Non-Pharmacological Therapies in Alzheimer's disease: A Systematic Review

INTRODUCTION

Alzheimer's disease (**AD**) is a degenerative neurological illness that is one of the most common causes of dementia and elderly disability in the United States. Recent reports suggest that, in 2018, almost 6 million Americans were living with AD. This figure is expected to increase to 14 million by 2050. AD is characterized by impaired short-term memory, altered communication, confusion, and behavioral changes. AD pathogenesis begins as much as two decades before overt symptoms appear. Early clinical evidence of cognitive decline without gross behavioral and/or physical dysfunction is diagnosed as Mild Cognitive Impairment (**MCI**). Later stages of dyscognition, neuropsychiatric symptoms, and loss of functional capacity is diagnosed as AD. Thus, MCI and AD are clinical stages within a spectrum of severity that encompass age-associated cognitive loss and functional decline.

Despite the tremendous financial investment into AD therapeutic discovery protocols, there are no known cures and there has not been a novel drug for AD introduced in about 15 years. The current crop of FDA approved drugs are limited to symptomatic relief and are not approved to treat the underlying disease process. In addition, recent late-stage Alzheimer's clinical trials have consistently produced negative results. This has led clinicians, researchers, and stakeholders to shift their focus towards interventional outcomes that aim to prevent or slow the progression of the disease earlier in the patient's lifespan. The growing number of diagnosed patients and subsequent economic burden makes AD one of the most pressing health and financial issues of our time.

The current dearth of pharmacological drug options highlights the need for additional prevention strategies and a robust evaluation of non-pharmacological treatments. In this report, we conducted an extensive search of non-pharmacological treatments assessed in AD, MCI, and normal aging. We identified 314 studies that met our inclusion criteria and subsequently organized them into various classifications.

We reviewed each therapy and identified important factors including market availability, stage of aging targeted, and expected post-treatment clinical outcomes, among others. We included published and peer-reviewed non-pharmacological therapies. General study categories included: pre-clinical (in-vitro and in-vivo), epidemiological/observational studies, active or completed non-randomized or randomized controlled trials (**RCT**), systematic/clinical reviews, and meta-analyses. To provide a measure of the quality and quantity of each non-pharmacological intervention, each therapy was rated on an ascending five-point scale known as the Level of Evidence (**LOE**) score. We did not conduct a meta-analysis for this specific review due to the extensive heterogeneity found among studies.

This report is not intended to assess the clinical meaningfulness or endorse any of the interventions discussed within it. Rather, the aim is to take stock of the most current literature on non-pharmacological therapies and identify potential opportunities for future research. In this report, we identified notable treatments (covered in detail within the "Case Studies" section), highlighted gaps in minority recruitment, and point to opportunities to bolster research efforts in low- and middle-income countries. In summary, this report builds upon previous findings by attempting to provide an up-to-date analysis of the current non-pharmacological research landscape and offer recommendations for future initiatives in Alzheimer's research.

Methods/Methodology

Primary Objective

The aim of this review was to assess the statistical quality, quantity of clinical trials (active and completed), and published literature on non-pharmacological therapies studied in patient groups identified as normal aging or at-risk, diagnosed with Mild Cognitive Impairment (**MCI**), or having dementia associated with Alzheimer's disease (**AD**). Search registries included clinicaltrials.gov; OVID; Medline; the Cochrane Central Register of Controlled Trials (**CENTRAL**); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; ICTRP; and NIH information repositories. The date of the most recent search was June 30, 2019.

Literature Review

A non-pharmacological treatment option was defined as any replicable intervention which may provide some quantifiable or relevant positive change in commonly reported symptoms or outcomes of normal aging, MCI, and Alzheimer's. Clinical trials or published reports were excluded if any aspect of the protocol used pharmacological therapies that were reviewed by the FDA's "Prescription Drug Approval Process" via the Center for Drug Evaluation and Research (**CDER**). Clinical trials and published studies written in English between 2000 and 2019 were reviewed for inclusion in the report using MESH terms, keywords, and combinations of terms/keywords such as "Alzheimer's disease, Mild Cognitive Impairment, normal aging, non-pharmacological treatments, randomized controlled trials, diet, exercise, vitamins, and treatments." Studies from all countries were reviewed for inclusion. We initially identified 1,234 potential candidates that were then further interrogated, filtered, and manually reviewed. Based upon our inclusion criteria (**Figure 1**), we identified 314 studies for this report. The remaining 920 discarded studies were grouped based upon the reason for exclusion (**Figure 2**). Despite our broad search parameters, we are aware that it would not be feasible to identify every appropriate study or trial for this review.

Figure 1. Inclusion Criteria

(1) Clinical trials must report the concomitant patient safety approvals to conduct research (e.g., Institutional Review Board approvals) & pre-clinical animal studies must report the associated animal welfare approvals.

(2) Reported interventions can only include non-pharmacalogical treatments (e.g., no mixed studies with FDA approved pharacological therapies).

(3) Studies must report the use of objective, measurable, and replicable outcomes that assess the efficacy of the treatment (e.g., behavioral and/or cognitive scores from well-accepted questionnaires).

