

COVER SHEET

TITLE: Mid-Life Dementia Risk Scores as a Predictor of CSF Biomarker and Cognitive Response to Simvastatin Therapy In Asymptomatic Adults At Risk for Alzheimer's Disease: The ESPRIT Trial

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ABSTRACT

Mid-Life Dementia Risk Scores as a Predictor of CSF Biomarker and Cognitive Response to Simvastatin Therapy In Asymptomatic Adults At Risk for Alzheimer's Disease: The ESPRIT Trial

(Abstract content here not to exceed 150 words)

BACKGROUND: Cardiovascular risk factors at mid-life are associated with an increased risk of developing Alzheimer's disease (AD).

OBJECTIVE: Determine relationships between baseline dementia risk, cognitive function, CSF biomarkers, and response to simvastatin.

METHODS: Middle-aged adult children of persons with AD were randomized to 9 months of 80mg simvastatin verses placebo. Statistical analysis included Spearman correlations and nonparametric modeling.

RESULTS:


In middle aged, asymptomatic adults at risk for AD, high dementia risk scores correlates with higher levels of CSF A β -40 (p=0.02), positively with Color Trails B time (r =0.355, p= <0.001), inversely with Stroop color word score (r = -0.289, p=0.0037), and positively with VSLT: Learning Score (β =0.65, p=0.032). Low dementia risk predicts a greater decrease in CSF p-tau-181, and greater improvement in HVLTL Learning Score (p=0.025) and processing speed index (p=0.005) for those on simvastatin compared to placebo. This study suggests low risk subjects benefit most from simvastatin therapy.

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Title: Mid-Life Dementia Risk Scores as a Predictor of CSF Biomarker and Cognitive Response to Simvastatin Therapy In Asymptomatic Adults At Risk for Alzheimer's Disease: The ESPRIT Trial

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Background:

Prevalence

Alzheimer's disease (AD) is a progressive neurodegenerative disease resulting in substantial loss of memory and executive function. It primarily affects the elderly population and therefore is of great concern in the coming decades. As the population in the United States continues to shift and change structure, there will be an increasing number of older adults suffering from age-related illness. In addition, life expectancy is also predicted to improve and increase the number of persons over 85 years old with an expected quadrupling of this age group by the year 2050 [1, 2]. It is predicted that the prevalence of AD in the US population will triple by the year 2050, reaching 13.2 million [1]. This dramatic increase will impact the healthcare system by placing increased demand for care of elderly patients with AD and resources to care givers. As the prevalence of AD continues to increase in the US and worldwide, it becomes crucial to discover preventative measures for AD prevent, targeting those who will most benefit from early intervention.

Environmental Risk

Mid-life cardiovascular risk factors have been associated with dementia in late life. Vascular risk factors that have been associated with the development of dementia include obesity, high total cholesterol levels, and increased systolic blood pressure (SBP) [3, 4]. Obesity, high total

cholesterol, and SBP are individually associated with a two-fold increase in risk of developing dementia in late life [5]. With clustering analysis, the risks combine in an additive manner in that persons with all three risk factors had a six fold increase in developing dementia compared to those who had no risk factors in mid-life [5]. Fortunately, these particular mid-life vascular risks are all potentially modifiable and thus are considered potential targets for preventive therapies[6].

Kivipelto Risk Score

Recent growth in the field of AD prevention includes the development of mid-life dementia risk score models [7, 8]. Applying disease risk stratification may benefit patients by allowing for proper treatment of disease earlier or by preventing the disease in those at the greatest risk [9]. Current models incorporate risk factors including, age, sex, education, and a host of other measures taken at mid-life to predict risk of developing AD in late life. A risk method developed by Barnes, et al. includes measures not commonly evaluated under standards of clinical care, such as grade of enlarged ventricles on MRI [7]. A comparable risk score developed by Kivipelto et al. is limited to clinically relevant measures that are frequently collected during routine clinical visits such as body mass index (BMI), total cholesterol, and physical activity [8]. However, Kivipelto's was developed in a European population which may alter the ability of the model to predict dementia risk in differing populations.

AD Pathology

Biological hallmarks of AD include β -amyloid plaque deposition and tau-associated neurofibrillary tangles in the brain upon autopsy. Related to these changes in the brain, cerebral spinal fluid (CSF) markers can be used to monitor the risk for disease. β -amyloid and tau are proteins in the CSF and have been identified as potential AD biomarkers. CSF tau is associated with higher levels in patients with AD, while CSF β -amyloid levels are decreased in comparison to controls [10]. CSF biomarker relationships in those at risk for AD are not well defined. However, it is hypothesized that modifying the levels of β -amyloid and tau in the CSF of preclinical AD patients may potentially delay or prevent AD.

