Published in final edited form as:
Clin Endocrinol (Oxf). 2014 July ; 81(1): 134–140. doi:10.1111/cen.12382.

Fetuin-A, a New Vascular Biomarker of Cognitive Decline in Older Adults

Gail A Laughlin, PhD[1], **Linda K. McEvoy, PhD**[2], **Elizabeth Barrett-Connor**[1], **Lori B. Daniels, MD, MAS**[1,3], and **Joachim H. Ix, MD**[4,5,6]

[1]Division of Epidemiology, Department of Family and Preventive Medicine, University of California San Diego

[2]Department of Radiology, University of California San Diego

[3]Division of Cardiology, Department of Medicine, University of California San Diego

[4]Division of Preventive Medicine, Department of Family and Preventive Medicine, University of California San Diego

[5]Nephrology Section, Veterans Affairs San Diego Healthcare System, San Diego, CA

[6]Division of Nephrology, Department of Medicine, University of California San Diego

Abstract

Objectives—Fetuin-A is an abundant plasma protein known to predict vascular disease. Fetuin-A levels are lower in patients with Alzheimer's disease in proportion to the severity of cognitive impairment, but their association with normal cognitive aging is unknown. We evaluated the association of serum fetuin-A levels with cognitive function in community-dwelling older adults.

Design/Patients/Measurements—A population-based study of 1382 older adults (median age 75) who had plasma fetuin-A levels and cognitive function evaluated in 1992–96; 855 had repeat cognitive function assessment a median of 4 years later.

Results—Adjusting for age, sex, education, and depression, higher levels of fetuin-A were associated with better baseline performance on the Mini-Mental Status Exam (MMSE) (P=0.012) and a tendency for better Trails Making B scores (P=0.066). In longitudinal analyses, the likelihood of a major decline (highest decile of change) in Trails B was 29% lower (P=0.010) for each SD higher baseline fetuin-A level; odds of major decline in MMSE was 42% lower (P=0.005) per SD higher fetuin-A for individuals with no known CVD, but were not related to fetuin-A in those with CVD (P=0.33). Fetuin-A was not related to Category Fluency performance. Results were independent of multiple vascular risk factors and comorbid conditions.

Conclusions—Higher plasma fetuin-A concentrations are associated with better performance on tests of global cognitive function and executive function and with less likelihood of major decline

Correspondence: Gail A Laughlin, PhD, Department of Family and Preventive Medicine, University of California San Diego, 9500 Gilman Drive, MC0725, La Jolla, CA 92093, Phone: (858) 822-2416, Fax: (858) 534-4642, glaughlin@ucsd.edu.

Conflicts of Interest:
The authors have no actual or potential conflicts of interest to declare.

in these cognitive abilities over a 4-year period. Fetuin-A may serve as a biological link between vascular disease and normal age-related cognitive decline.

Keywords

fetuin-A; cognitive function; vascular disease; inflammation; aging; epidemiology

INTRODUCTION

In the past decade, there has been increased focus on a vascular basis for age-related cognitive decline and dementia. Evidence suggests that vascular diseases including cardiovascular disease (CVD) and diabetes contribute to cognitive decline and dementia (1–3). Specific vascular risk factors such as hypertension (4) and hypercholesterolemia (5) have also been linked with more rapid cognitive decline and risk of dementia. Potential mechanisms for the influence of vascular risk factors on cognition have been proposed including reduced cerebral perfusion, cerebral atherosclerosis and vascular inflammation (4).

Fetuin-A is an abundant serum protein secreted from the liver that has multiple, and at times, disparate effects on vascular health (6). Fetuin-A acts as an inhibitor of vascular calcification by preventing spontaneous mineral precipitation in the vasculature (7, 8). By contrast, fetuin-A also inhibits insulin signaling and induces insulin resistance in muscle and fat (8, 9). In line with these contrasting biological actions, we, and others, have shown that lower plasma fetuin-A levels are associated with increased risk of subclinical and clinical CVD (10–12), whereas higher fetuin-A concentrations predict incident type 2 diabetes (13–15).

