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Sex Differences in the Association of Framingham Cardiac Risk Score with Cognitive Decline in Community-Dwelling Elders without Clinical Heart Disease

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Abstract

Objective—To investigate a possible link between cardiovascular risk factors and age-related cognitive decline, the association of the 1998 Framingham Cardiac Risk Score (FCRS) with the trajectory of cognitive function test (CFT) performance over 18 years was examined in adults 50 years and older without clinical heart disease at baseline.

Methods—Participants were 985 men and women who had assessments of cognitive function at three to four year intervals. The association of FCRS category with CFT score trajectory was examined using mixed effect models stratified by sex and controlling for age, education, and number of repeat cognitive assessments.

Results—At baseline, median FCRS corresponded to a 14% risk of a CHD event within 10 years for men and a 8% risk for women; 31% of men and 6% of women were at high (>20%) risk. In longitudinal analyses, women with FCRS risk >7% had a higher rate of decline on tests of verbal fluency (p 's <.05) and long term recall (p 's <.01) compared to low risk women; modest, but significant (p 's <.05), differences in the trajectory of MMSE and Trails B scores were also apparent. FCRS category was not related to the rate of decline in CFT performance in men.

Conclusions—For older women, very low levels of CHD risk were associated with preservation of cognitive function over 10 years, suggesting that maintenance of cardiovascular health may slow cognitive decline. The minimal association in men, who were at higher baseline risk, may be due to selective attrition of men with greater cognitive decline.

Keywords

aging; cardiovascular; cognitive function; prospective

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Relationship with Industry

None

INTRODUCTION

An increasing amount of laboratory and epidemiologic evidence suggests that cardiovascular disease (CVD) and dementia share common antecedents. Cardiovascular disease (CVD) is a known risk factor for cognitive decline and dementia(1–3). Recent studies suggest subclinical CVD may also be detrimental to cognitive function(1, 4–6). Whether the long-term trajectory of cognitive decline or maintenance in individuals without clinical heart disease is influenced by prior exposure to classic CVD risk factors is less certain. This information is important given the aging of the population, the fact that many CVD risk factors are modifiable, and because maintenance of cognitive function is an essential component of healthy aging.

Individual vascular risk factors have been associated with cognitive impairment (7–10). For example, longitudinal studies have shown that cognitive function decreases more rapidly in individuals with hypertension (8, 10) and type 2 diabetes has been consistently associated with a greater rate of cognitive decline and increased risk of cognitive impairment (9). Potential mechanisms for the influence of vascular risk factors on cognition are complex and include reduced cerebral perfusion, cerebral atherosclerosis and vascular inflammation (8). Diabetes may also contribute to cognitive decline via the production of advanced glycosylated end-products by hyperglycemia or via other diabetes-associated factors such as insulin resistance and microvascular disease(9, 11). Cumulative insults from multiple vascular risk factors may be especially harmful to cognitive ability.

The Framingham Cardiac Risk Score (FCRS) assigns an increasing score for increasing levels of classic CVD risk factors based on their ability to predict coronary heart disease (CHD) events in the Framingham cohort and weights them to produce a score giving the 10 year probability, or risk, of a CHD event (12). The predictive value of the FCRS for CHD events in asymptomatic men and women has been evaluated in numerous populations (13). Less attention has been given to whether the FCRS predicts other conditions thought to be related to vascular health including the decline of cognitive function with aging in individuals without clinical heart disease.

The objective of the present study was to investigate the association of the FCRS with the trajectory of cognitive decline over an average of 10 years in community-dwelling adults 50 years and older without clinical heart disease at baseline, and to test the independence of observed associations from other CVD risk factors which could affect vascular brain health.

METHODS

Study population

Participants were older community-dwelling adults enrolled in the Rancho Bernardo Study, a population-based study of healthy aging in a Southern California community. Between 1984 and 1987, 82% of surviving community-dwelling participants attended a research clinic visit when CHD risk factors were assessed. Cognitive function testing was first performed in 1988 to 1991 and was repeated using identical protocols at approximately four year intervals at four follow-up visits. The average time between the baseline CHD risk factor assessment and the first cognitive function assessment was 4.3 years; the total duration of follow-up was 18 years. The study protocol was approved by the Institutional Review Board of the University of California, San Diego; all participants gave written informed consent prior to participation.