Genetic Risk & Family History

Identified genetic risk factors for AD include a gene product involved in lipid metabolism and cellular repair processes called the apolipoprotein E (apoE) allele [11]. The majority of the population expresses apoE ϵ 3 allele form while the apoE ϵ 4 allele has been associated with a greater risk of developing AD [12]. ApoE ϵ 4 increases the formation of neurofibrillary tangles and amyloid plaques at the center of AD pathobiology. The direct mechanism of this association is yet to be defined, although hypotheses involving neuronal repair, protection, remodeling, and redistribution of degenerate cellular lipids have been suggested [12, 13]. Additionally, the association between asymptomatic changes in mesial temporal lobe activation and first degree family history exist independently of apoE ϵ 4 status [14], suggesting unidentified factors related to first degree family history may be predisposing individuals to early changes in the brain while remaining cognitively asymptomatic at mid-life.

Modifying Environmental Risk (Simvastatin)

Simvastatin is a commonly used cholesterol lowering medication that prevents biosynthesis of cholesterol in the body by inhibiting 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase. Genetic risk factors related to the development of AD are linked to lipid and cholesterol metabolism [12]. The association between mid-life cholesterol levels and late life development of AD suggests that mid-life simvastatin therapy may delay the initial onset of AD. Statins have also been shown to lower levels of β -amyloid proteins *in vitro* and *in vivo* which is considered to be protective for AD [15]. Cells cultured and treated with simvastatin showed decreased levels of β -amyloid peptides in the intracellular and the extracellular components of the tissue culture, while animal studies have shown simvastatin to decrease levels of β -amyloid in the CSF and brain homogenate and tau associated neurofibrillary tangles [15, 16]. Additionally, animal trials have shown that simvastatin therapy reverses cognitive deficits, while human trials regarding statin therapy have shown mixed results [17-19]. A four-month clinical trial of 40mg simvastatin verses placebo in asymptomatic middle-aged adults showed that simvastatin improved selective measures of cognitive function, but did not significantly modify CSF A β -42 or total tau levels, raising questions about the role of longer duration, higher dose simvastatin prevention therapy [20].

ESPRIT Trial

The ESPRIT trial is a single-site, prospective, randomized, controlled, double-blind clinical trial looking at the effects of nine months of high-dose simvastatin therapy in asymptomatic adults at risk for AD. Preliminary results from the ESPRIT trial show only marginal effects of

simvastatin on primary outcomes of CSF β -amyloid, CSF tau, and cognition [21]. It is unclear if certain dementia risk subgroups benefit from simvastatin intervention, warranting further investigation.

Research Questions Addressed

In an effort to determine those who best respond to nine months of high-dose simvastatin therapy we investigated the role of dementia risk stratification in relation to baseline measures and primary outcomes in the ESPRIT trial. In this study we: (1) determined baseline correlations between dementia risk scores, cognitive function and CSF biomarker levels, (2) evaluated the ability of an established dementia risk score model to predict simvastatin-related CSF biomarker and cognitive function changes in asymptomatic adults at risk for AD in comparison to placebo, and (3) determined the validity of dementia risk scores developed by Kivipelto et al as a predictor of cognitive and CSF biomarker response to nine months of simvastatin therapy in the ESPRIT trial population in comparison to a hypothesis driven regression models developed from ESPRIT baseline measures.

Research & Design:

The data used in this analysis is from the Evaluating Simvastatin's Potential Role in Therapy (ESPRIT) trial which is a single site, phase II clinical trial conducted at the University of Wisconsin – Madison. The primary outcome of this trial was to evaluate the impact of simvastatin on CSF biomarkers. The present report represents a post-hoc analysis of the effects of dementia risk on response to simvastatin therapy.

