



Meeting 4

# Brain Health

**Chair: Kirk Erickson**

Members: Chuck Hillman, Rich Macko, David Marquez, Ken Powell

# Experts and Consultants

- **Consultants:**
  - David E. Conroy, Ph. D.  
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# Subcommittee Questions

1. What is the relationship between physical activity and cognition?
2. What is the relationship between physical activity and quality-of-life?
3. What is the relationship between physical activity and (1) affect and (2) anxiety?
4. What is the relationship between physical activity and (1) sleep and (2) circadian rhythms?

# Question 1

1. What is the relationship between physical activity and cognition?
  - a) Does the relationship exist across the lifespan?
  - b) Does the relationship vary for individuals with normal to impaired cognitive function (i.e., dementia)?
  - c) What is the relationship between physical activity and biomarkers of brain health?
  - d) Is there a dose-response relationship? If yes, what is the shape of the relationship?
  - e) Does the relationship vary by age, sex, race/ethnicity or socio-economic status?
  
- Source of evidence to answer question
  - Systematic Reviews, Meta-Analyses

# Analytical Framework

## Systematic Review Question

What is the relationship between physical activity and cognition?

## Target Population

People of all ages

## Comparison

People who participate in varying levels of physical activity

## Intervention/Exposure

All types and intensities of physical activity, including free-living activities, play, and physical fitness