Eligibility criteria for the present analysis included attending the 1984–87 research clinic visit when CHD risk factors were assessed and completing from 2 to 5 cognitive function

assessments beginning with the 1988–91 visit. For the present analysis, participants had to be age 50 or older, postmenopausal (women), and with no history of CHD (myocardial infarction or coronary artery revascularization procedure) at the time of the CHD risk assessment. Of the 1578 men and women who attended the 1984–87 CHD assessment and had cognitive function assessments in 1988–91, 4 were excluded for age less than 50, 8 for pre-menopausal status, and 537 for no follow-up cognitive function assessment. An additional 52 were excluded for prevalent CHD. The remaining 394 men and 591 women are the focus of this study.

Cognitive function assessment

Five standardized tests chosen to assess different aspects of cognitive function were administered by a trained interviewer at the 1988–91 and follow-up clinic visits. The Mini-Mental State Examination (MMSE) (14, 15) briefly assesses multiple cognitive domains and is used as a test of global cognitive function; scores range from 0 to 30. Trail Making Test B (Trails B,) tests visuomotor scanning, tracking, attention and mental flexibility (16). Performance is rated by the time required to finish the test (300 seconds maximum); the greater the score, the poorer the performance. The Animals Naming Category Fluency test (17) assesses semantic association fluency and cognitive flexibility. The Buschke-Fuld Selective Reminding Test (18) assesses short- and long-term storage and retrieval of spoken words. Measures of long- and short-term recall were used for the present analysis. Higher scores on the short-term memory test indicate poorer performance (as they indicate words that did not enter long term storage). Based on recommendations from the Alzheimer's Disease Research Center of the University of California, San Diego, scores of ≤ 24 for the MMSE, ≥ 132 for Trails B, ≤ 12 for Category Fluency and < 14 for long term recall (LTR) were used to indicate categorically defined poor performance. Poor performance is not defined for short term recall.

Covariate and CHD risk factor assessment

During the baseline CHD assessment visit (1984–87), standardized questionnaires were used to obtain medical history, medication use, physical activity (exercise 3+ times per week, yes/no), and alcohol consumption (3+ drinks/week versus less or none) and current smoking (yes/no). Prevalent CHD was defined as physician diagnosis of myocardial infarction or coronary artery revascularization; prevalent cerebrovascular disease as transient ischemic attack or stroke. Current medication use was validated by examination of pills and prescriptions. Education was categorized as 5 levels (less than high school graduate, high school graduate, some college, college graduate, any graduate school). Depressed mood was assessed using the Beck Depression Inventory (BDI) (19).

Height, weight, and waist and hip girth were measured in the clinic with participants wearing light clothing and no shoes. Body mass index (BMI) (kg/m^2) and waist to hip ratio were used as estimates of overall and central adiposity, respectively. Blood pressures were measured twice in seated resting subjects using the Hypertension Detection and Follow-Up Program protocol (20); the mean of two readings was used in analyses.

Samples of fasting blood were obtained from participants after a requested overnight (12–16 hour) fast. Fasting plasma total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol and triglyceride levels were measured in a Center for Disease Control and Prevention Certified Lipid Research Clinic Laboratory. Total cholesterol and triglyceride levels were measured by enzymatic techniques using an ABA-200 biochromatic analyzer (Abbott Laboratories, Irving, TX). HDL was measured after precipitation of the other lipoproteins with heparin and manganese chloride. LDL was estimated using the Friedewald

formula(21). Plasma glucose levels were measured by the glucose oxidase method in a hospital laboratory.

FCRS and risk categories were calculated based on the 1998 criteria published by Wilson and colleagues(12). Based on CHD events observed over a 10-year period in the Framingham Heart Study, the FCRS assigns sex-specific points for age, LDL and HDL cholesterol, systolic and diastolic blood pressures, diabetes and current smoking and assigns a 10 year probability (or risk) of CHD events to each individual. Age greater than 75 was scored as 8 points for both sexes. Diabetes was defined by physician diagnosis, fasting plasma glucose ≥ 126 mg/dl, 2-h post-challenge glucose ≥ 200 mg/dl, or use of diabetes medications. Total point scores were used to define FCRS categories.