(4) Study population of interest can only include participants or animal models that are defintied as normal aging, MCI, and dementia associated with Alzheimer's disease (dementia associated with infections, chronic alcohol use, Traumatic Brain injury, or other causes will be excluded).

(5) Statistical methods and underlying rationale must be appropriate for the reported study design.

Figure 2. Flow Chart for Included Studies

Evidence Tables

To organize and tabulate the data/literature, we created evidence tables in Microsoft Excel. The general schematic of the evidence tables are shown below (**Figure 3**). All included interventions were first separated into two primary categories: **(1)** Diet/Exercise and **(2)** Other Interventions. Primary categories were then further divided into secondary categories. Within the primary category of Diet/Exercise, secondary categories were Overall Diet, Specific Foods, Vitamins, Minerals & Other Nutrients, Prescribed Nutrition, and Exercise. In the primary category of Other Interventions, secondary categories were Modifiable Risk Factors, Medical Devices, Cognitive Retraining, and Multimodal Interventions.

Topics and Their Descriptive Summaries

Each secondary category was further separated into topics within the evidence tables (**Figure 4**). Topics were defined as the treatment or therapy specifically studied for its potential effect (e.g., vitamin E is a topic nested within the secondary category of Vitamins and the broader primary category of Diet/Exercise). Each topic was then described by five descriptive summaries: (**1**) General Findings; (**2**) Acquisition of Treatment; (**3**) Stages of Cognition Targeted; (**4**) Expected Clinical Outcome; and (**5**) Level of Evidence (**LOE**) score. The **General Findings** descriptor provided a brief summary on the topic and its respective literature results.

Figure 3. Schematic of the Data Organized within the Evidence Tables.

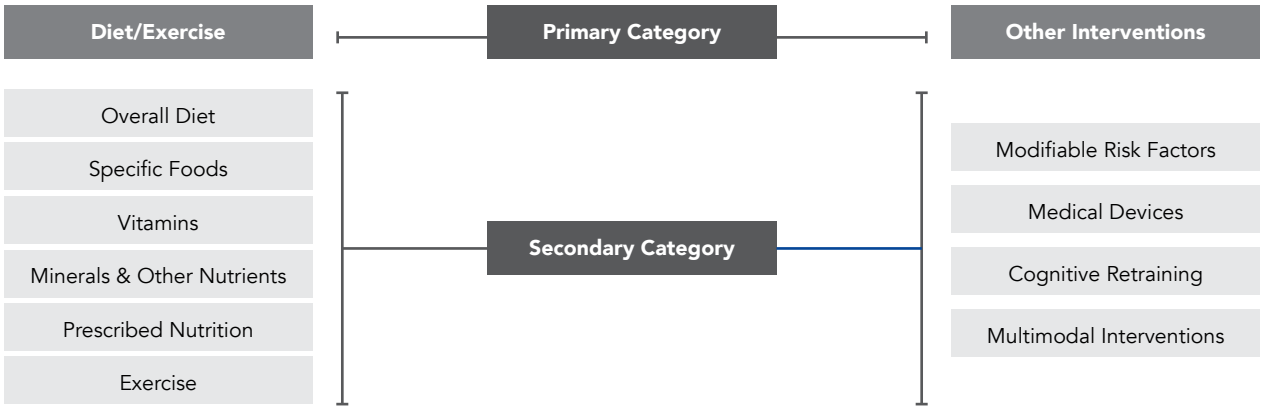
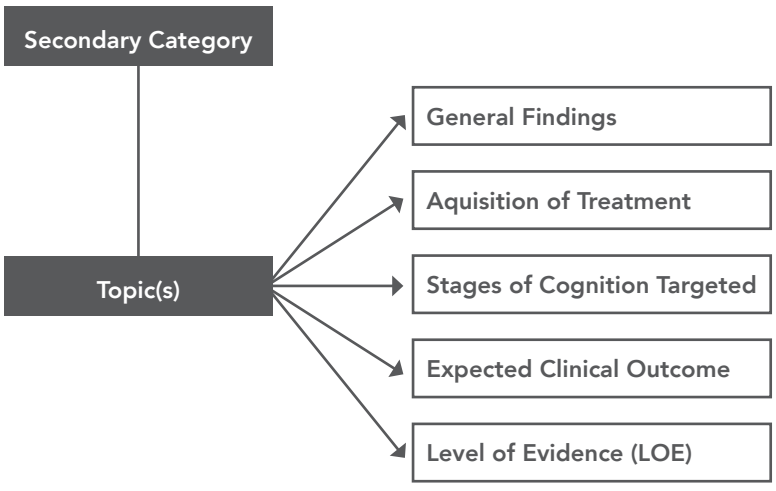


Figure 4. The five "descriptive summaries."



