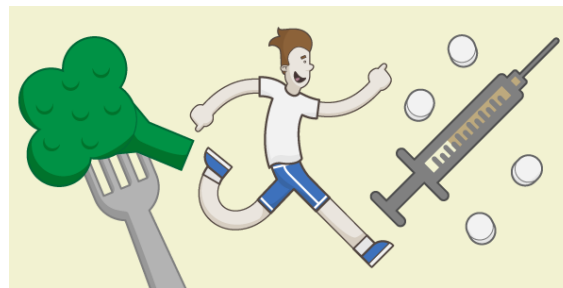


Adjourning Alzheimer's

Multidomain Interventions (Day 74)

The use of **multidomain interventions** to combat Alzheimer's is gaining ground. A multidomain intervention combines several single-domain interventions (such as medications, exercise, and dietary modification) to attack a disorder from as many angles as possible. Out of all the potential therapies we have discussed, multidomain interventions are the most difficult to follow. However, the right multidomain intervention could - potentially - impact the symptoms of Alzheimer's like no other.

Like dietary modification, multidomain interventions apply **multi-targeted epigenetic pressure over a sustained period of time**. In theory, a multidomain intervention can apply pressure from an even greater variety of angles compared to a dietary intervention. Let's look at the evidence supporting the two most talked-about multidomain interventions at the moment - FINGER and ReCODE.

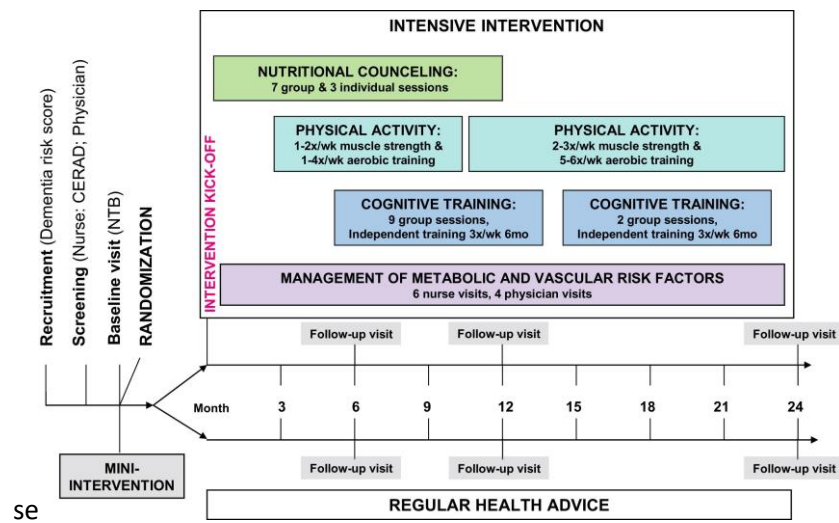


Multidomain interventions consist of several single-domain interventions, such as dietary modification, exercise, and medications.

In 2015, the **Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial** was published. This was a randomized controlled study in which 1,260 participants deemed "at risk" for cognitive impairment were randomized to a multidomain intervention group (consisting of four single-domain interventions) or a control group (general health advice) and followed for 2 years. Specifically, the four single-domain interventions were:

- (1) **Dietary modification** - Participants attended regular sessions where they were encouraged to eat a high-carbohydrate, low-fat diet consisting of 30% fat, 15% protein, and 50% carbohydrate by energy intake (15-20% fat, 20% protein, 60-65% carbohydrate by weight). The foods emphasized were fruits, vegetables, fish, cereals, low-fat milk and dairy, and vegetable margarine.
- (2) **Exercise** - Participants attended supervised aerobic or resistance exercise sessions (or both) one or more times a week.
- (3) **Cognitive training** - Participants attended regular sessions with psychologists, and regular social events were arranged.

(4) **Vascular risk factor education** - Participants met the study nurse regularly for vascular risk factor reduction advice.



The FINGER multidomain intervention - dietary modification, exercise, cognitive training, and vascular risk factor education.

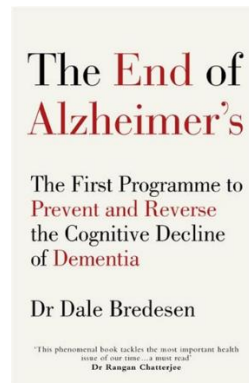
So, what were the results at the end of 2 years? There was a **very slight improvement in cognition** in the intervention group compared to the control group. These positive yet underwhelming results aside, there are several other factors to be aware of with regards to the FINGER study:

- (1) First, it examined **people “at risk” for cognitive impairment**, rather than people with Alzheimer’s.
- (2) Second, there were four interventions which collectively would have been **time-consuming** for the participants - a diet change plus regular exercise, cognitive training, and vascular risk factor reduction.
- (3) Third, even if we acknowledge the very slight improvement in the multidomain intervention group, we still cannot tell **which of the four single-domain interventions conferred the improvement**.