ESPRIT Trial Participants:

One hundred three asymptomatic middle-aged adults (ages 36-69 years) with a parental history of AD were recruited from the Wisconsin Registry for Alzheimer's Prevention (WRAP)[22] or from the community through newsletters, educational talks, health fairs, local clinics, and newspaper and magazine advertisements. WRAP participants that aligned with age requirements and other basic enrollment criteria of the ESPRIT trial were mailed a letter informing them of a new prevention study. Those interested were encouraged to contact the study coordinator to discuss eligibility. If eligible, the participant was enrolled. Prior to enrollment, a diagnosis of probable or definite AD in one or both parents was confirmed using the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [23] through clinical evaluation and/or chart review by physicians and neuropsychologists with expertise in dementia. Persons were excluded from study participation if they currently used cholesterol-lowering medications or medications known to interact with simvastatin, or if they had active liver disease, a past adverse reaction to a statin drug, or elevated creatine kinase (CK). The University of Wisconsin Human Subjects Committee approved this study. Informed consent was obtained from each participant.

ESPRIT Study Design:

Participants of the investigator-initiated ESPRIT trial attended 5 visits during the 9-month study (baseline, and months 1, 3, 6, and 9). An additional pre-study visit was conducted two weeks

prior to baseline for *APOE* analysis for participants not recruited from WRAP (WRAP participants already had *APOE* results completed). At baseline and month 9, all participants had fasting blood samples drawn, cognitive testing, a physical exam, and a lumbar puncture for CSF collection. At months 1 and 6, all participants had safety assessments including symptom questionnaires and blood tests for aspartate aminotransferase (AST) and alanine aminotransferase (ALT). At month 3 participants underwent cognitive testing and safety assessment. All data were collected at the University of Wisconsin Hospital and Clinical and Translational Research Core (CTRC).

At baseline, participants were randomized in a 1:1 ratio to receive simvastatin 40 mg nightly or matching placebo tablet. At month 1, the study drug dose was increased to simvastatin 80 mg nightly or matching placebo tablet. All study medications were manufactured by Merck and Co., Inc. for this investigator-initiated study and were identical in appearance. Randomization was conducted by the University of Wisconsin (UW) Pharmaceutical Research Center and was stratified based on *APOE4* allele status (positive or negative) and gender. Subjects and investigators were blinded to the identity of the study medication and to cholesterol-lowering effects during the course of the study. Study drug compliance was assessed by pill count in the Pharmaceutical Research Center.

ESPRIT CSF Collection

CSF collection was completed in the morning at approximately the same time at each visit [24]. Subjects were placed in the sitting or lateral decubitus position and the skin over the low

lumbar area was prepped and draped in a sterile manner. A 25-gauge needle was used to inject 1% lidocaine as a local anesthetic. A Sprotte 22- or 25-gauge spinal needle with introducer was inserted into the L3/4 or L4/5 interspace using sterile technique. Between 8 to 22 mL of CSF was collected using a standard clinical drip method directly into sterile collection tubes or, later in the study, by gentle extraction technique[25] into sterile 5-mL polypropylene syringes[26]. All CSF samples remained frozen until the time of analysis at the conclusion of the study. Each participant was called 24 hours after the procedure to inquire about any post-procedure adverse effects.

ESPRIT Cognitive Testing

On the morning of blood and CSF collection, all participants underwent cognitive testing by a trained technician according to protocols established for each test. The cognitive test battery targeted four domains:

| DOMAIN | SKILL | TEST |
|-----------------------|---|---------------------------------------|
| Memory/ Learning | Verbal Memory | List Learning (HVLТ) |
| | | Paragraph Recall (NYU) |
| | Nonverbal Memory | Visual Spatial Learning Test (VSLT) |
| | | Complex Figure Test – Recall |
| Language | Fluency | Letter-cued Fluency |
| | | Category-cued Fluency |
| Visual-Motor | Construction Drawing | Complex Figure Test – Copy |
| | Motor | Grooved Pegboard |
| | Attention | Ruff 2 and 7 Selective Attention Test |
| Executive Functioning | Vigilance | Symbol Search |
| | | Digit Symbol- Coding |
| | Working Memory: Selective and Divided Attention | Mental Control |
| | | Letter- Number Sequencing |
| | | Spatial Span |
| | | Stroop Color Word Interference Test |
| | | Color Trailmaking Test A and B |

memory and learning, language, visual-motor skills, and executive function (Table 1). Mini-Mental State Exam was administered at baseline to assess global cognitive function. To control for variations in instrumentation, technicians were trained to use standardized instructions for each test administered and the same technician tested a particular subject at each visit. Alternate forms of cognitive tests were used to reduce practice effects for tasks with a strong memory component. Cognitive exams have been previously validated in populations with

declining memory and function. Raw scores were used in analysis, correcting for age and education.