Fetuin-A may also influence vascular health via the inflammatory system. Fetuin-A is a negative acute phase reactant capable of attenuating inflammatory responses to injury and infection (16). At higher concentrations, fetuin-A suppresses the release of tumor necrosis factor (TNF) from lipopolysaccharide (LPS)-stimulated macrophages (17) and plasma levels of fetuin-A are negatively correlated with levels of CRP in dialysis patients (18) and in patients with acute coronary syndrome (19). Of importance to the present study, peripheral administration of fetuin-A has been shown to protect against early brain ischemic injury in a rodent model, possibly by attenuating the brain inflammatory response (20). In addition, a recent study showed lower levels of fetuin-A in individuals with mild-to-moderate Alzheimer's disease in direct proportion to the degree of cognitive impairment (21). TNF-α concentrations were significantly higher in patients than controls in this study and were inversely correlated with fetuin-A levels (21). Collectively, these findings are consistent with the hypothesis that low fetuin-A may function as a vascular risk factor linking vascular disease and diminishing cognitive function in aging adults. To our knowledge, the association between fetuin-A and cognitive ability has not been evaluated in a non-clinical population, nor has the ability of fetuin-A to predict decline in cognitive function over time.

The present study examined the association of plasma fetuin-A levels with cognitive function and cognitive decline among older adults from the Rancho Bernardo Study, a prospective observational study of healthy aging. Multiple domains of cognitive function were assessed using established neuropsychiatric instruments. Based on the existing

literature, we hypothesized that higher fetuin-A levels would be associated with better cognitive function in older individuals and with lower risk of cognitive decline over time. Because of our prior experience, we also tested for modification of associations by prevalent vascular disease and diabetes.

METHODS

Study population

Between 1972–74, community-dwelling residents living in Rancho Bernardo, California, aged 30–79 years were invited to participate in a study of heart disease risk factors, and 82% (n=5,052) enrolled. Nearly all were middle to upper-middle class and more than 90% had completed high school. The present analysis included participants in the 1992–96 clinic visit. This study was approved by the Institutional Review Board of the University of California San Diego; all participants gave written informed consent.

Eligibility criteria for the present analysis included 1) age 50 years or older when evaluated at the 1992–96 visit, 2) postmenopausal status for women, 3) availability of stored sera, and 4) availability of cognitive function test results. Of the 1781 participants who attended the 1992–96 clinic visit, 49 were excluded for age less than 50 years, 6 women for premenopausal status, 93 for insufficient stored plasma for fetuin-A determination, and 251 for no cognitive function assessment. The final baseline sample consisted of 541 men and 841 women. Of these, 325 men and 530 women returned for a second cognitive function assessment a median of 4.0 years later; these men and women comprise the cognitive change sample.

During the 1992–96 visit, information regarding medical history, medication use, physical activity, alcohol consumption and current smoking was obtained using standard questionnaires. Current medication use was validated by examination of pills and prescriptions brought to the clinic for that purpose and participants were asked to rate their overall health on a 5-point scale. Educational attainment was queried and classified as less than high school, high school graduate, some college, college graduate, or graduate school. Depressed mood was assessed using the Beck Depression Inventory (BDI).

Clinical measurements

Height, weight, and waist and hip girth were measured in the clinic with participants wearing light clothing and no shoes. Blood pressures were measured twice in seated resting subjects; the mean of the two measures was used in analyses. Blood samples were obtained by venipuncture between 0730 h and 1100 h after a requested 12 hour fast; serum and plasma were separated and frozen at −70° C. Fetuin-A levels were measured in duplicate in 2010 on EDTA plasma samples using a human enzyme linked immunosorbent assay kit (Epitope Diagnostics, San Diego, CA). This assay uses a 2-site “sandwich” technique with polyclonal antibodies that bind different epitopes of human fetuin-A. Intra- and inter-assay coefficients of variation (CV) were 2.4–4.7% and 9.5–9.9%, respectively, for the set of assays used for the present sample. Plasma lipids and measures of kidney and liver function

and Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) were determined by previously described methods (22).