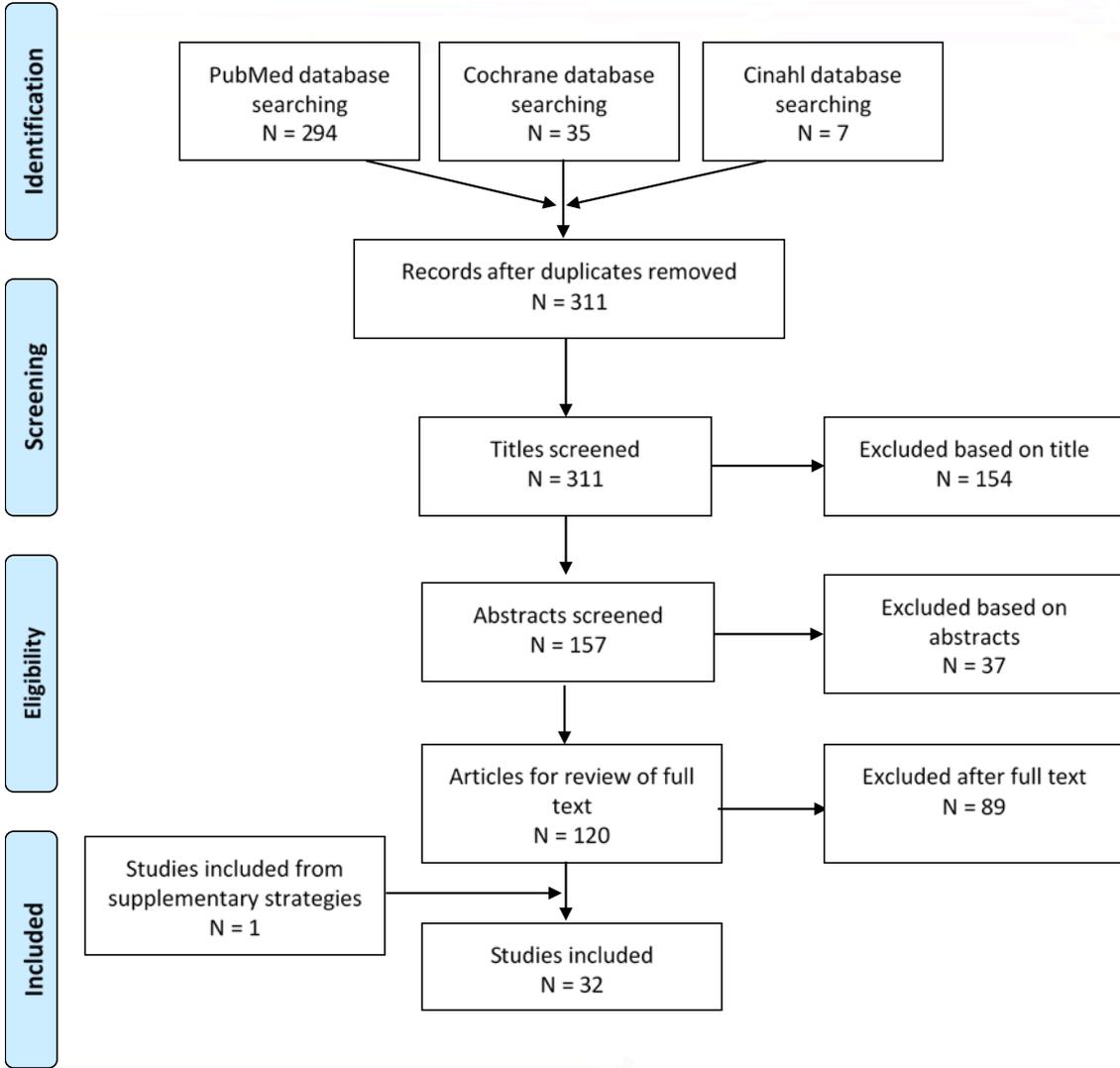
## Endpoint Health Outcomes

- Academic achievement
- ADHD
- Alzheimer's disease
- Cognitive decline
- Cognition
- Cognitive function
- Cognitive processing / cognitive processes
- Cognitive impairment
- Cognitive motor / motor cognition
- Dementia
- Impaired cognitive function
- Impaired memory
- Independence / Instrumental ADL / Basic ADL
- Intelligence
- Memory
- Mild cognitive impairment

## Key Definitions

- Cognition: The set of mental processes that contribute to perception, memory, intellect, and action. Cognitive function can be assessed using a variety of techniques including paper-pencil based tests, neuropsychological testing, and computerized testing methods. Cognitive functions are largely divided into different domains that capture both the type of process as well as the brain areas and circuits that support those functions. Working memory, visual attention, and long-term memory are all examples of different cognitive domains that are thought to be dependent on overlapping but yet largely separate neural systems.

# Search Results: High-Quality Reviews<sup>1</sup>



# Description of the Evidence

- Massive literature covering many different populations, study designs, and cognitive outcomes.
- Children, Aging, Dementia – largest categories
- 13 'categories' of papers were selected (32 papers):
  - Acute exercise (4 meta-analyses)
  - ADHD (2 meta-analyses; 1 systematic review)
  - Adolescents (1 meta-analysis; 1 systematic review)
  - Adult Lifespan (3 meta-analyses)
  - Aging (3 meta-analyses)
  - Children (4 systematic reviews)
  - Dementia (4 meta-analyses)
  - Mechanisms (1 meta-analysis; 3 systematic reviews)
  - Multiple Sclerosis (1 systematic review)
  - Parkinson's disease (1 systematic review)
  - Schizophrenia (1 meta-analysis)
  - Sedentary behavior (1 systematic review)
  - Stroke (1 systematic review)

# Description of the Evidence

- Number of studies and estimated sample sizes included in MA and SRs:
  - Acute (79+ studies; N=1000+)
  - ADHD (20+ studies; N=500+)
  - Adolescents (34+ studies; N=1400+)
  - Adult Lifespan (40+ studies; N=2000+)
  - Aging (25+ studies; N=2000+)
  - Children (64+ studies; N=1000+)
  - Dementia (20+ studies; N=33,000+)
  - Mechanisms (14+ studies; N=600+)
  - Multiple sclerosis (19 studies; N=1000+)
  - Parkinson's disease (8 studies; N=100)
  - Schizophrenia (10 studies; N=350+)
  - Sedentary behavior (7 studies; N=1000+)
  - Stroke (10 studies; N=400)
- Most papers summarized RCTs and a few (e.g., dementia) focused on prospective observational studies.

