NMRC AWARDS CEREMONY AND RESEARCH SYMPOSIUM 2016
24–25 February 2016
International Convention & Exhibition Centre
Raffles Boulevard Suntec City, Singapore

DESIGNING AND CONDUCTING PRIMARY AND SECONDARY PREVENTION TRIALS OF AGEING-RELATED DISORDERS IN THE COMMUNITY

TZE- PIN NG (MD)
Gerontology Research Programme, Departmentof Psychologcial Medicine, Yong Loo Lin School Of Medicine, National University Of Singapore

Primary and Secondary Prevention Trials in Older Persons

DEPRESSION

- Community-Based Screening and Primary Care Treatment of Depression in Older Persons (CEPIS Trial)

FRAILTY

- Frailty Intervention Trial (FIT)

DEMENTIA

- Insulin Sensitization Intervention Trial in Primary Care Patients with Pre-Diabetes and Diabetes and Mild Cognitive Impairment

Discussion Points

- Scientific and Experimental Design Issues
- Ethical and Regulatory Issues
- “Trials and Tribulations”

CEPIS (Community-based Early Psychiatric Intervention Strategy) Trial

- Pragmatic Trial:
- Screening of depression among older persons in the community and primary care treatment by private general practitioners

CEPIS Randomized Controlled Trial

- Clinical Trial Registration NCT00430404)
- Objective: To evaluate the feasibility and efficacy of collaborative care for the primary care treatment of late life depression in Singapore
- Hypothesis: collaborative care is more effective than usual care in reducing depressive symptoms in the primary care setting

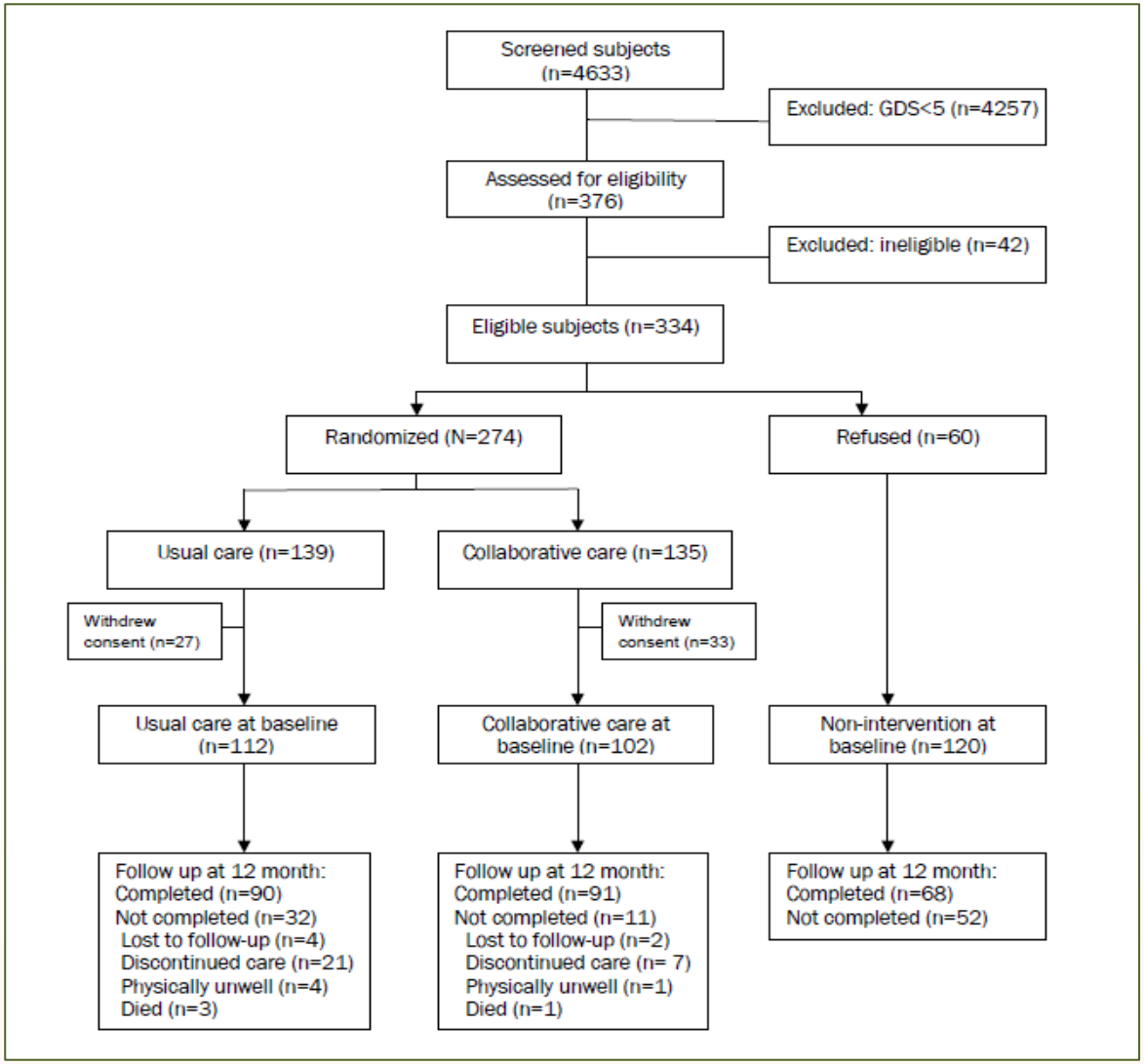
CEPIS Paradigm

- Setting: Innovative program of community-based outreach, screening and primary care aimed at improving access and treatment for depression among older persons
- CEPIS program:
- Neighborhood outreach through social service and activity center portals,
- Routine screening of depressive symptoms,
- Individual psychoeducation by community nurses to accept treatment,
- Primary care treatment by general practitioners (GPs) in neighborhood private practices.
- Elderly individuals were screened in 42 senior activity centers, 18 special needs services (day care and rehabilitation), 12 sheltered homes and 4 nursing homes

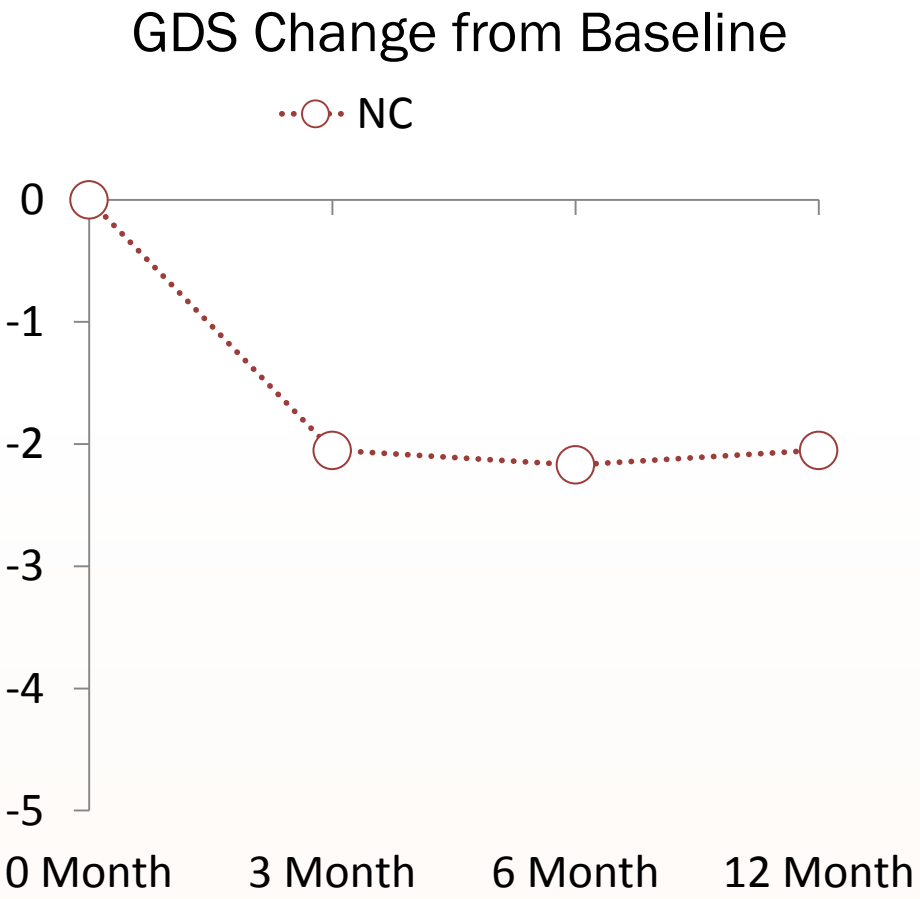
CEPIS Paradigm

- May 2007 to April 2008
- 4,633 individuals aged 60 or older were screened for depressive symptoms using the Geriatric Depression Scale (15-items GDS),
- 376 participants with GDS ≥5
- Exclusion: N=42, Alzheimer's disease, post-stroke and other dementias, mania, psychosis, alcohol abuse, other psychiatric disorders, recent three month psychiatric treatment, suicidality, and severe cognitive impairment (MMSE<18), and
- 120 participants refused referral for GP treatment.
- Remaining participants were randomized to either usual care (N=112) or collaborative care (N=102)

