WW-FINGERS Network
AAIC In-person Meeting
Los Angeles, CA
July 12, 2019
Summary

Attendees: There were representatives from the following countries and organizations: South Korea, USA, Luxembourg, Japan, United Kingdom, Spain, Canada, Singapore, Australia, Argentina, India, World Health Organization, U.S. National Institute of Aging, U.S. National Institutes of Health

1. WW-FINGERS

Certain research gaps in research have been identified, including harmonization of methods, sparse information from low and middle-income countries, midlife versus late life risk factors and a lack of large random controlled trials. The WW-FINGERS network includes around 25 countries that have harmonize methods with the network though certain adaptations are made to the specific country. A level system has been implemented to designate the participating countries phase in their study.

WW-FINGERS is developing a master protocol but will include appendices for each countries’ trial-specific details.
Future plans for the network include the inclusion of a multimodal lifestyle + pharmacological prevention intervention as well as creating a biorepository.

2. US POINTER

This is a 2-year study with the target to enroll 2000 cognitively normal, 60-79 years of age individuals who are at an increased risk for cognitive decline due to a sedentary lifestyle, poor diet, suboptimal cardiovascular health, and a 1st degree family history of significant memory impairment. A key to US POINTER is the partnership with the community and local Alzheimer’s Association chapters. The recruitment to intervention timeline:

- EMR search ➔ mailed questionnaires ➔ telephone interview ➔ randomization ➔ assigned to teams ➔ outcomes assessment

The groups are self-guided intervention versus structured intervention, there is no control group. The self-guided group will receive more support than usual standard of care. Suggestion was that countries might need to increase the dose of intensity, also US POINTER has an elaborate education curriculum to increase participant retention that can be shared to the countries in the network.

The first site at Winston-Salem, North Carolina started enrollment and recruitment. 34,000 recruitment mailings were sent out and currently there are 24 participants randomized. The study also has ancillary studies that will focus on brain imaging, sleep and the gut microbiome.

3. MIND CHINA

Prevalence of dementia is more in rural than urban areas. The goal of the study was to test whether multimodal intervention programs help cognitive and physical functioning in the rural dwelling. The study involves vascular risk interventions and a multimodal intervention. This is a cluster-randomized controlled multimodal intervention study, where a cluster is the village. Age 60-79 year olds, exclusion criteria people with dementia, who have a disability/severely impaired.


4. Singapore: SINGER

The SINGER study conducted randomized clinical trials of multiple interventions in elderly patients at risk of cognitive decline. People were enrolled in either FINGER or SINGER intervention models. For SINGER, exercise will be in an exercise facility and there was an adaptation to the diet, for example Asian type fruits. In addition, evaluations
for SINGER will use pen and paper, while FINGER will be computerized. SINGER is currently in the 3rd intake and hope to finish studies next year.

Lessons learned during this study is that SINGER participants had high vascular risks, subjects were motivated and there was a high diet compliance to both diets. Further, exercise and diet from FINGER was highly receptive in Singapore. The major difference was control of vascular risk factors.

5. Australia Maintain Your Brain (MYB)
MYB is an internet based study with a primary outcome of decreased cognitive decline over 3 years, a secondary outcome is decreased incidence of dementia over 8 years. Participants were recruited from 45 and Up Study that had 267,000 people. The target of Maintain Your Brain is 8,000. There are 2 groups: internet coaching and an information group. Cognition is measured using Cogstate and Cambridge Brain Science and the domains tested are Verbal Paired Associates learning, visual memory, executive function, speed of information processing, working memory. For testing of function the Amsterdam Short Term Memory Test is being used.

The study has completed validation and most completed year 1. Invitations were sent to 96,000 and 14,000 consented which resulted in 6,236 being randomized.

Challenges the study had was building an IT platform, this took 2 years; clinicians and IT communications; engagement & adherence to training programs; maintaining participant enthusiasm, both groups declined in enthusiasm over time; engaging informants of participants; and completion of quarterly assessments in 1 year. Some participants had computers that didn’t support the study’s software.

6. Australia AU ARROW
AU AAROW will have 3 sites and they will incorporate the same trial design as U.S. POINTER. The primary outcome is cognition and the examples of secondary outcomes are blood and CSF biomarkers, brain amyloid imaging FDG PET, MRI. The team is currently seeking funding.

7. Europe GOIZ-ZAINDU
GOIZ-ZAINDU is in the Basque country, they will adapt the FINGER study to the area and plan to demonstrate feasibility in the general population. This study is a 1-year multimodal intervention program including people over 60 years in age, not demented but must test below expected cognitive test performance.

Participants population over 60+ of age is 4,500, and randomized 126 people into either the intensive multimodal group (61 participants) or regular health advice group (65 participants). Primary outcome is the CAIDE dementia score. Each group has a monthly workshop lead by a neuropsychologist and were given the option to either complete via a
computer based or paper program, vast majority chose paper format. The adherence rate is 68-75%.

Currently the effort is to replicate this study in a larger number of participants.

8. Europe (SPAIN) PENSA
The PENSA study will evaluate the efficacy of epigallocatechin gallat (EGCG) in a randomized double blind trial. This study will include a home based cognition test and have an exercise component.

Planning to start September 2019 with the first batch of participants.

9. EURO-UK
EURO-UK studies are ready for 5- and 7-year follow-ups and will start 10 year follow up next year. There is a need to identify the right at risk target individuals. Results have found lower risk of functional decline, better health related quality of life, 60% lowered risk for multi-morbidity, 20% lower risk for hospitalization.