Acquisition of Treatment summarizes where/how a treatment may be administered or acquired. **Stages of Cognition Targeted** was described via three possibilities. The first was Normal Aging/Preclinical, where the patient has shown no evidence of cognitive or quality of life decline. The second was MCI, which represented memory problems greater than what is expected for the age group but without evidence of gross behavioral changes and no evidence of impairment sufficient to affect activities of daily living. The third possibility was Dementia/AD. Dementia describes a group of symptoms associated with a decline in memory or other thinking skills severe enough to reduce a person's ability to perform everyday activities. Although AD is not the sole causative factor of dementia, for this report we have only included non-pharmacological interventions targeting dementia in association with Alzheimer's disease (Dementia/AD). **Expected Clinical Outcome** was described in three ways: **(1)** prevention and/or a decrease in the rate of cognitive decline; **(2)** disease modifying; and **(3)** supportive and/or symptomatic improvement in a behavioral domain (e.g., improvement in mood). Due to the extensive criteria used for the **LOE** score, we have provided a more in-depth explanation below.

Due to the large number of studies that can be found within a topic, we used five descriptive summaries to provide an overview of the clinical research parameters studied. This organization, within the evidence tables, provides the key points encompassed within the literature without having to create an in-depth review of each topic.

Level of Evidence (LOE)

The Level of Evidence (**LOE**) score was derived exclusively to provide a statistic for each of the relevant topics with the primary aim of summarizing the underlying quality (statistical rigor) and quantity of the research activity (**Table 1**).The LOE score does not imply any type of clinical recommendation for patients or caregivers. Prior to publication, a separate panel of researchers reviewed the criteria to assess the scoring system's validity.

We used a 1-to-5 ascending rating system. A rating of **1** was given to topics represented by preclinical studies assessing potential biological activity in animals and/or test tubes. Topics with LOE scores of 1 have not been assessed in human trials. Finally, the reported statistical methods may not have been robust or adequately powered. A rating of **2** was given to a topic with at least one of the following: completed or active clinical trial, Observational/Prospective Study, Systematic/Clinical Review, or a Meta-analysis. Methodology and statistics reported were adequate for the study design. LOE scores of 1 and 2 allowed for topics to be separated based upon whether identified research studies were primarily conducted with animal models or human subjects. This scoring derivation was necessary as many non-pharmacological topics identified did not reasonably or scientifically need preclinical testing prior to usage in human subjects. A rating of **3** was given to topics with at least two completed preclinical studies and one completed clinical trial. In addition, at least one of the following criteria was met: one currently active clinical trial, an Observational/Prospective Study, a Systematic/Clinical review, or a Meta-analysis. All published methods used suitable statistical tests. A rating of **4** was given to topics with at least two completed preclinical studies, two completed clinical trials, and at least one currently active clinical trial. In addition, at least one of the following criteria was met: a Observational/Prospective study, a Systematic/Clinical Review, and/or a Meta-analysis. All studies reported appropriate statistical methods. A rating of **5** was given to topics with at least two published preclinical studies and three com-

Table 1. The Criteria for the Level of Evidence (LOE) Scoring System.

LOE SCORE	CRITERIA FOR SCORING
1	• At least one preclinical (animal study published in a peer reviewed journal. • No human trials have been conducted.
2	• At least one of the following involving human subjects/patients: ➔ Completed or active clinical trial ➔ Observational/Prospective Study ➔ Systematic/Clinical Review ➔ Meta-analysis
3	• At least two preclinical (animal) studies published in peer reviewed journals. • At least one completed clinical trial. • At least one of the following: ➔ Currently active clinical trial ➔ Observational/Prospective Study ➔ Systematic/Clinical Review ➔ Meta-analysis
4	• At least two preclinical (animal) studies published in peer reviewed journals. • At least two completed clinical trials. • At least one currently active clinical trial. • At least one of the following published in a peer-reviewed journal: ➔ Observational/Prospective Study ➔ Systematic/Clinical Review ➔ Meta-analysis
5	• At least two preclinical (animal) studies published in peer reviewed journals. • At least three completed clinical trials. • At least two currently active clinical trials (one of the two must have a recruitment target of n≥ 350). • At least two of the following published in a peer-reviewed journal (either in combination or multiples): ➔ Observational/Prospective Study ➔ Systematic/Clinical Review ➔ Meta-analysis

pleted clinical trials. In addition, two currently active clinical trials were identified. One of the two identified active clinical trial must have a recruitment target above *n*≥ 350. The rationale for using a recruitment floor of *n*≥ 350 stems from the FDA's published range on what is an appropriate number of subjects to recruit for a Phase III clinical trial (often considered to be the gold standard for assessing efficacy). Finally, at least two of the following criteria were met (in combination or multiples): an Observational/Prospective study, a Systematic/Clinical Review, and/or a Meta-analysis – all of which must be published in a peer-reviewed journal. All studies reported appropriate statistical methodology. Information compiled within evidence tables were used for internal review purposes and subsequently adapted into figures and tables found within this text.

Minority Recruitment and Inclusion

In order to assess patient population demographics, minority recruitment, and study enrollment protocols, we completed a separate but complimentary review of the 314 studies. Initially, we divided the studies based upon whether collecting demographic information was viable. Thus, all pre-clinical (animal) studies and systematic reviews were excluded. We then identified the number of active and completed studies with a focus on women or minority patient populations.