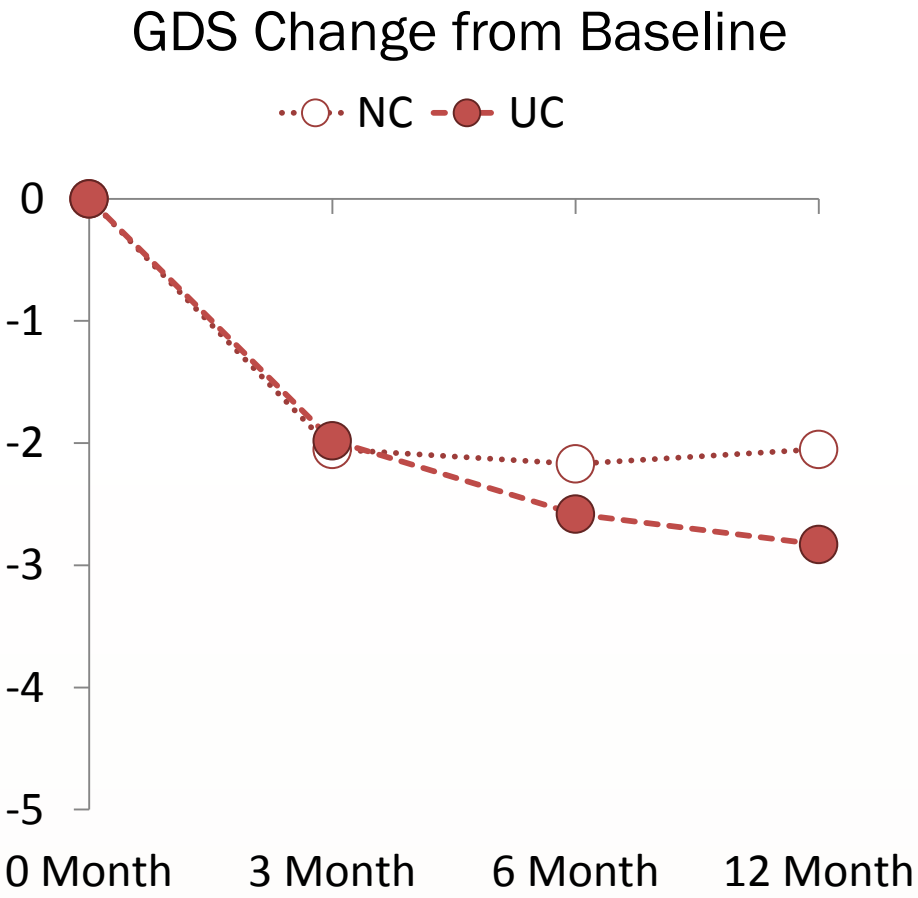
CEPIS CONSORT Flow Chart



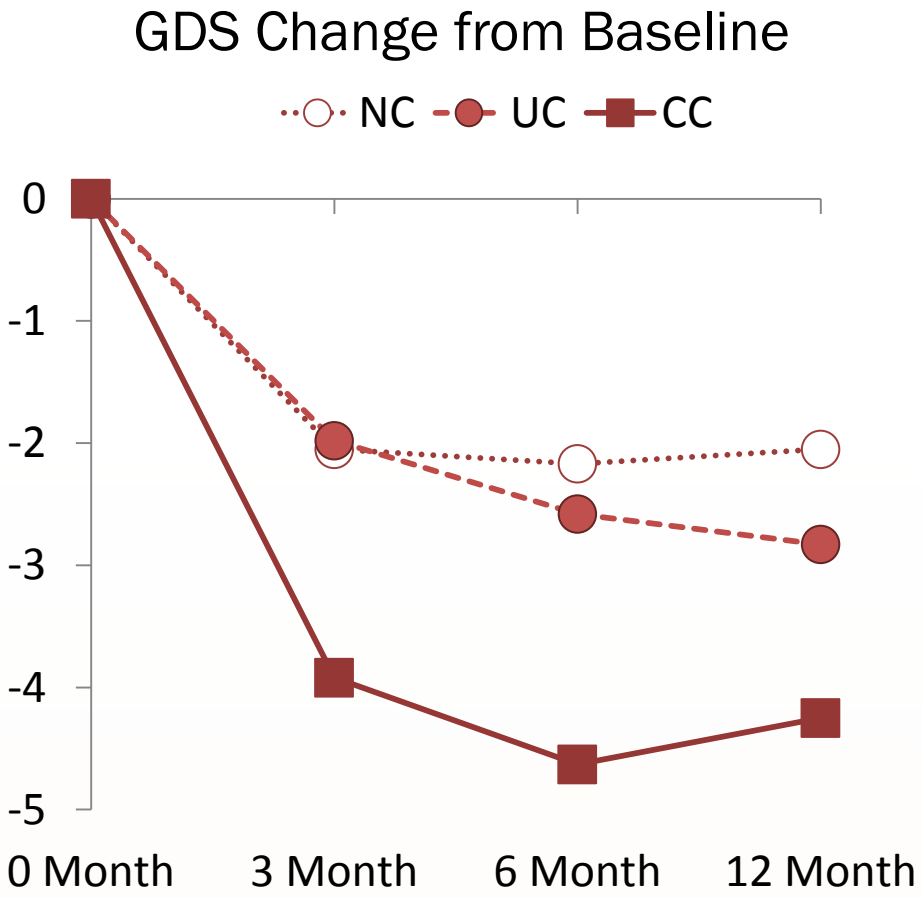
CEPIS Depression



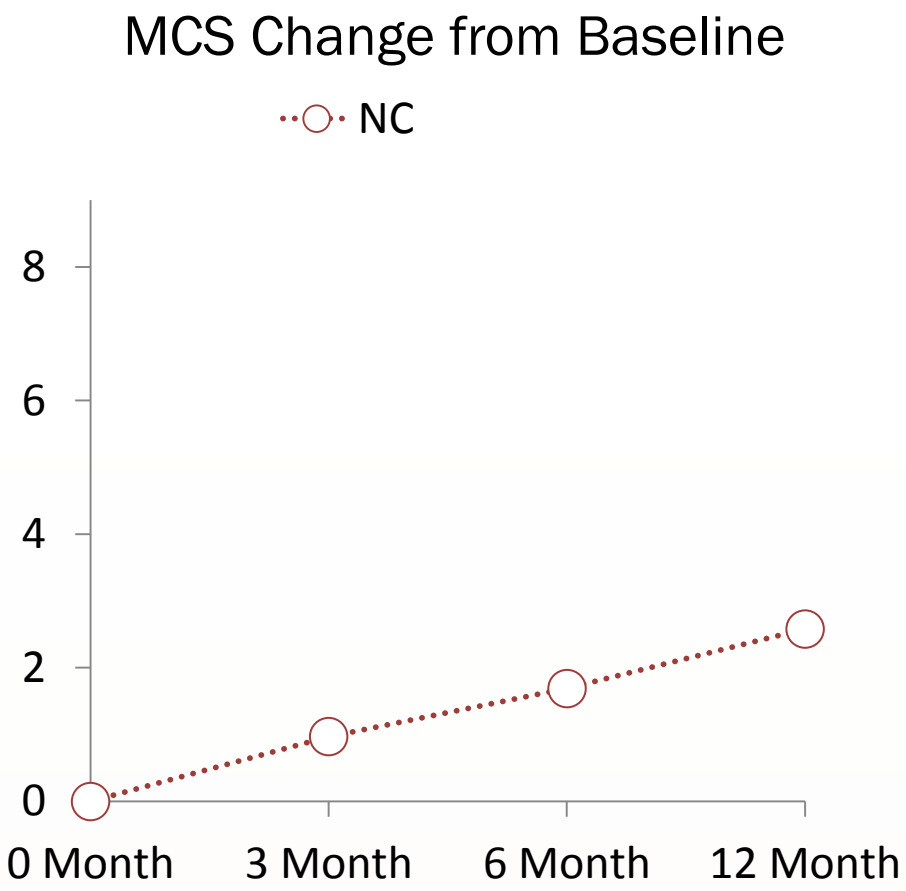
CEPIS Depression



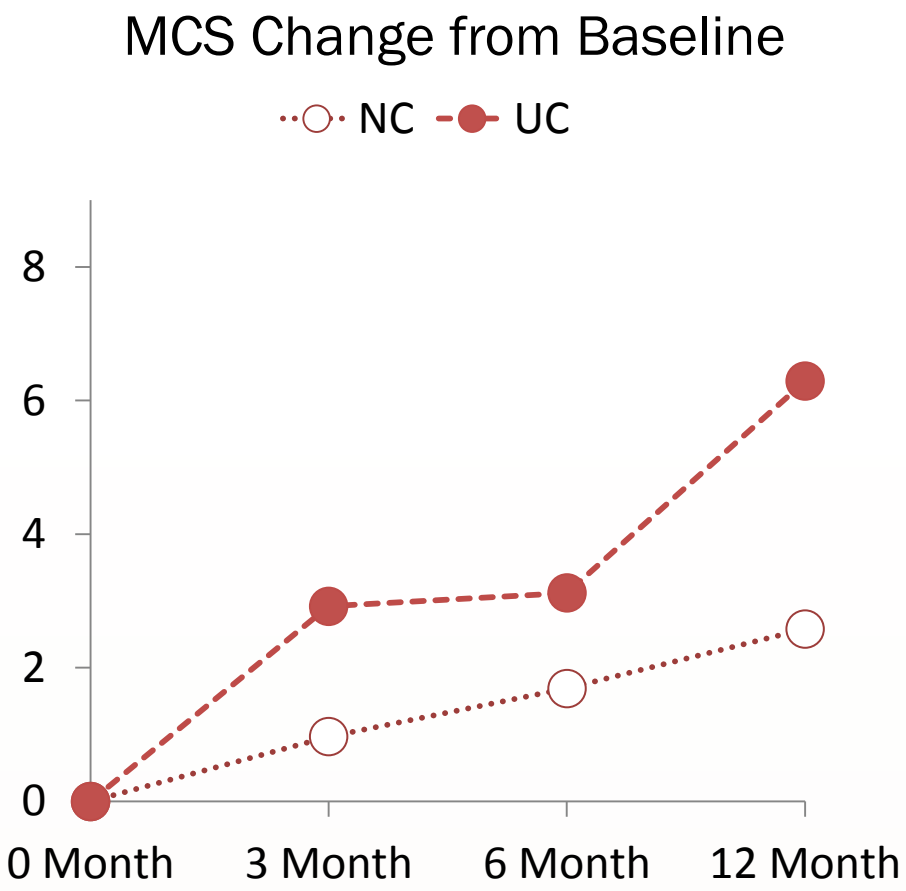
CEPIS Depression



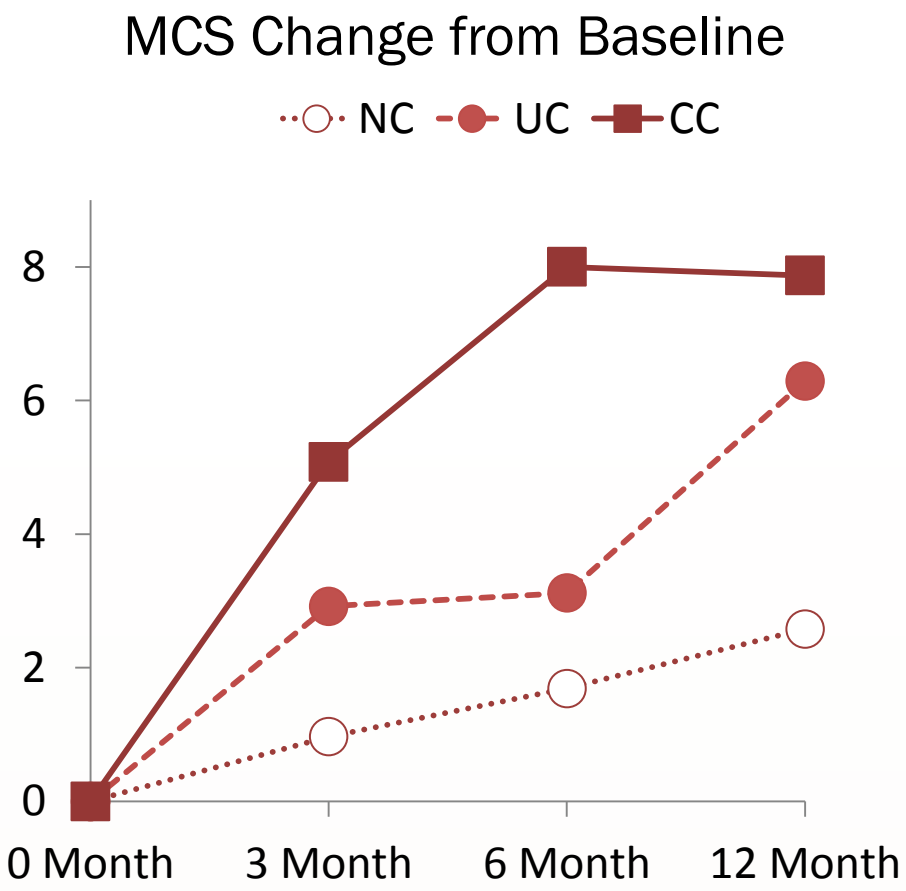
CEPIS Quality of Life



CEPIS Quality of Life



CEPIS Quality of Life



Discussion Points - 1

- Demonstrates that collaborative care is effective for primary care treatment of older persons with depression in Singapore
- Supports the applicability of the collaborative care model in some health care settings outside the US
- It is feasible to engage general practitioners in clinical research in Singapore
- Evaluates a package of modal interventions

Discussion Points - 1

- Clinically significant effect sizes
- Collaborative care vs Usual care at 6 month: Cohen's d=0.8
- Collaborative care vs Non-receipt of Care: Cohen's d=0.96
- Collaborative care vs usual care
- Response rate: 69% vs 45%
- Remission rate: 69% vs 51%
- Absolute rate differences of 24% and 18%
- Numbers needed to treat = 4 and 5.5

Discussion Points - 1

- Primary outcomes: GDS-15 depression severity at 3M and 6M
- Secondary outcomes:
  - BDI and HDRS depression severity at 3M and 6M
  - GDS-15, BDI and HDRS measures at 12 months
  - SF-12 MCS at 3, 6, and 12 months
  - Care satisfaction at 6 months
- Study was adequately powered with 80% probability to detect at least one point difference in estimated mean GDS scores (SD 2.5) between two equal-sized groups at $P<0.05$ with 100 patients in each intervention arm.
- For HDRS scores (SD of 7 points), 80% power to detect an estimated difference of 2·5 points between the groups, statistically significant at 5%, N=120 per intervention arm.

Discussion Points - 1

- The trial could not be un-blinded
- Usual care GPs may possibly redouble their ability to assess and treat depression, albeit without case management support.
- Equal levels of depression diagnosis, anti-depressants use and specialist referrals by both UC and CC doctors suggest possible contamination effects across trial arms
- Despite this, collaborative care evidently provided better outcomes than standard usual care, possibly through the key element of case management.

Frailty Interventional Trial

- Proof of principle: Frailty is reversible

Frailty Is Reversible

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Nutritional, Physical, Cognitive, and Combination Interventions and Frailty Reversal Among Older Adults: A Randomized Controlled Trial

Tze Pin Ng, MD,[a] Liang Feng, PhD,[a] Ma Shwe Zin Nyunt, PhD,[a] Lei Feng, PhD,[a] Mathew Niti, PhD,[b] Boon Yeow Tan, MMED,[c] Gribson Chan, MSc,[c] Sue Anne Khoo, MPsych(Clin),[d] Sue Mei Chan, MHlthSc (Mgmt),[d] Philip Yap, MRCP,[d] Keng Bee Yap, FRCP(Edin)[e]

[a]Gerontology Research Programme, Department of Psychological Medicine, National University of Singapore, Singapore; [b]Performance and Technology Assessment, Ministry of Health, Singapore; [c]St Luke's Hospital, Singapore; [d]Khoo Teck Puat Hospital, Singapore; [e]Alexandra Hospital, Singapore.

Singapore Frailty Intervention Trial

NMRC Grant (1108/2007)

Clinical Trial Registration: NCT00973258

Objectives

- To evaluate the effects of physical, nutritional, cognitive, and combination interventions versus usual care control in reducing CHS Frailty score and components (body mass, muscle strength, gait speed, exhaustion and physical activity), and secondary outcomes (hospitalizations, falls and dependency in activities of daily living) among community-dwelling pre-frail and frail older persons

Hypothesis

- Nutritional, Physical And Cognitive Training Interventions effectively reduce Frailty and its adverse health consequences

Study Participants

- Recruitment: October 2009 to August 2012
- Bukit Merah and Jurong
- Target population: community-living older persons ≥65 years who were pre-frail or frail (CHS score=1 to 5)
- Inclusion criteria:
  - Aged 65 and above;
  - Able to ambulate without personal assistance;
  - Living at home.
- Exclusion criteria:
  - Significant cognitive impairment (MMSE≤23),
  - Major depression,
  - Severe audio-visual impairment,
  - Any progressive, degenerative neurologic disease,
  - Terminal illness (life expectancy <12 months)
  - Participating in other interventional studies,
  - Unavailable to participate for the full duration of the study

Singapore Frailty Intervention Trial

- Parallel group randomized controlled trial
- Random allocation to 5 intervention arms of 6 months duration each
- Follow ups at 3 month, 6 month and 12 month
- Primary endpoints: CHS frailty score
- Secondary endpoints:
  - Frailty components: body mass, muscle strength, gait speed, exhaustion and physical activity
  - Depressive symptoms
  - Cognitive function
  - Hospitalizations, falls, activities of daily living dependency

Singapore Frailty Intervention Trial (FIT)

584 community-living older persons aged ≥65 years assessed for eligibility

314 ineligible
24 declined to participate

246 pre-frail and frail without cognitive impairment (MMSE 23/24) randomized

Nutriition (N=49)	Cognitive (N=50)	Physical (N=48)	Combined (N=49)	Placebo (N=50)
10 discontinued intervention -1 clinician decision -9 refused	9 discontinued intervention -1 unable to contact -8 refused	6 discontinued intervention -6 refused	12 discontinued intervention -2 clinician decision -10 refused	6 discontinued intervention -2 clinician -4 refused

Bassline (OM) and 3M, 6M, 12M Follow Up Visits
Frailty Assessments: strength, body weight, gait speed, energy and physical activity
Depression: GDS-15
Cognition: MMSE, Rey Auditory Verbal Learning Test, Brief Visuospatial Memory Test (Revised); Digit Span, Block Design, and Colour Trails Tests
IADL, BADL, Hospitalization, SF-12 Quality of Life

Intention-to-treat analysis: N=49	Intention-to-treat analysis: N=50	Intention-to-treat analysis: N=48	Intention-to-treat analysis: N=49	Intention-to-treat analysis: N=50

Interventions

Interventions of 24 weeks duration each

1. Nutritional supplementation (N=49)
2. Cognitive training (N=50)
3. Physical training (N=48)
4. Combination intervention (N=49)
5. Control (standard care, N=50)

Physical intervention:

- Physical exercise of moderate increasing intensity tailored to individual abilities
- 90 minutes duration, two days per week, for 12 weeks
- Classes (8 to 10 participants) were conducted by a qualified trainer
- Followed by 12 weeks of home-based individualized assignments.
- Designed to improve strength and balance for older adults, according to American College of Sports Medicine (ACSM) Guidelines
- Single set of 8 to 15 repetition maximum (RM), or 60 to 80% of 10RM, starting with <50% 1RM involving 8-10 major muscle groups

- Resistance exercises, integrated with functional tasks;
- Balance training exercises (functional strength, sensory input and added attentional demands)
- At three levels of increasing demand.

Nutritional intervention

- Commercial formula (Fortisip Multi Fibre, Nutricia)
- Iron and folate supplement (Sangobion, Merck),
- Vitamin B6 and vitamin B12 supplement (Neuroforte),
- Calcium and Vitamin D supplement (Caltrate)
- Taken daily for 24 weeks
- Augment caloric intake by 20% and provide one third of recommended daily allowances (RDA) of vitamins and minerals.
- Participants were encouraged to attain the maximal tolerable energy intake to gain 0.5 kg per week.