ESPRIT Laboratory Evaluation

All blood tests at baseline and months 3 and 9 were collected following a 12-hour fast. Blood tests collected at safety visits (months 1 and 6 measuring AST, ALT, and CK only) were non-fasting. Lipoprotein particles were analyzed by proton NMR spectroscopy at LipoScience, Inc. (Raleigh, NC). Lipoprotein particle concentrations of varying sizes were calculated from the measured amplitudes of their spectroscopically distinct lipid methyl group NMR signals. Weighted-average lipoprotein particle sizes were derived from the sum of the diameter of each subclass multiplied by its relative mass percentage based on the amplitude of its methyl NMR signal.[27] *APOE4* allele was measured using standard PCR and DNA sequencing techniques.

A MSD MULTI-ARRAY Human A β 40 Ultra-Sensitive (Meso Scale Discovery) kit was used to measure CSF A β 40 using an end-specific tag labeled with anti- A β 40 antibody [28]. CSF A β 42, total tau (T-tau), and phosphorylated tau 181 (p-tau 181) concentrations were measured with xMAP technology using the INNO-BIA AkzBio3 kit (Innogenetics).[29, 30] xMAP technology is based on flow cytometric separation of antibody-coated microspheres that are labeled with a specific mixture of two fluorescent dyes as previously described [30]. The technique allows for simultaneous measurement of several analytes in the same tube. Baseline and month 9 samples were run simultaneously at the conclusion of the study to reduce laboratory variability. All data has been stored in a secure database with double entry to insure correct values.

Dementia Risk Scores

Based on the model developed by Kivipelto and colleagues, dementia risk scores were assigned to all ESPRIT participants according to their baseline cardiovascular and demographic profile [8]. The Kivipelto et al model two (Table 2) was chosen for this analysis because it incorporates genetic risk (ApoE status) information collected in the ESPRIT trial. Distribution of dementia risk was evaluated between the two study arms.

| RISK FACTOR | CRITERIA | SCORE |
|----------------------------|----------|-------|
| Age | <47 | 0 |
| | 47-53 | 3 |
| | >53 | 5 |
| Education (years) | ≥10 | 0 |
| | 7-9 | 3 |
| | 0-6 | 4 |
| Sex | Female | 0 |
| | Male | 1 |
| Systolic BP (mmHg) | ≤140 | 0 |
| | >140 | 2 |
| BMI (kg/m ²) | ≤30 | 0 |
| | >30 | 2 |
| Total Cholesterol (mmol/L) | ≤6.5 | 0 |
| | >6.5 | 1 |
| Physical Activity | Active | 0 |
| | Inactive | 1 |
| APOE ε4 | Non- ε4 | 0 |
| | ε4 | 2 |

Statistical Analysis

Baseline cross-sectional analyses were used to identify pretreatment correlations. Spearman correlations were used to identify associations between dementia risk and cognition in the asymptomatic study population.

Cognitive function changes from baseline were evaluated using hypothesis-driven composite cognitive function scores. Cognitive exams targeting similar domains or regions of the brain were grouped for analysis. This includes a processing speed index which is the sum of two symbol search measures, a working memory composite summing spatial span measures, and letter number sequencing. Additionally, processing speed index, HLVT Total Learning Score,

HVLT Delayed Recall Score, and Stroop color word score were analyzed for changes from baseline to nine months between the simvastatin and control groups. Nine-month intervention changes were assessed using a linear mixed effects model incorporating cognitive exam scores collected at month 3.

Linear modeling techniques were used to model the combined effects of the Kivipelto dementia risk score and treatment on changes in CSF biomarkers after nine months of therapy. CSF biomarker levels were measured as concentration of A β -40, A β -42, t-tau, p-tau, and ratios of A β -42/A β -40, and tau/A β -42.

Linear modeling techniques were also used to evaluate the individual effects of various baseline characteristics and treatment on changes in CSF biomarker response and on changes in cognitive response. We performed backwards linear regression to develop multivariate models for predicting the changes in CSF biomarkers while keeping age, sex, and education in these models. These were adjusted R-squares and F-statistics to compare the fit of the various models. Prospective baseline measures to incorporate into risk regression model include LDL, HDL, systolic blood pressure, pulse pressure, total cholesterol, physical activity, age, education, sex, APOE status, alcohol use, interleukin-6, high-sensitivity c-reactive protein (hs-CRP), blood glucose, BMI, and blood pressure medication use. These variables were assessed across both treatment groups. Analyses were performed using SAS and R statistical computing environment.