The remaining studies were again separated based upon country of origin. This allowed us to focus on active clinical trials and studies based solely within the United States. U.S. based active clinical trials and their respective clinicaltrials.gov pages were further interrogated for recruitment protocols regarding age, gender, and race.

Finally, we reviewed whether these studies indicated their intent to publicly share Individual Participant Data (**IPD**).

Results

Topics Rated with an LOE Score of 1

Of the 314 identified studies, twenty-four studies obtained an LOE score of 1. All of the topics/therapies identified were either in such preliminary experimental stages or statistically underpowered that assessing the validity or potential of any of the results published was very difficult. Therefore, topics with LOE scores of 1 were excluded from the main components of the results below but are still mentioned within the broader issues broached in the discussion section.

Overall Summary

Within the two primary categories, we identified ten secondary categories (six in Diet/Exercise and four in Other Interventions) (**Figure 3**). **Tables 2 & 3** provide the identified topics and their respective LOE scores.

Key Findings in the primary category of "Diet/Exercise"

In the secondary category of Overall Diet, we identified two topics that met our search criteria: The Mediterranean-DASH Intervention for Neurodegeneration Delay (**MIND**) diet and the Modified Atkins Diet (**MAD**). The MIND diet was one of only four topics to obtain an LOE score of 5. We were able to identify two preclinical reports, two large observational studies (subjects n>900), three completed clinical trials, and two active clinical RCTs with one having a recruitment target of 604 participants. The MAD diet received an LOE score of 4. We identified two preclinical studies, three completed clinical trials, multiple active RCTs, and one comprehensive clinical review. However, none of the active RCT studies had recruitment targets that exceeded 120 participants. This is the primary reason the MAD diet did not obtain an LOE score of 5.

When assessing the secondary category of Specific Foods, we identified eleven topics. The highest rated topic, with an LOE score of 4, was chocolate/cocoa supplementation. In fact, cocoa supplementation was the only topic within the Specific Foods secondary category with an active clinical trial. Four of the eleven obtained an LOE score of 3 and the remaining six topics received an LOE score of 2 (**Table 2**).

Recent studies have shown that inflammatory processes may underlie the pathogenesis of AD. Within the Specific Foods secondary category, one topic stands out in particular: turmeric. Turmeric (curcumin) is known for its anti-inflammatory properties and has been studied in several other illnesses. Turmeric is the only topic within the Specific Foods secondary category to have completed three clinical trials with FDA Phase II designations. However, like other promising topics, understanding turmeric's efficacy is limited due to the small study populations. In order to adequately assess turmeric's potential, stakeholders should consider funding a fully powered multi-center double-blinded RCT. It may be expected that future funding efforts should focus on topics with higher LOE scores. However, that is not always the case.

Within the secondary category of Vitamins, we identified six topics. The highest rated topic was the B vitamin group (Folic Acid, Vitamin B6, and Vitamin B12), with an LOE score of 4. Vitamin E, Vitamin A, and Niacin received an LOE score of 3. Vitamin C and vitamin D + Calcium earned an LOE of 2 (**Table 2**). Review of the outcome measures within the studies for the topics in "Vitamins" all show mixed results. For example, a holistic review of vitamin E completed by the Cochrane Library, identified studies that showed positive and nonsignificant benefits. In fact, some of the positive outcomes were borderline statistically significant.

In the secondary category of Minerals and Other Nutrients, we identified seven topics. The highest rated topics, with LOE scores of 4, were Essential Fatty Acids and Bioactive Dietary Polyphenol Preparation (**BDPP**)/ Resveratrol. Magnesium Sulfate, Targeted Antioxidants (CO-Q-10), and Zinc all received an LOE score of 3. Chromium and Carnosine received an LOE score of 2. Within this secondary category, Essential Fatty Acids

had four clinical trials that were currently active with one even having a recruitment target of 320. For the topic of BDPP/Resveratrol, we identified two active clinical trials. However, recruitment targets were below 40 participants.

Within the secondary category of Prescribed Nutrition, we identified three topics: Souvenaid (Fortasyn Connect), Axona (Ketasyn), and Cerefolin. Souvenaid received an LOE score of 4 and the remaining two obtained an LOE score of 3. Prescribed nutritional products were specifically created to supplement food groups or organic molecules found to be consistently lacking within patients diagnosed with AD. Across all three medical foods, we identified several adequately powered and properly designed studies that showed statistically weak or insignificant outcomes.

The final secondary category was Exercise. In contrast to the prior secondary categories, we did not attempt to identify specific topics. Rather, we have one large encompassing topic known as Aerobic Exercise that obtained an LOE score of 5. In fact, Aerobic Exercise had the largest number of published studies, meta-analysis, longitudinal outcomes, prospective reviews, and active clinical trials among any of the topics researched. We did not include studies assessing anaerobic exercise, as clinical trials specifically studying such modalities are currently unavailable. Seven large RCT trials studying exercise are currently active within the United States. Two of the seven have recruitment targets above 600 subjects. Due to the vast number of active and completed clinical trials within the aerobic exercise topic, we included only the most representative clinical trials within the Evidence Tables. This prevented the cluttering of data and limited the repetition of similar study protocols. In general, trials studying Aerobic Exercise do show a correlation between physical activity and a reduction in the rate of cognitive decline.