Cognitive Training:

- First 12 weeks: two-hour weekly sessions of cognitive training designed to stimulate short-term memory, enhance attention and information processing skills, and reasoning and problem-solving abilities.
- Subsequent 12 weeks: fortnightly two-hour “booster” sessions revising cognitive skills
- Activities included learning strategies used to recall verbal and visual information, tasks such as “spot the differences”, categorical naming, and coding used to enhance attention and processing speed; and matrix reasoning exercises, mazes and tangram-like games aimed at enhancing reasoning and problem-solving abilities.

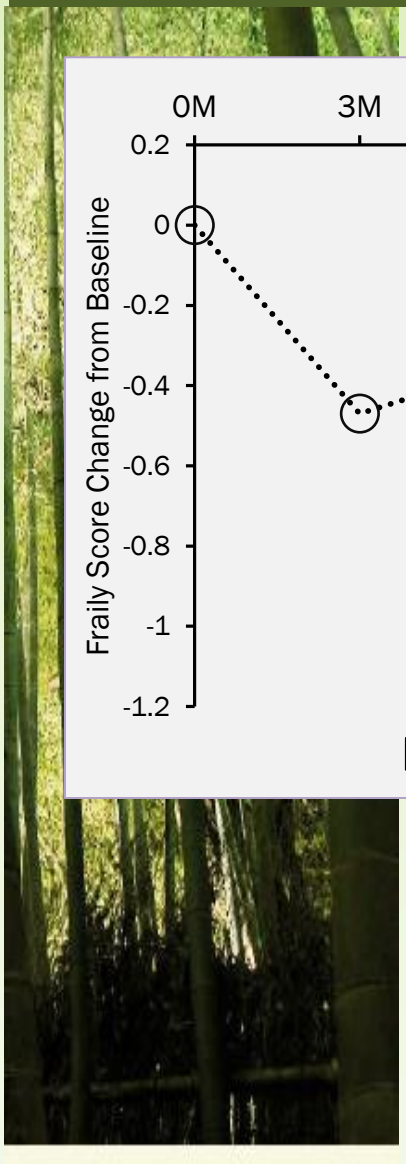
Combination intervention:

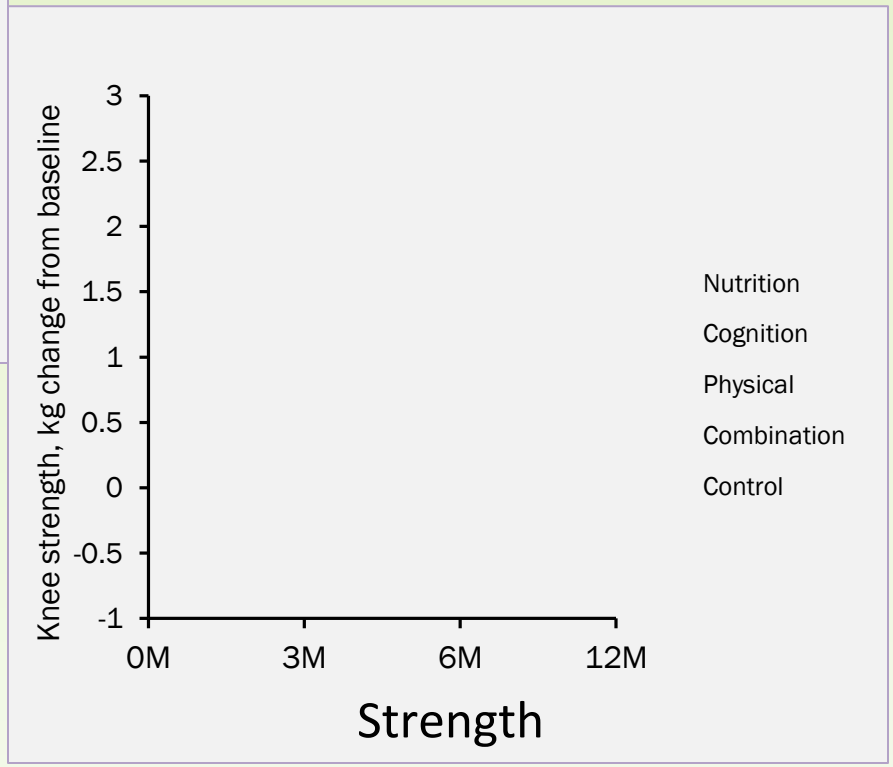
- Participants underwent all three interventions.

Control group

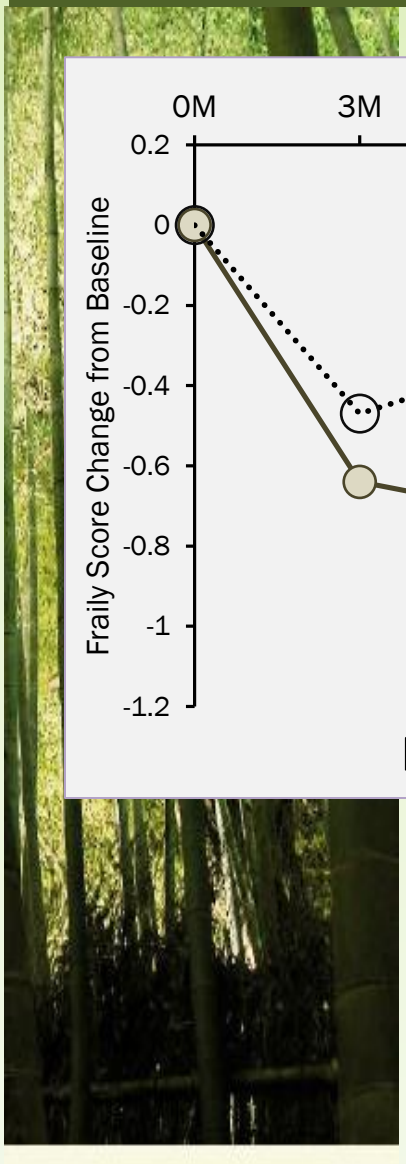
- Usual care from health and aged care services that were normally available to older people.
- Equal volume of artificially sweetened, vanilla-flavored liquid, two capsules and one tablet identical in appearance to the active nutritional supplements
- Participants were Instructed not to replace meals with the supplements
- Both the active supplement and placebo were administered by interventional nurses who had no knowledge of the participant's assignment status.

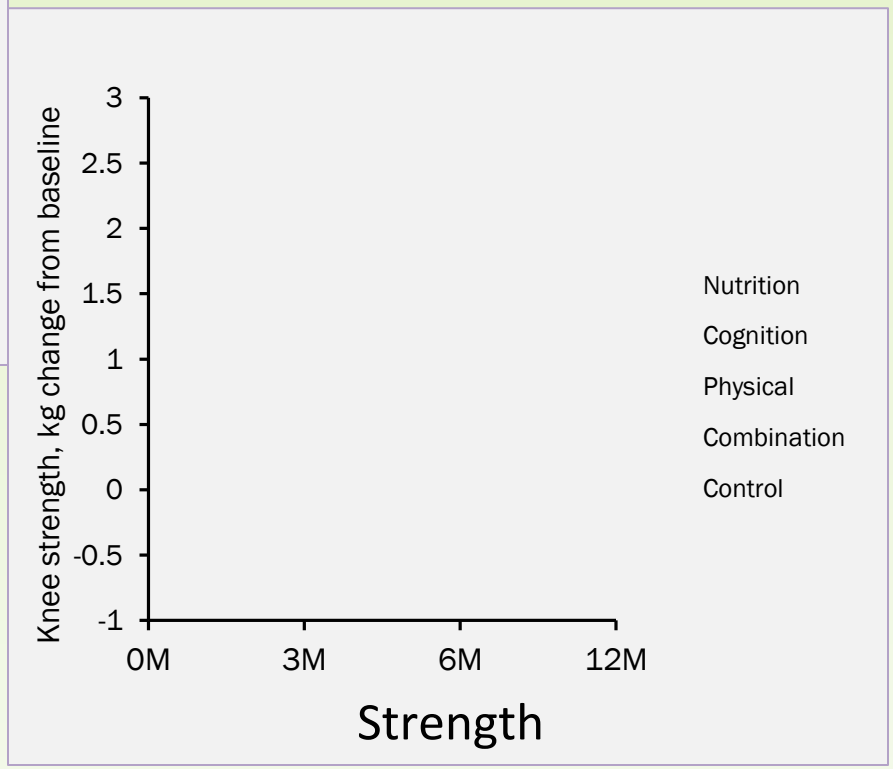
Frailty is reversible:



