Supplementary Material

METHODS

Study Protocol and search strategy

The PICO(T) (population, intervention, comparison, outcome, and [type]) (1) approach was used to develop our research question, while Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (1) were utilized as a guideline in this review. Our research question was as follows: "What are effects of multiple-modality exercise interventions aimed at improving cognition and neuroimaging outcomes in older adults without dementia?". Between August and October 2019, we searched the following bibliographical databases for potentially relevant documents: Cochrane Central Register of Controlled Trials, EMBASE, MEDLINE and Scopus. We also contacted authors directly to identify additional relevant material and to further determine eligibility of articles selected for full-text review. The final search strategy for MEDLINE can be found in the **Table** below (1).

Eligibility criteria

We selected peer-reviewed, published randomized controlled trials (RCTs) and non-randomized intervention studies (i.e., quasi-experimental) examining the effects of MME interventions on cognition (i.e., global and domain-specific cognitive function) and/or neuroimaging (e.g., brain function and structure) outcomes.

We defined MME interventions as those that included a combination of the following main exercise modalities: 1) AET aimed at improving aerobic capacity or cardiovascular fitness in which participants engaged in exercise involving large muscle groups, yielding substantial increase in heart rate and energy consumption (e.g., running, cycling, walking, dancing) (2,3); 2) RET aimed at improving muscle strength, endurance or power, defined as any type of muscle strengthening exercise in which participants moved against external resistance (e.g., machine-based weightlifting, free-weight training, rubber bands) (2,3). We also included studies that combined AET and RET with balance or flexibility exercises as complementary training. Balance and/or flexibility training was defined as activities aimed at increasing balance (e.g., static and dynamic balance exercises, single-leg stance standing, tandem walk) and flexibility (e.g., stretching, range of motion, and mobility exercises) (2,3). Other actives referred to as

'warm-up', 'cool-down' or 'recovery' were not considered. Considering the nature of this scoping review, we did not specify minimum or maximum length of exercise programs, whether components of AET or RET were administered in the same session or different sessions, and whether interventions were supervised, home-based or both.

We included studies that met the following inclusion criteria: 1) MME studies combining both AET and RET with or without additional balance/flexibility training, as defined above; 2) included older adults aged ≥ 55 years; 3) included individuals with or without cognitive impairment, but not dementia (i.e., cognitively healthy, self-reported cognitive or memory complaints, subjective cognitive/memory decline or impairment [SMI, MCI]); included at least one measure of cognition (e.g., global or domain-specific cognitive function), and/or neuroimaging outcomes relevant to cognitive function (e.g., functional network connectivity, grey matter volume); 5) included a comparator group (i.e., competing treatment group, active control group, or no-treatment control group); 6) published in English between January 1990 and October 2019; and 7) published in a peer-reviewed journal. We also included other articles from the same parent study that reported different relevant outcomes from the original publication; however, we excluded those reporting sensitivity analyses of primary outcomes already reported in the original publication.

Data charting process

A data charting form was created to determine which variables to extract. The first author (NCBSS) reviewed and updated the data charting form continuously to capture the most relevant information on study characteristics, including study design, population (e.g., age, cognitive status), experimental and control conditions, detailed exercise intervention, study outcomes, and main findings.

For the purpose of the outcomes of this review, we captured and reported on the cognitive domains assessed in each study and the specific tests employed to assess these domains. We defined global and domain-specific cognition as a broad range of neuropsychological constructs measured using instruments based on individual performance. For example, global cognitive functioning can be measured via the Mini-Mental State Examination (4), while executive functioning is measured by the Trial-Making Test, Part B (5). For the purpose of summarizing and contextualizing the evidence, we classified measures employed in the included studies under

four cognitive domains: global cognitive function, executive functioning, memory, and processing speed, following previous methods (6). In addition, we were particularly interested in the elements of the MME interventions employed in these studies to aid in contextualizing our results in light of the current guidelines for exercise prescriptions in older adults, as well as to facilitate recommendations for translation of the evidence. Therefore, when available, we extracted detailed information from each exercise training component administered (i.e., frequency, intensity, time [duration] and type) (7).

Synthesis of results

We organized our results based on study design. That is, reporting the evidence in the context of MME compared to the following conditions: a) competing treatment, defined as other experimental intervention aimed at improving cognition (e.g., cognitive training); b) active control, defined as conditions (e.g., education sessions) administered to control for confounding variables (e.g., socialization, attention); and c) no-treatment control, defined as a no-contact, no-intervention control conditions. Additionally, whenever applicable, we also contextualized the evidence based on participant cognitive status and other demographic characteristics. The details of each study, including intervention, assessment and main findings were reported in summary tables.

References

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4. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189–