Table 2. Topics and Their LOE Scores in the Primary Category of "Diet/Exercise"

Primary Category: Diet/Exercise	
Secondary Category: Overall Diet	
Topics	**LOE SCORE**
The MIND Diet	5
The MAD Diet	4
Secondary Category: Specific Foods	
Topics	**LOE SCORE**
Cocoa/Chocolate	4
Soy	3
Turmeric	3
Olive Oil	3
Green Tea	3
Cinnamon	2
Tomatoes	2
Saffron	2
Rosemary	2
Alcohol	2
Coffee	2
Secondary Category: Vitamins	
Topics	**LOE SCORE**
B Vitamins (Folic Acid, Vitamin B6, Vitamin B12)	4
Vitamin E	3
Vitamin A	3
Niacin/NAD+/Nicontinic Acid	3
Vitamin C	2
Vitamin D + Calcium	2
Secondary Category: Minerals & Other Nutrients	
Topics	**LOE SCORE**
Essential Fatty Acids	4
Bioactive Dietary Polyphenol Prep (BDPP)/Resveratrol	4
Magnesium Sulfate	3
Targeted Antioxidants (CO-Q-10)	3
Zinc	3
Chromium	2
Carnosine	2
Secondary Category: Prescribed Nutrition	
Topics	**LOE SCORE**
Souvenaid (Fortasyn Connect)	4
Axona (Ketasyn)	3
Cerefolin NAC	3
Secondary Category: Exercise	
Topics	**LOE SCORE**
Aerobic Exercise	5

Key Findings in the primary category of "Other Interventions"

Recent research has predicted that approximately one-third of all AD diagnosis could be prevented by changes in a patient's modifiable risk factors. Modifiable Risk Factors is both a secondary category and topic (similar to exercise). This secondary category/topic obtained an LOE score of 5 and is comprised of eight components that are consistently associated with positive cognitive benefits in the elderly. The eight components were body mass index (**BMI**), Type II Diabetes Mellitus (**T2DM**), Depression, Midlife Hypertension, Smoking, Physical Inactivity, Educational Attainment, and Sleep Disordered Breathing. The authors of this report decided to combine these eight components into a single topic due to the interconnected nature of the components and their associated outcomes. For example, if a patient attempts to decrease their weight, this may impact not only their BMI but also T2DM status, hypertension, physical inactivity, and even sleep disordered breathing. We recommend that future research initiatives focus on studying these modifiable risk factors together. Some work has already begun on this front, including most notably a recent multi-domain two-year RCT study conducted in Finland (the FINGER study), which will be discussed in detail below.

We identified ten topics within the Medical Devices secondary category. Of the ten topics, Deep Brain Stimulation (**DBS**), Transcranial Stimulation (**tCS**), and Continuous Positive Airway Pressure (**CPAP**) received an LOE score of 4. The topic of transcranial stimulation included three modalities: **(1)** transcranial alternating current stimulation (**tACS**); **(2)** transcranial magnetic stimulation (**TMS**); and **(3)** transcranial direct current stimulation (**tDCS**). One topic, electroconvulsive therapy (**ECT**), obtained an LOE score of 3. The remaining six topics earned an LOE score of 2. Transcranial Stimulation (**tCS**) will be covered in detail within the "Case Studies" section of this report.

Table 3. Topics and Their LOE Scores in the Primary Category of "Other Interventions"

Primary Category: Other Interventions	
Secondary Category: Modifiable Risk Factors	
Topics	**LOE SCORE**
Modifiable Risk Factors Body Mass Index, Type 2 Diabetes Mellitus Depression, Midlife Hypertension Smoking, Physical Inactivity Educational attainment, Sleep Disordered Breathing	5
Secondary Category: Medical Devices	
Topics	**LOE SCORE**
Deep Brain Stimulation (DBS)	4
Transcranial Stimulation (tCS)	4
Continuous Positive Airway Pressure (CPAP)	4
Electroconvulsive Therapy (ECT)	3
Low-Energy infrared/Laser LED Light (IRL)	2
Photobiomodulation (PBM)	2
Transcutaneous Vagal Nerve Stimluation (TVNS)	2
Hyperbaric Oxygen Chamber	2
Low Intensity Pulsed Ultrasound (LIPU)	2
Hearing Aid Placement	2
Secondary Category: Cognitive Retraining	
Topics	**LOE SCORE**
Cognitive Behavioral Therapy—Traditional	4
Cognitive Behavioral Therapy—Computerized	4
Tactile Tablet Stimulation	2
Serious Games	2
Auricular Point Acupressure	2
Musical-Lexical Based Therapy	2
Mindfulness Training	2
Smartphone Personal Assistant	2
Intense Piano Training Treatment	2
Secondary Category: Multimodal Interventions	
Topics	**LOE SCORE**
Cognitive Retraining + One Other Treatment	4
Aerobic Exercise + One Other Treatment	4
Risk Factor Modification + Cognitive Retraining + Exercise	5

