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Original Research

Sex-Driven Differences in the Effectiveness of Individualized Clinical Management of Alzheimer's Disease Risk

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Abstract

BACKGROUND: The Comparative Effectiveness Dementia & Alzheimer's Registry (CEDAR) trial demonstrated that individualized, multi-domain interventions improved cognition and reduced the risk of Alzheimer's disease (AD). As biological sex is a significant risk factor for AD, it is essential to explore the differential effectiveness of targeted clinical interventions in women vs. men.

METHODS: Patients were recruited from an Alzheimer's Prevention Clinic. Subjects with normal cognition, subjective cognitive decline, or asymptomatic preclinical AD were classified as "Prevention". Subjects with mild cognitive impairment due to AD or mild AD were classified as "Early Treatment." The primary outcome was the change from baseline to 18-months on the modified-Alzheimer's Prevention Cognitive Composite. Secondary outcomes included a cognitive aging composite, AD and cardiovascular (CV) risk scales, and serum biomarkers. Subjects who adhered to >60% of recommendations in the CEDAR trial were included in this a priori sub-group analysis to examine whether individualized intervention effects were modified by sex (n=80).

RESULTS: In the Prevention group, both women (p=0.0205) and men (p=0.0044) demonstrated improvements in cognition with no sex differences (p=0.5244). In the Early Treatment group, there were also no significant sex differences in cognition (p=0.3299). In the Prevention group, women demonstrated greater improvements in the Multi-Ethnic Study of Atherosclerosis risk score (MESA-RS) than men (difference=1.5, p=0.0013). Women in the Early Treatment group demonstrated greater improvements in CV Risk Factors, Aging and Incidence of Dementia (CAIDE) risk score (difference=2.3, p=0.0067), and the MESA-RS (difference=4.1, p<0.001).

CONCLUSIONS: Individualized multi-domain interventions are equally effective at improving cognition in women and men. However, personally-tailored interventions led to greater improvements in calculated AD and CV risk, and CV blood biomarkers, in women compared to men. Future study in larger cohorts is necessary to further define sex differences in AD risk reduction in clinical practice.

Key words: Alzheimer's Prevention Clinic, Alzheimer's disease; precision medicine, sex-driven differences.

Introduction

Alzheimer's disease (AD) develops over an extended preclinical period, with amyloid plaques, neurofibrillary tangles, and glucose hypo-metabolism occurring at least 15-20 years before the onset of symptoms (1-4). Considering the limited progress with developing effective, disease-modifying therapeutics to treat AD, along with the fact that an estimated 46 million Americans have preclinical AD, clinical and research efforts have begun to focus on delaying, or possibly preventing, progression to dementia (5).

Research has continued to identify modifiable risk factors throughout the lifespan for AD, such as hypertension, diabetes, and cardiovascular (CV) disease, among others (6-8). Population-attributable risk models have suggested that managing such risk factors can prevent up to one-third of dementia cases, highlighting the immense potential that lies in addressing modifiable risk factors. Several large-scale, randomized controlled trials (RCTs) have shown that multi-domain lifestyle-based interventions, including nutrition, exercise, and cognitive training, can ameliorate vascular and lifestyle-related risk factors, maintain cognitive function, and reduce the risk of dementia (9-12). In an effort to translate these findings into clinical practice, the Comparative Effectiveness Dementia & Alzheimer's Registry (CEDAR) study showed that individualized clinical management using multi-domain interventions geared for AD risk reduction was feasible in an outpatient clinic setting. Significant improvements in cognition were found from baseline to 18-months when compared with two matched historical control cohorts (National Alzheimer's Coordinating Center; Rush Memory and Aging Project). Reductions in calculated AD and CV risk scores, and improvements in serum AD risk biomarkers were also found (13).

While it is encouraging that multi-domain

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interventions may reduce modifiable AD risk, the effectiveness of these approaches has not yet been robustly investigated with consideration for sex. Research has suggested that after increasing age, the most significant risk factor for AD dementia is female sex—two-thirds of AD patients are females (14, 15). Statistical models have indicated that even when accounting for gender-dependent mortality rates, age at death, and differences in lifespan, women still have twice the risk of incidence (16, 17). Furthermore, a growing body of evidence suggests there are stark differences in brain anatomy, function, and age-related morphological changes between men and women (17). Women have been shown to accumulate greater neurofibrillary tangle burden than men when compared at the same amyloid burden level, suggesting an earlier onset of AD (18). One theory posits that estrogen is neuroprotective against AD. As women age, their estrogen levels sharply decline, contributing to the development and progression of AD (19). In men, age-related decline in testosterone levels is associated with increased risk for AD (19). However, men lose testosterone at a significantly slower rate than women lose estrogen (19). Additionally, women traditionally had fewer opportunities for educational attainment and thus have weaker cognitive reserves when compared to men (20).

To our knowledge, the CEDAR study was among the first clinical research trials to evaluate the effectiveness of evidence-based individually-tailored, multi-domain interventions on cognition, AD/CV risk scores, and AD risk biomarkers in real-world clinical practice.

