RESULTS FROM THE SYSTEMATIC MULTI-DOMAIN ALZHEIMER’S RISK REDUCTION TRIAL (SMARRT)

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CONFLICT OF INTERESTS

• I have no conflict of interest to report.
• Details of all authors conflict of interest can be found at: https://www.j-alz.com/manuscript-disclosures/18-0634r2
BACKGROUND

• Alzheimer disease and related dementias (ADRD) are highly prevalent, costly and feared.
• Urgent unmet need for prevention and treatment
• Medications have limited impact on ADRD prevention and treatment and might have severe adverse effects.
• Multicomponent interventions to address ADRD have been recommended.
• 40% of ADRD risk might be modifiable by targeting lifestyle, medical and behavioral risk factors
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk for dementia (95% CI)</th>
<th>SMARRT Selected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less Education</td>
<td>1.6 (1.3-2.0)</td>
<td></td>
</tr>
<tr>
<td>Hearing Loss</td>
<td>1.9 (1.4-2.7)</td>
<td></td>
</tr>
<tr>
<td>Traumatic Brain Injury</td>
<td>1.8 (1.5-2.2)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.6 (1.2-2.2)</td>
<td>X</td>
</tr>
<tr>
<td>Alcohol (&gt;21 units/wk)</td>
<td>1.2 (1.1-1.3)</td>
<td></td>
</tr>
<tr>
<td>Obesity (BMI 30+)</td>
<td>1.6 (1.3-1.9)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1.6 (1.2-2.2)</td>
<td>X</td>
</tr>
<tr>
<td>Depression</td>
<td>1.9 (1.6-2.3)</td>
<td>X</td>
</tr>
<tr>
<td>Social Isolation</td>
<td>1.6 (1.3-1.9)</td>
<td>X</td>
</tr>
<tr>
<td>Physical Inactivity</td>
<td>1.4 (1.2-1.7)</td>
<td>X</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.5 (1.3-1.8)</td>
<td>X</td>
</tr>
<tr>
<td>Air pollution</td>
<td>1.1 (1.1-1.1)</td>
<td></td>
</tr>
<tr>
<td>Risky Medication</td>
<td>1.1-1.5 (1.0-1.5)</td>
<td>X</td>
</tr>
<tr>
<td>Sleep</td>
<td>1.2 (1.1-1.3)</td>
<td>X</td>
</tr>
<tr>
<td>Cognitive Activity</td>
<td>1.8 (1.4-2.3)</td>
<td>X</td>
</tr>
</tbody>
</table>

BACKGROUND

• A recent Cochrane Review (2021) of multi-domain dementia interventions found a small beneficial effect on cognitive functioning (mean difference 0.03 sd on neuropsychological test batteries)
• The FINGER trial showed a small increase in cognitive functioning after a 2-year intervention (Ngandu et al, Lancet, 2015)
• However, several multidomain trials have been negative (MAPT, preDIVA etc)
• Few multi-domain studies conducted in US
• None with a personalized approach
THE SYSTEMATIC MULTI-DOMAIN ALZHEIMER’S RISK REDUCTION TRIAL (SMARRT)

A pilot RCT comparing a 2-year personalized risk reduction intervention (SMARRT) to a health education control condition in adults aged 70-89 with two or more identified risk factors
INCLUSION & EXCLUSION

Setting

• Kaiser Permanente Washington

Inclusion Criteria

• Age 70-89
• English Language Fluency
• 2+ risk factors for AD/ADRD

Exclusion Criteria

• Reside in skilled nursing facility
• Receive palliative or hospice care,
• High comorbidity score (Charlson score of > 5)
• Serious mental illness
• Parkinson’s, Amyotrophic Lateral Sclerosis, or Multiple Sclerosis
• Severe visual impairment
• Diagnosis of dementia or Cognitive Abilities Screening Instrument Score <25 indicative of ADRD
RANDOMIZATION

• Interested and eligible participants were randomized 1:1 to either SMARRT personalized intervention or Health Education (HE) control,
• Stratified on clinic, age, and race/ethnicity
Translating Research Evidence into Clinical Geriatric Mental Healthcare

ASSESSMENT

Baseline

Randomize

SMARRT Intervention

Health Education

6-month assessment

12-month assessment

18-month assessment

24-month assessment

Health coach sessions

General info by mail

Stop
CONTROL GROUP: HEALTH EDUCATION

• HE group received mailed educational materials every three months

• The materials, from the Alzheimer’s Association and KPWA on dementia risk reduction, which including addressing risk factors targeted in the SMARTT intervention

What is cardiovascular disease?
Cardiovascular disease refers to the disease of the heart and blood vessels and can include coronary heart disease, atherosclerosis (blocking and narrowing of the arteries), deep vein thrombosis (blood clot) and stroke. Often there are no overt symptoms of cardiovascular disease and a heart attack or stroke may be the first indication of underlying disease.

What is the link between dementia and heart disease?
Quite simply, the brain needs a healthy heart and healthy blood vessels to provide a good blood supply to keep brain cells functioning well.