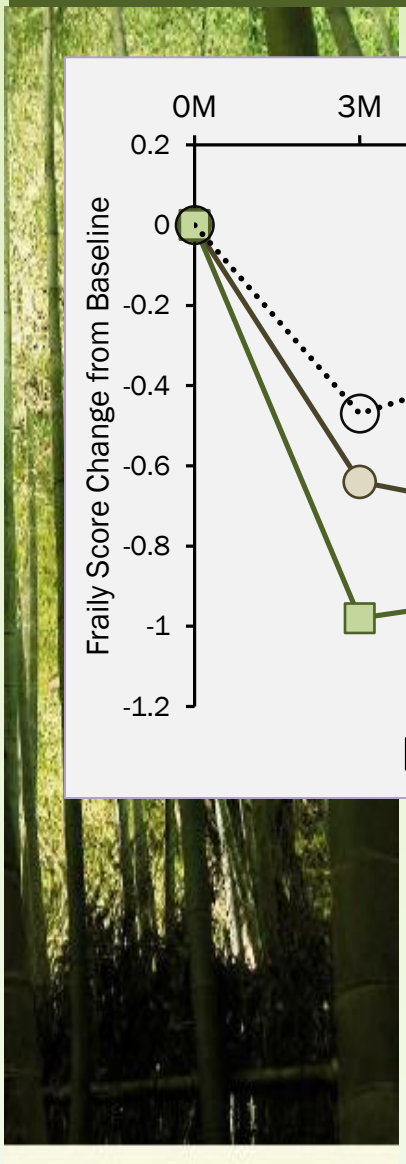


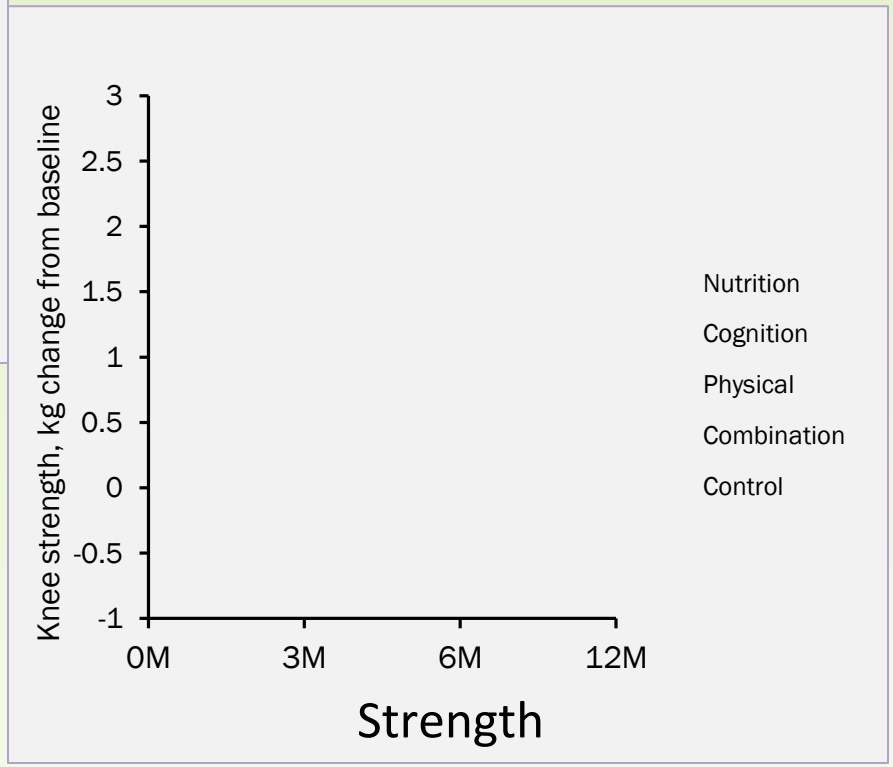
Frailty is reversible



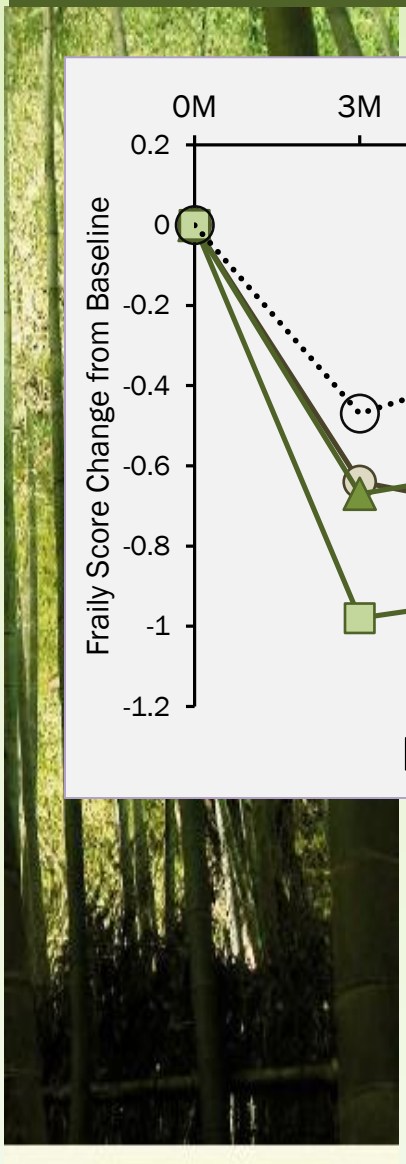


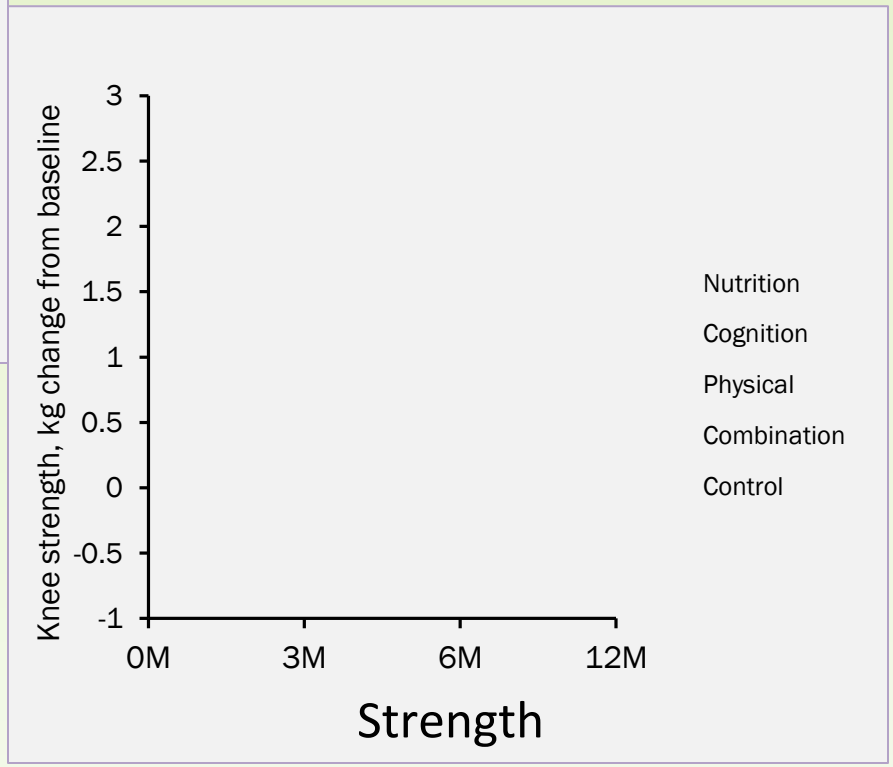
Frailty is reversible



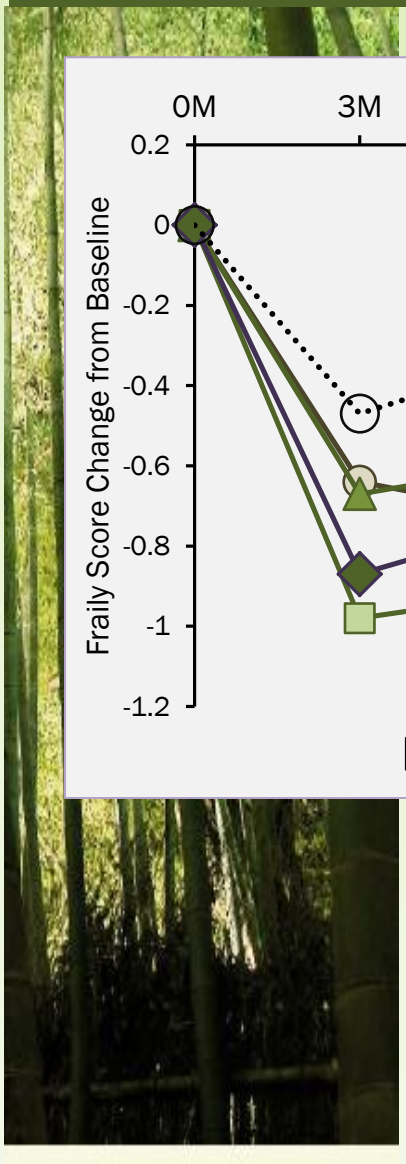


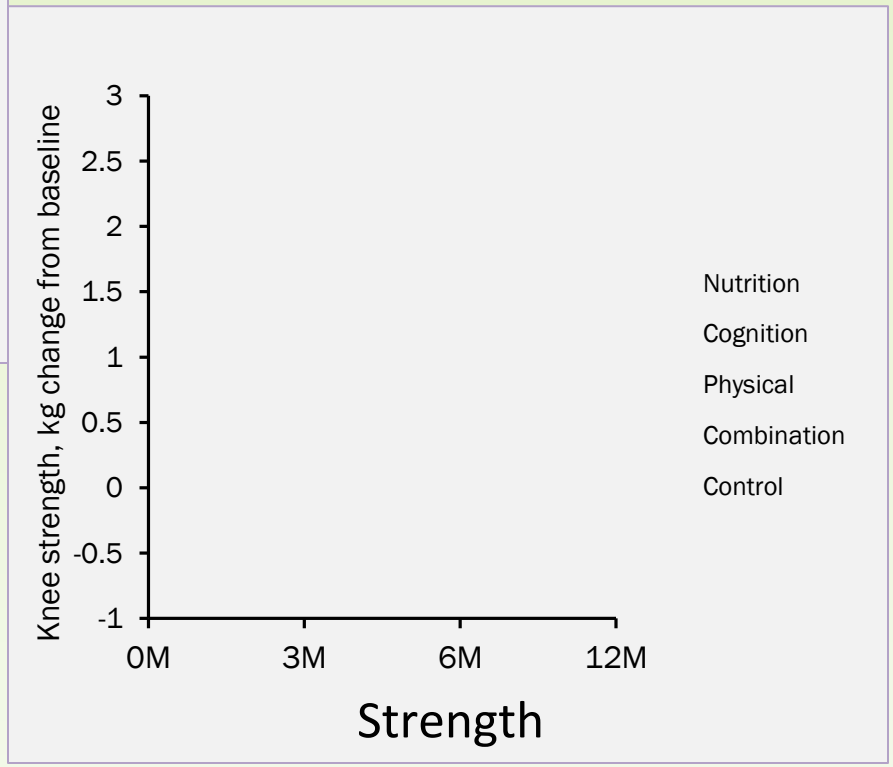
Frailty is reversible



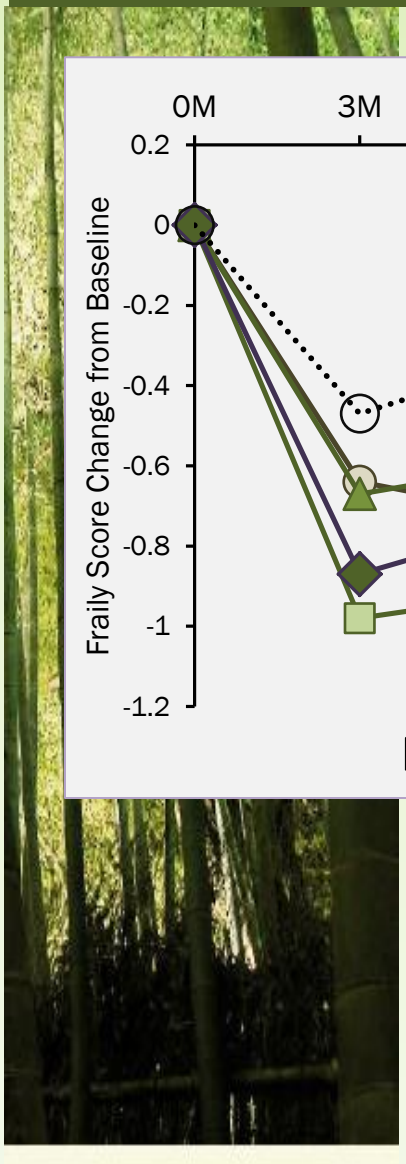


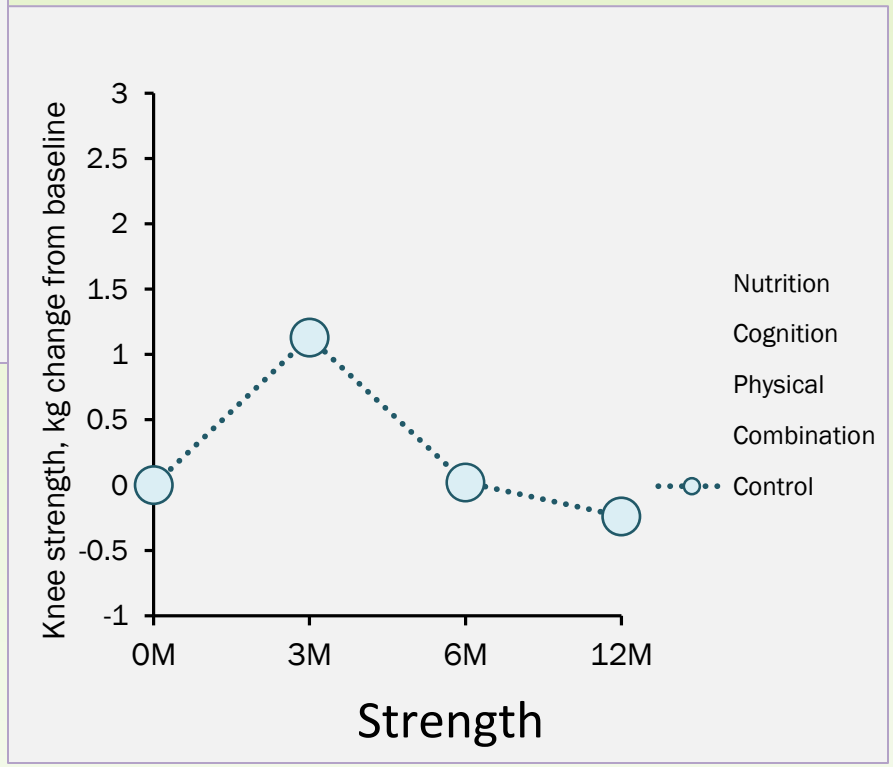
Frailty is reversible



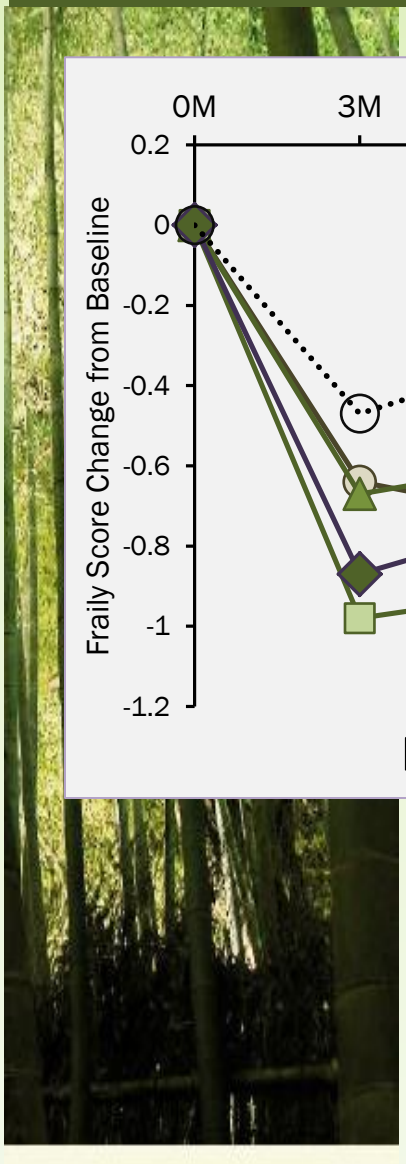


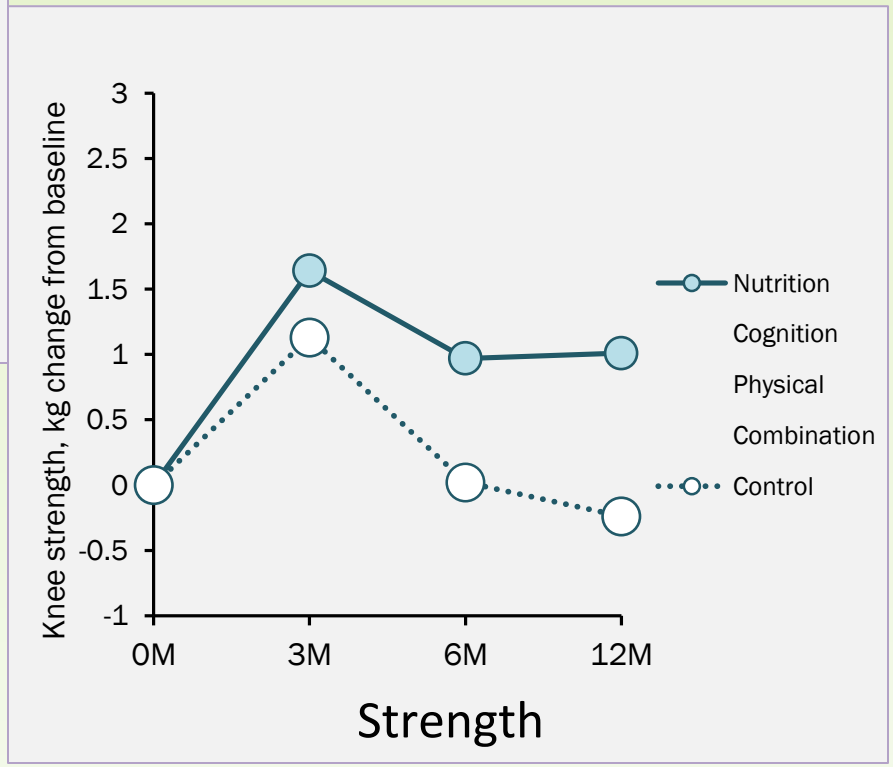
Frailty is reversible



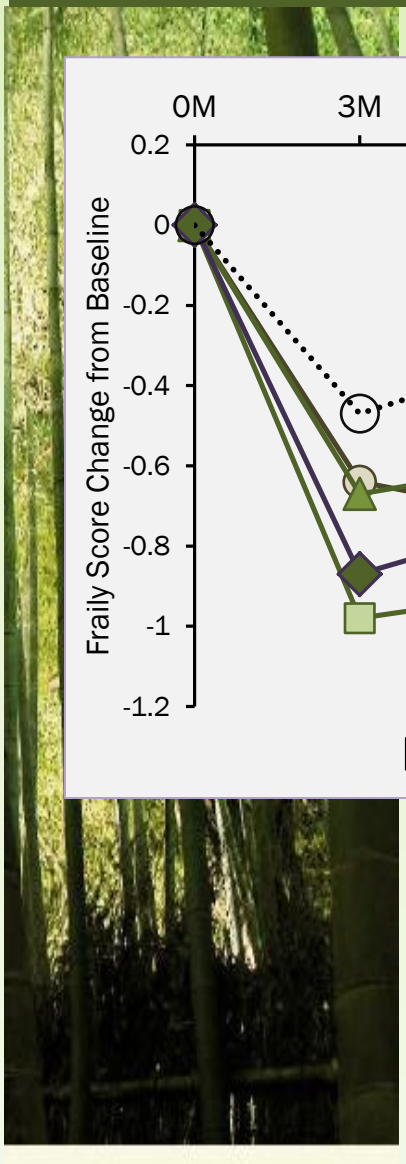


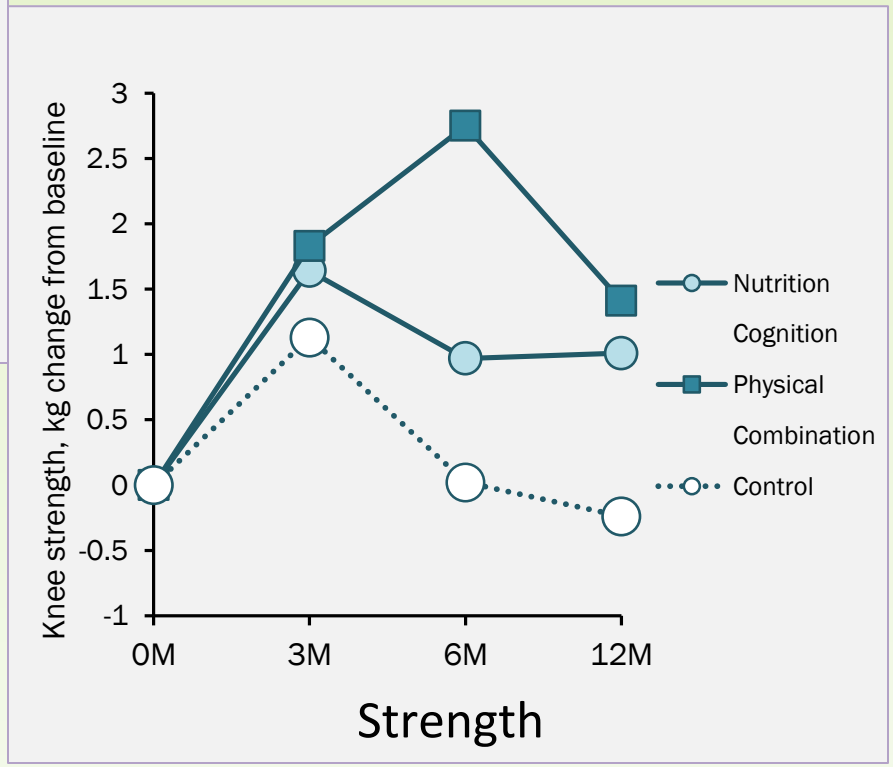
Frailty is reversible



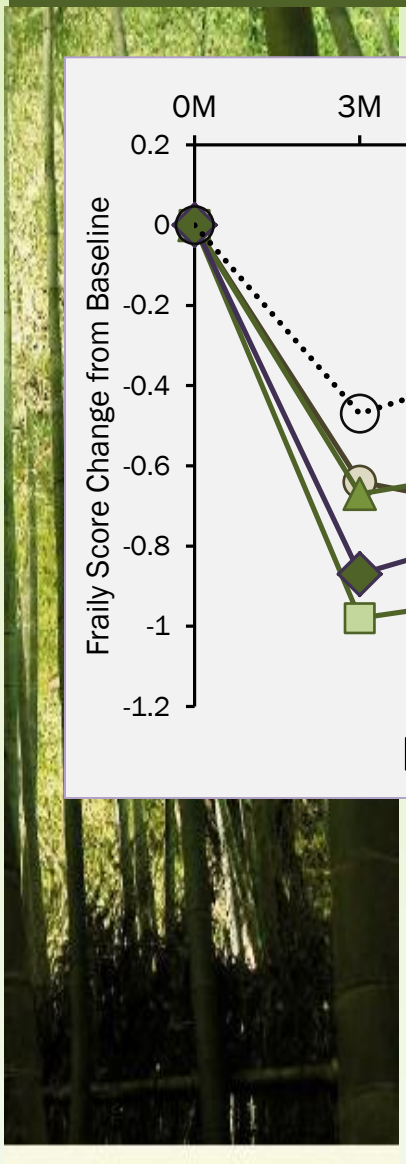


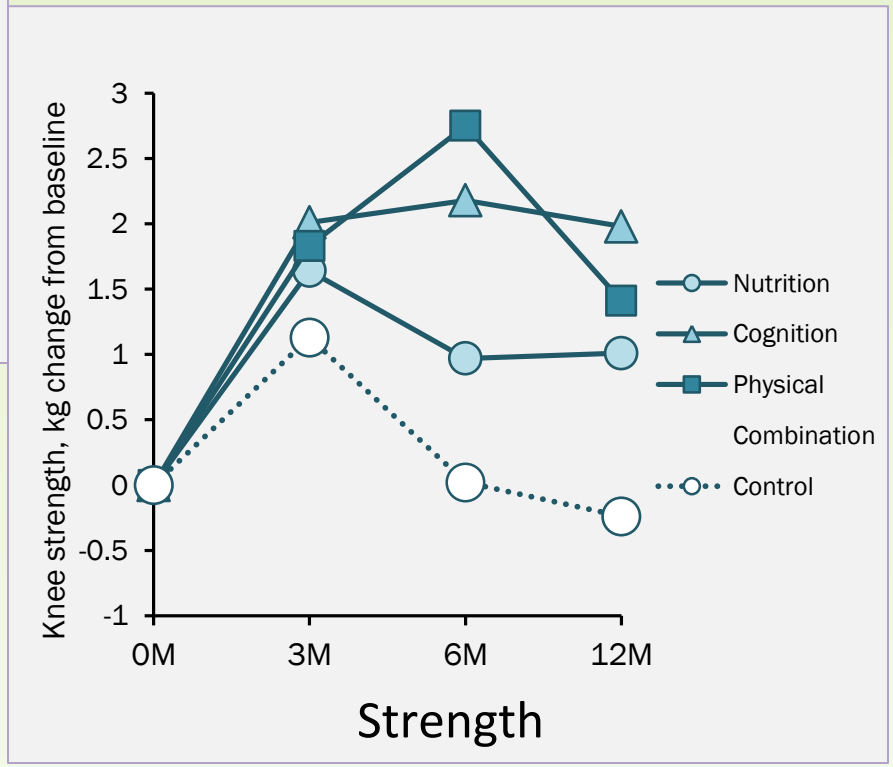
Frailty is reversible



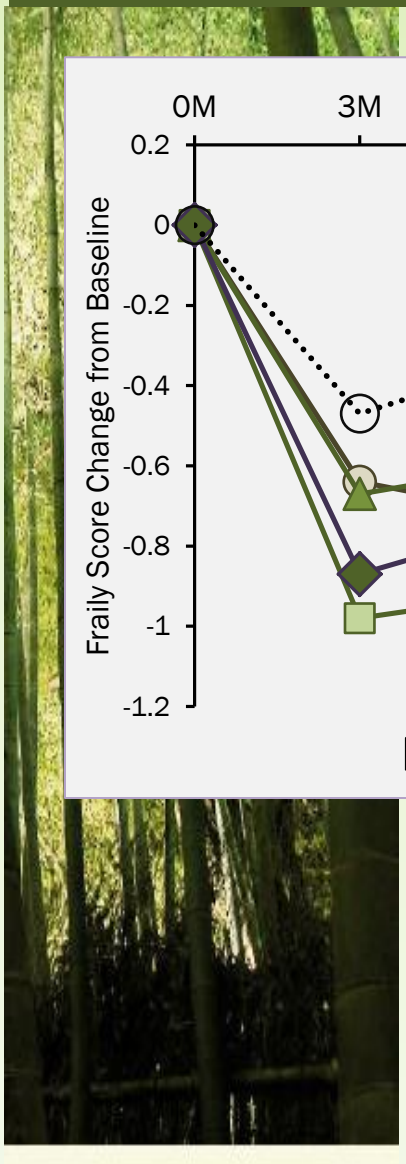


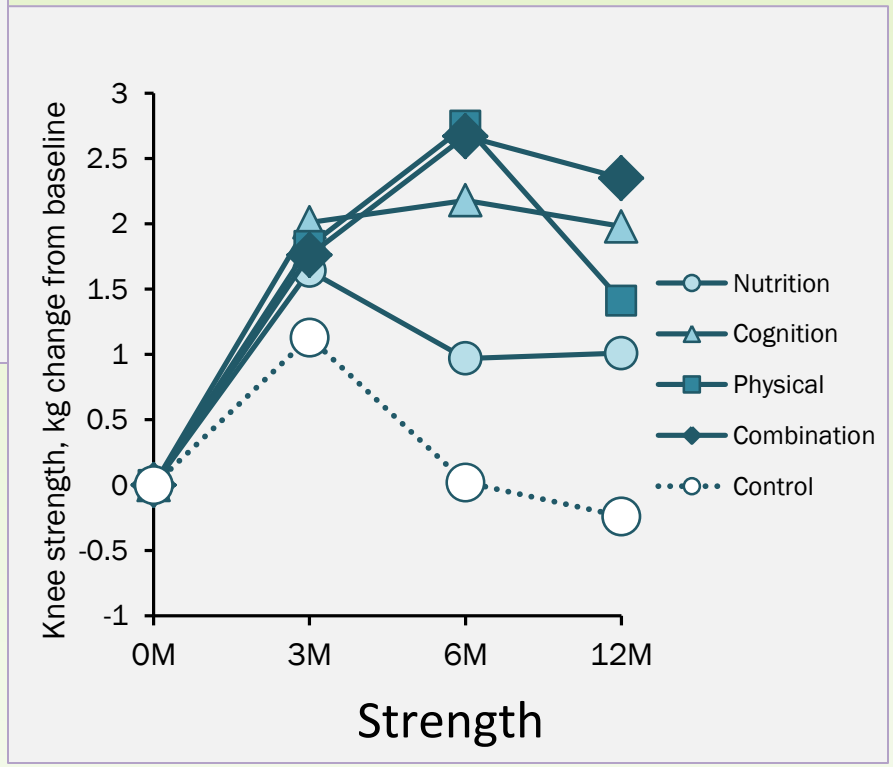
Frailty is reversible



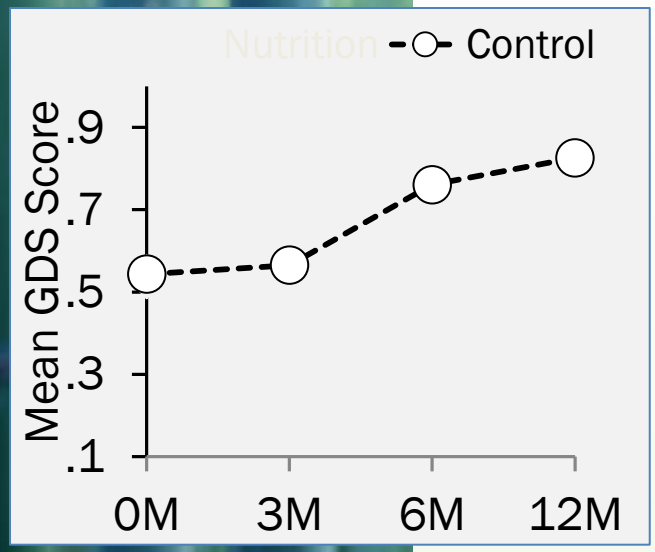


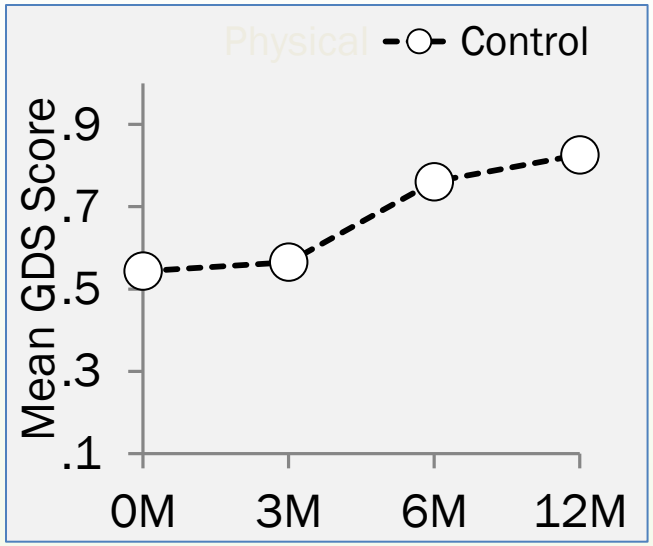