In this sub-analysis, we sought to examine if sex significantly affects the cognitive, CV, and AD risk outcomes in subjects who follow individually-tailored, multi-domain interventions.

Methods

Study Design and Participants

The CEDAR study procedures, baseline population characteristics, and primary results have been previously described in detail (13, 21). In the original study, participants were separated into two groups based on compliance to recommendations: participants who followed >60% of the recommendations were classified as "higher-compliance," whereas participants who followed ≤60% were classified as "lower-compliance." In this sub-group analysis, we evaluated the differential effectiveness of the clinical approach itself when considering sex in higher-compliance participants (n=80) from the original study cohort (n=154). Within this cohort, similar to the original study, participants were grouped based on baseline diagnoses: normal cognition, subjective cognitive decline, and preclinical AD participants were classified as "Prevention." Mild cognitive impairment (MCI) due to AD and mild AD were classified as "Early Treatment."

All participants were recruited at the Alzheimer's Prevention Clinic at Weill Cornell Medicine & New-York Presbyterian. Inclusion criteria assessed via an initial telephone screen included a family history of AD and no or minimal cognitive complaints. Exclusion criteria assessed during an in-person evaluation included a diagnosis of moderate-to-severe AD dementia or other dementia; disorders affecting safe engagement in interventions (e.g., malignant disease, major depression, psychotic disorder); or coincident participation in another trial. Participants with a clinical diagnosis of MCI or early mild dementia with negative amyloid neuroimaging were also excluded.

Institutional Review Board approval was obtained on February 16th, 2015, and patients were consented to participate in the Comparative Effectiveness Dementia & Alzheimer's Registry (Protocol #1408015423). Trial registered at ClinicalTrials.gov (NCT03687710).

Procedures

This methodology was outlined in detail in prior publication. In brief, after undergoing baseline clinical assessments, which included a detailed clinical history, physical examination, anthropometrics, blood biomarkers, apolipoprotein-ε4 (APOE-e4) genotyping, and cognitive assessment, patients were given individually-tailored, multi-domain intervention recommendations informed by these clinical and biomarker data. Recommendation categories included patient education/genetic counseling, individualized pharmacological approaches (medications/vitamins/supplements), non-pharmacological approaches (exercise counseling, dietary counseling, vascular risk reduction, sleep hygiene, cognitive engagement, stress reduction, general medical care), and other evidence-based interventions (13, 21). Table 1 outlines which interventions were recommended based on the presence of specific risk factors, as well as differences in various interventions with regards to sex. Additionally, Appendix B in the supplementary material outlines a more detailed application of Table I and our previously published clinical approach (21). It is important to note that these interventions are evidence-based and their clinical application requires a comprehensive evaluation from a qualified healthcare provider. Furthermore, it is necessary for providers to stay current on new research in this field, as evidence continues to emerge on the effectiveness of different interventions across several risk categories, including stress management (e.g., kirtan kriya) (22, 23), nutrition (24), and exercise (25).

Each participant was seen for longitudinal follow-up visits every 6-months, during which continual refinement of interventions would occur. Upon follow-up, each participant was graded as "compliant" or "not compliant" with each recommendation. Afterward, a composite compliance score was calculated as a

