



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

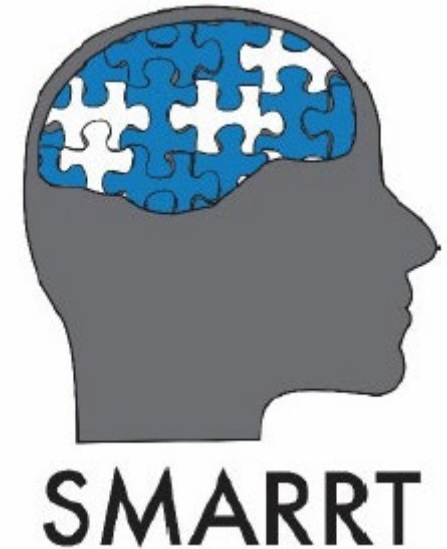
| Risk Factor | Relative Risk for dementia (95% CI) | SMARRT Selected |
|------------------------|-------------------------------------|-----------------|
| Less Education | 1.6 (1.3-2.0) | |
| Hearing Loss | 1.9 (1.4-2.7) | |
| Traumatic Brain Injury | 1.8 (1.5-2.2) | |
| Hypertension | 1.6 (1.2-2.2) | X |
| Alcohol (>21 units/wk) | 1.2 (1.1-1.3) | |
| Obesity (BMI 30+) | 1.6 (1.3-1.9) | |
| Smoking | 1.6 (1.2-2.2) | X |
| Depression | 1.9 (1.6-2.3) | X |
| Social Isolation | 1.6 (1.3-1.9) | X |
| Physical Inactivity | 1.4 (1.2-1.7) | X |
| Diabetes | 1.5 (1.3-1.8) | X |
| Air pollution | 1.1 (1.1-1.1) | |
| Risky Medication | *1.1-1.5 (1.0-1.5) | X |
| Sleep | 1.2 (1.1-1.3) | X |
| Cognitive Activity | 1.8 (1.4-2.3) | X |