# Draft Key Findings

- Despite significant heterogeneity in (1) populations, (2) outcomes, (3) exposures, the effect sizes reported were highly consistent:
  - Effects were of small-moderate size (Hedge's  $g=0.1-0.5$ ).
  - Generally larger effect sizes for studies of longer duration.
  - Some evidence for effect moderation by sex
- Effects were also consistent in impaired populations.
  - E.g., Schizophrenia effects sizes were similar to dementia and ADHD ( $\sim 0.3$ )

# Draft Conclusion Statement

- Conclusion Statement:
  - Moderate evidence indicates a consistent association between greater amounts of physical activity and cognition including performance on academic achievement tests and neuropsychological tests such as processing speed, memory, and executive function, and risk for dementia.
  - Demonstrated across numerous populations and individuals representing a gradient of normal to impaired cognitive health status.
  - Considerable consistency in the findings given the variety of experimental designs and cognitive outcomes.
  - These effects are found across a variety of forms of physical activity including aerobic activity (e.g., brisk walking), strength training, yoga, and play activities (e.g., tag or other low organizational games) in children.
  - Such improvements are temporary following acute bouts of physical activity, and more sustained following participation in a physical activity routine.
- **PAGAC Grade: Moderate**

# Draft Conclusion Statement

- Conclusion Statement:
  - a) Does the relationship exist across the lifespan?
    - Young Children (< 5 years)
      - 7 studies (Carson et al., 2016) – positive effects but high risk of bias
      - **PAGAC Grade: Grade Not Assignable**
    - Preadolescent Children (5-13 years)
      - 40+ studies (Donnelly et al. 2016) – significant positive effects; most robust on measures of executive functioning, attention, academic achievement
      - 12 studies (Janssen et al., 2014) – acute exercise; non-significant effects on measures of attention; methodological limitations
      - 9 experimental studies (Bustamante et al., 2016) – positive effects in obese children
      - **PAGAC Grade: Moderate**
    - Adolescent Children (14-18 years)
      - 5 longitudinal/intervention (Esteban-Cornejo et al., 2015) – 75% of studies reporting positive associations
      - 10 studies (Spruit et al., 2015) – effect size: 0.367; methodological limitations
      - **PAGAC Grade: Grade Not Assignable**

# Draft Conclusion Statement

- Conclusion Statement:
  - a) Does the relationship exist across the lifespan?
    - Young Adulthood (18-24 years)
      - 29 studies (Smith et al. 2010) – effect size of 0.12-0.15; largest effects on executive function, attention, processing speed
      - 21 studies (Roig et al., 2013) – focused on short and long term memory in acute and long term physical activity; effect size of .15 for studies longer than 6 months on short term memory
      - Ludyga et al. (2016) – most acute exercise studies in young adults; effect size = 0.35; executive functions
      - **PAGAC Grade: Moderate**
    - Middle Adulthood (25-50 years)
      - **PAGAC Grade: Grade Not Assignable**
    - Older Adulthood (50+ years)
      - 18 studies (Colcombe 2003) – effect size = 0.478; studies with durations > 6 months had greater effect sizes
      - 6 studies (Wu et al., 2013) – effect size of Tai Chi = 0.20-0.46 depending on cognitive domain
      - 25 studies (Kelly et al., 2014) – effects for attention and processing speed; not significant effects for other studies
      - **PAGAC Grade: Moderate**

# Draft Conclusion Statement

- Conclusion Statement:
  - (b) Does the relationship vary for individuals with normal to impaired cognitive function (i.e., dementia)?
    - Attention deficit hyperactivity disorder (ADHD):
      - 0.58 (Cerillo et al., 2015)
      - 0.77 (Den Heijer et al., 2016)
      - 0.181 (Tan et al., 2016)
    - Schizophrenia:
      - 0.43 (Firth et al., 2016)
    - Dementia and Alzheimer's Disease (AD)
      - 38% reduced risk of cognitive decline (Sofi et al., 2011)
      - 60% reduced risk of Alzheimer's disease (Beckett et al., 2015)
    - Multiple sclerosis (MS)
      - Conflicting results; executive function showing most consistent results (Morrison et al., 2016)
    - Parkinson's Disease (PD)
      - Significant improvements in executive functions (Murray et al., 2014)
    - Stroke
      - Significant improvements in global, attention, memory, visuospatial (Zheng et al., 2016)
  - **PAGAC Grade: Moderate**