Table 1. Example Personalized Interventions

Risk Factor	Individual Factor	Recommended Intervention
Hypertension	Midlife(44)	BP target of 120/70s or lower(45, 46); Consider ARBs (especially candesartan (47) and telmisartan(48)) or ACE inhibitors (45, 46); Avoid CNS-active beta blockers (49)
Insulin Resistance / Diagnosis of Type 2 Diabetes	With unhealthy lifestyle(44)	Lifestyle counseling
	Already healthy lifestyle	Consider treatment with semaglutide or metformin (50); Supplement such as cocoa flavanols(44)
	May pose higher risk for females(51)	As above; Tighter targets for control
	May pose higher risk for APOE4 carriers (52)	Strongly consider early intervention with semaglutide or metformin (50); Supplement such as cocoa flavanols (44)
Hyperlipidemia	Due to elevated sterol absorption Due to elevated sterol production Due to elevated sterol production in females	Ezetimibe(53); refer to preventive cardiologist Hydrophilic statin therapy(54); refer to preventive cardiologist May benefit more from rosuvastatin for primary prevention(55); refer to preventive cardiologist
	Refractory to mono-therapy	May benefit more with combination therapy (e.g., statin and ezetimibe(53)); refer to preventive cardiologist to discuss PCSK9i
Elevated homocysteine		B complex vitamins (folate, pyridoxine, cobalamin (56, 57))
Vitamin B12 deficiency	With absorption deficit(56)	Oral vs IM B12 supplementation; Nutritional counseling (58)
	With absorption and/or potential genetic methylation deficit (e.g., MTHFR)	Methylated B12 or B complex; Consider B12 injections (59)
Vitamin D deficiency		Cholecalciferol +/- daily brief exposure to sunlight (60, 61)
Sleep Apnea	Type of Apnea	CPAP or other treatment as indicated; referral to sleep specialist
Low RBC omega-3 (EPA/DHA)/Omega-3 Index	With APOE4	Nutritional counseling (24) + supplementation at a ratio of DHA (~2g):EPA (~600-800mg) (62, 63)
	Without APOE4	Nutritional counseling +/- individualized ratio of DHA:EPA supplementation (64, 65)
Physical inactivity		Intensive and individualized exercise counseling (25, 66)
	With APOE4	May benefit from greater ratio of high-intensity interval training (HIIT) compared to non-APOE4 carriers (67)
	Female	Greater ratio of cardiovascular to resistance training (68-77)
	Male	Equal-to-greater ratio of resistance to cardiovascular training
	Elevated visceral body fat	Cardiovascular exercises, such as fast walking (Zone 2, 65-70% of maximum heart rate), running, swimming, and cycling
	Low muscle mass	Resistance training to improve strength and endurance, often with use of weights
Poor diet	Female	Sex-specific nutritional counseling (78-81)
	Male	Sex-specific nutritional counseling (78-81)
Elevated Cystatin or reduced GFR		Early referral to internal medicine and/or nephrology (82)
Suboptimal Cognitive Activity or Reserve	May pose higher risk for females (83, 84)	Adult education and/or cognitive training; Second language training or musical training (85, 86)
Social Isolation	May pose higher risk for males (87-89)	Referral to social worker or geriatric care manager; Encourage activity programs and social engagement (90, 91)
Chronic Stress, Depression, and/or Anxiety	Depression may pose higher risk in males (92)	Mindfulness training (93, 94), meditation (22, 23, 95), periodic vacations (96); Cognitive Behavioral Therapy (97); Exercise counseling(98) +/- medication
	Stress and anxiety may pose higher risk in females (99-101); Females may be more vulnerable to depression risk in the Perimenopausal period (102, 103)	As above; may also benefit more from vacation and meditation (96, 104)
Perimenopause (<5-7 years after start of menopause transition)	Symptomatic age <65 (105, 106)	Careful consideration of risk/benefits of type, route and dose of HRT(107) for an individualized period of time(108)
	With APOE4(108)	
	Induced Menopause(109)	
	Diagnosis of Type II Diabetes(110), Coronary artery disease, and/or hormone-sensitive cancer history	Careful consideration of orally-administered HRT given higher risk. If treatment indicated, consider alternatives such as low-dose topical

percentage of recommendations adhered to on a scale of 1–10 (1 represents 0–10% of recommendations, etc.), assessed independently by two clinicians based on patient discussion and patient Likert-scale ratings. Clinicians then collectively assigned an overall compliance score prior to reviewing any follow-up data. Higher-compliance participants were pre-specified as following >60% of all recommendations given, versus lower-compliance participants (≤60%).

Outcomes

The primary outcome was the change in performance on the modified-Alzheimer's Prevention Initiative Cognitive Composite (m-APCC) from baseline to 18-months. Statistical comparisons were performed between women and men within higher-compliance groups within each diagnostic classification (13, 26).

Secondary outcomes included changes on a composite of neuropsychological tests associated with non-pathological cognitive aging (CogAging), two AD risk scales (Australian National University–AD Risk Index (ANU-ADRI), Cardiovascular Risk Factors, Aging and Incidence of Dementia (CAIDE), two CV risk scores (American College of Cardiology/American Heart Association (ACC/AHA), Multi-Ethnic Study of Atherosclerosis (MESA), and AD risk biomarkers (27-30). Exploratory outcomes were chosen a priori based on evidence supporting their use in assessment of AD and/or cardiovascular disease risk. Additionally, when indicated, these measures were used to inform clinical management decisions that target modifiable AD/CVD risk factors. Exploratory outcomes included change in three risk scales, the Mayo Clinic Mild Cognitive Impairment Risk Score (Mayo MCI-RS), Mid-Life Disease Risk Score, and Vascular Risk for Late-Onset Alzheimer's Disease Risk Score (Vascular Risk for LOAD RS) (31-33).

All outcomes are shown in Table 2.

Statistical Methods

General

Participants were grouped based on biological sex and clinical diagnosis. Two-sided P-values were used for all comparisons, with no correction for multiplicity due to the a priori intent to investigate the primary outcome across Diagnosis×Sex groups. All secondary and exploratory analyses may be considered hypothesis-generating and not confirmatory.

Mixed Model Repeated Measures (MMRM)

Change from baseline in all outcomes was analyzed at 18 months for the Full Analysis Set (FAS) using MMRM that included all available data for all participants with at least one follow-up visit. Least squares mean (LSMEAN) estimates at each visit were reported and groups were compared with least squares differences (LSDIFFs). The primary model included diagnostic classification (Prevention/Early Treatment) and sex (male/female) with Diagnosis×Sex interaction, as well as age, baseline score, baseline Mini-Mental State Examination, and visit. The interaction between quantitative compliance and diagnosis group was used to assess whether limiting the analysis to higher-compliance affected the sex sub-groups differently. SAS® V9.4 PROC MIXED was used.

Compliance Adjusted Model

Since participant characteristics may affect compliance levels, predictors of compliance were assessed by fitting a stepwise regression model. To assess the specific impact of compliance, significant baseline predictors of compliance (at α<.05) were identified and corrected for as covariates in the adjusted MMRM, which also included a term for Baseline×Time interaction. LSMEANs estimates from the Diagnosis×Sex interaction using the adjusted model are shown for the primary analysis.

