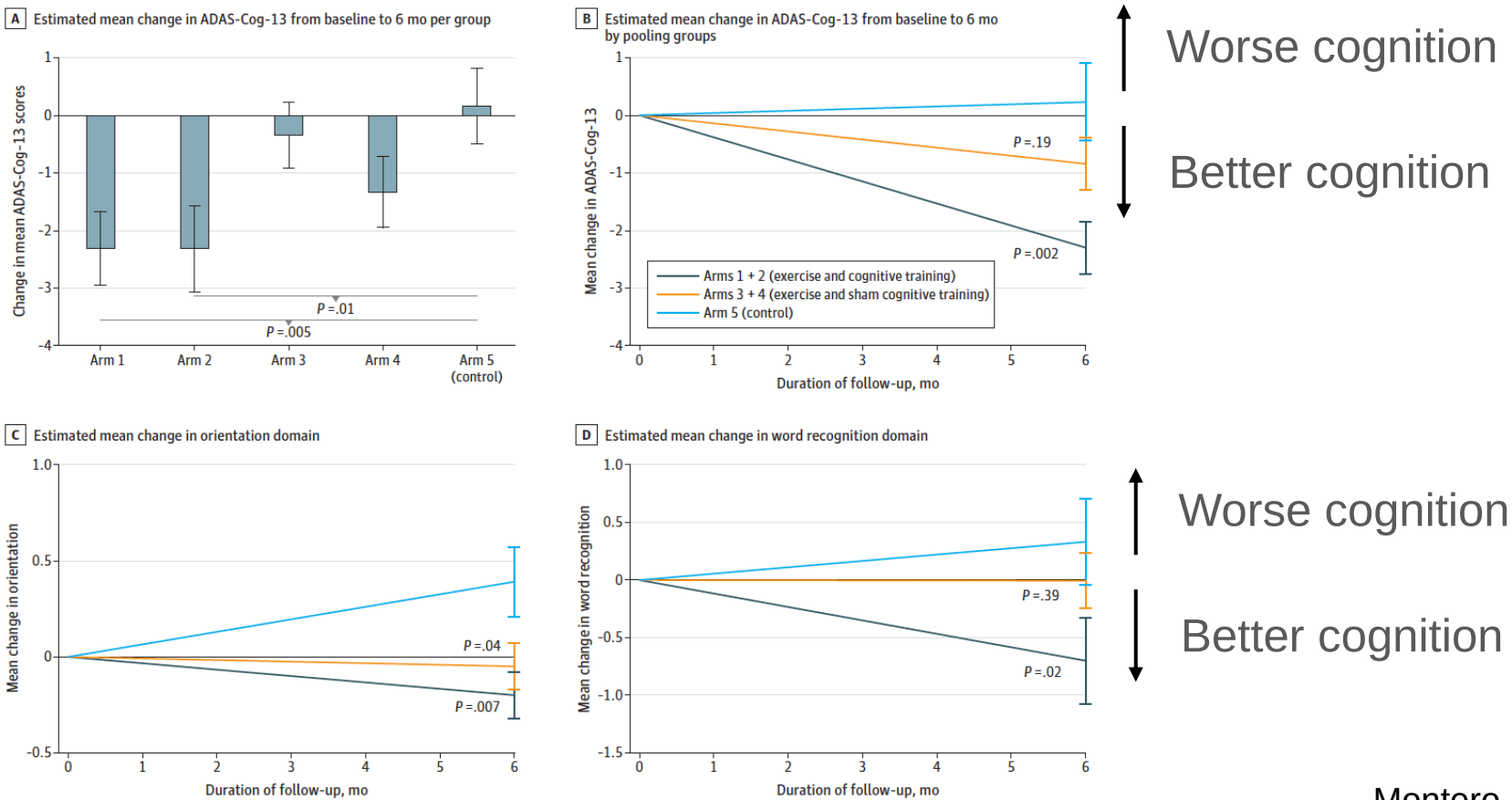
Original Investigation | Geriatrics

Effects of Exercise Alone or Combined With Cognitive Training and Vitamin D Supplementation to Improve Cognition in Adults With Mild Cognitive Impairment

A Randomized Clinical Trial

Manuel Montero-Odasso, MD, PhD; Guangyong Zou, PhD; Mark Speechley, PhD; Quincy J. Almeida, PhD; Teresa Liu-Ambrose, PhD; Laura E. Middleton, PhD; Richard Camicioli, MD; Nick W. Bray, PhD; Karen Z. H. Li, PhD; Sarah Fraser, PhD; Frederico Pieruccini-Faria, PhD; Nicolas Berryman, PhD; Maxime Lussier, PhD; J. Kevin Shoemaker, PhD; Surim Son, MSc; Louis Bherer, PhD; for the Canadian Gait and Cognition Network