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 & EXCLUSION⁷

Setting

- Kaiser Permanente Washington

Inclusion Criteria

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

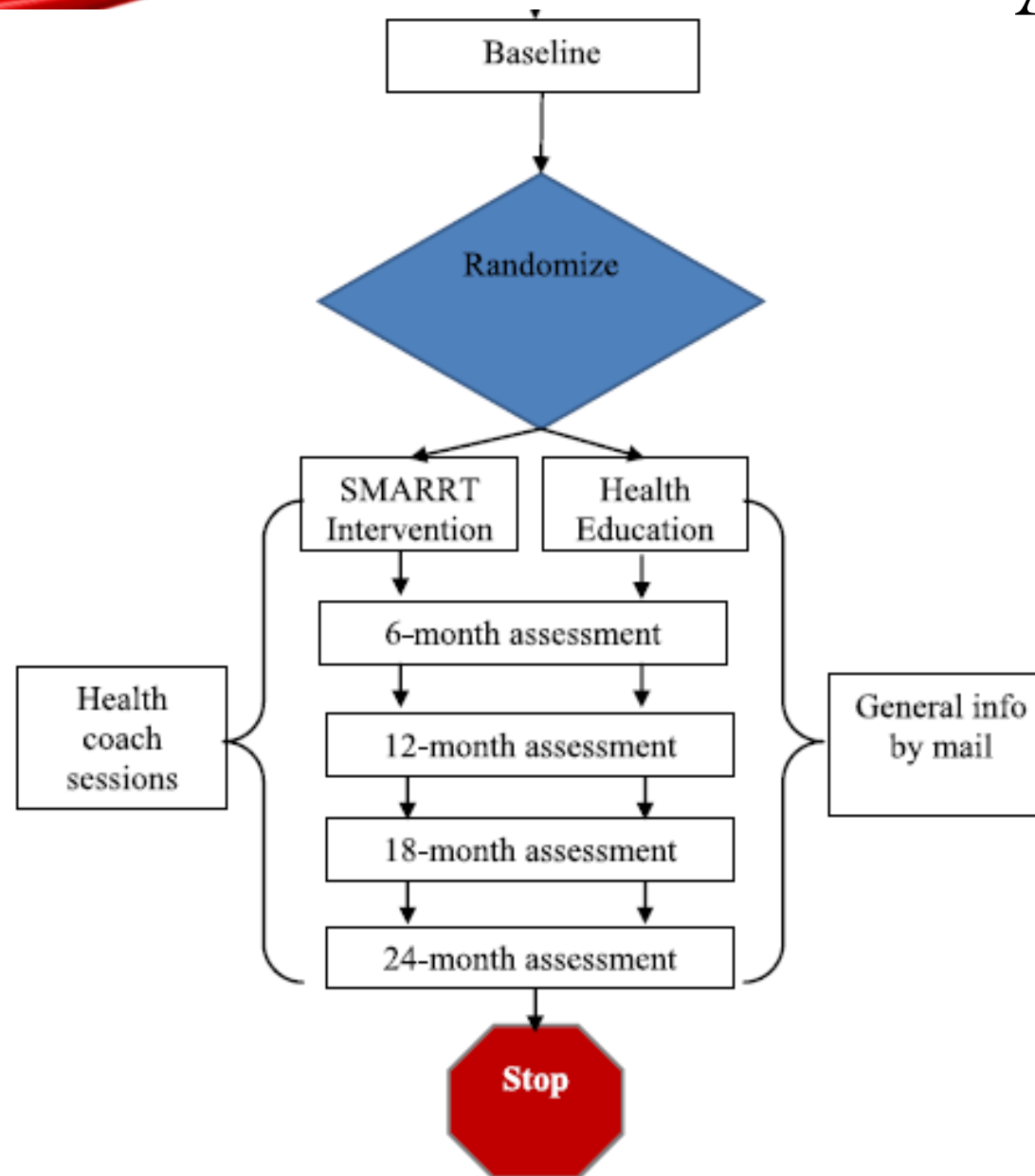
Exclusion Criteria

- 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 SMART personalized intervention or Health Education (HE) control,
- Stratified on clinic, age, and race/ethnicity

ASSESSMENT⁹



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 SMARRT intervention

Brain & Heart Health What's the Connection?

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

What is cardiovascular disease?

Cardiovascular disease refers to the disease of the heart and blood vessels and can include coronary heart disease, atherosclerosis (clogging and narrowing of the arteries), deep vein thrombosis (blood clots) 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. Over the years, a growing body of research has found a strong connection between cardiovascular risk factors (such as high blood pressure and blood cholesterol levels) and dementia. Findings have shown that what is good for our heart is also good for our brain.

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

SMART INTERVENTION: TARGETED RISK FACTORS

Risk Factor addressed by RN

Risky Medications

Hypertension

Diabetes

Risk Factors addressed by HC

Depression

Sleep

Physical Inactivity

Social Isolation

Tobacco Use

Diet

Cognitive Activity

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 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.

| | |
|---|--|
|  | <ul style="list-style-type: none"> ✓ Physical Activity ✓ High blood pressure ✓ Medications that impact brain health |
|  | <ul style="list-style-type: none"> ✓ Brain training activities ✓ Following a healthy diet for your brain health |
|  | <ul style="list-style-type: none"> ✓ Social activities ✓ Sleep ✓ Healthy mood ✓ Not smoking ✓ No diabetes |

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:

Date:

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)