Results

Baseline Demographics

Baseline characteristics are described in Table 3. The mean age of all participants was 60.4 (SD 12.4) years old, with no differences between men and women in the Prevention group (p=0.605) and in the Early Treatment group (p=0.804). There were differences found in body mass index (BMI) between women and men in both the Prevention (p=0.002) and Early Treatment (p=0.004) groups.

Predictors of Compliance

The baseline compliance model identified three baseline parameters that significantly predicted compliance: baseline HbA1c (p<.0001), baseline ACC/AHA risk score (p<.0001), and baseline homocysteine (p=.0225). These parameters were included as co-variates in the Compliance Adjusted Model. The interactive analysis for quantitative compliance and sex resulted in a statistically insignificant interaction (p=0.4518). Each extra point of compliance (complying with an additional 10% of recommendations) resulted in 0.09 point improvement in m-APCC at 18 months within the female group (p=0.7347), and 0.41 points of improvement within the male group (p=0.3133).

Table 2. Outcomes

Cognitive Measures	Biomarker Measures	Risk Scores (RS)
Primary Outcome	*Secondary Outcomes*	*Secondary Outcomes*
Modified Alzheimer's Prevention Cognitive Composite (m-APCC)	LDL-C Direct	Australian National University-AD Risk Index (ANU-ADRI)
	HDL-C	Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE)
Secondary Outcome	Triglycerides	American College of Cardiology / American Heart Association Cardiovascular (ACC-AHA)
Cognitive Aging Composite (CogAging)	Lp(a) Mass	Multi-Ethnic Study of Atherosclerosis (MESA)
	Fibrinogen	
Exploratory Outcomes	HbA1c	*Exploratory Outcomes*
NIH Toolbox	HOMA-IR	Mayo Clinic Mild Cognitive Impairment Risk Score
-RAVLT Trial1	Homocysteine	Mid-Life Disease Risk Score
-RAVLT Trial2	Cystatin C	Vascular Risk for Late-Onset Alzheimer's Disease Risk Score
-RAVLT Trial3	hs-CRP	
-RAVLT Delayed Recall	25-hydroxy-Vitamin D	*Biometric Measures*
-RAVLT: Total Recognition Score		
-Dimensional Change Card Sort	*Exploratory*	*Exploratory Outcomes*
-Flanker Inhibitory Attention & Control	Total Cholesterol	Heart Rate (Pulse)
-Pattern Comparison	Non-HDL-C	Diastolic Blood Pressure (BP)
-Odor Identification	Apo B	Systolic Blood Pressure (BP)
-Oral Symbol Digit	LDL-P	Total Body Weight (TBW)
FAS Letter Fluency	HDL-P	Dry Lean Mass (DLM)
Animal Naming Test	sdLDL-C	Percent DLM
Boston Naming	Apo A-I	Fat Free Mass (FFM)
Total MMSE score	Fasting glucose	Percent FFM
MMSE Orientation to Time	Fasting insulin	Percent Fat
MMSE Orientation to Place	Adiponectin	Basal Metabolic Rate (BMR)
MMSE Figure Copying	Saturated Fat Total	Daily Energy Expenditure (DEE)
Delayed Recall	Trans Fat Total	
Face Name-Facial Recognition	cis-Monounsaturated Total	
Face Name-Cued First Letter	Omega-3 Total	
Face Name-Multiple Choice	Omega-3 Fatty Acids - EPA	
Name	Omega-3 Fatty Acids - DHA	
Cogstate: Detection	Alpha-Linolenic Acid (ALA)	
Cogstate: Identification	Vitamin B12	
Cogstate: One Back Accuracy		
Cogstate: One Back Speed		
Cogstate: One Card Learning		

Differences found in Prevention Group

Cognition

For m-APCC at 18 months, women in the Prevention group improved by 4.7 (2.0) points (p=0.021) and men improved by 7.1 (2.4) points (p=0.004), with no significant difference between these groups (difference= 2.3 [3.1], p=0.524).

For CogAging scores at 18 months, women in the Prevention group improved by 0.5 (1.6) points (p=0.753) and men improved by 5.8 (1.9) points (p=0.003). There was no significant difference between these groups (difference= 5.3 [2.5], p=0.083).

Risk Scales

For ANU-ADRI at 18-months, women in the Prevention group decreased by 3.9 (1.5) points (p=0.011) and men decreased by 3.8 (1.7) points (p=0.027), with no significant difference between these groups (difference= 0.07 [2.3], p=0.979).

For CAIDE at 18 months, women in the Prevention group decreased by 0.4 (0.3) points (p=0.099) and men increased by 0.4 (0.3) points (p=0.166), with no significant difference between these groups (difference= 0.9 [0.4], p=0.082).

For ACC/AHA at 18 months, women in the Prevention group significantly decreased by 4.4 (1.0) points (p=<0.0001) and men decreased by 2.2 (1.2) points (p=0.057), with no significant difference between these groups (difference= 2.2 [1.5], p=0.245).