Cognitive function assessment

Three standardized tests, chosen to assess different aspects of cognitive function, were administered by a trained interviewer at both the baseline and follow-up clinic visits. The Mini-Mental State Examination (MMSE) (23) assesses orientation, registration, attention, calculation, language and recall and is used as a test of global cognitive function. Trail Making Test B (Trails B, from the Halstead-Reitan Neuropsychological Test Battery) tests visuomotor scanning and executive function (24). Performance is rated by the time required to finish the test (maximum 300 sec); the higher the score, the poorer the test performance. The Animals Naming Category Fluency test assesses semantic fluency and executive function (25).

Prevalent conditions

Prevalent CVD was defined as physician-diagnosed myocardial infarction, coronary artery revascularization, congestive heart failure, stroke or transient ischemic attack, carotid surgery, peripheral artery surgery, or physician-diagnosed intermittent claudication. Diabetes was defined by physician diagnosis, fasting plasma glucose ≥6.99 mmol/L, 2-hr post-challenge glucose ≥11.1 mmol/L, or use of diabetes medications. Hypertension was defined as blood pressure ≥140/90 mm Hg or use of antihypertensive medication. Comorbidities recorded included thyroid, liver, kidney and heart disease, diabetes, cancer (non-skin), emphysema, arthritis, hip fracture and hypertension. The metabolic syndrome was defined according to NCEP ATP III criteria.

Statistical Analysis

General linear models were performed to compare those with follow-up cognitive function data to those without repeat cognitive assessment. Associations between fetuin-A and baseline cognitive function test (CFT) score and 4-year change in CFT score were determined by linear regression analyses. To facilitate comparison of associations among the three CFTs, results are reported as standardized β-coefficients. The change in CFT performance score was defined as the difference in each test score (follow-up value minus baseline value) divided by the number of years between assessments, and multiplied by 4 (the median years between assessments).

Pre-specified scores of ≤24 for the MMSE, ≥132 for Trails B, and ≤12 for Category Fluency were used to indicate categorically defined poor performance. Major cognitive decline was defined as a reduction in performance that fell within the highest decile as assessed by the four-year change score, a previously used approach (26). Associations between fetuin-A and baseline cognitive impairment and major cognitive decline were tested by logistic regressions.

Base models for linear and logistic regressions were adjusted for age, sex, education, and BDI score (as a continuous variable). To correct for regression to the mean, models for 4-year change and major cognitive decline were additionally adjusted for the mean of the

baseline and follow-up test score. Secondary models tested biologically plausible effect modifiers (age, sex, diabetes, prevalent CVD) and the influence of potential confounders and covariates. A single model tested for confounding by vascular disease by adjusting for CVD risk factors shown to be related to fetuin-A levels (12) (BMI, exercise, alcohol use, smoking, LDL cholesterol, triglycerides, eGFR and HOMA IR). Quadratic associations and interactions by sex were tested for all base regression models; none were found. Because fetuin-A levels differ significantly for women using oral estrogens compared to non-estrogen using women and compared to men (12), we also created a variable for group (women using oral estrogen, women not using oral estrogen, and men). Substituting this variable for sex did not materially change results for any model, and there was no evidence of any interaction by group (P>0.74 for all).

Exact P-values for two-sided tests are shown; $P<0.05$ was considered statistically significant for all analyses including interaction terms. Data were analyzed using SPSS (v18.0; SPSS Inc., Chicago, IL).

RESULTS

Characteristics for the participants at baseline and for those who returned for the follow-up cognitive assessment are presented in Table 1. The mean age of the 1382 participants at the baseline visit was 75 years (range 50 to 98); 61% (n=1025) were female, of whom 328 (39%) reported current use of oral estrogens. Fetuin-A levels (median, IQR in g/L) were highest in women using oral estrogens (0.54, 0.47–0.63), intermediate for women not using oral estrogens (0.51, 0.44– 0.57), and lowest for men (0.50, 0.44–0.56) ($P<0.001$ for all); the standard deviation was 0.10 g/L for each group. Fetuin-A levels decreased with age (r = −0.22, $P<0.001$ overall).