Statistical analysis

General linear models were performed to compare those with and without complete data and to compare baseline CFT scores by Framingham risk category; all models were adjusted for age and education. The relation of FCRS to longitudinal cognitive function data was examined using mixed effects regression models. This statistical approach handles inconsistent measurement intervals within and across participants and accounts for within-subject correlation between repeated measures. Separate models were created for each CFT. Models included 'fixed' effect terms which model the mean trajectory of subjects as a function of the covariates: baseline age, education, and time (years since baseline). Models also include 'random' effect coefficients which allow individual subject baseline levels (intercept) and rates of decline (slope) to vary randomly about the mean trajectory described by the fixed effect terms. Interaction terms of all covariates with time were included to test whether the influence changed over time. Quadratic (time-squared) terms were tested because of the long follow-up period (up to 18 years). Additionally, a participation effect (defined as the number of cognition assessments) was added as a fixed main effect to reflect loss to follow-up (due to death, illness, etc.); an interaction term was used to test the influence of the participation effect on trajectory (slope).

The FCRS was modeled as a sex-specific categorical variable. The coefficient for each FCRS category indicates its influence on each CFT score at baseline (intercept). The coefficient for the interaction of each FCRS category with time indicates its influence on the rate of change (slope) for each CFT score over time. Secondary models tested confounding or effect modification by age at baseline, adiposity (BMI and waist to hip ratio), depressed mood, prior estrogen use, prevalent cerebrovascular disease, and lifestyle variables (alcohol intake, physical activity, current smoking). Based on a priori reasoning, all analyses were sex-specific. Plots of modeled mean trajectories were created including all parameters and using sex-specific means for the covariates baseline age, education and number of cognitive assessments.

Following the recommendation of Rothman(22), no adjustment was made for multiple comparisons; rather exact *P*-values for two-sided tests are shown; $p \leq 0.05$ was considered statistically significant. Data were analyzed using SAS v9.1 (SAS Institute, Cary, NC) and SPSS v15.0 (SPSS Inc, Chicago, IL).

RESULTS

Baseline characteristics

The average age of the 985 men and women with CVD risk factor assessment and serial cognitive function testing was 66.8 years (SD, 8.5) at the 1984–87 CVD visit. Means and the prevalence of relevant characteristics are summarized in Table 1. The median FCRS corresponded to a 14% (intermediate) risk of a CHD event within 10 years for men and a 7%

(low) risk for women. Using traditional FCRS categories, the majority (72%) of women were classified as low risk (<10%), whereas only 30% of men were low risk. Conversely, only 6% (n=34) of women were classified as high risk (>20%) compared to almost a third of men.

The mean scores for MMSE, Trails B, category fluency and long term recall at the first assessment (1988–91) were well outside traditional cut points for poor cognitive performance for both sexes, reflecting the relatively healthy, well-educated, community-dwelling cohort (Table 2). Proportionally more men than women scored in the poor performance range for the MMSE and long term recall tests, whereas more women scored in the impaired range for Trails B. Age and education-adjusted baseline CFT scores and the prevalence of poor CFT scores at baseline did not differ by FCRS category in either sex.

The proportion of participants excluded due to prevalent CHD did not differ by sex (13.5% of women, 13.0% of men, $p=0.79$). Compared to those who did not return for another cognitive function assessment, those who had one or more repeated assessments were on average younger (66.8 vs 74.2 years), had better performance on the MMSE (27.5 vs 26.1), Trails B (118.3 vs 166.1), category fluency (18.8 vs 16.1), short term recall (6.1 vs 7.5) and long term recall (33.5 vs 24.7), and lower FCRS (7.3 vs 8.9 points), all $P<.001$.

Cognitive Function Trajectories by FCRS Category

The average number of repeat cognitive assessments was 3.4 and did not differ between men and women ($p=0.58$). Overall, 32% of participants had two cognitive assessments, 19% had three, 20% had four and 29% participated in all five cognitive function examinations over the 18 year period. The median length of cognitive function follow-up was 9.8 years (range 2.5 – 17.4). During follow-up, 191 women (32.3%) and 171 men (43.4%) died; 47% of deaths in women and 38% of deaths in men were attributed to CVD. Men and women in the high and intermediate FCRS risk categories were less likely to return for all cognitive assessments and more likely to die during follow-up than those with low risk, all $P<.001$.