Figure 2. Change in ADAS-Cog-13 Scores During the 6-Month Intervention



Montero-Odasso et al, 2023 *JAMA Open*

SYNERGIC Trial Limitations

- We could not reach the 200 participants due to COVID-19 Pandemic restrictions, which may have affected power for detecting efficacy for some of the interventions on secondary cognitive outcomes
- Drop out was 17%, being 50% related due the early termination for COVID restrictions
- Vitamin D intake was not an exclusion criteria so the majority of the participants had a normal-high serum level of vitamin D

SYNERGIC Trial Conclusions

- Combining exercise + cognitive training has synergistic effect to improve cognition and mobility that the single modalities

- Multi-domain, personalized combination of progressive aerobic + resistance training coupled with cognitive training is feasible to do in older adults with cognitive impairment (MCI)

- ADAS-Cog 13 changes were in the medium-large effect size (0.70) and close to clinical significant changes (3 point range)

- "*The study demonstrates that people with MCI can do something that may influence their cognitive trajectory*" said Ronald C. Petersen

- Adding Vitamin D did not enhance cognition or mobility

Secondary Outcomes – Brain connectivity

GeroScience (2023) 45:1967–1985
https://doi.org/10.1007/s11357-023-00805-6

ORIGINAL ARTICLE

Combining exercise with cognitive training and vitamin D_3 to improve functional brain connectivity (FBC) in older adults with mild cognitive impairment (MCI). Results from the SYNERGIC trial

Nick W. Bray · Frederico Pieruccini-Faria · Suzanne T. Witt · Robert Bartha · Timothy J. Doherty · Lindsay S. Nagamatsu · Quincy J. Almeida · Teresa Liu-Ambrose · Laura E. Middleton · Louis Bherer · Manuel Montero-Odasso

GeroScience (2023) 45:1033–1048
https://doi.org/10.1007/s11357-022-00702-4

ORIGINAL ARTICLE

Frailty and functional brain connectivity (FBC) in older adults with mild cognitive impairment (MCI): baseline results from the SYNERGIC Trial

Nick W. Bray · Frederico Pieruccini-Faria · Suzanne T. Witt · Kenneth Rockwood · Robert Bartha · Timothy J. Doherty · Lindsay S. Nagamatsu · Quincy J. Almeida · Teresa Liu-Ambrose · Laura E. Middleton · Louis Bherer · Manuel Montero-Odasso

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Nick W Bray

Depressive Symptoms
(Secondary outcomes)

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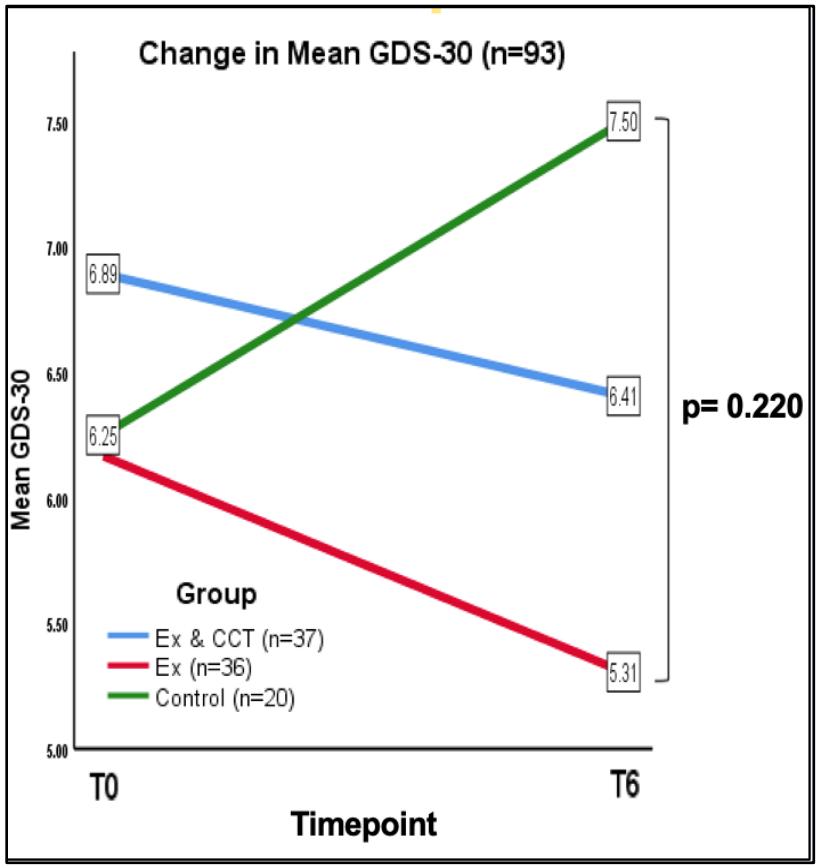
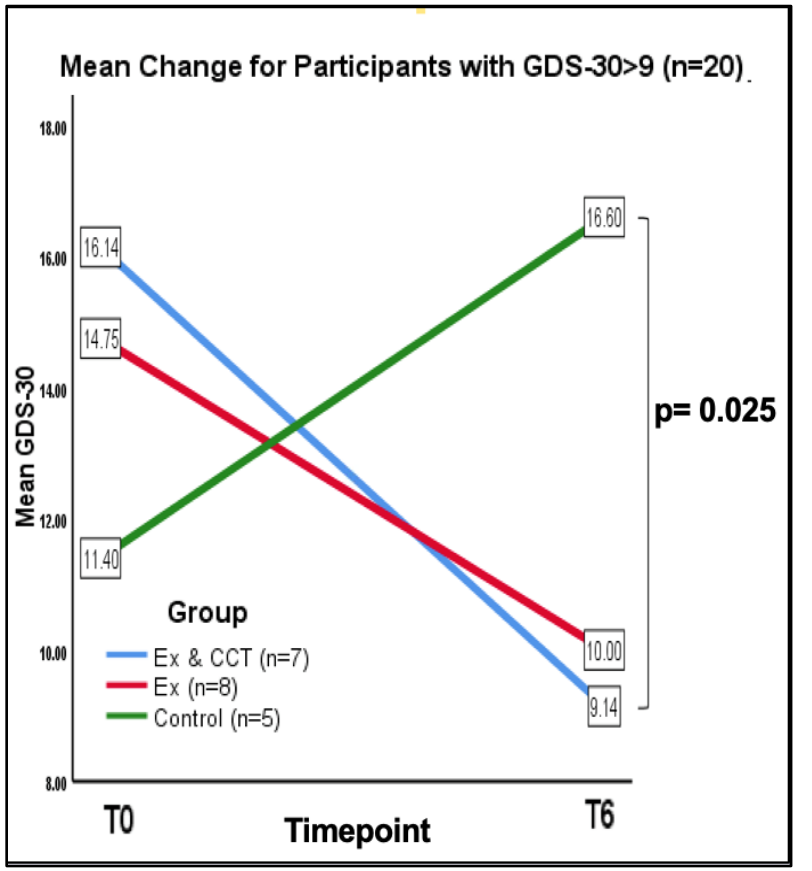
The Effect of a Multimodal Exercise Intervention Combined with Computerized Cognitive Training on Neuropsychiatric Symptoms in Older Adults with Mild Cognitive Impairment: A Preliminary Report