In 2014, United States neurologist **Dale Bredeesen** published a multidomain intervention program later dubbed the **Reversal of Cognitive Decline (ReCODE)** protocol. He published two single-arm studies in 2014 and 2016, each of which followed ten patients with varying degrees of cognitive impairment, for around 2 years. In 2018, he published a larger single-arm study of 100 patients.

The **ReCODE multidomain intervention** is unique in that it is essentially a “personalized program” tailored towards the main factors thought to be driving each person’s Alzheimer’s. For example, one person’s Alzheimer’s might be thought to be driven more by nutrient deprivation, whereas that of another might be thought to be driven more by mold exposure. Once the main risk factors are identified, a personalized program is instituted.

The ReCODE personalized program **differs for each person**. For one person, it included the elimination of simple carbohydrates, removal of gluten and processed foods, increase in vegetables, fruits, and non-farmed fish, yoga training, meditation for 20 minutes twice daily, melatonin, increase in sleep from 4-5 hours to 7-8 hours a night, methylcobalamin, vitamin D, fish oil, coenzyme Q10, optimized oral hygiene with an electronic toothbrush and flosser, the reinstatement of hormone replacement therapy, fasting for 12 hours a day including 3 hours before bedtime, and exercising for 30 minutes 4-6 times a week. Whew! Clearly, this was a very dedicated participant. However, there were many other people from the ReCODE studies with similarly comprehensive personalized programs.



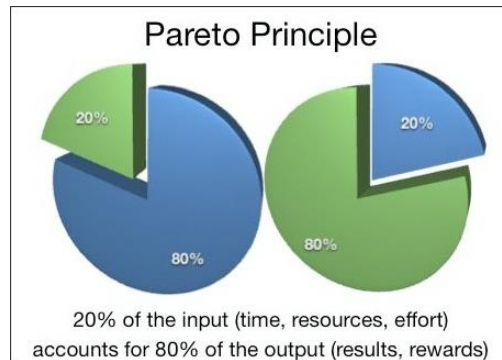
Bredesen wrote a book about ReCODE with the above title; if you see a book about “ending” something that has existed for thousands of years, just be careful about the author’s claim.

So, what were the results at the end of approximately 2 years? Most people showed **improvements in cognition**; some improvements were impressive, with a subset of people even returning to work. Moreover, there were some exceptional cases, notably a man who had an increase in hippocampal volume from the 17th to the 75th percentile (translation - an 8.5% increase in volume) after 10 months. These results seem good, but there are **several important factors** to be aware of with ReCODE:

- (1) First, even compared to FINGER, ReCODE is **time-consuming and expensive**; in his original paper, Bredesen himself wrote that none of the participants followed the entire protocol; it requires a lot of dedication and many tests and supplements that cost thousands (even tens of thousands) of dollars, a price beyond the financial reach of many people.
- (2) Second, we cannot tell **which single-domain intervention conferred improvement** in the ReCODE studies; perhaps two or three of the single-domain interventions conferred most of the improvement.
- (3) Third (most crucially), there was **no control group** in any of the ReCODE studies, and without a control group, we cannot tease out the contribution from a placebo effect (a well-described effect where people improve for the simple reason that they expect to; it can be strong).

ReCODE faces **several difficulties**. First, it is not a realistic option for many people with Alzheimer’s; the time and financial commitments are beyond what most can afford. Second, we need to know which single-domain interventions are conferring the improvement; this idea is illustrated by the Pareto Principle, which states that 80% of the outputs for any event come from 20% of the inputs. For

example, if it was known that the dietary modification and increase in sleep were responsible for 80% of the ReCODE improvements, then we might be able to achieve most of the improvements by just focusing on diet and sleep. Third, ReCODE needs to be tested with a control group in a **randomized controlled study**; frankly, a single-arm study is too prone to placebo effect and other sources of bias - the true test of a therapy is whether it survives a properly-designed randomized controlled study.



The Pareto Principle states that 80% of the outputs of an event come from 20% of the inputs; it makes sense to figure out which of the inputs are the really important 20%.

Let's sum up. Multidomain interventions may have promise in Alzheimer's, but they face several major difficulties. They are often time-consuming and costly, involve interventions that may not be doing anything at all, and in the case of ReCODE are highly prone to placebo effect and other potential sources of bias. If these difficulties could be addressed, then multidomain interventions, which potentially can incorporate all the potential therapies we have discussed plus more, **could become more achievable** and used by many people to impact the Alzheimer's pathological process.

Yet as things stand, applying a multidomain intervention is out of reach for many, **taking most people too far past the edge**, beyond the place where you challenge yourself. Yet we have a chance to improve the evidence for them right now. Given that the multidomain interventions contain a dietary modification, I sincerely hope you will join us for **The Alzheimer's Dietary Study**, so that we may find out if the dietary component of FINGER and ReCODE is effective or not, for they each emphasize two different diets - very similar to the two diets we will test against each other, as a matter of fact.

Matt (Neurologist, Waikato Hospital).

References

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- (4) Bredesen et al. 2018. Reversal of Cognitive Decline: 100 Patients. *J Alzheimers Dis Parkinsonism* 8(5), 1-6.