Results

Subject Characteristics:

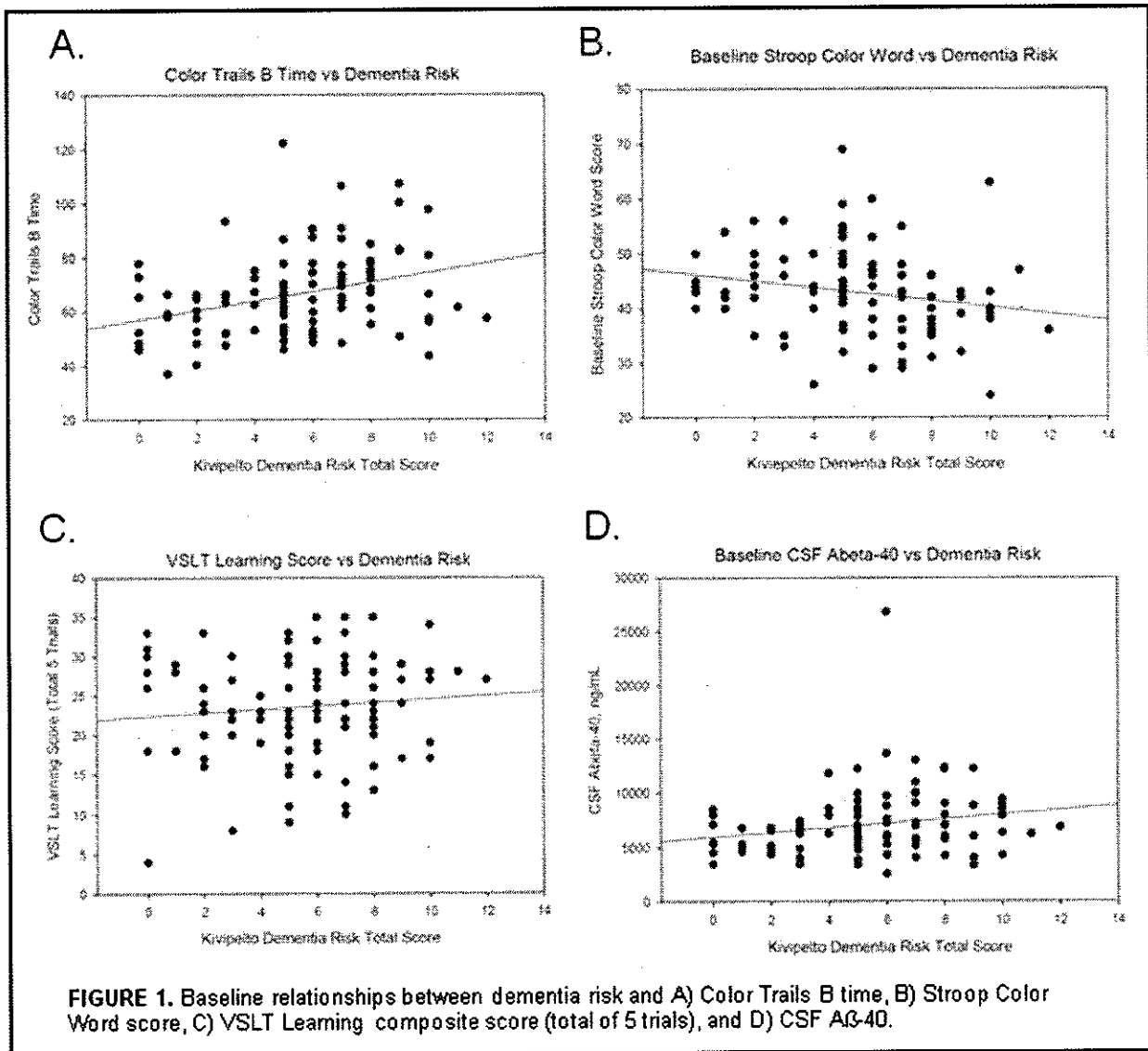
Participant characteristics are described in table 3. Subjects were predominately Caucasian, cognitively normal at baseline as evidenced by the Mini Mental State Examination, and had