Sex-specific results for FCRS categories from mixed models adjusted for baseline age, education and number of cognitive assessments are presented in Table 3. Results are presented for both sexes by traditional FCRS risk categories: low (<10%), intermediate (10–20%), and high (>20%). Because of the small number of categorically defined high risk women (n=34), results for women are also presented stratified by FCRS tertiles. This categorization was chosen because the distribution of traditional FCRS risk categories for men approximates tertiles. [The number of women in each tertile is not evenly distributed because of a large number of identical scores in the lowest tertile.] Plots of CFT score trajectory models by FCRS category in men and by FCRS tertile in women are presented in Figure 1. These plots are based on all model coefficients using sex-specific mean values for covariates.

For women, the rate of CFT decline was significantly associated with FCRS for 4 of the 5 CFTs in analyses stratifying by traditional FCRS risk categories or by FCRS tertiles (Table 3). As shown in Figure 1, the decline in verbal fluency and long term recall scores was delayed and slowed in women in the lowest FCRS tertile, with women in the two highest FCRS tertiles showing similar and more rapid rates of decline. Significant quadratic FCRS by time coefficients for each of these tests indicated that these differences diminished as the cohort aged. In contrast, statistically significant differences in CFT trajectory by FCRS tertile for MMSE and Trails B in women were relatively small and only evident at later time points. FCRS tertile was not related to the trajectory of short term recall test performance in women. In men, FCRS category was not related to the rate of decline in CFT performance for any test. The difference in results for men and women was supported by significant

($p < 0.10$) sex by FCRS by time interactions for Trails B ($p = 0.06$), short term recall ($p = 0.01$), long term recall ($p = 0.01$), but not for MMSE ($p = 0.19$) or Category Fluency ($p = 0.30$). Main effect coefficients for the FCRS categories were not statistically significant for any CFT in either sex, indicating that baseline CFT scores did not differ by FCRS category. Although men in the lowest risk category showed, on average, lower performance on Trails B, category fluency and long term recall at baseline than those in the higher risk categories, these baseline differences were not significant, and rate of change did not differ among the three risk groups.

Because raw CFT scores were used in the analyses, regression coefficients are not comparable across test measures. To provide a sense of magnitude of effect, the influence of FCRS tertile on CFT scores for women at 10 years of follow-up was calculated from the models using population means for all covariates. Compared to low risk women, scores for verbal fluency at 10 years were an identical 1.3 points lower for women in the second and third FCRS tertiles; corresponding values for long term recall were 4.2 and 3.7 point lower scores for the two highest tertiles at 10 years. Based on education-adjusted baseline scores, these differences are equivalent to a 7 year increase in age for verbal fluency and an 8 to 9 year increase in age for long term recall.

Secondary trajectory analyses

In secondary analyses (data not shown), there was no evidence of effect modification by age at baseline (<70 vs 70+ years) or by number of cognitive function assessments for any test in either sex. In addition, results were essentially unaltered in separate analyses adjusting for adiposity (BMI, waist-to-hip ratio), depressed mood (BDI), estrogen use (in women), or lifestyle (physical activity, alcohol intake). Adjusting for or excluding those with prevalent cerebrovascular disease ($N = 36$) also did not appreciably alter results for either sex. Finally, to examine the same level of very low risk in men as was used for women, analyses were repeated categorizing men by <7% risk ($n = 34$) versus all higher; there were no significant differences in rate of decline for any CFT using this cut point.

DISCUSSION

In this cohort of community-dwelling adults without clinical heart disease, the FCRS was associated with the rate of cognitive decline in women, but not men. Women with very low CHD risk based on a FCRS <7% maintained a higher level of cognitive function over time than women with higher CHD risk. Differences in the rate of decline on tests of semantic verbal fluency and long term verbal recall were apparent early in follow-up and continued over 10 years. CHD risk in women was also modestly, but significantly, associated with the longitudinal trajectory of scores on the MMSE, a screening test for global cognitive function, and Trails B, a measure of visuomotor tracking and executive function, but only near the end of follow-up. In contrast, the pattern of cognitive decline did not differ by CHD risk profile in men, even though more men than women were at intermediate or high CHD risk.