# Draft Conclusion Statement

- Conclusion Statement:
  - (c ) What is the relationship between physical activity and biomarkers of brain health?
    - Grey matter morphology (i.e., volume, density, and thickness), white matter integrity, cortical electrophysiology and neural networks including cognitive evoked responses, circulating neurotrophic factors linked to cognitive function and neuroplasticity, cerebral blood flow, task-evoked functional activity, resting state functional connectivity, MR spectroscopy, and positron emission tomography (PET).
    - Right hippocampus volume = 0.26 (Li et al., 2016)
    - Brain Derived Neurotrophic Factor = 0.39 (Dinoff et al., 2016)
    - Volume and function = 0.20-0.30 (Halloway et al., 2016)
    - White matter = “small effect” (Sexton et al., 2016)
  - **PAGAC Grade: Moderate**

# Draft Conclusion Statement

- Conclusion Statement:
  - (d) Is there a dose-response relationship? If yes, what is the shape of the relationship?
    - Conflicting dose-response relationships have been observed for physical activity on cognition across populations, cognitive outcomes, and experimental approach.
  - **PAGAC Grade: Grade Not Assignable**

# Draft Conclusion Statement

- Conclusion Statement:
  - (e) Does the relationship vary by age, sex, race/ethnicity or socio-economic status?
    - Stronger effect of physical activity on cognition in older compared to younger adults (Smith et al., 2010).
    - Within older adults, evidence exists for a stronger effect of physical activity in women compared to men (Colcombe & Kramer, 2003).
    - No evidence for an effect of physical activity on cognition as a function of SES, race/ethnicity, or BMI.
  - **PAGAC Grade: Limited**

# Draft Research Recommendations

- Conduct research in children <6 yrs of age and middle-aged adults
- Longitudinal studies on older adults with multiple co-morbidities
- Better understand biomarkers with brain health and the relative role of genetic and environmental risk factors
- Improve understanding of effects of physical activity in individuals with cognitive impairment
- Improve understanding of dose-response relationship
- Improve understanding of impact of sedentary behavior on cognitive outcomes
- Improve understanding of demographic factors on moderating effect of the physical activity-cognition relationship

# Committee Discussion

1. What is the relationship between physical activity and cognition?
  - a) Does the relationship exist across the lifespan?
  - b) Does the relationship vary for individuals with normal to impaired cognitive function (i.e., dementia)?
  - c) What is the relationship between physical activity and biomarkers of brain health?
  - d) Is there a dose-response relationship? If yes, what is the shape of the relationship?
  - e) Does the relationship vary by age, sex, race/ethnicity or socio-economic status?

# Question 2

2. What is the relationship between physical activity and quality-of-life?
  - a) Is there a dose-response relationship? If yes, what is the shape of the relationship?
  - b) Does the relationship vary by age, sex, race/ethnicity or socio-economic status?
- Source of evidence to answer question
  - TBD

# Analytical Framework

## Systematic Review Question

What is the relationship between physical activity and quality-of-life?

## Target Population

People of all ages, including healthy people and people with psychiatric disorders or cognitive impairment

## Comparison

People who participate in varying levels of physical activity

## Intervention/Exposure

All types and intensities of physical activity, including free-living activities, and play