The secondary category of Cognitive Retraining had eleven total topics. For the treatment of cognitive behavioral therapy (**CBT**), we created two topics based upon whether CBT was administered via a traditional regimen (where the patient would have to visit the health care provider) or whether it was computerized (where the patient could complete the CBT session at home). Both CBT topics earned an LOE score of 4. The rationale for this split allowed us to determine which subtype (traditional or computerized) was becoming the preferred clinical/research route. As expected, the number of active clinical trials using computerized CBT (six clinical trials) outweighed traditional versions of CBT (two clinical trials) interventions. The remaining topics of tactile tablet stimulation, serious games, auricular point acupressure, animal assisted therapy, acupuncture, musical-lexical based therapy, mindfulness training, smartphone personal assistant, and intense piano training treatment obtained an LOE score of 2. A notable computerized CBT therapy available now, known as BrainHQ, was derived from a completed FDA Phase II/III trial (NCT00298558). BrainHQ will be covered in detail within the "Case Studies" section of this report.

Three topics were identified within the Multimodal Interventions secondary category: **(1)** cognitive retraining plus one other treatment; **(2)** aerobic exercise plus one other treatment; and **(3)** risk factor modification plus cognitive retraining plus aerobic exercise. The first two "multi-modal interventions" obtained an LOE score of 4.

The topic of "risk factor modification plus cognitive retraining plus aerobic exercise" earned an LOE of 5. This is due in part to a groundbreaking study conducted in Finland known as the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (**FINGER**) study. The FINGER study was one of the first large multi-center RCT trials to show modifying lifestyle behaviors can drastically reduce the risk of a dementia diagnosis in elderly participants. Specifically, this multi-domain two-year RCT study found that a combination of exercise, brain games, diet, and social activity synergistically prevented the decline of cognitive function in adults with significant risk for dementia. The outcomes from the FINGER study are unmatched by any pharmacological intervention. In fact, the FINGER study is scheduled for replication in twenty-five countries, including the United States where it recently launched as the U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (**POINTER**) study. The U.S. POINTER Study started in January 2019 and has a recruitment target of 2,000 participants. The FINGER/U.S. POINTER study will be covered in detail within the "Case Studies" section of this report.

Case Studies

Based on the findings of this report, there are a number of non-pharmacological treatments being studied currently that document notable progress in the field's understanding of AD and offer opportunities for promising future research. The following case studies shine a light on some of the most cutting edge thinking in the field to date.

Transcranial Stimulation (tCS)

Transcranial stimulation (tCS) comprises three similar but distinct interventions: transcranial alternating current stimulation (tACS); transcranial magnetic stimulation (TMS); and transcranial direct current stimulation (tDCS). To recap, we identified multiple preclinical studies, many completed RCTs, and even six active clinical trials within the tCS topic. The concept of tCS is not novel and has been used for many years to treat depression and several other disorders. It has been tested for safety in many other clinical trials, has benefited from decades of published literature, has received FDA approval for other illnesses, and continues to receive a high level of clinical interest (as evidenced by the six active clinical trials). However, it is surprising that such a well-studied intervention does not have a single active or upcoming trial that meets the requirements for an FDA Phase III RCT. In fact, five of the six active trials did not exceed a study sample above 100. Policymakers looking to fund future trials should ask principal investigators to design studies that encompass large and representative sample

sizes. The continued funding of small RCTs (when several similar trials have already been completed) is unlikely to give researchers the evidence they need to conclude whether tCS is a viable therapy.

BrainHQ

Computer-based CBTs are increasing in popularity and have become a prevalent intervention used in clinical studies observing cognitive dysfunction. There are controversies that persist in regards to the therapeutic outcomes of such software programs. This may be due to "cognition" having several domains such as reasoning speed, processing speed, short-term memory, long-term memory, and attention. However, one therapeutic outcome with a specific population is very clear: The use of computerized cognitive training programs in normal aging, regardless of the domain studied, significantly improved cognitive and real-world performance. This is backed up by several large studies, well-executed clinical trials, and published meta-analyses.

BrainHQ, a commercially available cognitive retraining program, has published several peer-reviewed articles using the cohort from the ACTIVE study (NCT00298558) to show significant declines in the risk of a dementia diagnosis for older adults. However, upon closer inspection of the underlying data, BrainHQ participants showed only slight improvements in the domains of reasoning and processing speed and nonsignificant effects on memory.[1] Another concern with computer-based CBTs, such as BrainHQ, is the lack of a large currently active multicenter clinical trial for MCI and dementia/AD. Although there is strong evidence that computer exercises can reduce future risk of dementia in normal aging, there are no specific cognitive retraining protocols that have shown the ability to reverse symptoms in MCI or AD. We recommend that large multicenter RCT studies be conducted using BrainHQ or a similar type of computerized CBT for MCI or dementia/AD patient populations.