| TABLE 3. PARTICIPANT BASELINE CHARACTERISTICS | | | | |
|--|-----------------|--------------------|-----------------|---------------------------------|
| Characteristics | All Subjects | Simvastatin (N=51) | Placebo (N=49) | p Value (Simvastatin & placebo) |
| Age, mean (SD), yrs | 52.8 (7.96) | 53.3 (7.4) | 52.4 (8.5) | 0.607 |
| Women, No. (%) | 70 (70) | 35 (68.6) | 35 (71.4) | 0.760 |
| Education, mean (SD), yrs | 16.2 (2.85) | 16.1 (2.5) | 16.3 (3.2) | 0.788 |
| MMSE score, mean (SD) | 29.5 (0.7) | 29.5 (0.8) | 29.6 (0.6) | 0.799 |
| APOE4 carrier, No (%) | 38 (38) | 21 (41.2) | 17 (34.7) | 0.504 |
| Current smoker*, No. (%) | 8 (8) | 2 (3.9) | 6 (12.2) | 0.125 |
| Body Mass Index, mean (SD), kg/m ² | 27.85 (5.5) | 27.8 (5.3) | 27.9 (5.7) | 0.882 |
| Physical exercise**, No. (%) | 69 (70.4) | 36 (72.0) | 33 (68.8) | 0.985 |
| Systolic blood pressure, mean (SD) mmHg | 121.5 (13.3) | 121.9 (13.0) | 121.1 (13.7) | 0.772 |
| Kivipelto Dementia Risk Score, mean (SD) | 5.48 (3.0) | 5.8 (2.8) | 5.1 (3.1) | 0.404 |
| Current use of antihypertensive, No (%) | 13 (13) | 6 (11.8) | 7 (14.3) | 0.708 |
| Fasting Blood Tests | | | | |
| Total cholesterol, mean (SD), mg/dL | 190.3 (32.4) | 192.8 (36.4) | 187.6 (27.7) | 0.882 |
| Triglycerides, mean (SD), mg/dL | 100.4 (44.4) | 96.6 (43.3) | 104.3 (45.7) | 0.326 |
| HDL-C, mean (SD), mg/dL | 55.7 (16.4) | 54.4 (15.7) | 57.0 (17.2) | 0.517 |
| LDL-C, mean (SD), mg/dL | 118.6 (28.8) | 123.8 (31.7) | 113.1 (24.5) | 0.090 |
| CSF Fluid Measures | | | | |
| CSF Aβ-42†, mean (SD), ng/mL | 518.8 (265.9) | 345.6 (77.1) | 331.0 (83.7) | 0.361 |
| CSF Aβ-40#, mean (SD), ng/mL | 7071.8 (3132.5) | 6960.9 (2282.9) | 7192.4 (3874.4) | 0.739 |
| CSF Total tau†, mean (SD), ng/mL | 70.0 (63.3) | 63.0 (23.3) | 77.8 (88.5) | 0.652 |
| CSF p-tau-181†, mean (SD), ng/mL | 37.3 (17.9) | 37.2 (16.2) | 37.4 (19.9) | 0.743 |
| CSF Aβ-42/Aβ-40, mean (SD) | 0.073 (0.015) | 0.074 (0.015) | 0.071 (0.015) | 0.298 |
| CSF Total tau/Aβ-42, mean (SD) | 0.216 (0.194) | 0.194 (0.106) | 0.241 (0.258) | 0.188 |
| Values are mean (SD) unless indicated. MMSE=Mini Mental State Examination, out of 30; APOE4=apolipoprotein E ε4 allele; HDL-C=high density lipoprotein cholesterol; LDL-C=low density lipoprotein cholesterol. *Current smoker defined as smoked in the previous month. **Physical exercise defined as greater than once a week (30+ min). † Using ALZ bio 3 method, polystyrene collection tube. # Using triplex method, polystyrene collection tube. | | | | |

fairly average vascular risk profiles. All subjects had confirmed parental diagnosis of AD prior to enrollment. Kivipelto dementia risk scores were balanced between simvastatin and control (Table 3). Cognitive performance and CSF biomarkers did not significantly differ at baseline between treatment and controls (Table 3).

Cognitive Function

Baseline cross sectional analyses (n=100) revealed dementia risk scores correlated positively with Color Trails B time ($r = 0.355$, $p = < 0.001$) (Figure 1.A) and inversely with Stroop color word score ($r = -0.289$, $p = 0.0037$) (Figure 1.B), measures of executive function and processing speed. Dementia risk was also correlated with nonverbal memory. The composite VSLT: Learning Score ($\beta = 0.65$, $p = 0.032$) correlated significantly with dementia risk (Figure 1.C). No baseline relationships were noted between dementia risk scores and verbal memory, visual-motor, or language measures.