Authors:
Adrian Espiritu
Joel Mahon
Amer Burhan
Manuel Montero-Odasso

↑ Worse symptom

↓ Better symptom





Espiritu et al, *in prep*

Exercise, Gait Speed, and Primary Motor Cortex Metabolism in Mild Cognitive Impairment: A ^{1}H-MRS Analysis from the SYNERGIC Trial

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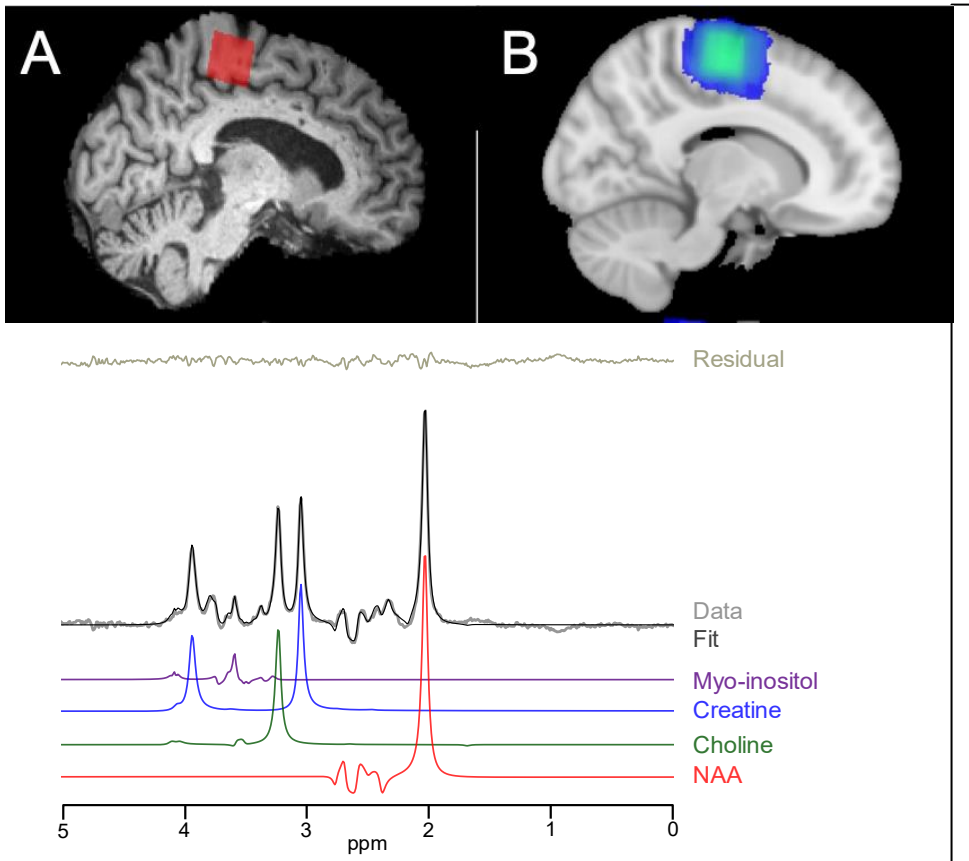
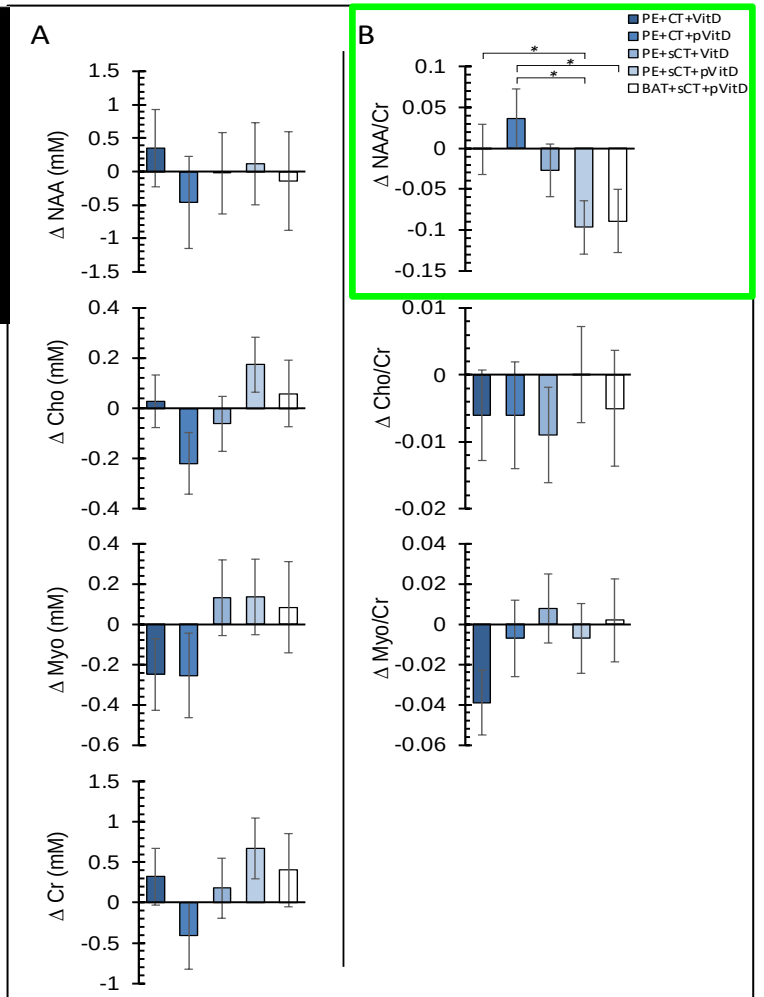
Jack Elkas, Frederico Pieruccini-Faria, Guangyong Zou, Amer Burham, Mark Speechley, Quincy J. Almeida, Teresa Liu-Ambrose, Laura E. Middleton, Richard Camicioli, Nick W. Bray, Karen Z.H. Li, Sarah Fraser, Nicolas Berryman, Maxime Lussier, J. Kevin Shoemaker, Surim Son, the Canadian Gait and Cognition Network, Louis Bherer, Manuel Montero-Odasso, Robert Bartha*