The FINGER Study

The FINGER Study, published in June 2015, is one of the most seminal non-pharmacological studies to be reported in recent years. The premise behind the FINGER study was to assess whether lifestyle changes can effect the risk of cognitive decline. Over 1,200 people were recruited for this multi-domain two-year clinical trial. It was considered a pioneering feat, because, prior to the FINGER study, lifestyle components were mainly assessed in an epidemiological or observational fashion. Although results from past studies have shown a link between lifestyle changes and a patient's risk of developing dementia, the lack of an RCT trial (considered the gold standard when it comes to research) prevented researchers from providing causal evidence. The FINGER study is also notable because of its methodology and research design. For example, the control and intervention group were almost equal in size (n=629 and n=631, respectively). This allowed valid conclusions to be drawn from parametric statistical analyses. Senior researchers were transparent and provided multiple ancillary reports, inclusion of adverse events, drop out rates, and other important indices related to the groups studied. Further, data was collected from six sites throughout Finland. This multi-center approach ensures subjects within the sample are truly representative of the overall population.

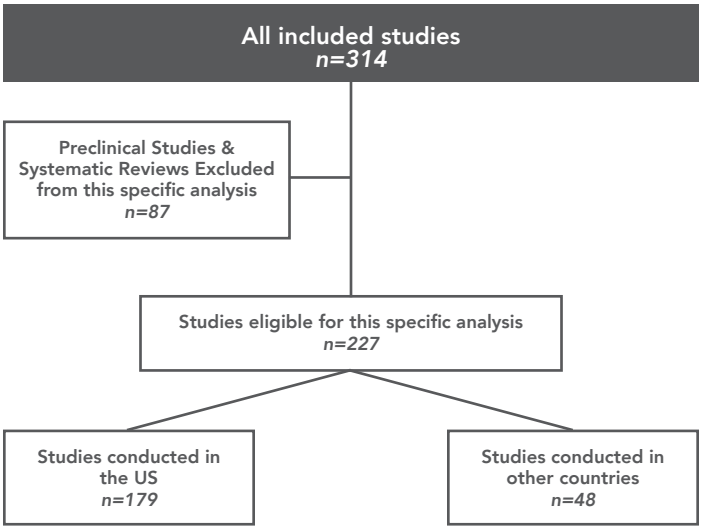
Prior to the FINGER study, many large cohort RCTs assessed the effect of a single independent variable or recruited from a single region/area. However, the FINGER study's results, novel approach to assessing multiple independent variables, and adherence to multi-site recruitment strategies proved how vital a well-planned study design is to powering and interpreting the primary outcomes envisioned. In addition, the FINGER study proves that AD is complex and multifaceted. Thus, researchers should consider multiple explanatory variables when conducting RCTs going forward. In summary, we strongly believe that the FINGER study provides a proof-of-concept protocol design that should serve as a viable blueprint for future trials in AD research. The FINGER study will be replicated within the U.S. as the POINTER study (clinical trial #: NCT03688126) in the near future.

1 "'Brain training' cut dementia risk in healthy adults – U.S. study." Reuters. July 24, 2016. https://www.brainhq.com/news/brain-training-cut-dementia-risk-in-healthy-adults-u-s-study/

Minority Recruitment

To assess whether current clinical trials were focusing on minority recruitment (women and other under represented populations), we devised an analysis of clinical studies based in the United States. For this specific analysis, we initially excluded 87 of the 314 studies as they were either Preclinical studies or Systematic Reviews (**Figure 5**). Of the remaining 227 studies, 48 were removed based upon country of origin (Figure 5). A final total of 179 studies conducted within the U.S. were identified.

Figure 5. Schematic for Identifying Active U.S. Clinical Trials.



Of the 179 studies conducted in the U.S., we identified 12 that specifically focused on non-pharmacological interventions in women or other underrepresented minority groups, such as African Americans. From the remaining 167 trials conducted within the U.S., we identified 56 trials that were currently active. In order to gauge the demographic criteria for inclusion, recruitment protocols, and study populations of these 56 trials, we reviewed the associated clinicaltrials.gov page or the ancillary methods paper. Specific indices identified were age, gender, minority recruitment protocols, and whether the trial leaders intended to share Individual Participant Data (**IPD**).

We found that all 56 active clinical trials published their recruitment strategy for age and gender. However, only 4 of the 56 (~7%) mentioned a specific or even general strategy for recruiting minority populations. Additionally, only 13 studies plan to share IPD information. The remaining 43 studies are either undecided, do not mention the IPD, or state they do not intend to disclose the information.

Table 4. Proportion of Active U.S. Clinical Trials and Associated Indices within Their Recruitment Strategy.

Active Clinical Trials in U.S. (n =56)	
Age	56/56 (100%)
Gender	56/56 (100%)
Minority Recruitment Plan	04/56 (7.1%)
Plan to Share IPD	
Yes	13/56 (23.2%)
No	17/56 (30.3%)
Undecided	13/56 (23.2%)
N/A	13/56 (23.2%)

Discussion

This report provides a comprehensive assessment of the non-pharmacological literature currently available and builds upon previously published findings. In order to obtain a truly holistic review we did not limit our searches to a particular subtype of intervention (e.g., cognitive-based treatments). Even with the expanded search net, we maintained a rigorous inclusion criterion, which allowed us to identify the most relevant findings and research. Within our total review, we identified fifty-five topics that were within our two primary subcategories. Only seventeen of the fifty-five (~30.9%) obtained an LOE score of 4 or 5.