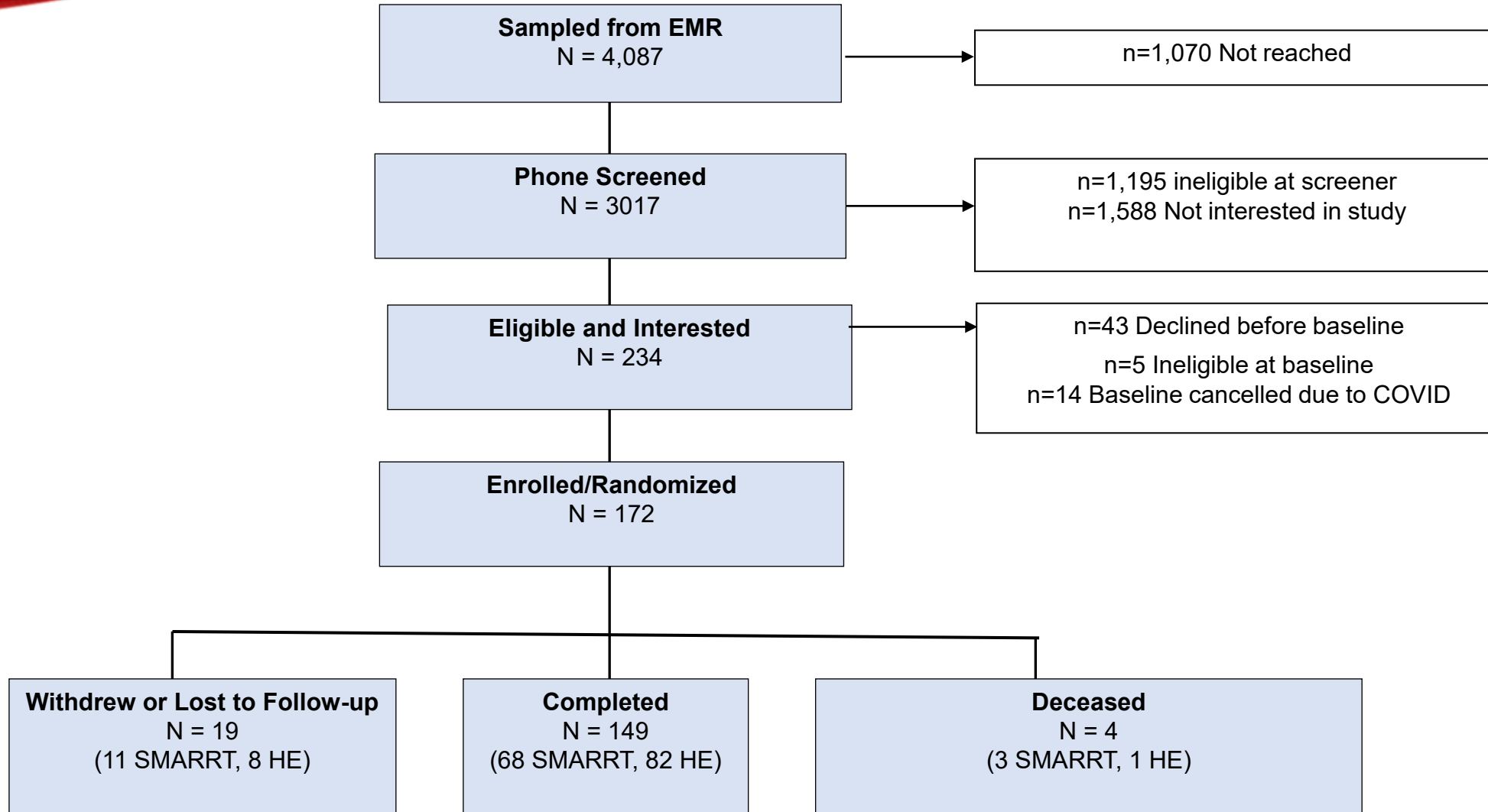
Other Outcomes

- Satisfaction
- Quantitate Analysis of intervention

RESULTS



RECRUITMENT¹⁷



BASELINE CHARACTERISTICS

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

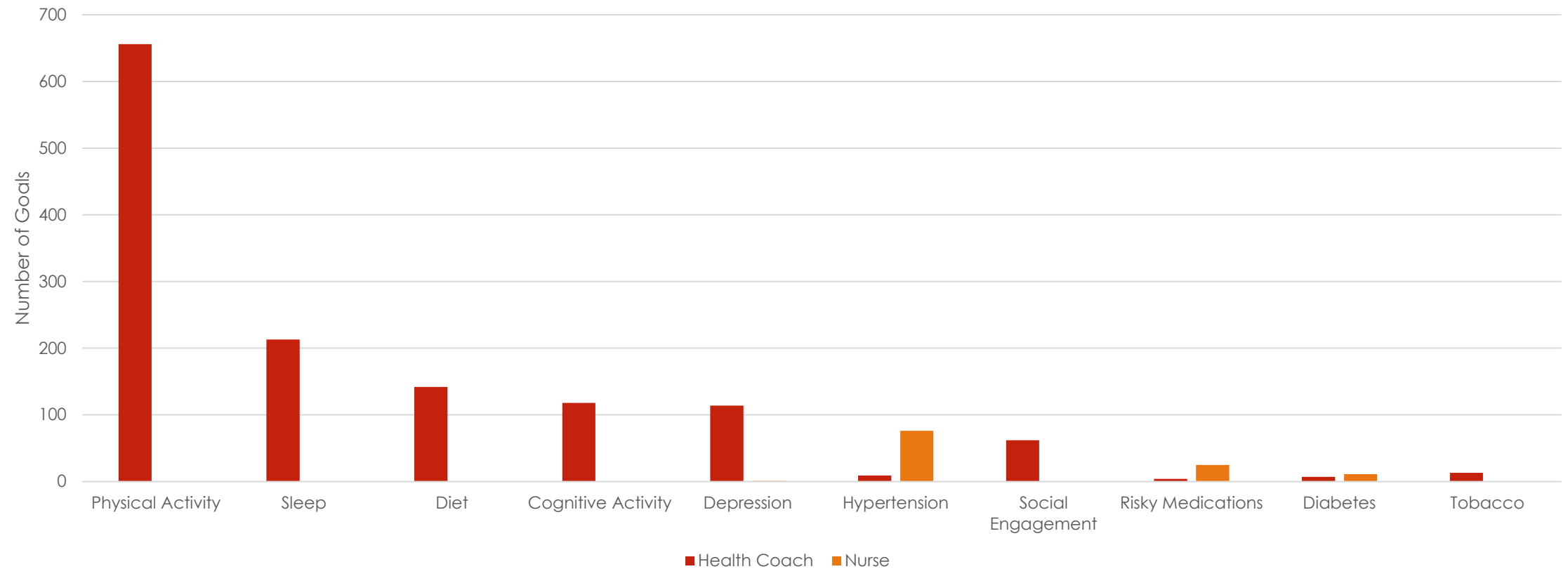
BASELINE RISK FACTORS