For MESA at 18 months, women in the Prevention

Table 3. Patient Demographics and Baseline Characteristics

Variable	Subcategory or statistic	Prevention		Early Treatment		Total N=80
		Female (N=33)	Male (N=32)	Female (N=8)	Male (N=7)	
Diagnosis	MCI			6 (75.0%)	5 (71.4%)	11 (13.8%)
	Mild AD			2 (25.0%)	2 (28.6%)	4 (5.0%)
	Normal	25 (75.8%)	19 (59.4%)			44 (55.0%)
	Pre-clinical AD	0 (0%)	4 (12.5%)			4 (5.0%)
	Subjective Cognitive Decline	8 (24.2%)	9 (28.1%)			17 (21.3%)
APOE-e4 Group*	Heterozygotes	12 (36.4%)	13 (40.6%)	2 (25.0%)	1 (14.3%)	28 (35.0%)
	Homozygotes	3 (9.1%)	3 (9.4%)	2 (25.0%)	2 (28.6%)	9 (11.3%)
	Non-Carriers	18 (54.5%)	16 (50.0%)	4 (50.0%)	4 (57.1%)	42 (52.5%)
Race	White	30 (90.9%)	29 (90.6%)	5 (62.5%)	4 (57.1%)	68 (85.0%)
	Other	2 (6.1%)	2 (6.3%)	2 (25.0%)	1 (14.3%)	7 (8.8%)
	Missing	1 (3.0%)	1 (3.1%)	1 (12.5%)	2 (28.6%)	5 (6.3%)
Age	Mean (SD)	56.6 (11.24)	58.3 (11.7)	72.6 (6.3)	73.6 (8.1)	60.4 (12.4)
	Diff. (p-value)	1.72 (0.6049)		0.946 (0.8039)		
BMI	Mean (SD)	23.7 (3.8)	26.4 (3.0)	22.4 (2.1)	26.5 (0.6)	24.8 (3.6)
	Diff. (p-value)	2.69 (0.0024)		4.09 (0.0040)		
Education Level	Mean (SD)	16.1 (1.11)	16.0 (0.8)	15.6 (0.9)	15.8 (0.8)	16.1 (0.9)
	Diff. (p-value)	0.07 (0.7721)		0.17 (0.7016)		

group significantly decreased by 2.2 (0.2) points (p<0.0001) and men significantly decreased by 0.8 (0.3) points (p=0.007), with women significantly improving more than men (difference= 1.5 [0.4], p=0.001).

Biomarkers

In the Prevention group, women showed improvements in HDL-C (9.7 [3.8], p=0.013). Men showed worsening of Cystatin C (0.1 [0.0], p=0.004) and improvement in HOMA-IR (0.7 [0.3], p=0.034). Women improved HDL-c more than men (difference= 13.8 [5.9], p=0.050), and men improved HOMA-IR more than women (difference= 1.0 [0.4], p=0.042).

No significant changes were seen within and between women and men for the remaining secondary outcomes (Table IV).

Differences found in Early Treatment Group

Cognition

For the m-APCC at 18 months, women in the Early Treatment group improved by 1.4 (4.0) points (p=0.734) and men improved by 7.9 (5.3) points (p=0.138), with no significant difference between the groups (difference= 6.5 [6.6], p=0.330).

For CogAging scores at 18 months, women in the Early Treatment group improved by 3.6 (3.3) points (p=0.266) and men improved by 5.4 (4.2) points (p=0.207), with no significant difference between the groups (difference= 1.7 [5.3], p=0.743).

Risk Scales

For ANU-ADRI at 18 months, women in the Early Treatment group increased by 1.2 (2.9) points (p=0.687) and men decreased by 8.2 (4.1) points (p=0.051), with no significant difference between the groups (difference= 9.3 [5.0], p=0.063).

For CAIDE at 18 months, women in the Early Treatment group decreased by 1.4 (0.5) points (p=0.007) and men increased by 0.9 (0.7) points (p=0.187), with women significantly improving more than men (difference= 2.3 [0.8], p=0.007).

For ACC/AHA at 18 months, women in the Early Treatment group decreased by 5.5 (2.0) points (p=0.006) and men decreased by 5.6 (2.5) points (p=0.032), with no significant difference between the groups (difference= 0.0 [3.2], p=0.991).

For MESA at 18 months, women in the Early Treatment group decreased by 2.9 (0.5) points (p<0.0001) and men decreased by 1.2 (0.6) points (p=0.049), with women significantly improving more than men (difference= 4.1 [0.8], p<0.0001).