Fetuin-A and Cognitive Function

Mean baseline scores for each CFT and associations with fetuin-A are presented in Table 2. In linear regressions adjusting for age, sex, education and BDI score, higher levels of fetuin-A were associated with better performance on the MMSE ($P=0.012$) and marginally associated with better Trails B scores ($P=0.066$). Fetuin-A levels were not related to Category Fluency scores. For MMSE, there was a significant interaction by age such that higher fetuin-A associated with better MMSE test performance for individuals age 75 and older ($P=0.004$), but not for those less than age 75 ($P=0.94$). The association of fetuin-A did not differ by age for Trails B or Category Fluency, and did not vary by prevalent CVD or diabetes for any CFT (P for interactions all >0.30).

Next we tested whether fetuin-A levels were related to scoring in the cognitive impairment range for each CFT (Table 2). For each SD higher fetuin-A level, the odds of cognitive impairments were 23% lower ($P=0.067$) for the MMSE and 15% lower ($P=0.009$) for Trails B. Fetuin-A levels were not related to impaired performance on the Category Fluency test.

Associations for cognitive impairment did not differ by age, prevalent CVD or diabetes, and results were not altered by sequential adjustment for fetuin-A – related CVD risk factors, prevalent CVD or diabetes (data not shown).

Fetuin-A and Cognitive Function Decline

We evaluated the association of fetuin-A with change in CFT score performance in a subset of 855 men and women who returned for a second CFT assessment a median of 4 years later. Characteristics of this subset are shown in Table 1. Compared to those with a follow-up CFT, those who did not return were older (means 77.2 vs 73.4 years), more likely to have prevalent CVD (29.0 vs 19.1%, $P<0.001$), and had poorer scores on the MMSE (mean 27.2 vs 28.4), Trails B (155.6 vs 122.3) and Category Fluency (16.1 vs 18.1) tests (all $P<0.001$); 31% died within 4 years of the baseline visit. Age and sex-adjusted fetuin-A levels were significantly higher in those who returned compared to those who did not (means 0.52 vs 0.50 g/L, respectively, $P=0.001$).

There was no significant association of fetuin-A levels with 4-year change in MMSE or Category Fluency scores. Higher fetuin-A was associated with less decline in Trails B performance ($P=0.015$). These results did not vary by age or diabetes and were not altered by additional adjustment for fetuin-A – related CVD risk factors, prevalent CVD or diabetes.

For each CFT, individuals with change scores in the poorest performing decile were defined as having major cognitive decline for that test. As shown in Table 3, higher baseline fetuin-A levels were associated with lower odds of a major decline in MMSE ($P=0.048$) and Trails B scores ($P=0.010$), but were not related to major decline in Category Fluency ($P=0.74$). The fetuin-A association with MMSE varied by prevalent CVD (P for interaction = 0.015) such that the odds of major decline in MMSE were reduced by 42% (95%CI 16–60%, $P=0.005$) for each SD higher baseline fetuin-A in individuals without CVD, but were not significantly related to fetuin-A levels in those with prevalent CVD ($P=0.33$). These disparate associations were not altered by sequential adjustment for lifestyle, classic CVD risk factors, kidney function, markers of health status, metabolic syndrome or diabetes, or by excluding individuals with metabolic syndrome, diabetes or stroke history (Table 4). Likewise, the association of fetuin-A with major decline in Trails B score was not altered in models adjusting for or excluding the same factors (data not shown). Associations of fetuin-A did not vary by prevalent CVD for major decline in Trails B or Category Fluency performance, and did not vary by diabetes for major decline in any CFT.

DISCUSSION

To our knowledge, this is the first study to evaluate the association of plasma fetuin-A levels with cognitive function and cognitive decline in a large population of community-dwelling older men and women. We observed protective associations of fetuin-A with two tests commonly used to screen for cognitive impairment: MMSE, a measure of global cognitive function, and Trails B, a test of executive function. Higher fetuin-A was associated with better scores on the MMSE and Trails B and with reduced odds of scoring in the impaired range for both tests. In addition, each SD higher fetuin-A level was associated with a statistically significant 29% reduction in the likelihood of a major decline in Trails B scores over the following 4 years. Notably, the odds of a major decline in MMSE scores over the same time period was 42% lower for each SD higher fetuin-A, but only among participants without CVD. These associations did not vary by sex and were not explained by a wide range of vascular risk factors and comorbidities.