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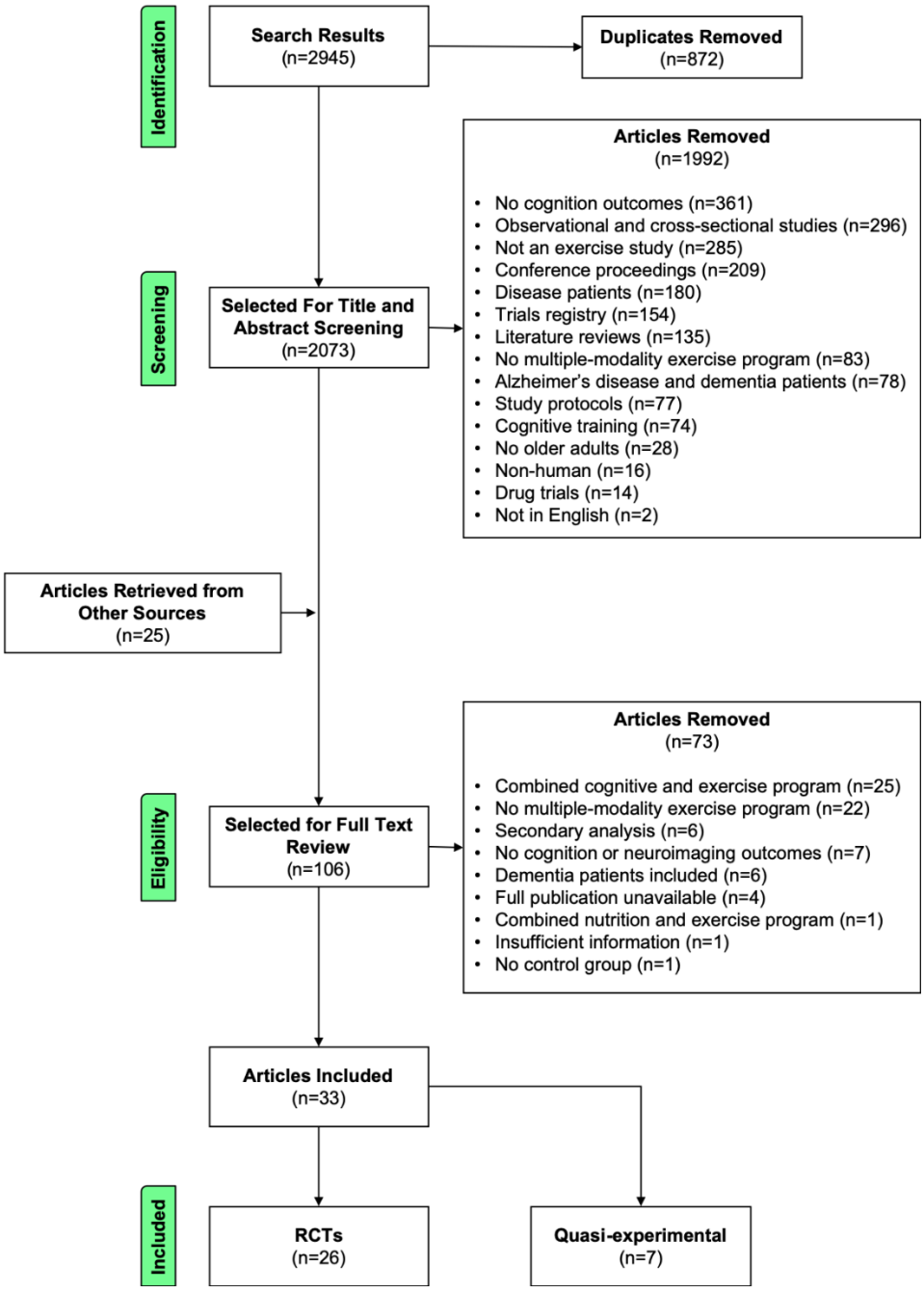
5. Tombaugh TN. Trail Making Test A and B: Normative data stratified by age and education. Arch Clin Neuropsychol. 2004;19(2):203–14.
6. Falck RS, Davis JC, Best JR, Crockett RA, Liu-Ambrose T. Impact of exercise training on physical and cognitive function among older adults: a systematic review and meta-analysis. Vol. 79, Neurobiology of Aging. Elsevier Inc; 2019. p. 119–30.
7. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. In: 9th ed. Baltimore: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2014. p. 456.

Supplementary Table 1. Final search strategy for MEDLINE

MEDLINE search parameters
1. Aged/ or Aging/ or older adults.mp.
2. (Elderly or Elders).mp.
3. Seniors.mp.
4. Multiple-Modality.mp.
5. Combined.mp.
6. Global.mp.
7. Integrated.mp.
8. (Multi-component or Multicomponent).mp.
9. (Multi-domain or Multidomain).mp.
10. (Multi-faceted or Multifaceted).mp.
11. (Multi-modal* or Multimodal).mp.
12. Exercise/
13. (Aerobic exercise or Aerobic training).mp.
14. (Balance exercise or Balance training).mp.
15. (Cardiovascular exercise or Cardiovascular training).mp.
16. Endurance exercise.mp. or Endurance Training/
17. (Functional exercise or Functional training).mp.
18. (Physical activity or Physical exercise or Physical training).mp.
19. Resistance training.mp. or Resistance Training/
20. (Strength exercise or Strength training).mp.
21. Walking.mp. or Walking/
22. Cognition/
23. Brain/
24. Brain function*.mp.
25. Cognitive function*.mp.
26. Global cognitive function*.mp.
27. Mental ability.mp.
28. Neurocognition.mp.
29. Neurocognitive function*.mp.
30. Attention/
31. Concentration.mp.
32. Decision Making/
33. Dual-task*.mp.
34. Executive function*.mp. or Executive Function/
35. (Information processing speed or Processing speed).mp.
36. Memory/
37. Memory function*.mp.
38. Mental flexibility.mp.
39. Problem Solving.mp. or Problem Solving/
40. Reasoning.mp.
41. Thinking/
42. Thinking ability.mp.
43. Alzheimer's disease/
44. (Cognitive complaint* or Subjective cognitive complaint*).mp.
45. Cognitive Dysfunction/
46. Cognitive impairment.mp.
47. Dementia/
48. Healthy.mp.
49. (Mild-cognitive impairment or MCI).mp.
50. Memory impairment.mp.
51. Dementia, Vascular/
52. Subjective memory impairment.mp.

53. (Memory complaint* or Subjective memory complaint*).mp. 54. or/1-3 [**Older adults] 55. or/4-11 [**Multiple-modality] 56. or/12-21 [**Exercise types] 57. or/22-42 [**Cognition, all terms] 58. or/43-53 [**Clinical status] 59. and/54-58 [**All]



Supplementary Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-ScR) flow diagram for the scoping review process