Table 4. Outcomes for Prevention Group

Prevention	Males		Females		Males v. Females	
	LSMean (SE)	p-val	LSMean (SE)	p-val	LSMean (SE)	p-val
Cognition						
m-APCC	7.1 (2.4)	0.0044	4.7 (2.0)	0.0205	2.3 (3.1)	0.5244
Cognitive Aging Score	-5.8 (1.9)	0.0032	-0.5 (1.6)	0.7525	5.3 (2.5)	0.0833
Risk Scales						
ANU-ADRI	-3.8 (1.7)	0.0272	-3.9 (1.5)	0.0112	0.1 (2.3)	0.9794
ACC/AHA	-2.2 (1.2)	0.0570	-4.4 (1.0)	<0.001	-2.2 (1.5)	0.2445
MESA-RS	-0.8 (0.3)	0.0068	-2.2 (0.2)	<0.001	-1.5 (0.4)	0.0013
CAIDE	0.4 (0.3)	0.1661	-0.4 (0.3)	0.0989	-0.9 (0.4)	0.0822
Mid-Life Disease Risk Score*	0.4 (0.3)	0.1520	-0.5 (0.2)	0.0280	-0.9 (0.4)	0.0408
MAYO MCI-RS*	-0.9 (0.1)	<0.001	-1.1 (0.1)	<0.001	-0.2 (0.2)	0.4925
Vascular Risk for LOAD-RS*	-0.3 (0.7)	0.6566	-0.9 (0.6)	0.1009	-0.6 (0.9)	0.5448
Biomarkers						
LDL-C Direct	-3 (9.9)	0.7647	3.7 (8.4)	0.6620	6.7 (13)	0.6730
HDL-C	-4 (4.4)	0.3645	9.7 (3.8)	0.0133	13.8 (5.9)	0.0498
Triglycerides	-4.1 (14.4)	0.7773	4.9 (12.4)	0.6906	9 (19)	0.6866
Fibrinogen	-24.9 (24.1)	0.3059	2.2 (20.6)	0.9144	27.1 (31.7)	0.4565
HbA1c	0 (0.1)	0.8799	0 (0.1)	0.6476	0 (0.1)	0.8819
HOMA-IR	-0.7 (0.3)	0.0344	0.3 (0.2)	0.2010	1 (0.4)	0.0416
Homocysteine	-0.5 (0.7)	0.4760	-0.1 (0.6)	0.8982	0.4 (0.9)	0.6926
Cystatin C	0.1 (0)	0.0035	0 (0)	0.3264	-0.1 (0.1)	0.1891
25-hydroxy-Vitamin D	1.1 (4.2)	0.7932	4.2 (3.4)	0.2249	3.1 (5.4)	0.6365
hs-CRP	-0.4 (0.4)	0.3861	-0.5 (0.4)	0.2001	-0.1 (0.5)	0.8621
Exploratory						
Total Cholesterol*	-5.4 (11.4)	0.6377	11.3 (9.7)	0.2467	16.7 (14.9)	0.3580
Non-HDL-C*	-2.6 (10.9)	0.8131	3.5 (9)	0.6981	6.1 (14.1)	0.7206
Apo B*	-2.6 (7.1)	0.7180	3.5 (6)	0.5640	6.1 (9.3)	0.5853
LDL-P*	-39.5 (126.5)	0.7556	37.7 (107.6)	0.7271	77.2 (166)	0.6888
sdLDL-C*	-0.6 (2.9)	0.8433	-0.7 (2.5)	0.7880	-0.1 (3.8)	0.9856
Glucose*	-6 (3)	0.0504	0.7 (2.5)	0.7907	6.6 (3.9)	0.1587
Adiponectin*	-0.6 (1.1)	0.6066	4.5 (1)	<0.001	5.1 (1.5)	0.0061
Saturated Total*	-0.8 (0.7)	0.2393	0 (0.6)	0.9825	0.8 (0.9)	0.4369
Trans Total*	0 (0)	0.2683	-0.1 (0)	0.0937	-0.1 (0)	0.1135
cis-Monounsaturated Total*	2 (1.2)	0.0906	-0.6 (1)	0.5154	-2.6 (1.5)	0.1502
Omega-3 Total*	0 (0.8)	0.9705	0.9 (0.6)	0.1387	0.9 (1)	0.4323

* indicates exploratory outcome measure

Biomarkers

In Early Treatment participants, women showed improvement in HbA1c (-0.3 [0.1], p=0.025), blood glucose (-12.8 [4.9], p=0.011), and LDL-C (-44.4 [16.9] points, p=0.010). Men showed an increase in Cystatin C by (0.3 [0.1], p=0.006). Between women and men, there were differences seen in Cystatin C (difference= 0.4 [0.1], p=0.006) and HbA1c (difference= 0.6 [0.2], p=0.016).

No significant changes were seen within and between women and men for the remaining secondary outcomes (Table V).