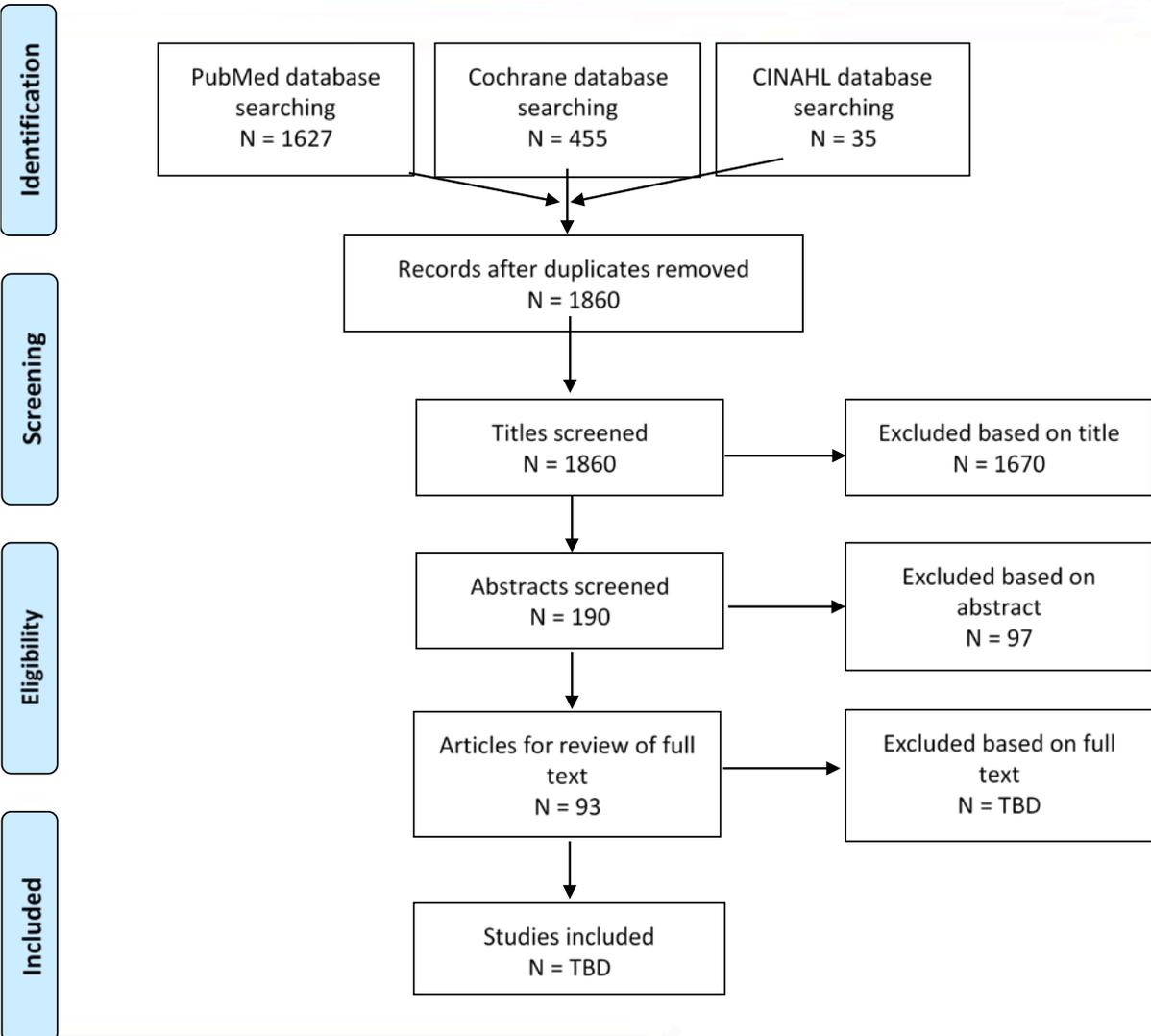
## Endpoint Health Outcomes

- Quality of Life
- Life Satisfaction
- Health-Related Quality of Life
- Social Quality of Life

## Key Definitions

- Quality of Life: “Quality of life, rather than being a description of patients’ health status, is a reflection of the way that patients perceive and react to their health status and to other, nonmedical aspects of their lives” (Source: Gill TM, Feinstein AR. A critical appraisal of the quality of quality-of-life measurements. *JAMA*. 1994;272:619-626.)