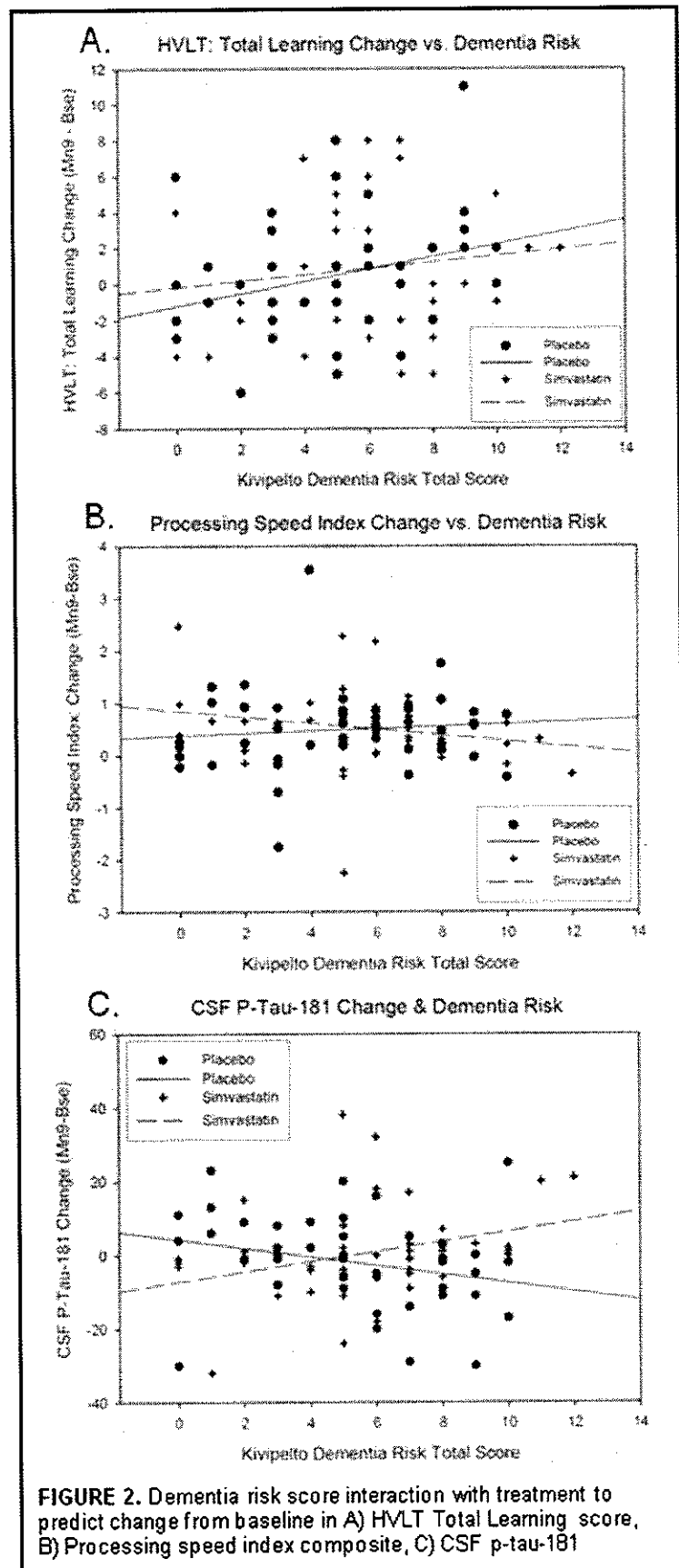
While the simvastatin group as a whole did not have any improvement in cognitive tests above the placebo group at month 9, lower dementia risk scores significantly interacted with treatment to predict a greater increase in HVLT Learning Score (T1+T2+T3) overtime ($p=0.025$) (Figure 2.A) and improvement in processing speed index ($p=0.005$) respectively (Figure 2.B). HVLT: Learning Score did not significantly differ ($p=0.760$) between control (mean=29.6, SD=3.6) and treatment (mean=29.5, SD=3.1) groups at baseline. Processing speed index composite score was also similar ($p=0.629$) between controls (mean=0.06, SD=0.87) and treatment (mean=

-0.05, SD=0.86), suggesting these changes were related to treatment and dementia risk and not a consequence of baseline variation.