Table 5. Outcomes for Early Treatment Group

Early Treatment	Males		Females		Males v. Females	
	LSMean (SE)	p-val	LSMean(SE)	p-val	LSMean(SE)	p-val
Cognition						
m-APCC	7.9 (5.3)	0.1383	1.4 (4.0)	0.7337	6.5 (6.6)	0.3299
Negative Cognitive Aging Score	-5.4 (4.2)	0.2073	-3.6 (3.3)	0.2659	1.7 (5.3)	0.7427
Risk Scales						
ANU-ADRI	-8.2 (4.1)	0.051	1.2 (2.9)	0.6873	9.3 (5.0)	0.0626
ACC/AHA	-5.6 (2.5)	0.0317	-5.5 (2.0)	0.0059	0.0 (3.2)	0.9908
MESA-RS	1.2 (0.6)	0.0487	-2.9 (0.5)	<0.001	-4.1 (0.8)	<0.001
CAIDE	0.9 (0.7)	0.1872	-1.4 (0.5)	0.0067	-2.3 (0.8)	0.0067
Mid-Life Disease Risk Score*	0.2 (0.6)	0.7645	-1.3 (0.5)	0.0066	-1.5 (0.8)	0.0644
MAYO MCI-RS*	-1.4 (0.3)	<0.001	-1.2 (0.2)	<0.001	0.2 (0.4)	0.6646
Vascular Risk for LOAD-RS*	1.5 (1.5)	0.3048	0.6 (1.1)	0.6133	-1 (1.8)	0.6030
Biomarkers						
LDL-C Direct	6.4 (21.7)	0.7707	-44.4 (16.9)	0.0103	-50.8 (27.5)	0.0657
HDL-C	-6.4 (10)	0.5258	9 (7.7)	0.2459	15.3 (12.6)	0.2220
Triglycerides	56.6 (31.9)	0.0802	-17 (24.8)	0.4938	-73.6 (40.4)	0.0680
Fibrinogen	-57.4 (53.7)	0.2885	-35.9 (41.9)	0.3942	21.5 (68.1)	0.7532
HbA1c	0.3 (0.2)	0.1726	-0.3 (0.1)	0.0250	-0.6 (0.2)	0.0159
HOMA-IR	-0.2 (0.8)	0.7741	0.1 (0.5)	0.8060	0.3 (0.9)	0.7111
Homocysteine	-0.1 (1.5)	0.9720	0.1 (1.2)	0.9153	0.2 (1.9)	0.9253
Cystatin C	0.3 (0.1)	0.0058	-0.1 (0.1)	0.1581	-0.4 (0.1)	0.0055
25-hydroxy-Vitamin D	-1.9 (8.8)	0.8286	7.2 (6.7)	0.2898	9.1 (11.1)	0.4146
hs-CRP	-0.8 (0.9)	0.3943	-0.4 (0.7)	0.6058	0.4 (1.2)	0.7332
Exploratory						
Total Cholesterol*	-1.8 (25.2)	0.9429	-44.2 (19.2)	0.0237	-42.4 (31.6)	0.1795
Non-HDL-C*	8.4 (23.3)	0.7207	-54.7 (18.9)	0.0049	-63.1 (30)	0.0402
Apo B*	0.8 (15.6)	0.9568	-38.1 (12.1)	0.0024	-38.9 (19.8)	0.0104
LDL-P*	-342.6 (283.5)	0.2308	-714.6 (219.4)	0.0017	-372 (358.5)	0.2904
sdLDL-C*	2.7 (6.4)	0.6714	-9.8 (4.8)	0.0465	-12.5 (8)	0.1241
Glucose*	-6.3 (6.4)	0.3268	-12.8 (4.9)	0.0111	-6.5 (8)	0.4255
Adiponectin*	-2.7 (2.8)	0.3409	0.8 (2)	0.6978	3.4 (3.4)	0.3215
Saturated Total*	1 (1.6)	0.5314	-0.2 (1.2)	0.8655	-1.2 (2)	0.5482
Trans Total*	0.1 (0.1)	0.2864	0 (0.1)	0.5669	-0.1 (0.1)	0.5828
cis-Monounsaturated Total*	3.4 (2.5)	0.1813	-2.9 (1.9)	0.1331	-6.4 (3.2)	0.0477
Omega-3 Total*	0.7 (1.7)	0.6915	1 (1.3)	0.4296	0.4 (2.1)	0.8660

* indicates exploratory outcome measure

Discussion

To our knowledge, this is the first study to examine the differential effectiveness of individualized modifiable AD risk reduction between women and men. Previous studies have focused on the role of hormones and sex-specific risk factors when examining differences in AD risk(34), but none have examined if individualized multi-domain interventions result in differences in outcomes related to cognition and AD risk blood biomarkers. While no meaningful differences were seen in the primary outcome of cognitive improvement, we found significant improvements in secondary outcomes including CV risk scales and lipid biomarkers in women compared

to men. Further research is needed to draw more definitive conclusions, but our findings suggest that the individualized management approach used by the CEDAR study in a real-world clinic may offer equal cognitive benefits to both women and men, as well as better mitigation of calculated AD and CV risk in women compared to men. Further research with larger cohorts is needed to examine if these better outcomes for women have a significant impact on their risk of developing AD.

In the Prevention group, both women and men improved their m-APCC scores without significant differences between these groups suggesting that an individualized approach that takes sex into consideration may be effective and warranted. Prior studies have suggested that in AD, men demonstrate more rapid rates of cognitive decline than women (35, 36), while other studies support the opposite (37). A recent study suggested that women and men have similar rates of cognitive decline until much later in life when women suffer from a sharp decline (38, 39). Our work highlights the need for larger studies that focus on sex differences in AD-related cognitive trajectories, as the existing body of knowledge lacks conclusive evidence on this issue.