Frailty is reversible

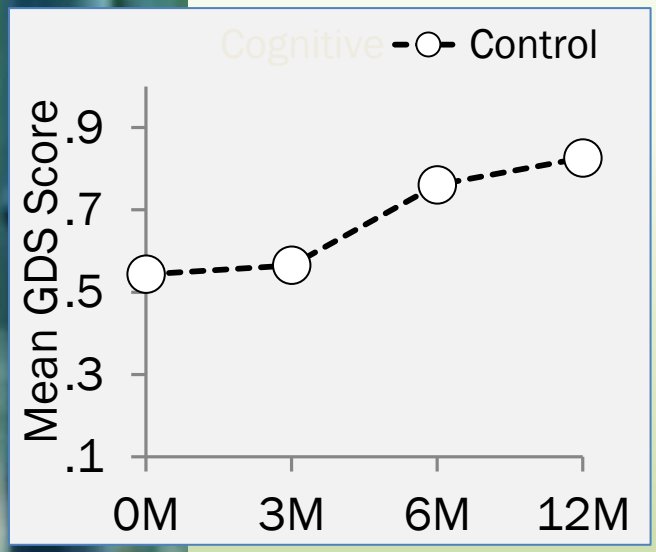


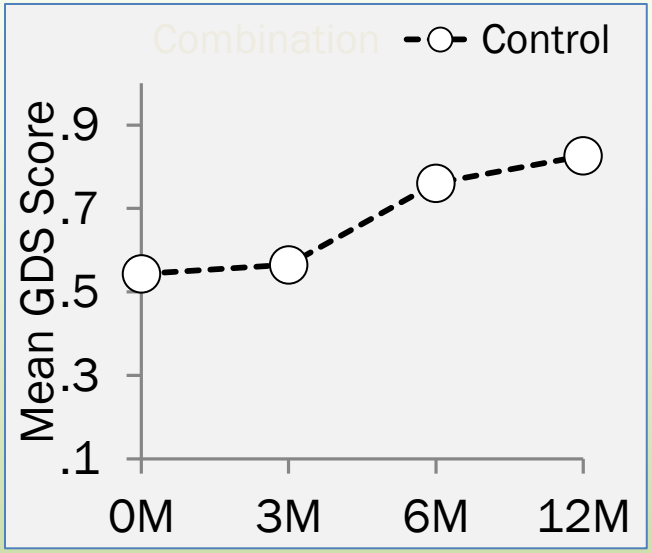


Depressive Symptoms Outcome

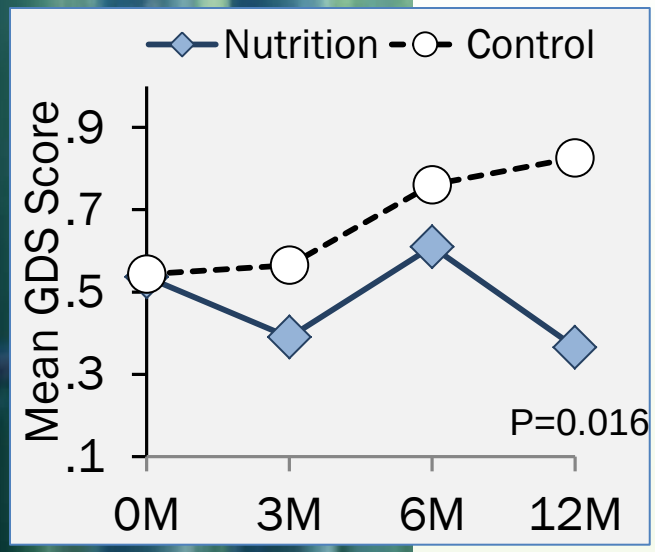


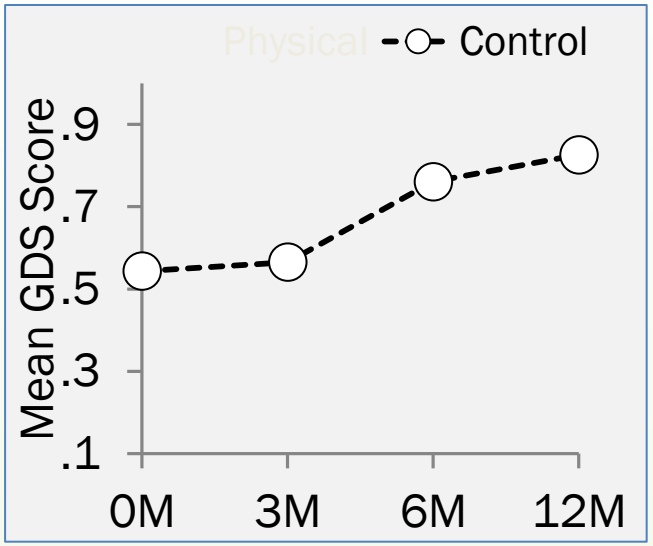


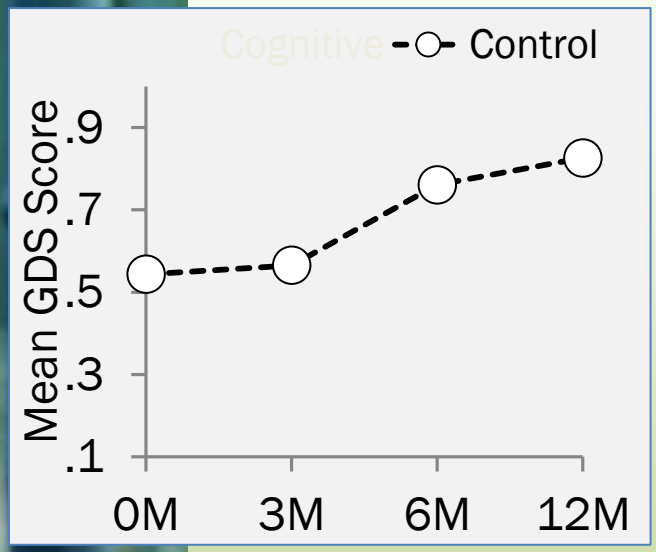


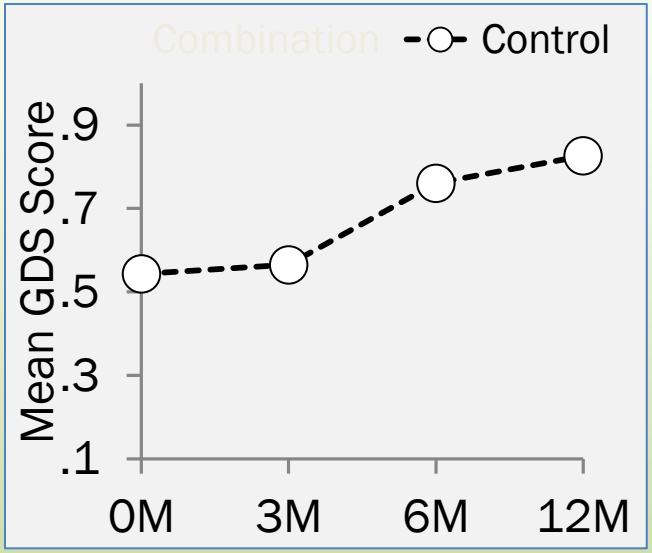


Depressive Symptoms Outcome

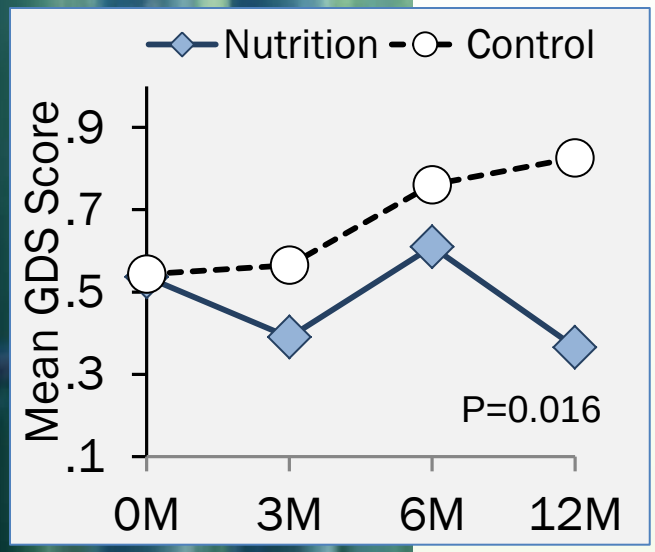


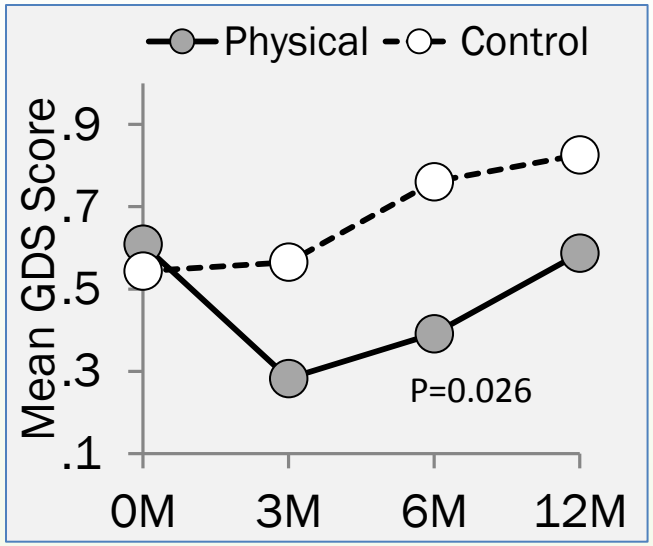


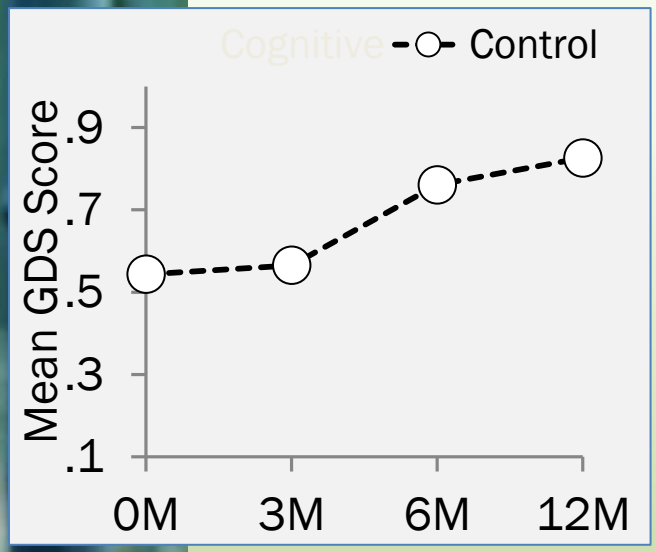


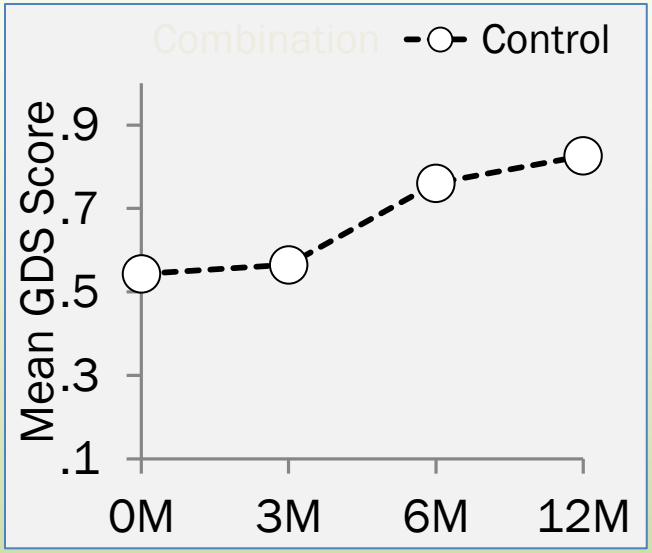


Depressive Symptoms Outcome

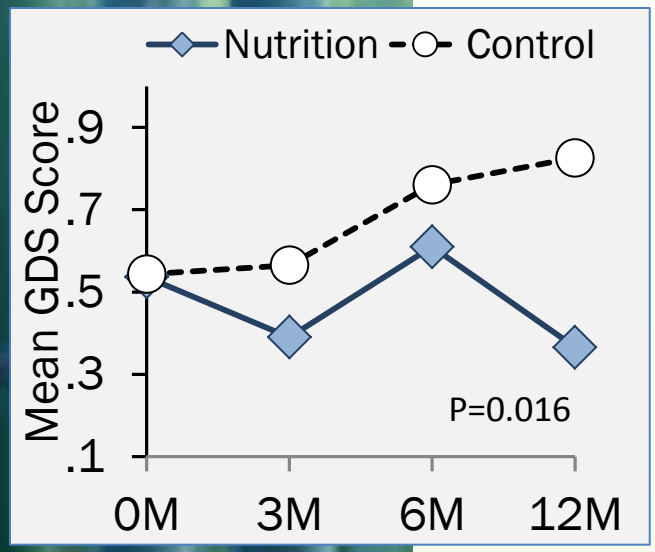


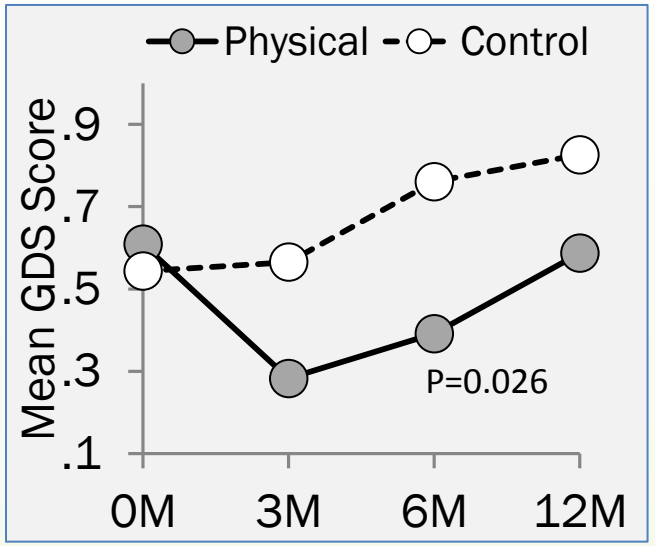


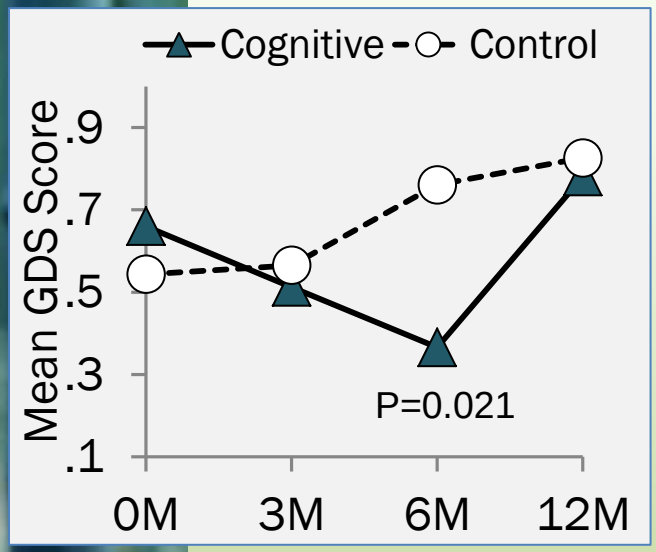


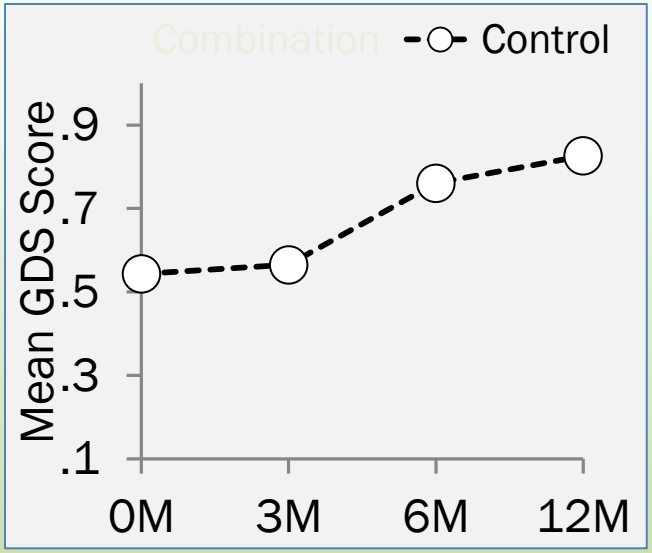


Depressive Symptoms Outcome

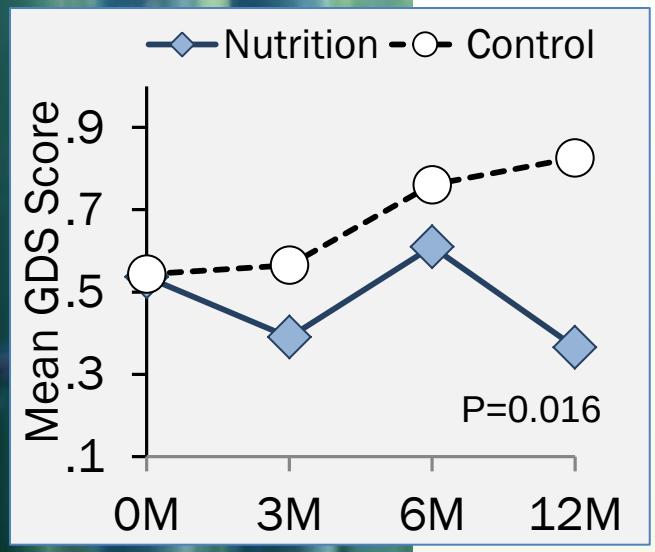


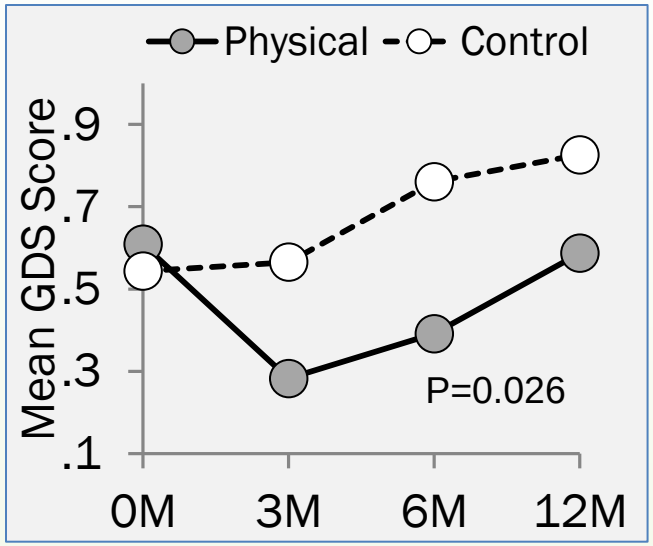


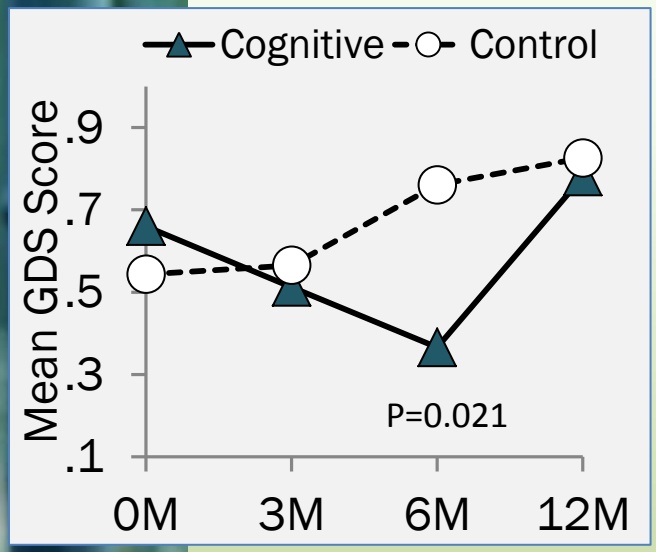


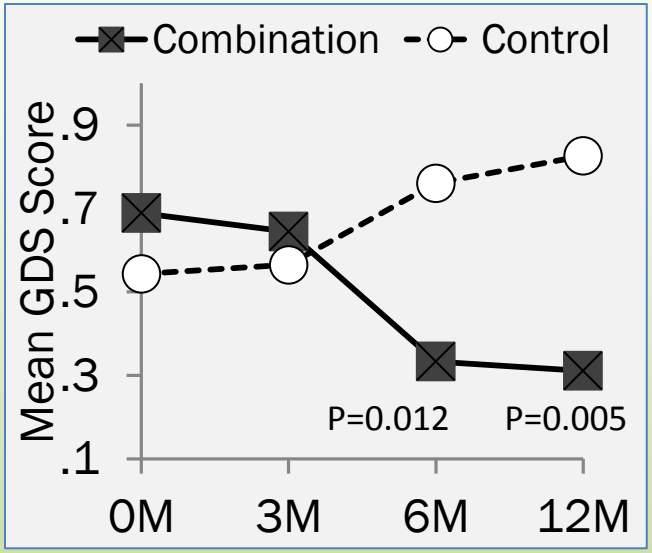


Depressive Symptoms Outcome