To our knowledge, this is the first study to investigate the association of the FCRS with trajectory of cognitive function in adults 50 years and older. A number of studies have evaluated various components of the FCRS; results are inconclusive for some factors and robust for others. For example, in the MacArthur Study of Successful Aging, increases in HDL cholesterol levels over a 2.5 year period were associated with reduced risk of cognitive decline over the following 4.5 years(23), but there was no association of total, LDL or HDL cholesterol levels with decline in cognitive performance among 1147 older adults in a multi-ethnic urban population(24). One of the best-established risk factors is diabetes. In a review

of 25 longitudinal observational studies(25), type 2 diabetes was consistently associated with a greater rate of cognitive decline and increased risk of cognitive impairment.

There are several plausible mechanisms whereby higher CHD risk could lead to more rapid loss of cognitive function. The presence of subclinical atherosclerotic disease has been associated with concurrent impairments in cognitive function(4, 6), more rapid decline in cognitive performance(4, 5, 26)and increased risk of dementia(1). Prolonged exposure to the cluster of CVD risk factors included in the FCRS may lead to unidentified atherosclerotic disease resulting in impaired cerebral blood flow, “silent” infarcts, or inflammatory injury with a subsequent decline in cognitive function. Cerebral white matter lesions, a predictor of cognitive impairment(27), are also more common in individuals with atherosclerosis(28, 29). Individual FCRS risk factors may also work through mechanisms not related to atherosclerosis. For example, the increase in blood viscosity in diabetics(30)may contribute to reduced cerebral blood flow(31)and cognitive decline, and the renin-angiotensin system could be involved in the association of blood pressure with cognition(32). An accumulation of insults from multiple factors is likely to underlie the association of composite CHD risk scores with cognitive decline.

The FCRS does not include some factors which could be important in the etiology of both heart disease and cognitive decline. The associations (or lack of associations) between FCRS and cognitive trajectory observed in the present study persisted in analyses adjusting for overall and central adiposity and were insensitive to other potential confounders including depressed mood, physical activity and alcohol consumption. Adjustment for or exclusion of the small number of participants with prevalent cerebrovascular disease also failed to explain either the protective association of low FCRS risk with cognitive decline in women, or its absence in men.

What could explain the sex-specific association of CHD risk with cognitive performance in this population and is it generalizable to other populations? Not all CHD risk factors have adverse associations with cognitive function in elders. For example, in some studies, higher total cholesterol levels(33) or higher blood pressure(34, 35)were associated with better cognitive performance. These protective associations are observed most often in the oldest old(1). Thus, composite risk scores such as the FCRS may cancel out protective and harmful associations with individual risk factors, especially when measured late in life. In the present study, stratifying by age at baseline, did not alter results for either sex, thus this phenomenon does not explain the absent associations in men. Another possibility is that above a certain low threshold of CHD risk, there are no differences in rate of cognitive decline; at least in a population of relatively healthy, well-educated adults like those in this study. The low number of men (n=34) with very low risk (<7%) in the present study precluded definitive testing of this hypothesis.

The association of CHD risk with cognitive decline in women, but not men, may also be related to sex differences in vascular physiology. Shaw and colleagues(36)have proposed that coronary microvascular dysfunction is more prevalent in women than men, due in part to the combination of smaller arterial size and more vascular remodeling in women. The same mechanisms may lead to more microvascular damage in the female brain, resulting in silent cerebral infarcts and hypoperfusion. Reports that white matter hyperintensities in the brain, which are thought to reflect small-vessel vascular disease(37), are more common in women than men (38), support this view.

Finally, it is possible that selective attrition may have prevented detection of an association in men. Longitudinal studies in the elderly are vulnerable to truncation of data by death (39). Although in this study the proportion excluded for prevalent CHD at baseline did not differ

by sex, work by Kurland and colleagues suggests that women can survive with cognitive decline better than men(39)and more men than women died during follow-up. Thus, men whose cognitive abilities declined during follow-up may have been more likely to die than women with similar cognitive impairments, obscuring any association with vascular risk in men.