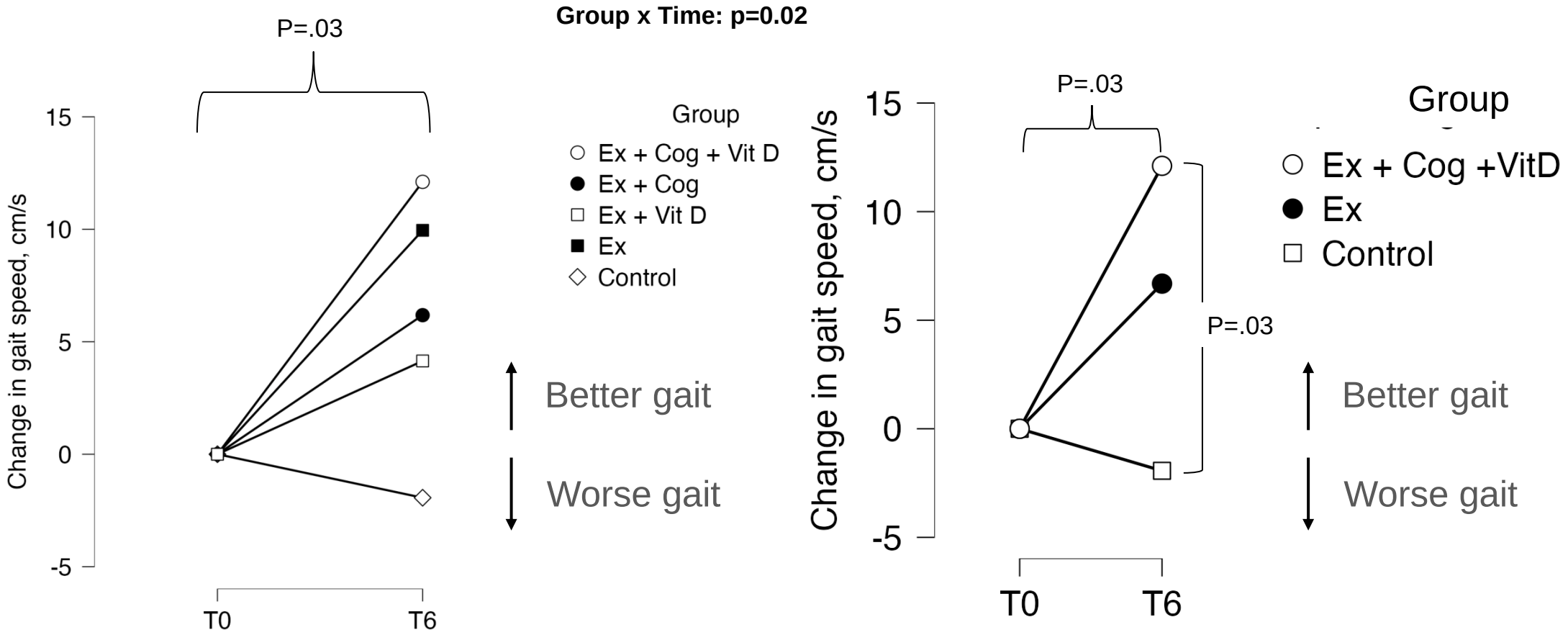
Protective effects of combined interventions on motor cortex

↑ Better for neurons

↓ Worse for neurons

Elkas et al *in prep*

Positive effects of combined interventions on gait performance



Pieruccini-Faria et al *in prep*

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SYNERGIC @Home

Pilot Launched in New Brunswick

New Nouveau
Brunswick

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neurodégénérescence
associée au vieillissement

SYNERGIC @Home
1 site

Pam Jarrett
(Dalhousie and Memorial University)