Despite the overall number of identified RCTs and published findings, the proportion of high-quality studies was extremely low. Limitations included small sample sizes. Other problems identified were ambiguous specification of interventions, lack of rigorous outcome collection, inconsistent updates to federal databases, and untimely reporting of results.

Following the completion of this project on non-pharmacological interventions, we have identified gaps within the research literature. These gaps, if addressed, will provide novel insight that may prove to be valuable to the broader research community. First, we believe that promising research deserves confirmation studies. Upon review, we found that in many cases, the most promising interventions were not followed up by a larger confirmation study. Future confirmation studies that are designed using the gold standard of research (multicenter double-blinded randomized placebo control trials) would be of tremendous value to the patient population and the scientific community. In addition, we also found that many trials did not have the most up-to-date information available for review. Although standard data reporting protocols exist, they can be difficult to enforce. Future policymakers must prioritize this issue, as accurate and transparent data reporting are crucial to future success in the field.

A second concern is the lack of non-pharmacological interventions studying racial and ethnic minorities and women. Current and recently completed large studies often do not have patient populations that are representative of the demographic make-up of the American public. Our analysis found that of the 179 studies (both active and completed trials) in the United States, only 12 specifically focused on women and minority populations. Upon further reviewing the active clinical trials, only 4 studies (of a total 56) published a minority recruitment plan. Moreover, only 13 of the 56 indicated that they plan to publicly share their Individual Participant Data (IPD). Despite general consensus on the importance of recruiting minority populations and ensuring transparency with regard to data collection, our analysis shows that these efforts continue to fall short. Given that some racial and ethnic minorities face a greater risk of developing AD – for example, studies have shown that African Americans are twice as likely and Latinos are 1.5 times as likely to develop Alzheimer's than non-Hispanic whites – only makes this point all the more important. Further, the Latino and African American populations age sixty-five and older will grow 224% and 114%, respectively, by 2030, compared to a 65% growth rate for non-Hispanic white Americans. As dementia risk increases with advanced age, this demographic trend underscores the need to develop risk-reduction strategies targeting these communities. We strongly believe that more time and resources must be invested in developing non-pharmacological interventions tailored to high-risk communities to ensure feasibility and scalability via community health programming.

During the review of pertinent literature, we identified twenty-four studies that received an LOE score of 1 due to their preliminary results. Upon closer inspection of published reports, a majority of the studies were conducted and completed in low- and lower-middle-income countries (**LMIC**). We believe that this observation presents a promising opportunity. Although a majority of AD research is still conducted in North America and Europe, the recent success of studies with large subject recruitment in China, Japan, and India underscores the value of well-coordinated global research efforts.

Thus, future policies should aim to support global grant funding mechanisms. This will provide researchers based in LMICs the chance to develop substantive multi-center clinical research projects that could lead to the reporting of results that are more robust. Grant mechanisms should allow for consultations with statisticians to help inform adequate study designs, opportunities to take short-courses (laboratory/general procedures), and travel to conferences where they could interact with other researchers and report preliminary findings. We believe that inclusion of more AD researchers will provide a tremendous benefit to our understanding of Alzheimer's disease.

Conclusions

In this review, we sought to quantify and tabulate the breadth of non-pharmacological treatments being explored within AD research. Having identified a significant number of completed trials that do not meet several basic guidelines, did not recruit a representative sample population, and are not being followed by confirmatory trials, we conclude these issues require decisive action. In order to tackle AD and discover groundbreaking therapies, future researchers and policymakers must identify a more standardized approach to recruitment, prioritize funding for the most promising pilot studies, and aim to cultivate a pipeline that reflects the broad range of cutting-edge theories and approaches to attacking the disease.

Authors

Rakib Rayhan
Georgetown University Medical Center,
Howard University Department of Physiology/Biophysics

Patrick Rochelle
ResearchersAgainstAlzheimer's

Drew Holzapfel
UsAgainstAlzheimer's

George Vradenburg
UsAgainstAlzheimer's

Acknowledgements

A special thank you to the researchers who took time to review and provide feedback on the report, including: Dr. David Morgan, Ph.D., Michigan State University; Dr. Miia Kivipelto, M.D., Ph.D., Karolinska Institute; and Dr. William Vega, Ph.D., University of Southern California.

We would also like to thank the following researchers for providing input and feedback on the Level of Evidence (LOE) score outlined in this report. They include: Dr. Stuart Washington, Ph.D., Georgetown University; Dr. Kebreten Manaye, M.D., Howard University; Dr. Jahn O' Neil, Ph.D., Howard University; Dr. Syed Khundmiri, Ph.D., Howard University; and Dr. James N. Baraniuk, M.D., Georgetown University.

Contact

For inquiries about the report,
please contact Drew Holzapfel at
dholzapfel@usagainstalzheimers.org.

For media inquiries, please contact
melissagreen@rational360.com.