If confirmed in other populations, our findings may have important clinical relevance. Age-related cognitive decline is a major contributor to functional decline, loss of independence and lower quality of life in older adults(40, 41). The delay in cognitive decline in women with very low CHD risk was equivalent to almost 10 years younger age. Thus, maintaining optimal blood pressure and healthy lipid levels, not smoking, and avoiding diabetes may enable older women to enjoy a higher level of cognitive ability longer into their senior years, while simultaneously protecting the cardiovascular system.

Study Strengths and Limitations

Strengths of this study include its population-based cohort and longitudinal design. FCRS components were collected at baseline with standardized measurements and assessments of multiple cognitive domains were obtained at up to five clinic research visits over an 18 year period. We were able to adjust and stratify the data for known major confounders, which is important in elderly populations where many factors may affect cognitive function. The main limitations are survival and participation bias, an unavoidable characteristic of cohort studies of the elderly. Participants with higher CHD risk were less likely to return for cognitive function assessments and more likely to die from CVD-related causes during follow-up. The resulting inevitable focus on healthier individuals with lower risk of cognitive decline may have led to an under estimation of the true association between CHD risk and cognitive decline. Analyses were not adjusted for multiple comparisons which may have increased the likelihood of Type I errors, that is, false positive results; however, the consistency of associations across multiple cognitive function tests in women argues in favor of their validity. In addition, not adjusting for multiple comparisons reduces the likelihood that the absence of significant associations in men was due to Type II (false negative) errors.

The Rancho Bernardo Study is almost entirely white and middle to upper-middle class, and the mean education level was high, thus results may not be generalizable to less advantaged groups or to other ethnicities. However, this homogeneity is an advantage in that it reduces confounding due to socioeconomic status, education and access to health care. Finally, although multiple cognitive domains were assessed, it is possible that untested domains may have yielded additional associations.

Conclusions

In conclusion, this study showed that very low levels of CHD risk were independently associated with preservation of cognitive function over 10 years in women 50 years and older. If confirmed, these results suggest that maintaining CHD risk factors at optimal levels not only protects the heart, but may also delay loss of cognitive ability in older women. The absence of a similar protective association in men may be related to selective attrition or may be because so few men were at such low cardiovascular risk. Studies of younger men with lower risk are needed to clarify whether vascular health influences the trajectory of cognitive decline in men.

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Abbreviations

CVD	cardiovascular disease
CHD	coronary heart disease
CFT	cognitive function test
FCRS	Framingham Cardiac Risk Score
MMSE	Mini-Mental State Examination
BMI	body mass index
LDL	low density lipoprotein
HDL	high density lipoprotein
BDI	Beck depression inventory

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Figure 1.

Modeled cognitive function test score trajectories by Framingham coronary heart disease risk category among 591 postmenopausal women and 394 men, 50 years and older at baseline. Framingham Cardiac Risk Scores are stratified by traditional risk groupings for men and by tertiles for women. Plots are based on all model coefficients using sex-specific mean values for covariates (age, educational level, and number of cognitive assessments). Note that for Trail-Making Test B and short-term recall the y axis is reversed because increasing scores indicate poorer performance. The symbols are included for reference only and do not represent discrete data points. Residual covariance parameter estimates for the models from the top to the bottom plot are 2.2, 1100, 9.1, 17.8, and 64 for the women and 2.2, 852, 9.6, 17.9, and 63 for the men, respectively. MMSE = Mini-Mental State Examination; CFT = cognitive function test; BSTR = baseline short-term recall; BLTR = baseline long-term recall.