Chris McGibbon
(U of New Brunswick)

Manuel Montero-Odasso
(Western)

SYNERGIC@HOME A pilot, feasibility RCT using "in-home" physical exercises + cognitive training interventions delivered online to improve cognition in elderly with MCI, SCI, and CI (with risk factors).

SYNERGIC @Home

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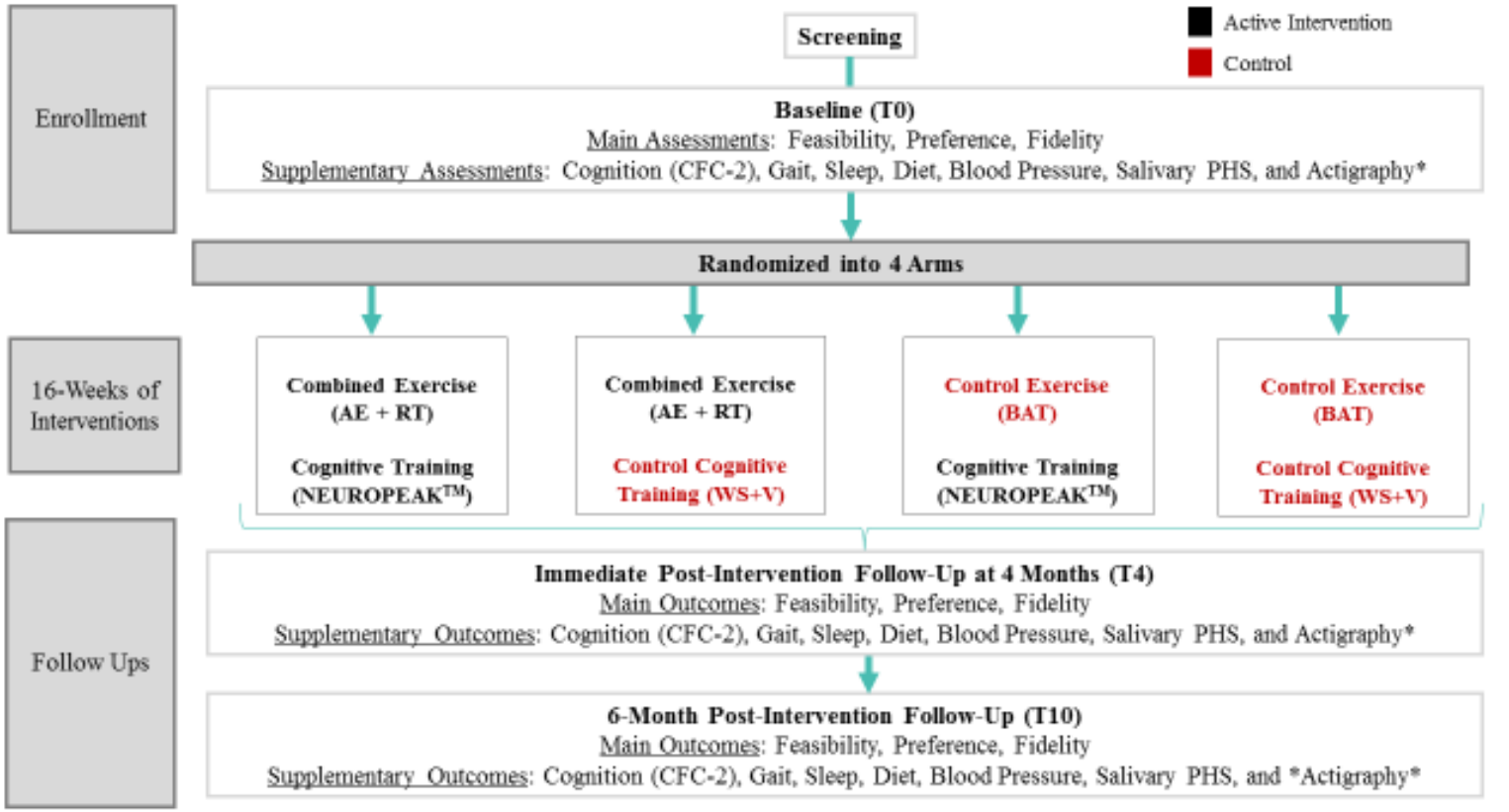
Purpose:
to assess feasibility of implementing multidomain interventions at home, preference for each intervention type, and adherence-compliance in MCI, SCI, and CI (with 2 or more risk factors).