The association between the risk factors for cardiovascular disease and dementia is strong, with a close link between brain health and heart health.

Brain & Heart Health
What's the Connection?

What can I do to reduce my risk of dementia and cardiovascular disease?

Have regular check-ups
All adult Americans from the age of 18 years should have their blood pressure checked regularly and follow their doctor’s advice about having their blood cholesterol and blood glucose levels tested. Generally, it is recommended that adults aged 45 years and older see their doctor regularly for a heart and stroke risk assessment.

Take medicines as directed
As well as leading a healthy lifestyle, some people will need to take medicines for the long term to manage their blood pressure, blood cholesterol or blood glucose levels, and to reduce their risk of heart attack, stroke and dementia. If you have to take medicines, follow your doctor’s advice and see him or her regularly to make sure the medicines are working properly.

Lead a healthy lifestyle
To help control your risk of developing dementia and cardiovascular disease you should:
• Eat healthy
• Reduce excess body weight
• Be physically active
• Be smoke-free
• Limit your alcohol intake
• Be socially active
### SMARRT INTERVENTION: TARGETED RISK FACTORS

<table>
<thead>
<tr>
<th>Risk Factor addressed by RN</th>
<th>Risk Factor addressed by HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risky Medications</td>
<td>Depression</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Sleep</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Physical Inactivity</td>
</tr>
<tr>
<td></td>
<td>Social Isolation</td>
</tr>
<tr>
<td></td>
<td>Tobacco Use</td>
</tr>
<tr>
<td></td>
<td>Diet</td>
</tr>
<tr>
<td></td>
<td>Cognitive Activity</td>
</tr>
</tbody>
</table>
NURSE CARE MANAGER

Nurse trained in Motivational Interviewing

Provided:

- Risk Factor review and personalized feedback
- Medication Review
- Action Planning
- Communication with PCP
HEALTH COACH

Health coaches trained in motivational interviewing provided:

- Personalized feedback on risk factors
- Discussion of which risk factors are most important and which they feel ready to address now
- Review of relevant risk factor modules
- Action planning with personalized goal setting, linking to values, encouragement to self-monitor
Personalized Profile of Your Risk Factors for Dementia

- Did you know that 30% (3 in 10) cases of dementia may be caused by modifiable risk factors? Over the past few weeks, you’ve answered many of our questions about different risks you may have for developing dementia.

- The good news is that there are many things you are doing that will help protect you from developing dementia (indicated with a green traffic light). Your coach will help you keep up the good work with these health habits.

- There are also several risk factors that nearly all of us could do a better job of building into their lifestyle (indicated with a yellow traffic light).

- There are some risk factors that may put you at higher risk for developing dementia (indicated with a red traffic light).

- Your health coach will work with you over the next 2 years to make improvements in these areas.

RISK FACTOR:

- risky medications
- exercise
- mood
- brain activities
- diabetes
- social activity
- sleep
- smoking
- diet
- hypertension

Personalized Action Plan:

Setting goals is an important first step toward improving brain health.

Why is this health factor important to me?

Goal:

What steps will I take? Be specific (when, where, with whom):

What might get in the way?

What can I do to make it easier?

Continue with this goal? Y N Notes:
ANALYSIS

Primary Outcome: 2-year cognitive change in on the Modified Neuropsychological Test Battery z-score
• Baseline done in person, but due to COVID switched to remote assessment altering the data collection

Secondary Outcomes:
1) 2-year change in composite AD risk factors z-score
2) Quality of life (composite score) PROMIS Global Health Measure

Analysis
• Used linear mixed models to compare changes from baseline, averaged over follow-up by intention-to-treat, adjusted for sex, race/ethnicity, education, comorbidity score, and phone assessment (to control for Covid)

Other Outcomes
• Satisfaction
• Quantitate Analysis of intervention
RESULTS
Sampled from EMR
N = 4,087

Phone Screened
N = 3017

Eligible and Interested
N = 234

Enrolled/Randomized
N = 172

Withdrew or Lost to Follow-up
N = 19
193 MMARRT, 8 HE

Completed
N = 149
68 MMARRT, 82 HE

Deceased
N = 4
(3 MMARRT, 1 HE)

n=1,070 Not reached

n=1,195 ineligible at screener
n=1,588 Not interested in study

n=43 Declined before baseline
n=5 Ineligible at baseline
n=14 Baseline cancelled due to COVID
## BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Mean(SD) or N(%)</th>
<th>Control (n=90)</th>
<th>Intervention (n=82)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>75.6 (4.7)</td>
<td>75.8 (4.9)</td>
<td>0.82</td>
</tr>
<tr>
<td>Female</td>
<td>51 (56.7%)</td>
<td>57 (70.4%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>White</td>
<td>76 (84.4%)</td>
<td>64 (78.0%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>9 (6.7%)</td>
<td>9 (11.0%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>5 (5.6%)</td>
<td>3 (3.7%)</td>
<td></td>
</tr>
<tr>
<td>American Indian</td>
<td>4 (4.4%)</td>
<td>2 (2.4%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (4.4%)</td>
<td>4 (4.9%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic Ethnicity</td>
<td>5 (6.5%)</td>
<td>2(3.1%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Education, years</td>
<td>16.4 (2.4)</td>
<td>16.0 (2.8)</td>
<td>0.34</td>
</tr>
<tr>
<td>Elixhauser Comorbidity Score</td>
<td>2.3 (1.7)</td>
<td>2.8 (1.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>CASI Telephone</td>
<td>29.8 (1.8)</td>
<td>29.6 (2.1)</td>
<td>0.48</td>
</tr>
</tbody>
</table>
## BASELINE RISK FACTORS

