CRITICAL APPRAISAL OF: THE LIFE RANDOMIZED TRIAL

Effect of a 24-Month Physical Activity Intervention vs Health Education on Cognitive Outcomes in Sedentary Older Adults

Wednesday 16 December, 1-2pm, Library room 4

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PLAN

1. Summary of study
2. 10 Questions for critical appraisal
3. Conclusions
4. Discussion
5. Questions

SUMMARY OF STUDY

- Objective: To find out if a 24 month physical activity program results in better cognitive function/lower risk of mild cognitive impairment or dementia compared with a health education program
- Design: single-blinded randomized clinical trial
- N=1635
- Setting: 8 US centers
- Subjects: sedentary adults 70-89 years old, at risk of mobility disability, but able to walk 400m
- Intervention: (n=818) structured, moderate intensity physical activity program including walking, resistance training, flexibility exercises
- Control: (n=817) Health education program with workshops and upper body stretching

SUMMARY OF STUDY

- Intervention

- Results at 24 months:
  - Adjusted DSC task scores not different (46.26 PA vs 46.28 HE, p=0.97)
  - Adjusted HVLT-R scores not different (7.22 PA vs 7.25 HE, P=0.84)

  - "No differences for any other cognitive or composite measures seen"

  - Older(>80), less PA at baseline had better executive function composite scores vs HE (PA vs HE, P=0.01)

  - Incident MCI or dementia occurred in 98 in PA group vs. 91 in the HE group (OR 1.08, 95% CI 0.80-1.46)

- Conclusion: In sedentary older adults (in US), a 24month moderate intensity PA did not result in cognitive improvements vs. HE

1. IS THE STUDY QUESTION RELEVANT?

- Hypothesis: Physical activity for 24 months would result in better cognitive function and lower incidence of all cause mild cognitive impairment or dementia, compared to health education

- 1 in 14 adults over 65 years old have dementia
- 40% increase expected over next 12 years
- Relevant to current government initiatives to combat dementia
- Evidence based medicine

David Cameron sets out a new, long-term strategy focused on boosting research, improving care and raising public awareness about dementia.
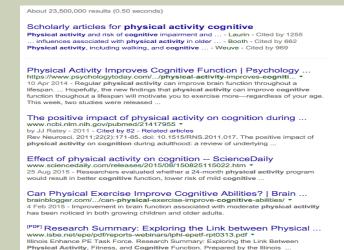
Britain will expand its efforts to combat dementia over the next 5 years, the Prime Minister David Cameron said today as he set out a new, long-term strategy focused on boosting research, improving care and raising public awareness about the condition.

Britain has emerged as the world leader in fighting dementia since 2010 with investment in research doubled, hundreds of thousands of NHS staff given specialist training and 1 million 'Dementia Friends' taking part in awareness sessions across the country.

The Prime Minister wants to build on that momentum both in the UK and worldwide. The Prime Minister's Challenge on Dementia 2020 is the next phase in the country's effort to combat the condition and includes:

2. DOES THE STUDY ADD ANYTHING NEW?

- Conclusion: The intervention (24 months of physical activity) did not result in improvements in global or domain-specific cognitive function.

- Largest, longest RCT of physical activity intervention in older adults at increased risk for mobility disability

- Mental activity and eXercise trial also found aerobic activity not better than stretching control or mental activity control on cognition

- Action for Health in Diabetes trial – no benefit of diet + physical activity on cognitive function x 8 years

3. WHAT TYPE OF RESEARCH QUESTION IS BEING ASKED?

- **Efficacy of treatment**
  - Physical activity vs. health education
- **Group/population of patient**
  - Community living participants in 8 centres in the USA
  - N=1635
  - Sedentary adults age 70-89 years old
  - At risk for mobility disability but able to walk 400m
    - *This might be a lot or a little based on your point of view*
    - *What relevance does this have towards cognitive outcomes?*

4. WAS THE STUDY DESIGN APPROPRIATE FOR THE RESEARCH QUESTION?

- **Intervention**
  - Computer-randomized assignment of intervention/control (stratified by field center and sex)
  - PA: walking, strength, flexibility, balance training
  - 2 center-based sessions a week + 3-4 home-based sessions a week
  - Center-based session progressed towards
    - 30 min walking- moderate intensity
    - 10 min lower extremity strength training + ankle weights
    - 10 min balance training + large muscle group flexibility exercises
- **Health Education (Control)**
  - 26 x weekly health education workshops(60-90 min), then
  - Monthly sessions after
  - Presentations, demonstrations, guest speakers, field trips
  - Topics: Travel safety, legal and financial issues, nutrition
  - Unlikely to increase physical activity