Methodology/Design:
64 participants with MCI, SCI, or CI (with risk factors), aged ≥60 years enrolled and randomized into one of 4 arms.



AE: aerobic exercise, RT: resistance training; PHS = Polygenic Hazard Score*Using ActiGraph GT9X.

Significance and results. The SYNERGIC@HOME trial will:

✓Test feasibility of remote, COVID-friendly delivery of interventions and assessments.
✓Informed our large trial @home (SYNERGIC 2 trial).
✓Evaluated factors related to intervention compliance in older populations.

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The Future…

The most reliable way to predict the future is to create it.

~ Abraham Lincoln

The Future…

1. Personalized “menus” – Precision medicine
2. Mobile or Digital platforms – Wearables and virtual reality to stimulate the brain
3. At Home Interventions
4. Exercise is key – Goal oriented exercise
5. Dual-task training? Sequential or concurrent?
6. Physical exercise “holy grail” and emerging evidence is showing that combining that with cognitive training may have a synergistic effect
7. Effective coaching

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SYNERGIC 2.0 Trial

Weston Family
Foundation

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neurodégénérescence
associée au vieillissement

SYNERGIC 2.0 Trial
8 sites

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(U of Alberta)

Teresa Liu-Ambrose
(UBC)

Karen Li
(Concordia)

Chris McGibbon
(U of New Brunswick)

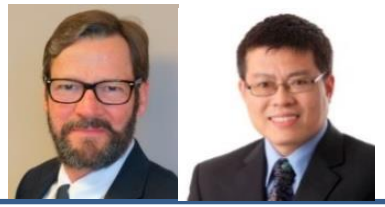
Sarah Fraser
(U of Ottawa)

Manuel Montero-Odasso
(Western)