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

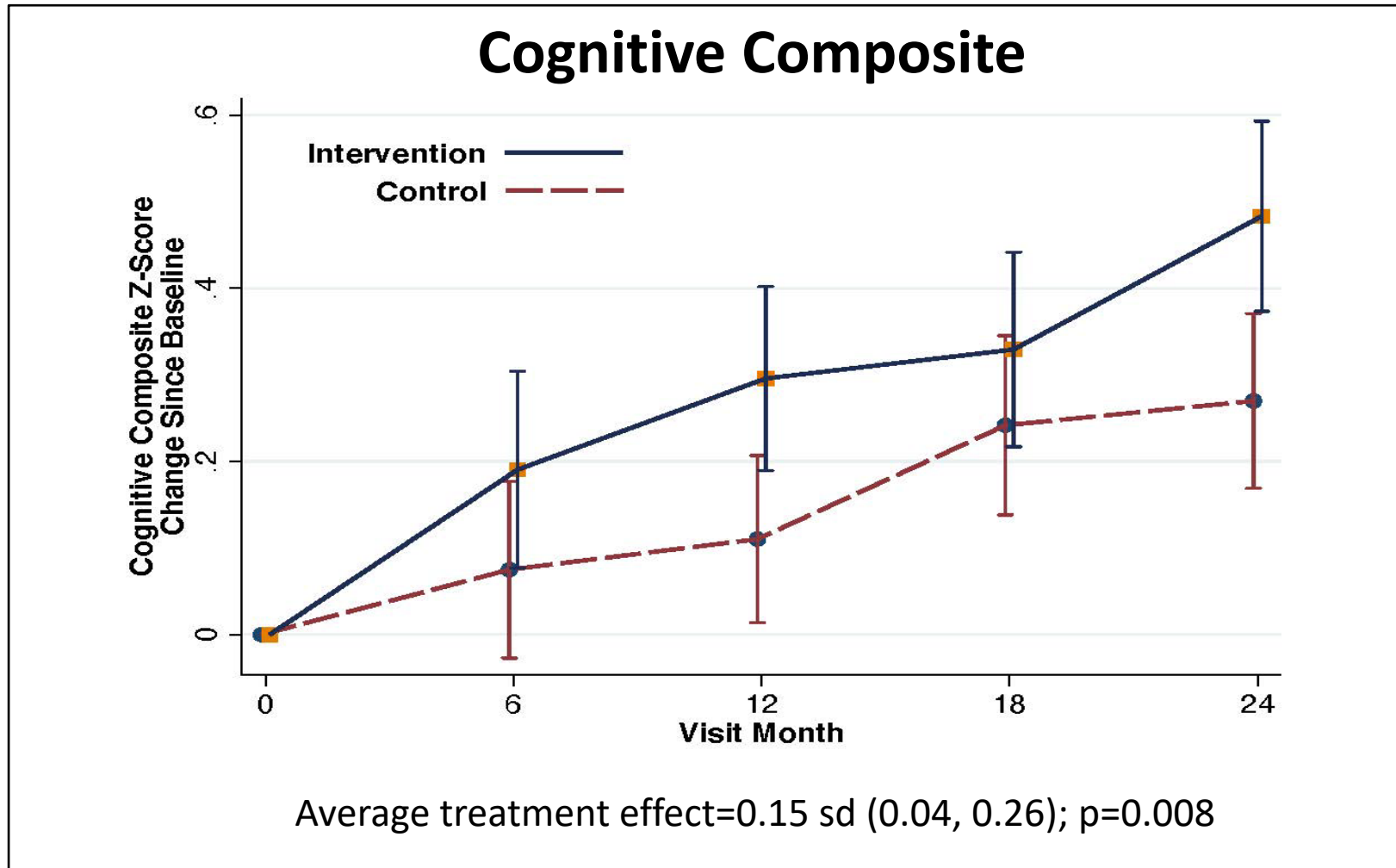
RISK FACTORS WORKED ON

| | Number (%) of Participants | |
|---------------------------|----------------------------|-----------|
| | Health Coach | Nurse |
| Physical Activity | 78 (95.1) | |
| Hypertension | 8 (9.8) | 59 (72.0) |
| Cognitive Activity | 49 (59.8) | |
| Sleep | 43 (52.4) | |
| Diet | 39 (47.6) | |
| Depression | 37 (45.1) | 1 (1.2) |
| Social Engagement | 34 (41.5) | |
| Risky Meds | 4 (4.9) | 18 (22.0) |
| Diabetes | 3 (3.7) | 10 (12.2) |
| Tobacco | 4 (4.9) | |