<table>
<thead>
<tr>
<th>Mean(SD) or N(%)</th>
<th>Control (n=90)</th>
<th>Intervention (n=82)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>73 (81.1%)</td>
<td>64 (78.0%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Poorly controlled hypertension</td>
<td>43 (47.8%)</td>
<td>41 (50.0%)</td>
<td>0.88</td>
</tr>
<tr>
<td>Poor sleep</td>
<td>43 (48.3%)</td>
<td>40 (48.8%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Risky medications</td>
<td>18 (20.0%)</td>
<td>15 (18.3%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Depression</td>
<td>15 (16.9%)</td>
<td>15 (18.3%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Poorly controlled diabetes</td>
<td>8 (8.9%)</td>
<td>12 (14.6%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Social isolation</td>
<td>8 (9.0%)</td>
<td>12 (14.6%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Smoking</td>
<td>6 (6.7%)</td>
<td>8 (9.8%)</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>Number of Risk Factors</strong></td>
<td>2.4 (0.6)</td>
<td>2.5 (0.7)</td>
<td>0.17</td>
</tr>
</tbody>
</table>
## RISK FACTORS WORKED ON

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Health Coach</th>
<th>Nurse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Activity</td>
<td>78 (95.1)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (9.8)</td>
<td>59 (72.0)</td>
</tr>
<tr>
<td>Cognitive Activity</td>
<td>49 (59.8)</td>
<td></td>
</tr>
<tr>
<td>Sleep</td>
<td>43 (52.4)</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>39 (47.6)</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>37 (45.1)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Social Engagement</td>
<td>34 (41.5)</td>
<td></td>
</tr>
<tr>
<td>Risky Meds</td>
<td>4 (4.9)</td>
<td>18 (22.0)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3 (3.7)</td>
<td>10 (12.2)</td>
</tr>
<tr>
<td>Tobacco</td>
<td>4 (4.9)</td>
<td></td>
</tr>
</tbody>
</table>
NUMBER OF GOALS SET FOR RISK FACTORS
Average treatment effect = 0.15 sd (0.04, 0.26); p = 0.008
RESULTS: SECONDARY OUTCOMES

Risk Factor Composite

Average treatment effect = 0.11 sd (0.02, 0.21); p = 0.02
RESULTS: SECONDARY OUTCOMES

Average treatment effect = 1.11 ± 0.08 to 2.14; p = 0.03

Quality of Life

![Graph showing Quality of Life over time with intervention and control groups. The graph illustrates the change in Quality of Life since baseline across different visit months. The average treatment effect is highlighted as 1.11 ± 0.08 to 2.14 with a p-value of 0.03.](image-url)
RESULTS: SATISFACTION

Survey given to participants at 24-month visit
4-point scale: 1=not satisfied, 2=a little satisfied, 3=satisfied, 4=very satisfied

<table>
<thead>
<tr>
<th></th>
<th>Intervention Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>Between group significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfaction with study overall</td>
<td>3.7 (.45)</td>
<td>3.5 (.66)</td>
<td>p=.02</td>
</tr>
<tr>
<td>Satisfaction with study’s ability to improve health</td>
<td>3.4 (.68)</td>
<td>2.9 (1.0)</td>
<td>p&lt;.001</td>
</tr>
</tbody>
</table>
RESULTS: ADVERSE EVENTS

• All SAEs (deaths, serious illness, hospitalizations) were unrelated to the study and were equal by group (SMARRT=24, HE=23, p=0.59)

• The intervention group reported 14 AEs possibly related to treatment (e.g., pain); no treatment-related AEs in the HE group

• Exploratory outcome:
  • Incident low CASI score (<27) or diagnosis of MCI/ dementia, N=13
  • 5 in the intervention (6.9%) and 8 in the HE group (9.6%), p=0.55
CONCLUSIONS

• The SMARRT intervention led to modest statistically significant improvements in cognition and targeted risk factors, as well as quality of life over 2 years

• Participants are satisfied with the intervention

• SAE and AE are minimal for this type of intervention

• Effect size greater than prior multidomain trials despite COVID
LESSONS LEARNED

• COVID limited our assessment of some cognitive and risk factor outcomes, but increased the pragmatic nature of the study (i.e., remote intervention and data collection)

• Physical activity, sleep and diet were the most common goals set with the Health Coach.

• Hypertension and risky medications are the most common goals set with the Nurse.

• Risky medication work should include OTCs

• Effectiveness may be attributable to a personalized approach.

• This study paves the way for a larger multi-site personalized trial for AD prevention
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