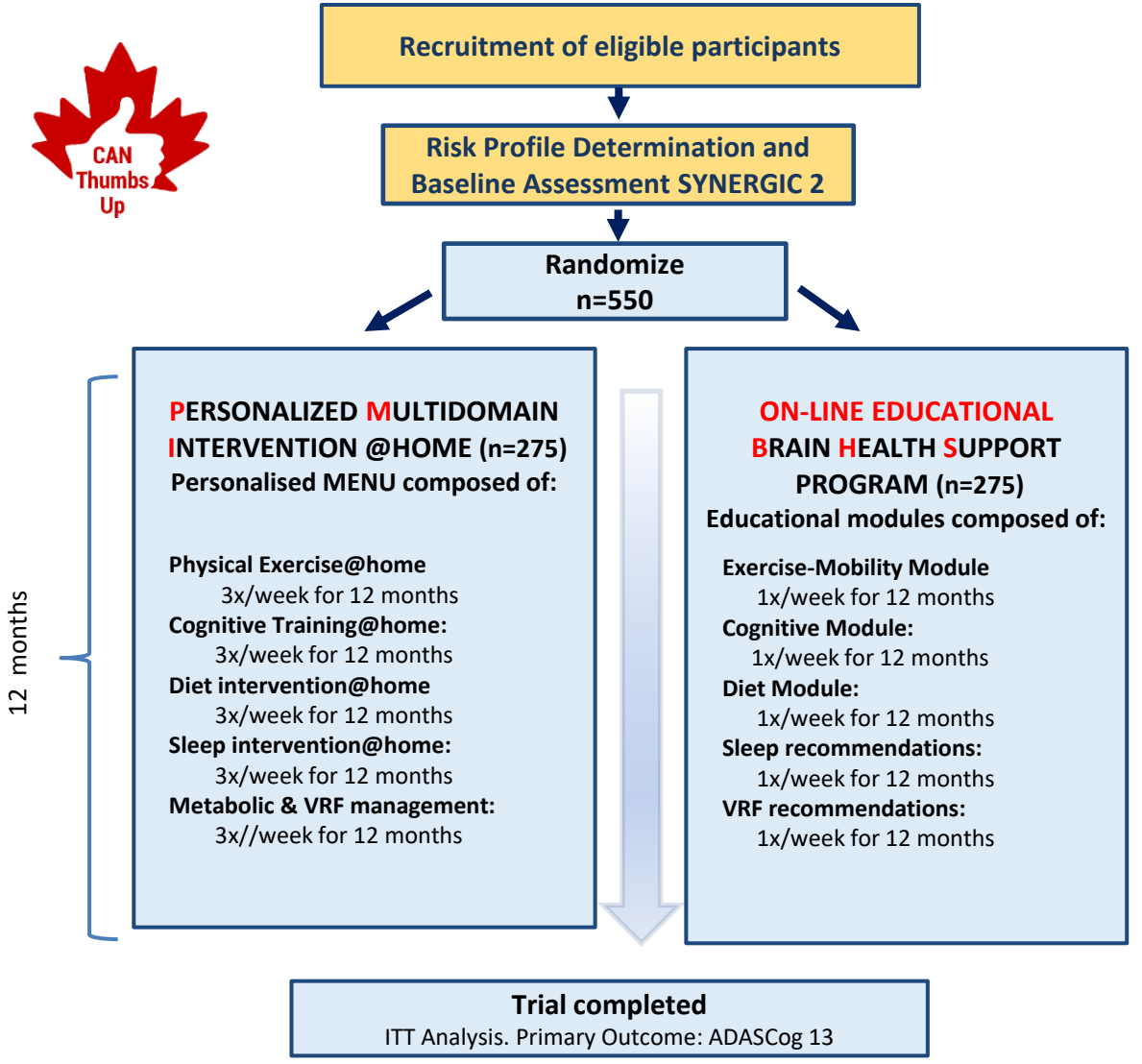
Howard Chertkow
(Baycrest)

Laura Middleton
(U of Waterloo)

Methodologists



SYNERGIC 2 - Trial Consort Flowchart



RCT, @home Personalized Multidomain lifestyle Interventions for 12 months

Older adults with MCI and ≥2 lifestyle risk factors for dementia

PMI@Home:

-**individually tailored interventions (menu)** based on **patient profiles:** multimodal exercise, cognitive training, and sleep enhancement, diet coaching, metabolic/vascular risk factor coaching,

-effective coaching

Primary Outcome: ADSCog13 at 12 months (PMI group will show a 25% better performance in ADAS-Cog 13 at month 12 with an effect size of 0.22 SD)

Efficacy declared when difference between PMI and BHS in change scores of PO at end point is statistically significant at 2-sided 5% level