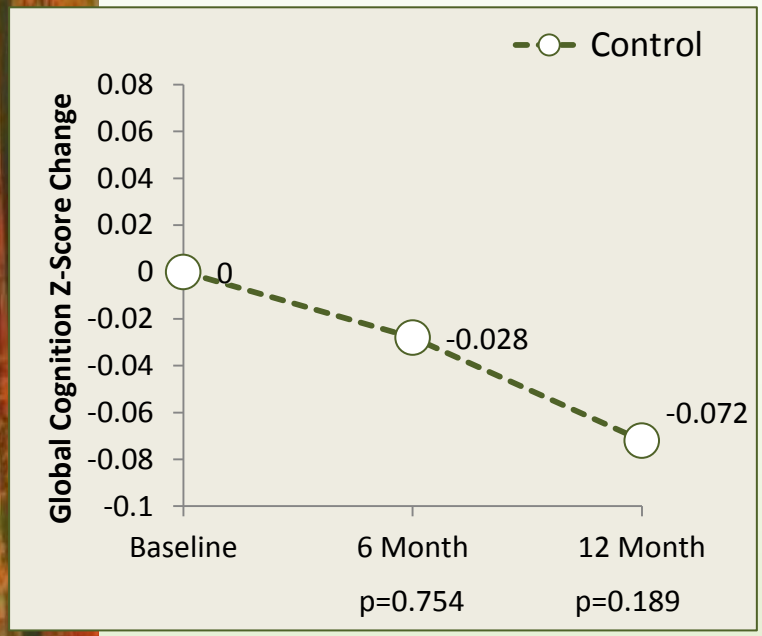




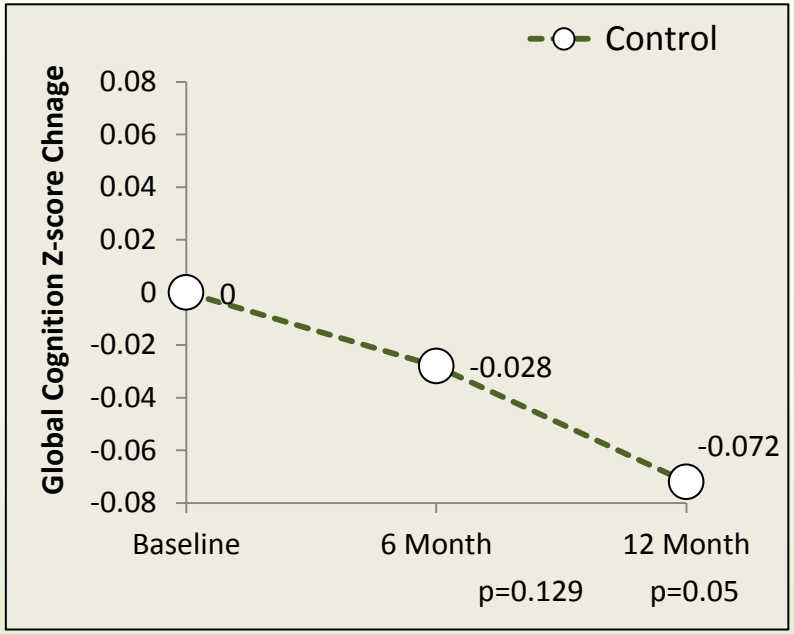


Global Cognition Outcome

Cognitive Training

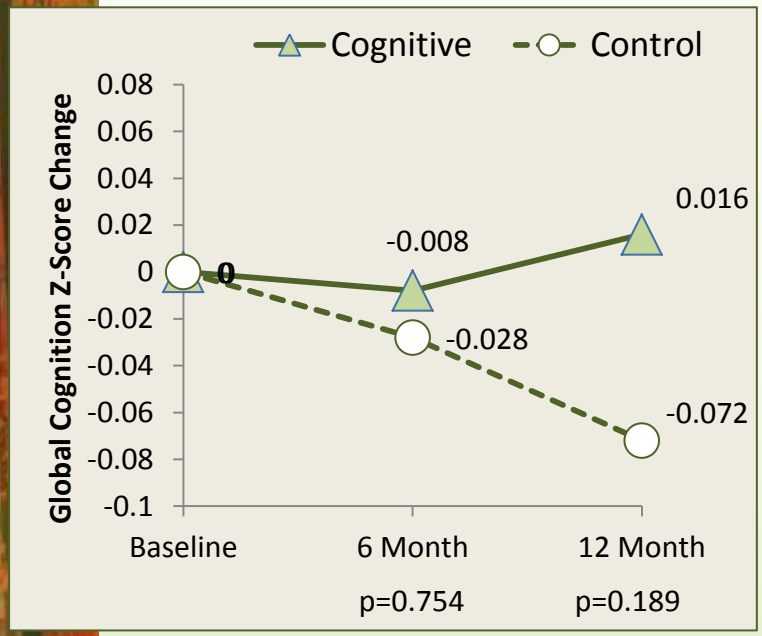


Combination

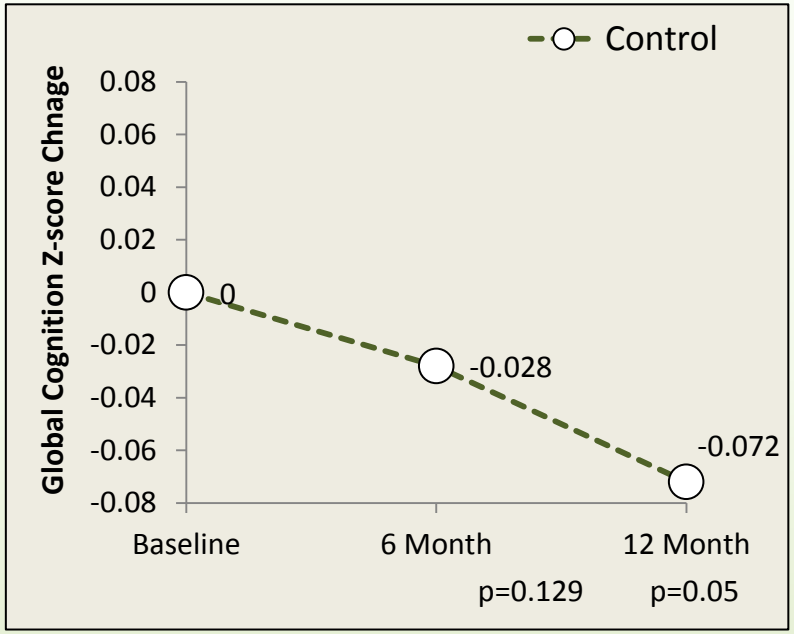


Global Cognition Outcome

Cognitive Training

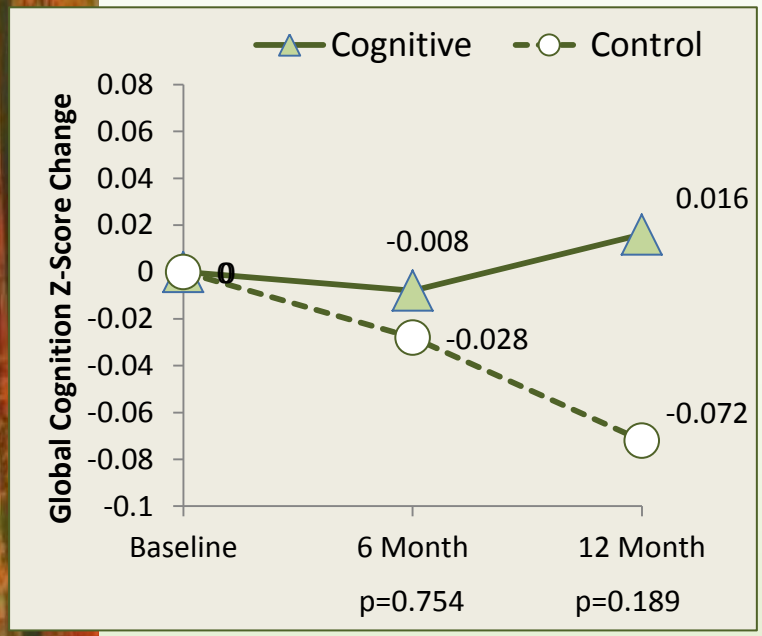


Combination

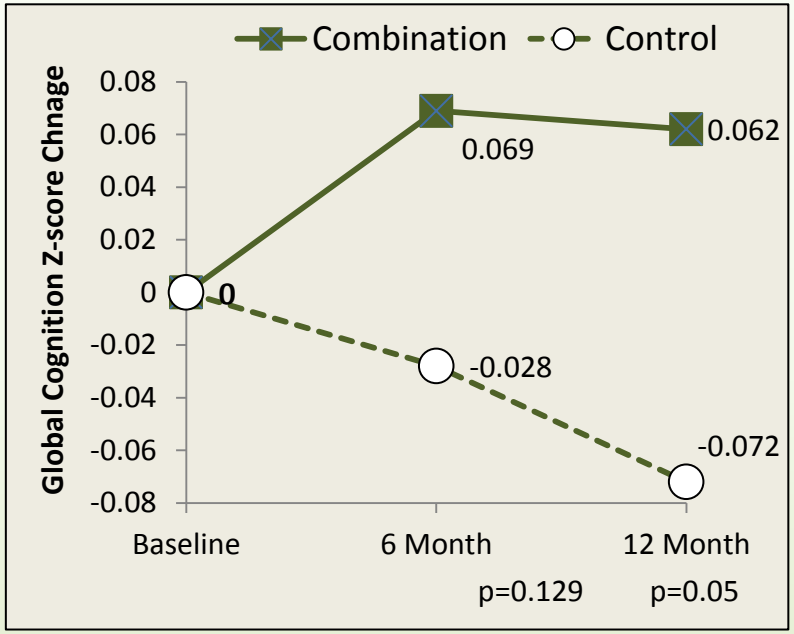


Global Cognition Outcome

Cognitive Training

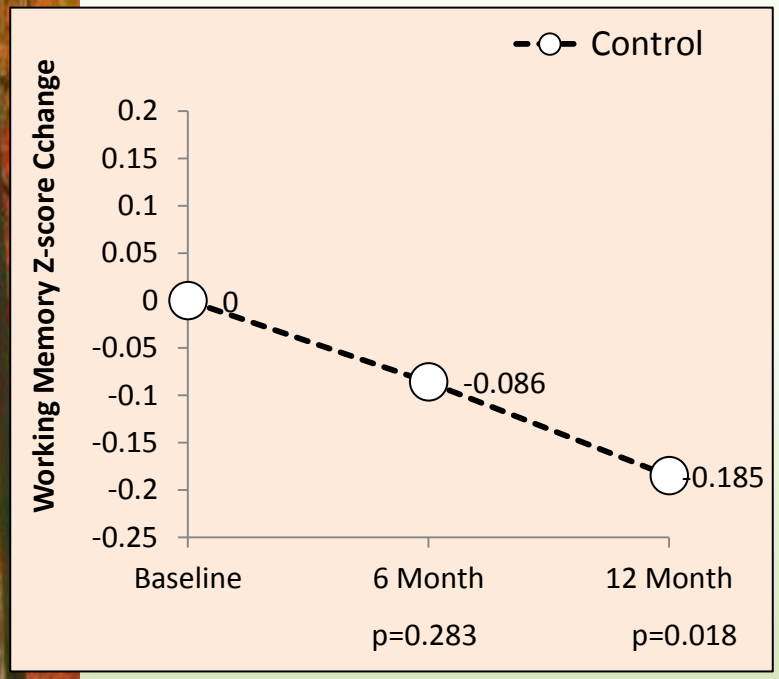


Combination

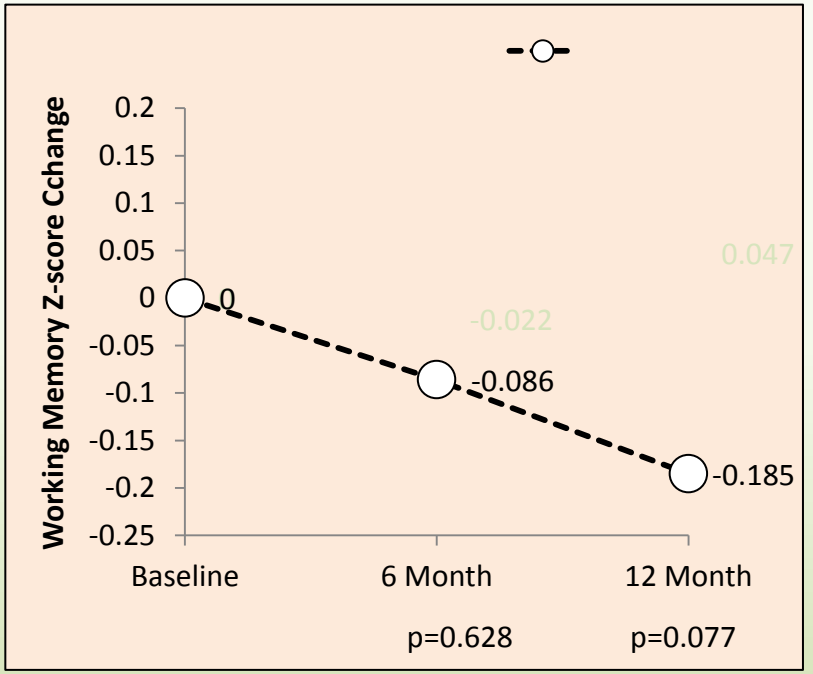


Working Memory Outcome

Cognitive Training

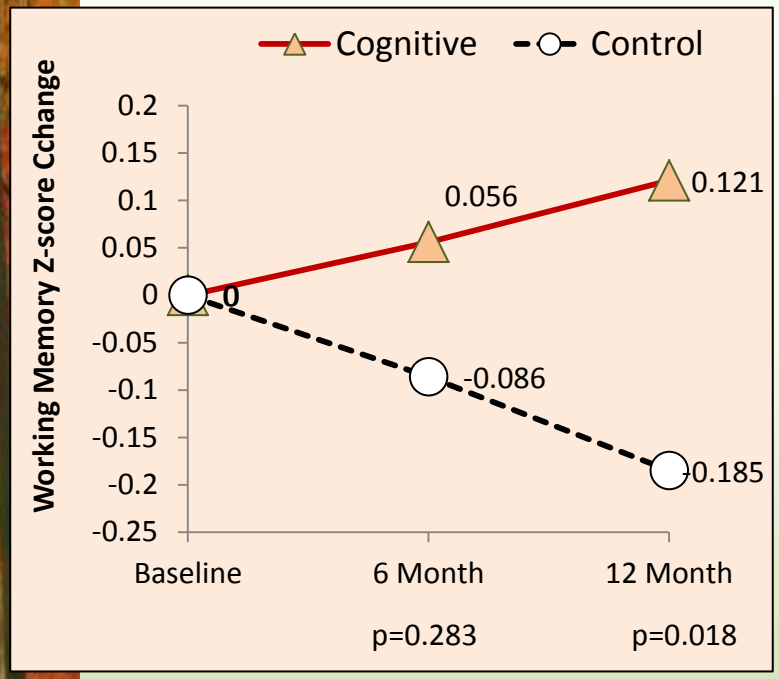


Combination

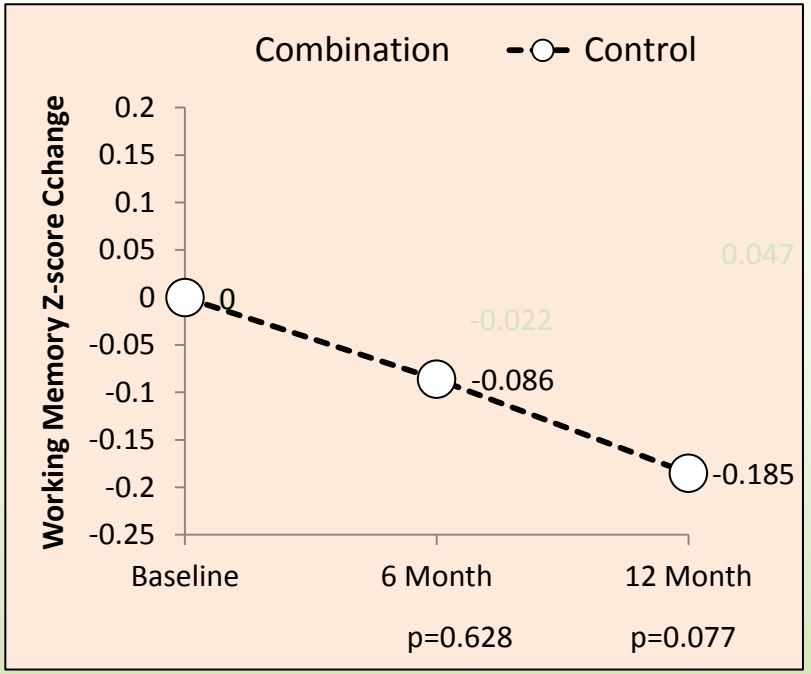


Working Memory Outcome

Cognitive Training

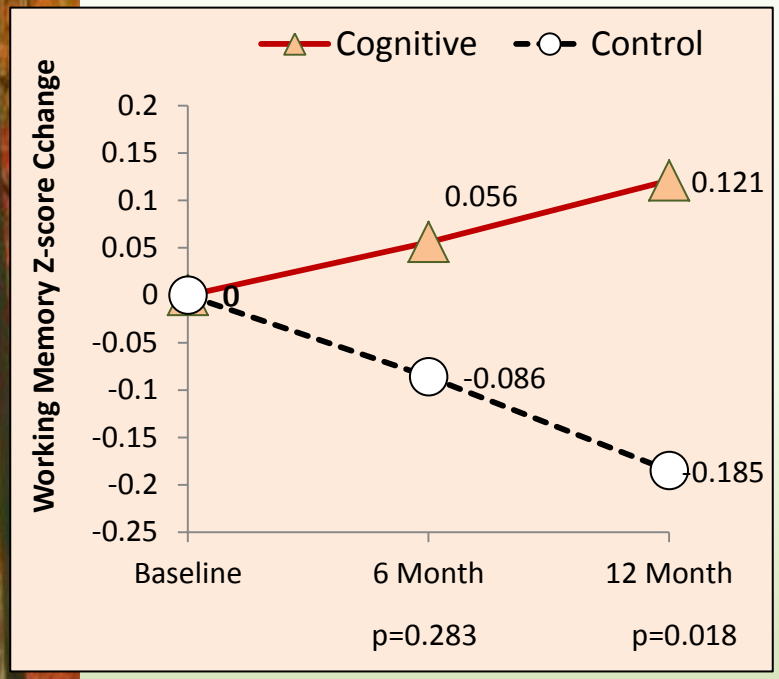


Combination

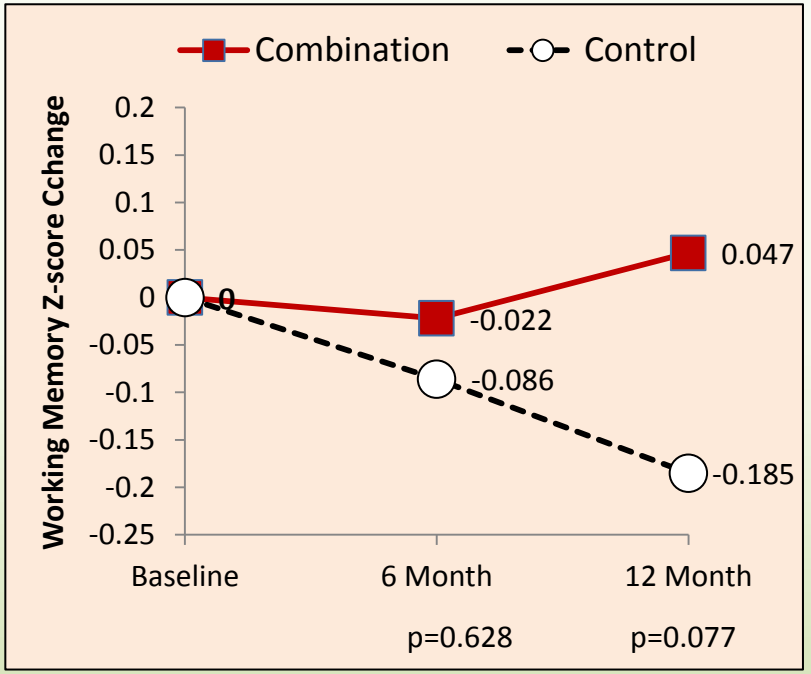


Working Memory Outcome

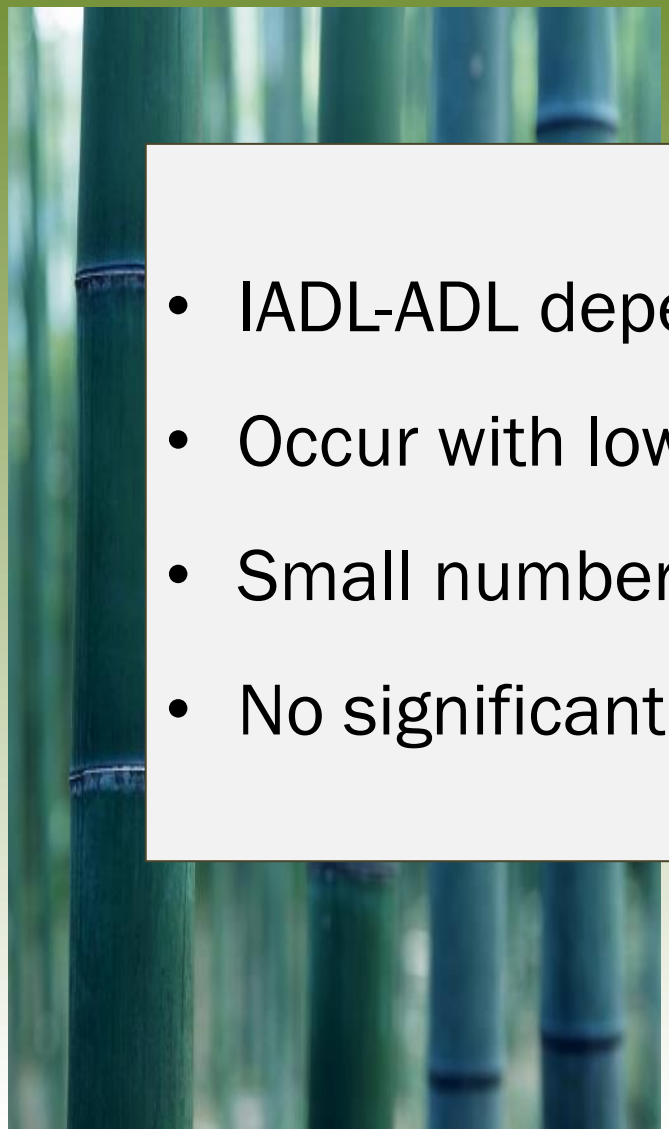
Cognitive Training



Combination



Adverse Health Outcomes



- IADL-ADL dependency, hospitalization and falls