# Search Results: High-Quality Reviews<sup>1</sup>



# Draft Description of the Evidence

- Large heterogeneous literature covering many different populations, study designs, and Quality of Life outcomes (momentary to satisfaction with life)
- Older adult, Adults, Schizophrenia– largest categories
- 7 'categories' of papers were selected:
  - Older adults (10 systematic reviews, 4 meta-analyses)
  - Adults (13 systematic reviews, 2 meta-analyses, 1 pooled analysis)
  - Schizophrenia (2 systematic reviews, 1 meta-analyses)
  - Depression (2 systematic reviews, 1 meta-analyses)
  - Youth (2 systematic reviews, 1 meta-analyses)
  - Dementia (1 systematic review, 1 meta-analyses)
  - Grouped/Miscellaneous mental illness (3 systematic reviews, 2 meta-analyses)

# Draft Key Findings

- For Older Adults, effects were of small-moderate size (effect size = 0.1-0.5)
  - Significant improvements for physical function component of health-related QoL (effect size= 0.41, 95% CI, 0.19 to 0.64) (Kelley, 11 RCTs)
  - No significant improvement for mental function component of HR QoL (-0.16, 95% CI, -0.81 to 0.5)
  - Significant improvements for community dwelling older adults; includes RCTs using 150 min/week (Morey)
  - No significant improvements for frail / institutionalized older adults

# Draft Key Findings

- For Adults, effects were null to small (SMD = 0.11, 95% CI, -.03 to 0.24)
  - Subdomains significantly improved:
    - Physical health (SMD = 0.22; 0.07 to 0.37) and psychological well-being (SMD = 0.21; 0.06 to 0.36)
  - Subdomains not improved:
    - Social relations and Level of independence

# Draft Key Findings

- For Schizophrenia, effects were of moderate size (Hedges'  $g = 0.55$ )
  - Effects were of similar size for aerobic (7 trials) and yoga (3 trials) (Hedges'  $g = 0.58$ ); only 1 trial on anaerobic training
  - Effects were significant for physical, social and environmental QoL but not mental QoL (n.s.)

# Draft Key Findings

- For Dementia, effect sizes not currently available
  - No significant effect on dementia-specific QOL scales (carer-rated ADR-QOL; self-rated QOL-AD)
  - Limited RCT data suggests moderate effect on Physical Role Function HR-QOL (SF-36); possible bias from concurrent behavioral management program (Teri 2003, JAMA)
  - Findings relevant to specific diagnosis of AD (by clinical or NINCDS - ADRDA Criterion), generally excluding severe dementia cases

# Draft Key Findings

- For Youth and Grouped, a grade was not assignable due to too few studies and small N within those studies
- It is not possible to draw strong conclusions about dose-response relations at present
- We have not yet evaluated other potential moderators in detail – e.g., age, sex, race/ethnicity, socioeconomic status

# Draft Conclusion Statement

- DRAFT - Conclusion Statement QOL and PA

Strong evidence suggests that the physical component of HR-QOL improves as a result of participation in physical activity when compared with minimal or no-treatment controls for adults and older adults, but not frail older adults, or those with AD dementia

No evidence that the mental domain of HR-QOL improves as a result of participation in physical activity in adults, older and frail adults, and in AD populations

Strong evidence suggests that physical, social and environmental, but not mental components of QoL improve as a result of participation in physical activity in individuals with schizophrenia

Evidence related to global QoL cannot yet be determined

# *Draft* Implications

- Conclusions about the sufficiency of evidence are pending final analysis
- Physical activity may positively impact QOL

# Draft Research Recommendations

- Conduct more rigorous randomized controlled trials, to examine QoL changes with control conditions
- Conduct studies with larger sample sizes
- Incorporate QoL outcomes into prospective observational studies

# Draft Research Recommendations

- Conduct more studies on QoL global, i.e., life satisfaction
- Conduct more studies/analyses of non-aerobic PA and QoL
- PA is a dynamic behavior and its impacts on QOL may be acute, so future work should consider investigating within-person associations linking PA and QOL at the daily level

# Committee Discussion

2. What is the relationship between physical activity and well-being and quality-of-life?

- a) Is there a dose-response relationship? If yes, what is the shape of the relationship?
- b) Does the relationship vary by age, sex, race/ethnicity or socio-economic status?