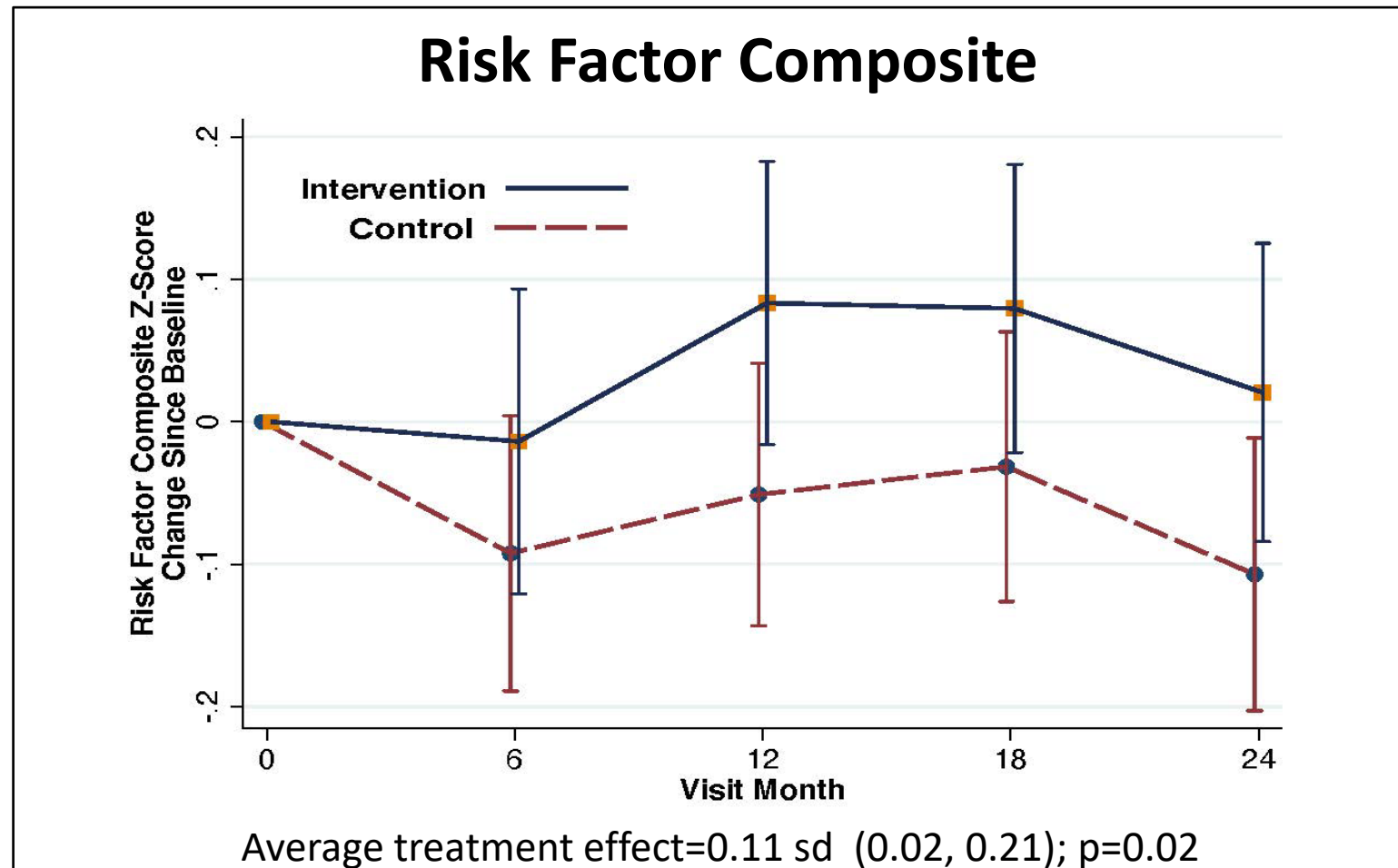
NUMBER OF GOALS SET FOR RISK FACTORS



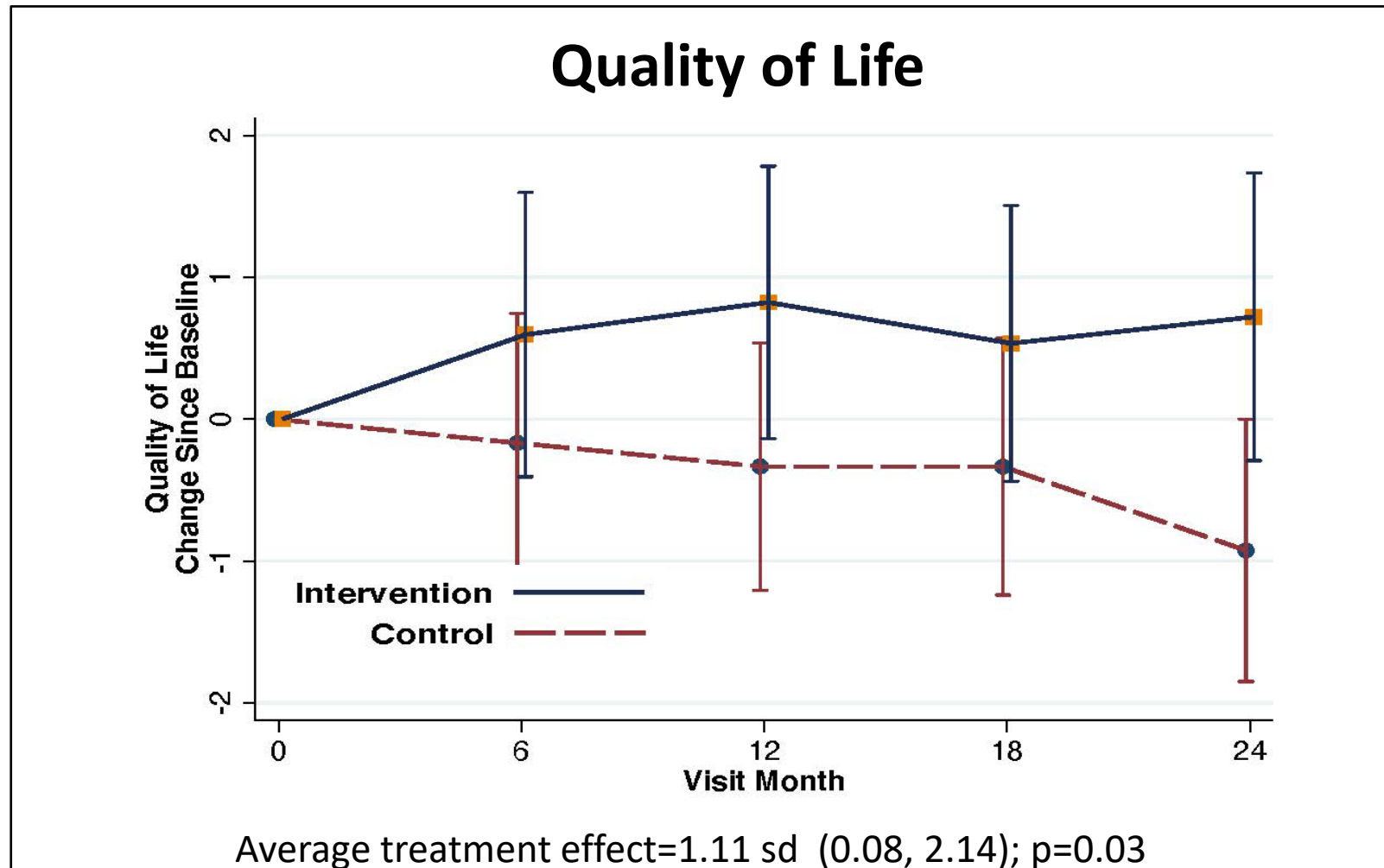
RESULTS: MAIN OUTCOME



RESULTS: SECONDARY OUTCOMES



RESULTS: SECONDARY OUTCOMES



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

| | Intervention Mean (SD) | Control Mean (SD) | Between group significance |
|--|-----------------------------------|------------------------------|---------------------------------------|
| Satisfaction with study overall | 3.7 (.45) | 3.5 (.66) | p=.02 |
| Satisfaction with study's ability to improve health | 3.4 (.68) | 2.9 (1.0) | p<.001 |

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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