In Early Treatment participants, women improved more than men on both the CAIDE and the MESA. In Prevention participants, women improved more than men on the MESA. The CAIDE is a validated risk index that calculates late-life dementia risk based on midlife vascular risk factors (e.g., body mass index, blood pressure, cholesterol smoking status), while the MESA estimates one's risk of CV disease incidence over the next ten years using traditional risk factors. These results suggest that women saw greater reductions in their CV risk than men, and later on in the AD spectrum, this reduced CV risk may subsequently reduce the risk of AD. In support of these results, we found that women saw significant improvements in a number of vascular biomarkers, and this may be driving the CV disease risk reduction. Nevertheless, due to the small number of participants in these sub-groups, the significance of these findings are limited. This limitation is further discussed below.

Women in the Prevention group saw significant improvements in HDL cholesterol compared to men. Furthermore, women in the Early Treatment group saw significant improvements in several lipid biomarkers, including total cholesterol, LDL-C, LDL-P, and ApoB. Men in the Early Treatment saw no significant changes in any lipid biomarkers, and the differences between women and men were not found to be significant. However, these findings, when considered alongside the changes found in risk scales, suggest that when patients are further along on the AD spectrum, women may see greater CV benefit than men. It is uncertain why Prevention and Early Treatment women demonstrated improvements in different lipid biomarkers, though differences in age and consequently, estrogen levels may play an important role. Several studies have shown that estrogen can modulate LDL cholesterol absorption, and this relationship will be important to evaluate in further studies (40-42).

Differences found in metabolic markers were more difficult to interpret. Men in the Prevention group saw significantly more improvement in HOMA-IR than Prevention women, while women in the Early Treatment group significantly improved in HbA1c more than Early Treatment men. HOMA-IR and HbA1c have been proven to serve as effective markers for insulin resistance and diabetes diagnoses, which are among the leading risk factors for AD dementia (9). Thus, it is essential that future studies explore the effectiveness of multi-domain interventions targeting glucose metabolism with respect to differences in age, sex, and AD progression.

Our study has several limitations, with a key limitation being that this is a sub-group analysis. Dividing the original sample population into smaller sub-groups resulted in reduced statistical power, as such, detection of significant interactions may have been limited. Due to the small number of participants in the study, specifically in the Early Treatment sub-groups, as well as the vast outcome measures, it is important that our findings are to be considered hypothesis-generating and non-confirmatory. To address this gap, the study authors are in process of expanding a clinical research consortium (currently 6 sites in the United States, 1 in Canada and 1 in the United Kingdom) to expand the cohort, harmonize measures, and yield larger sample sizes upon which more valid conclusions can be made.

An expanded consortium would improve not only the sample size, but also the recruitment of a study population that is more diverse with respect to race, geography, and educational background. Although more than one-third of participants lived outside the New York metropolitan area, our cohort was predominantly Caucasian (85.0%) and, on average, well-educated (16.1 years), and this is an important limitation of our study. The original intent of this study was to have two sites, with the second site (Alzheimer's Prevention Clinic and Research Center of Puerto Rico) recruiting 100 subjects to begin enrollment in August 2016. Due to a natural disaster (Hurricane Maria, September 2017) that had devastating effects on the clinic, all clinical research operations were halted.

Furthermore, significant differences were found within and between various sub-groups, and we must consider the increased likelihood of false-positive findings due to multiple comparisons across a broad spectrum of outcomes (43). Due to the nature of our analyses, we were not able to determine whether changes in any specific biomarkers were associated with change in cognition in women versus men. With the necessary sample size and power, future studies should seek to perform a Bayesian hierarchical analysis to identify biomarkers that are primarily associated with cognition changes. Nevertheless, future studies must continue to explore differences found in the effectiveness of AD risk reduction strategies within and between sub-groups defined by

important baseline characteristics, such as age, sex, and genetic risk factors, as this can expand the body of evidence to inform individualized clinical paradigms.

To investigate sex differences in response to treatment, these analyses only included the participants marked as higher-compliance in the original CEDAR study, and this is an important limitation. This was done to assess for differences in intervention effects within a study cohort that had adhered to a majority of multi-domain interventions recommended. We believe this was the best way to assess for differential response to interventions, as conducting these analyses in lower-compliance participants may have resulted in false-positive findings that were not attributed to following the intervention. Nevertheless, due to the random nature of patient compliance and the inability to randomly assign participants to compliance levels, the sample size is considerably smaller compared to the original CEDAR study. Furthermore, only including higher-compliance participants may introduce bias to our results. We hope to conduct further analyses to continue exploring sex differences within a larger, more diverse sample of participants.

Conclusion

Individualized multi-domain interventions are equally effective in improving cognition in women and men. However, these interventions led to greater AD and CV risk reduction in women compared to men. Future study in larger cohorts with a priori primary and/or secondary outcomes is necessary to examine the effects of sex on AD risk reduction interventions.

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Conflict of interest: Dr. Isaacson has served as a scientific advisor for Acadia, Biogen, Genentech/Roche, Lilly, and Novo Nordisk. The other authors have nothing to disclose.

Ethical standard: All procedures performed in this study involving human participants were approved by and in accordance with the ethical standards of the IRB. Informed consent was obtained from all participants.

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