- Occur with low frequency (2.1% to 8.7%)
- Small numbers (N=1 to 6)
- No significant differences versus control

Discussion Points - 1

- Non-diseased study population
- Functional outcomes
- Selection criteria: safe but over-restrictive
- Biological samples at baseline and follow up: investigate biological mechanisms and markers
- Multiple interventional groups
- Physical frailty was primary outcome
- A priori hypothesis testing: individual active intervention versus control
- Power and sample size: $p<0.0125$
- Depression and cognition were secondary outcomes
- Hospitalization, IADL disability and falls were low frequency events

Discussion Points - 2

- Non-drug intervention: less safety concerns
- Recruitment of community-living elderly subjects requires good community relations network
- Usual Care Control was sub-optimal
- ‘Purity’ of interventional modality is difficult to achieve

Trials and Tribulations

- Under-budget
- Delayed start-up
- Slow recruitment

Acknowledgement

- The Frailty Intervention Trial was supported by a grant funding from the National Medical Research Council. Ministry of Health (NMRC/1108/2007):

  "Randomized Controlled Trial of Community-based Nutritional, Physical and Cognitive Training Intervention Programmes for At Risk Frail Elderly"

- The Singapore Longitudinal Ageing Studies (SLAS) were supported by grant funding from Biomedical Research Council, Agency for Science, Technology and Research (ASTAR): 03/1/21/17/214; 08/1/21/19/567

Acknowledgement

Thanks for support in kind:

- Geylang East Home for the Aged
- Presbyterian Community Services
- Thye Hua Kwan Moral Society (Moral Neighbourhood Links),
- Yuhua Neighbourhood Link
- Henderson Senior Citizens' Home
- NTUC Eldercare Co-op Ltd
- Thong Kheng Seniors Activity Centre (Queenstown Centre)
- Redhill Moral Seniors Activity Centre
- St Luke Eldercare Services

THANK YOU