AD Biomarkers

Baseline analyses revealed higher dementia risk correlated to increased levels of CSF A β -40 ($r=0.242$, $p=0.018$), shown in Figure 1.D. Relationships between dementia risk and baseline tau and A β 42 proteins were not observed.

Treatment effect analyses with covariate adjusted modeling, using baseline levels as a predictor showed that lower dementia risk scores significantly interacted with treatment to predict a greater decline ($\beta=1.72$, $p=0.048$) in CSF p-tau-181 for subjects on simvastatin in comparison to



placebo (Figure 2.C). This relationship could not be described by treatment ($p=0.164$) or dementia risk ($p=0.314$) alone. Baseline p-tau-181 levels did not significantly differ at baseline (Table 3). No significant treatment interactions were noted between dementia risk scores and CSF β -amyloid levels.

Dementia Risk Model

Backwards regression models including treatment and vascular risk factors did not predict changes in primary outcomes. Although the treatment variable fell out of the backwards regression, a model including baseline HDL, LDL, alcohol consumption and baseline CSF IL-6 remained significant ($p= 0.0027$) and explained approximately 17% of the variance in changes in CSF A β -42 over the course of the study. Similarly, models to describe cognitive changes over time did have treatment as a significant predictor. After backwards regression, only baseline age significantly ($p=0.042$) predicted a small percentage (4.4%) of the variance in HVLT: Delayed Recall Score over nine months.

Discussion:

In asymptomatic, middle-aged, adult children of persons with AD, higher dementia risk scores predict worse cognitive performance in executive function and processing speed, tests sensitive to early decline in AD. High dementia risk also correlates to higher levels of CSF A β -40, an established biomarker for AD. Cognitive correlations align with the current assumption that those developing dementia will display decreased mental capacity. Interestingly, baseline correlations between dementia risk and CSF β -amyloid are hypothesized to be inversely

correlated in declining populations; however CSF levels of β -amyloid in middle aged adults are not yet established. Further research is necessary to determine if dementia risk and CSF β -amyloid are directly correlated at mid-life, as suggested by this risk analysis.

Dementia risk significantly interacts with treatment to predict a greater improvement in cognitive measures for subjects with low dementia risk. Low dementia risk scores also predict a greater decrease in p-tau-181 levels on simvastatin compared to placebo. Although it is hypothesized decreasing the levels of CSF tau is protective in older populations, the role of CSF tau biomarkers in middle aged populations are not clearly defined.

Study findings suggest that those with low dementia risk show the most benefit from simvastatin therapy in respect to CSF biomarker modification and cognitive improvement. Additionally, subjects with low dementia risk demonstrated better cognitive performance in executive function and nonverbal memory and increased CSF β -amyloid at baseline, which are associated with healthy aging. Backwards regression modeling suggests the Kivipelto risk score is appropriate to predict changes in response to therapy in this increased risk population in comparison to models developed from baseline characteristics. Baseline models were not able to predict response to treatment.

This study is distinct from previous studies in that risk stratification is employed to cluster participants. Additionally, having a parental history of AD places this study group at a higher risk than can be explained by identified genetic factors, which makes this a particularly

interesting group to study. Although various environmental and lifestyle risk factors have been associated with developing dementia through large scale cross-sectional analyses [31, 32], few, if any studies to date, have combined the use of risk ratios and controlled clinical intervention trials targeting AD prevention in a middle-aged, healthy population.

Limitations

Most of the study participants were fairly low risk. A wider range of risk for AD in study participants may provide more information regarding the role of higher baseline risk and prevention therapies. Additionally, the ESPRIT population is more educated and overall a healthier population than the population from which the risk score model was developed. The Kivipelto model does not include family history of AD, which has shown to be associated with early brain changes even after controlling for known genetic risk factors. These caveats may alter the ability of the Kivipelto et al model to predict dementia risk in the ESPRIT or other similar at-risk populations.

Study limitations include sample size and length of study. As each study arm includes 50 participants, more participants would allow for more powerful, conclusive analysis. Additionally, it may be that individuals have to remain on simvastatin therapy for 1-2 years before we will see significant effects of therapy.

Future Directions

Further research is necessary to determine how quantified dementia risk predicts response to longer duration simvastatin therapy and its role in clinical trial recruitment and clinical care. Additionally, it is unclear how dementia risk influences newly developing AD biomarkers, neuroimaging, and the modification of various vascular risk factors in a middle aged, at risk population. While currently there is little known about the prevention of AD and mid-life dementia risk, future developments in AD prevention look promising.

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