- MIND AD
  - This has the same format as FINGER with a target group of prodromal AD defined with biomarkers. The goal is 125 participants. 1 arm multimodal intervention and medical food.
- UK FINGER
  - APOE enrichment, complex multi-domain intervention and pharma contribution (drug repurposing approach); new technology (repeated measures, follow up).
- EURO-FINGERS: there will be a master protocol and each country will have their own section. There will also be an online registry for recruitment.

10. CANADA THUMBS UP
Canada THUMBS UP currently has partial funding with an expected project launch of January 2020 of Phase A recruitment of a trial ready cohort of 2,000, there will be 2 phases with an emphasis on people with increased risk.

11. Latin America (LATAM)
LATAM is an initiative to develop joint regional efforts for the prevention of cognitive deterioration and dementia and share, compare and harmonize data. Twenty-nine Latin countries are interested consisting of high income and upper middle income, there are currently no low and middle income countries.

Sample size is 100 elderly adults per country, 60-77 years old, at risk of cognitive deterioration (50 per group: control and intervention). The study will evaluate self-guided versus more structured intervention and will evaluate participants at 6 and 12 months.

12. INDIA
Challenges for this study include diversity of language, education and socioeconomic factors. The study in India includes an Urban cohort - Tata longitudinal study of Aging (TLSA) and Rural Cohort Srinivasapura Gaging, Neuroscience… (SANSCOG). Populations for each group are: SANSCOG n=20,000, TLSA n=10,000. Urban cohort is high in diabetes, cholesterol, homocysteine, body mass index and white matter hyperintensity.

The study does not have access to PET ligands for beta amyloid and tau and cannot obtain CSF from people who are not ill. Outcome measures have to come from retinal imaging, etc. It is more likely to be able to conduct an intervention lifestyle in the highly educated urban cohort.

13. JAPAN J-MINT
The J-MINT study started 2 months ago and is a multicenter open-label randomized control trial with participants ages 65-85 years who have mild cognitive dysfunction. The study excludes individuals with a MMSE score less than 24.

There is a multicomponent exercise program and also a diet component. They will use a sensitive composite score as primary outcome and measure plasma biomarkers, development of polygenic risk score, mechanism of cognitive improvement, etc.

14. South Korea: Superbrain
Study to prevent cognitive impairment and protect brain health through lifestyle intervention. Participants who have vascular and metabolic risk factors and will engage in cognitive training, social activity, exercise and nutrition.

Outcome measures are: RBANS, MMSE, CDR, motivational questionnaires, sleep questionnaire, exploratory evaluation such as the microbiome, etc. The sample size is 150 participants and the study is single blind with 2 doctor’s visits and 6 nurse visits every 4 weeks. Exercise program 3 times per week, 60 minutes, implement support videos for the participants.

15. Master Protocol: Outcomes
The next step in the WW FINGERS network is to develop a Master Protocol. The goal is to develop a master protocol to encompass the Alzheimer’s disease continuum. The primary outcome is global cognitive composite score. For secondary outcomes, divide lists into compulsory versus recommended. Also should include exploratory outcomes and ancillary studies.

There is harmonization in the primary cognitive outcome across FINGER and POINTER, which is cognitive domain: episodic memory was measured using CERAD in FINGER and in U.S. POINTER they are using the Free and Cued Selective Reminding Test. For executive function & processing speed FINGER used concept shifting test and Stroop test.
One model that was proposed was for harmonization of cognitive outcomes across WW-FINGERS using episodic verbal memory and visual memory and each country will fill in what test they will use to measure these. The suggestion was to recommend a couple of standard tests that all countries can administer. If countries are not using the exact same measures results may differ but it should still be a representation of narrow domains, the focus can be on the pattern of result. The WW-FINGERS network need to have a standardization on how challenging the tests are.

All WW-FINGER network country leads agreed with this approach of identifying tests that will fit in the categories. Phase 2 will be to assess which tests are acceptable.

- **Action Item:** A committee will be formed from each country to establish the list.

It was discussed that batteries should be consistent on length. COhort Studies of Memory in an International Consortium (COSMIC) and Integrative Analysis of Longitudinal Studies of Aging and Dementia (IALSA) have conducted work similar to this.

**Key secondary outcomes:** Cognitive domains, subgroup analysis for primary & secondary outcomes. The network will specify core secondary outcomes and then allow countries to select if it is secondary or exploratory for their study.

- **Action Item:** Will convene a workgroup and provide a report for next year’s AAIC.

**Intervention:** Core elements - multiple lifestyles: diet, exercise, cognitive training and social stimulation, vascular risk management, group and individual visits …

**Diet:** Specify physiologic parameters such as nutrient levels as well as cardiovascular measures. Example, 4 key ingredients for brain health can be identified and then each country can adapt their foods to that list. Create a diet profile, SINGER and FINGER diets based on recommended sugars, fats, vitamin E, DHA, folic and fat compensation that play into brain health based on the literature.

**Exercise:** Need to quantify intensity, not just days/week. MIND CHINA use an actigraph, in China at lot are still working and have high level of steps in the 20,000 range. LATAM uses a wearable as well.

- **Action Item:** Create a survey to distribute to the network.

16. **Data Sharing**

The objective is to have a consensus and the main recommendation is to facilitate data sharing as early as possible where standardization, data acquisition techniques and assessments should be included. Screening and pre-randomization baseline data should be available within 12 months of study completion.
What data sharing can mean: 2 main alternatives, share the actual individual level data (files) between the partners in the network and maybe making them available for people outside of the network. It was a recommendation to identify a minimal data set (MDS) proposal, the characteristics will be simple and no room for interpretation. Anonymization can be difficult in different countries.

- **Action Item:** Establish a work group to identify climate around global data sharing, evaluate different alternatives for data sharing/combined data analyses, develop principles for data harmonization, and formulate a data access protocol. The work group will draft a written proposal on data harmonization and data sharing timelines.