5. DID THE STUDY METHODS ADDRESS THE MOST IMPORTANT POTENTIAL SOURCES OF BIAS?

- Assessments done by staff 'blinded' to treatment group– avoids observer bias
- Demographics, PMH, MH, quality of life, functional limitation- self reported- at risk of reporting bias
- Physical activity measured by self-report using "Community Health Activities Model Program for Seniors questionnaire" – at risk of self-reporting bias
- Actigraph accelerometer used to measure total minutes of atleast moderate activity (>760 counts/min) over 7 days – avoids self-reporting bias
- MCI and Dementia was determined by panel of 2/8 if 3MSE was </=88 using all results and history – risk of interpretation bias

6. WAS THE STUDY PERFORMED ACCORDING TO THE ORIGINAL PROTOCOL?

- Article stated:
  - "The LIFE protocol specified DSC total score and HVLT-R immediate and delayed recall subscales mean as the 2 primary cognitive outcomes for assessing cognitive decline"
- Incident outcomes of MCI and dementia were not fully prepared for

7. DOES THE STUDY TEST A STATED HYPOTHESIS?

- H1: 24 months of physical activity results in better cognitive function and lower incidence of MCI/dementia compared to health education
- HO: 24 months of physcail activity does not result in better cognitive function and lower incidence of MCI/dementia compared to health education

- Cognitive assessment at baseline and 24 months
  - 3MSE- 100 points, global cognitive function
  - DSE- Digit symbol coding task of the Wechsler Adult Intelligence Scale, 3rd edition, psychomotor speed, attention, working memory
  - HVLR-R- Revised Hopkins Verbal Learning Test, list learning and recall taslk
  - Revised Rey-Osterrieth Complex Figure, visuospatial function(copy) and figural memory (immediate recall)
- At 24 months, also:
  - Boston Naming Test, language measure
- Trail Making Test, Part A- attention, concentration, psychomotor speed
  - Part B- executive function
  - Category fluency test

CONT'D

- Computerised cognitive function tests
  - N-back task
  - Eriksen Flanker task
  - Task switching exercise
- Center for Epidemiology Studies- Depression scores
- Self-reported disability
- Self-reported Functional Assessment Questionnaire – functional status assessment given to those 3MSE scores </=88

8. WERE THE STATISTICAL ANALYSIS PERFORMED CORRECTLY?

- Outcomes tested according to intention to treat principle
- Analysis for covariance at 24 months
- Covariate adjustment for field center, sex, and baseline value
- Computerised battery of tests- winsorised to limit extremes
- Composite scores for HVLT-R, n-back, task switching, and Flanker tasks – averaging the Z-scores from their components
- Composite scores formed by using averages of all available data
- Statistical analysis- used SAS version 9.4
- 2 sided inferences $p < 0.05$ considered statistically significant
- Targeted sample size 1600(actual 1635) expected to provide 87% power to detect mean differences between groups of 0.15 SD for cognitive tests

STATISTICAL ANALYSIS

818 Randomized to receive physical activity intervention

  800 Received physical activity intervention as randomized

    18 Did not receive physical activity intervention as randomized

      4 Due to illness or health

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704 Analysis sample for 24-mo interviewer-administered battery

  96 Missed 24-mo interviewer-administered battery

    29 Telephone or proxy interview

    26 Withdrew

    21 Died

    20 Unknown reason

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696 Analysis sample for 18- or 30-mo computer-administered battery

  104 Missed 18- or 30-mo computer-administered battery

    6 Telephone interview

    22 Withdrew

    11 Died

    5 Vision impairment

    10 Computer malfunction

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817 Randomized to receive health education intervention

  805 Received health education intervention as randomized

    12 Did not receive health education intervention as randomized (unknown reason)

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710 Analysis sample for 24-mo interviewer-administered battery

  95 Missed 24-mo interviewer-administered battery

    31 Telephone or proxy interview

    18 Withdrew

    21 Died

    25 Unknown reason

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698 Analysis sample for 18- or 30-mo computer-administered battery