Table 1

Baseline (1984–87) demographics, CVD risk factors, and Framingham Heart Scores

	Men (N=394)	Women N=(591)	p-value*
Characteristic	Mean (SD)	Mean (SD)	
Age (yrs)	65.9 (8.4)	67.3 (8.6)	.01
BMI (kg/m ²)	26.1 (3.1)	24.0 (3.5)	<.001
Waist Girth (cm)	93.8 (8.5)	77.4 (9.1)	<.001
Beck Depression Score	4.3 (3.4)	5.9 (4.3)	<.001
	Percent	Percent	
Education			<.001
Graduate school	23.2	6.7	
College graduate	29.8	21.0	
Some college	27.2	36.7	
High school graduate	17.7	32.4	
<High school graduate	2.1	3.2	
Alcohol (3+ drinks/wk)	63.2	49.9	<.001
Current smoker	11.2	13.5	<.001
Exercise (3+ times/wk)	86.8	82.6	.008
Current estrogen use		31.9	
Prior estrogen use		41.2	
CVD Risk Factors	Mean (SD)	Mean (SD)	
Systolic blood pressure (mm Hg)	132.9 (18.1)	133.8 (20.7)	<.001
Diastolic blood pressure (mmHg)	78.5 (8.9)	74.9 (8.9)	<.001
Total cholesterol (mg/dl)	214.6 (38.8)	228.6 (40.0)	<.001
LDL cholesterol (mg/dl)	137.8 (35.1)	136.8 (38.9)	.62
HDL cholesterol (mg/dl)	53.1 (13.9)	70.2 (18.1)	<.001
Triglycerides (mg/dl) [‡]	102.9 (43.1)	95.5 (29.0)	.04
Diabetes (%)	12.7	10.2	<.001
Framingham Risk Score			
Median CHD risk (%)	14	8	<.001
% Low risk (<10%)	29.7	71.7	<.001
% Intermediate risk (10–20%)	38.6	22.5	
% High risk (>20%)	31.7	5.8	

* p-value for sex differences adjusting for age

[‡] values are geometric means

Table 2

Sex differences in baseline (1991–95) cognitive function test performance

	Men (N=394)	Women N=(591)	p-value *
Cognitive Function Test Scores	Mean (SD)	Mean (SD)	
MMSE	27.4 (1.8)	27.7 (1.5)	.003
Trails B [†]	106.6 (45.8)	124.9 (58.3)	<.001
Category fluency	19.9 (4.9)	18.0 (4.7)	<.001
Short term recall [†]	7.2 (4.5)	5.2 (3.7)	<.001
Long term recall	29.8 (12.7)	36.1 (11.7)	<.001
Poor Performance	Percent	Percent	
MMSE <24	4.0	1.0	.001
Trails B >132	25.1	33.4	.003
Category fluency <12	9.0	9.3	.211
Long term recall <14	13.4	4.6	<.001

*
p-values are for age and education adjusted comparisons

[†] Higher scores indicate poorer performance

Table 3
Association of Framingham Heart Score (FCRS) with Trajectory of Cognitive Function Test Scores

	N	MMSE		Trails B		Verbal Fluency		Short term recall		Long term recall	
		Linear	Quad	Linear	Quad	Linear	Quad	Linear	Quad	Linear	Quad
<u>Men</u>											
FCRS category											
Low (<10%)	117	Ref	ref	ref	ref	ref	ref	ref	ref	ref	Ref
Intermediate (10–20%)	152	.017	---	.237	---	.026	---	.090	---	.047	
High (>20%)	125	.017	---	.804	---	.026	---	-.047	---	.045	
<u>Women</u>											
FCRS category											
Low (<10%)	424	Ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Intermediate (10–20%)	133	.086	-.008*	-3.200*	.402 [†]	-.080	.004	.020	---	-.301	.009
High (>20%)	34	.276 [†]	-.020 [†]	-2.685	.327	-.637 [†]	.047 [†]	.102	---	-1.442*	.124 [†]
<u>Women</u>											
FCRS tertile											
1: <7 points (<7%)	265	Ref	ref	ref	ref	ref	ref	ref	ref	Ref	ref
2: 7–9 points (7–9%)	159	-.015	-.001	-1.634	.196*	-.167	.010	.048	---	-1.069 [†]	.067*
3: >9 points (>9%)	167	.120*	-.011 [†]	-3.542 [†]	.444 [†]	-.270*	.018*	.055	---	-1.010 [†]	.065*

Beta-coefficients are for factor*time for the linear term and factor*time*time for the quadratic (quad) term

Ref=reference levels;

* p<.05,

† p<.01

Results for women included separate models for FCRS category and FCRS tertile

Models are adjusted for baseline age, education status and number of cognitive function assessments

--- indicates no significant quadratic term