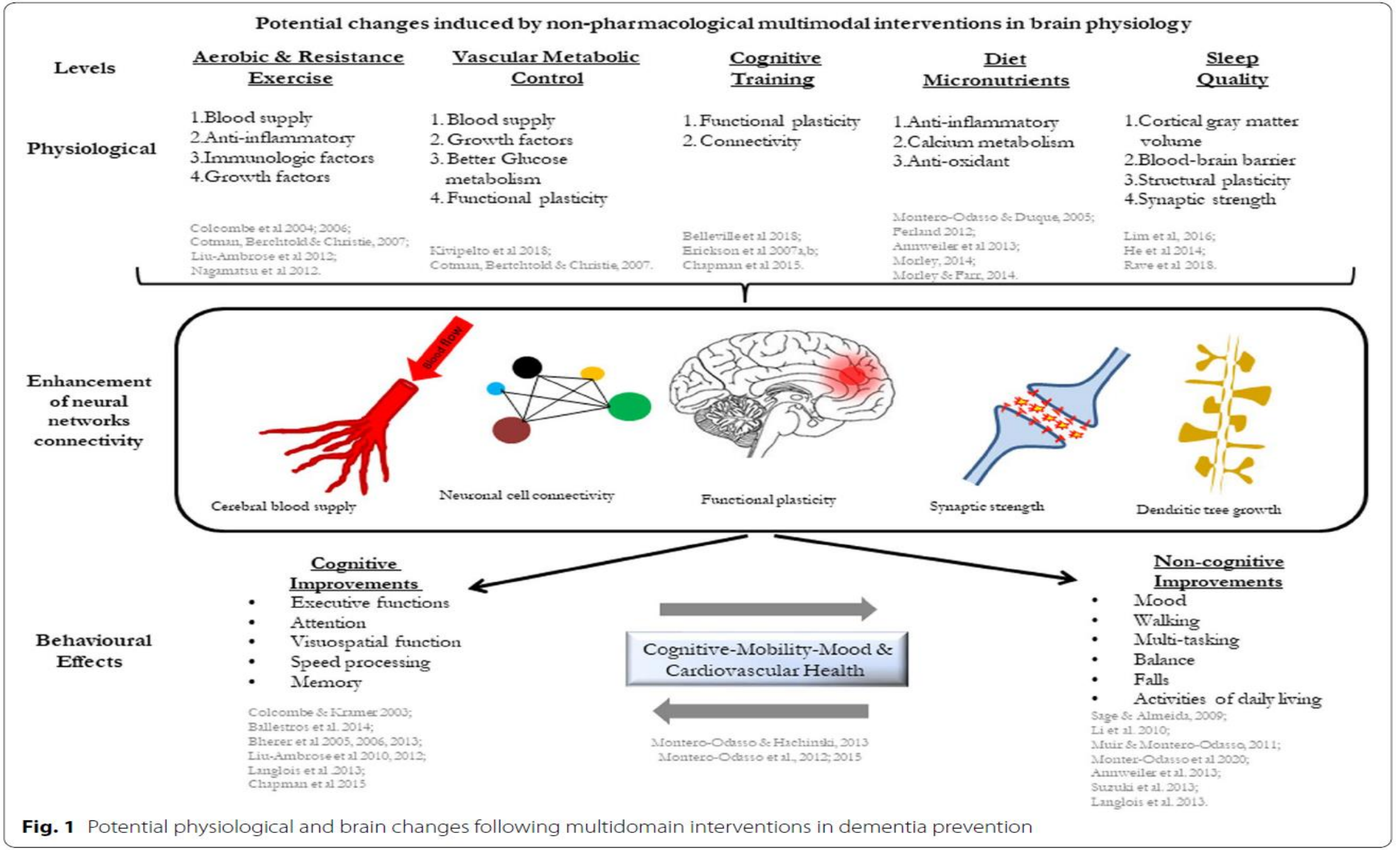


Fig. 1 Potential physiological and brain changes following multidomain interventions in dementia prevention

Montero-Odasso *et al. Alzheimer's Research & Therapy (2022) 14:94* https://doi.org/10.1186/s13195-022-01036-1

SYNERGIC-2 Digital Platform Dashboard

The Future

Welcome Back John!

MY AWARDS AND BADGES

LOG OUT

MY PERSONALIZED INTERVENTIONS THIS WEEK

- Physical Exercise
- Cognitive Training
- Diet
- Heart Health
- Sleep

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MY LATEST PROGRESSES

MESSAGES

You have 1 unread message

NEED HELP?

CALL US

519-685-4000 Ext 45629

FORUM

CHAT NOW

TAKE HOME MESSAGES

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1 - Cognitive impairment, dementia and Alzheimer's disease are multifactorial with several potentially modifiable risk factors including vascular risk factors, physical activity levels, diet and other lifestyle factors.

2 - Owing to this multifactorial etiology, multidomain interventions that target several risk factors and mechanisms simultaneously might be needed for effective prevention.

3 - Large RCTs of multidomain lifestyle interventions to prevent cognitive impairment shows encouraging results, particularly when targeting individuals at higher risk. **Role of personalized medicine: SYNERGIC Trial**

4 - A life-course approach is needed to facilitate optimal lifestyle intervention strategies for different age groups and for individuals with different risk profiles.

5 - Identification of interventions that are effective and sustainable in different geographic, economic and cultural settings should be the focus of future.

SYNERGIC 2.0 TRIAL

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- 31 scientists involved in SYNERGIC 2 Trial
- 550 participants being recruited
- 8 Canadian Cities participating
- $218 billion projected savings in Canada's Healthcare System over 30 years

Are you 60 to 85 years old?

Do you have trouble remembering things?

Come join us!

For more information, contact (519) 685 4292 ext. 45629
or info@gaitandbrain.com

Thank you!

Gait & Brain Team

Parkwood Institute, London ON

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Munira Sultana	***Laila Zaman***
Shamim Mortuza	***Susan Muir-Hunter***
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Dr Ryota Sakurai
Australia
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Dr Alavaro Casas - Dr Nicolas Martinez

GAIT & BRAIN LAB — LAWSON HEALTH RESEARCH INSTITUTE

LAWSON HEALTH RESEARCH INSTITUTE

Weston Family Foundation

ONTARIO BRAIN INSTITUTE INSTITUT ONTARIEN DU CERVEAU

CIHR IRSC
Canadian Institutes of Health Research Instituts de recherche en santé du Canada

Ontario
MINISTRY OF RESEARCH & INNOVATION

Canadian Consortium on Neurodegeneration in Aging.
The Canadian Component of CIHR's International Collaborative Research Strategy for Alzheimer's Disease.

1878
Western

St JOSEPH's HEALTH CARE LONDON