  107 Missed 18- or 30-mo computer-administered battery

    1 Telephone interview

    11 Withdrew

    9 Died

    5 Vision impairment

    7 Computer malfunction

9. DO THE DATA JUSTIFY THE CONCLUSIONS?

Table 2. Adjusted Raw and z-Transformed Follow-up Cognitive Function Scores

	Mean (95% CI)			
	Physical Activity (n = 735)[a]	Health Education (n = 741)[a]	Difference Between Groups	P Value
Digit Symbol Coding task				
Raw score	46.26 (45.75 to 46.82)	46.28 (45.72 to 46.83)	−0.01 (−0.80 to 0.77)	.97
z Score	−0.003 (−0.046 to 0.040)	−0.002 (−0.045 to 0.041)	−0.001 (−0.063 to 0.060)	
Revised Hopkins Verbal Learning Test				
Immediate word recall				
Raw score	22.83 (22.52 to 23.14)	22.97 (22.67 to 23.28)	−0.14 (−0.58 to 0.29)	.52
z Score	−0.073 (−0.132 to −0.014)	−0.046 (−0.105 to 0.013)	−0.027 (−0.110 to 0.055)	
Delayed word recall				
Raw score	7.22 (7.03 to 7.41)	7.25 (7.06 to 7.44)	−0.03 (−0.29 to 0.24)	.84
z Score	−0.167 (−0.234 to −0.100)	−0.157 (−0.224 to −0.090)	−0.010 (−0.103 to 0.084)	
Composite z score[b]	−0.130 (−0.187 to −0.073)	−0.106 (−0.163 to −0.049)	−0.024 (−0.105 to 0.057)	.56
Executive function				
Percentage correct on n-back task				
1-back	83.7 (82.5 to 84.9)	82.9 (81.8 to 84.1)	0.7 (−0.9 to 2.4)	.39
2-back	53.2 (51.6 to 54.8)	51.9 (50.4 to 53.5)	1.3 (−0.9 to 3.5)	.26
Reaction time on task switching, s				
No	1.47 (1.42 to 1.51)	1.46 (1.42 to 1.51)	0.01 (−0.06 to 0.07)	.86
Yes	2.43 (2.37 to 2.49)	2.39 (2.33 to 2.45)	0.04 (−0.05 to 0.13)	.37
Reaction time on Flanker task, s				
Congruent	0.65 (0.64 to 0.67)	0.67 (0.66 to 0.68)	−0.02 (−0.03 to −0.01)	.04
Incongruent	0.73 (0.72 to 0.74)	0.75 (0.73 to 0.76)	−0.02 (−0.04 to 0)	.07
Composite z score[b]	−0.003 (−0.060 to 0.054)	−0.025 (−0.080 to 0.030)	0.022 (−0.057 to 0.101)	.59
Mean global composite z score[b,c]	−0.052 (−0.099 to −0.005)	−0.081 (−0.128 to −0.034)	0.029 (−0.038 to 0.095)	.40

Conclusion: In sedentary older adults (in US), a 24month moderate intensity PA did not result in cognitive improvements vs. HE

CONT'D

Table 3. Incident Mild Cognitive Impairment or Dementia at 24 Months

	No./Total (%)		Odds Ratio (95% CI)[a]	P Value
	Physical Activity	Health Education		
Mild cognitive impairment[b]	70/686 (10.2)	62/682 (9.1)	1.14 (0.79-1.62)	.48
Dementia[c]	28/743 (3.8)[d]	29/747 (3.9)[d]	0.96 (0.57-1.63)	.88
Mild cognitive impairment or dementia	98/743 (13.2)[d]	91/747 (12.1)[d]	1.08 (0.80-1.46)	.61

This study was not sufficiently powered for these incident outcomes.

Conclusion: In sedentary older adults (in US), a 24month moderate intensity PA did not result in cognitive improvements vs. HE

10. ARE THERE ANY CONFLICTS OF INTEREST?

- **Dr Sink had funding from:**
  - National institute on Ageing for several Alzheimer's disease cooperative studies
  - Navidea – grant funding
    - Research PET imagine ageing used in diagnosing Alzheimer's disease
- **Dr Cohen**
  - McKnight Brain Research Foundation – grant funding
- **Dr Lopez**
  - Baxter, Lilly, Grifols, Lundbeck – consultant
- **Dr McDermott**
  - Regeneron – Grant funding
    - Praluent- inhibitor antibody for familial Hypercholesterolaemia or atherosclerotic cardiovascular disease
    - *If this disease does not benefit from exercise but instead, medication, that is in the interests of this pharmaceutical company*
- **Dr Reid**
  - Eli Lilly and Co – consultant
    - Cardiovascular drugs
    - Diabetes drugs- insulin, metformin, gliptins, etc.
    - Neuroscience- antidepressants, antipsychotics, etc.
  - Bay Cove Human Services

10 QUESTIONS

- 1. Relevant? Yes
- 2. Something new? Yes
- 3. Type of research question? Re: Efficacy
- 4. Appropriate study design? Could be better
- 5. Address bias? Could be better
- 6. Study in line with Protocol? Mostly
- 7. Test the stated hypothesis? Kind of
- 8. Statistical analysis correct? Apparently
- 9. Do the data justify the conclusions? Possibly
- 10. Any conflicts of interest? Yes

DISCUSSION

- Is health education a true 'control'? Or is there an impact of it on cognitive decline?
- How reflective are these questionnaires of actual functioning in independent living?
- Cognitive function remained stable for 2 years for all participants- "We can not rule out that both interventions were successful at maintaining cognitive function"
- Was the amount of physical activity enough?
- How good was the adherence to physical activity as adherence wanes/ the gains diminish
- 2/3rds of the participants had college degrees- maybe they take longer than 2 years for cognitive decline

ANY QUESTIONS?

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