Evidence of a role for fetuin-A in neurodegenerative processes is sparse, but accumulating (6). Smith and colleagues (21) found lower circulating concentrations of fetuin-A in 34 patients with mild-to-moderate Alzheimer's disease compared to 34 age-matched controls. Notably, plasma fetuin-A levels were strongly correlated with MMSE scores ($r=-0.54$, $P=0.002$) among the Alzheimer's patients, even after adjustment for other predictor variables, suggesting fetuin-A may be related to the severity or progression of disease. The authors concluded that lower plasma concentrations of fetuin-A in patients with Alzheimer's disease might be explained, in part, by the presence of subclinical inflammation since plasma TNF-α levels were significantly higher in patients than controls and were inversely correlated with fetuin-A levels ($r=-0.50$, $P=0.003$).

A potentially important role for fetuin-A in regulating inflammatory responses is under active investigation. The underlying biology is complex, and as with many fetuin-A functions, depends on the biological setting (16). For example, fetuin-A induces TNF-α and IL-6 expression in differentiated adipocytes (27). Conversely, hepatic synthesis of fetuin-A is suppressed by increasing levels of pro-inflammatory cytokines; leading fetuin-A to be described as a negative acute phase reactant (28, 29). Thus, higher fetuin-A levels in our study may simply be a marker of the absence of peripheral inflammatory activation. Other studies suggest a more direct role for fetuin-A in regulating inflammatory responses. At higher concentrations, fetuin-A abolishes the response of macrophage to bacterial lipopolysaccharide (17) and inhibits the intrinsic inflammatory response to carrageenan in rats (30). Importantly, peripheral administration of fetuin-A attenuated the central inflammatory response in a rat model of cerebral ischemia (20) and dramatically reduced TNF expression levels in the ischemic tissues. This study found a time-dependent increase in cerebral fetuin-A levels in brain tissues, demonstrating that fetuin-A is capable of crossing the blood brain barrier, at least in the transient state of elevated permeability characteristic of ischemic injury (31). Taken together, the existing data suggest a potential role for endogenous fetuin-A as an anti-inflammatory and neuroprotective factor that may be of particular relevance to Alzheimer's disease.

The current study provides evidence that fetuin-A may also provide protection against normal age-related cognitive decline. It extends the link between low fetuin-A levels and cardiovascular disease to a possible association with neurodegenerative changes. We were unable to test an anti-inflammation hypothesis for the association of higher fetuin-A with reduced risk of major cognitive decline in our study, since levels of inflammatory markers were not available. Adjustment for a large number of potential explanatory covariates including classic CVD risk factors, lifestyle variables, kidney function and health status had minimal influence on results. Thus, mechanisms other than conventional pathogenic pathways are likely to be involved in the biology underlying the fetuin-A associations. Inflammation may be one. Longitudinal studies with repeat measures of fetuin-A, inflammatory markers and cognitive function should provide more insight into this possibility.

Although some of our results have marginal statistical significance, when taken in concert our findings suggest that fetuin-A has protective associations with current cognitive ability and is even more robustly related to major decline in global cognitive function and executive

function over a relatively short period (4 years). We used a population-based definition for major decline; however, the degree of change in the highest decile of decline for the MMSE was 4 points, in line with recommended clinical cut-points for detecting significant change over a 5-year period (32). This degree of change in the poorest performing 10% of our participants contrasts with an average annual decline in MMSE scores of about 4 points in patients with Alzheimer's disease (33), highlighting the high-functioning cognitive status of the Rancho Bernardo cohort. Nonetheless, a 4-point decline in MMSE score even over a 5-year period is considered to be sufficient clinical basis for referring an individual for further neuropsychological examination (23, 32).

Fetuin-A levels were not associated with a test of category fluency. Performance on category fluency tests relies on executive functions subserved by frontal areas, as well as semantic knowledge subserved by temporal areas (34). Although Trails B is also a test of executive function, the neural substrates for the multiple functions measured with Trails B involve systems distributed throughout the brain (35). MMSE performance is also dependent on multiple brain systems. The selectivity of fetuin-A associations with MMSE and Trails B performance in the present study suggests the underlying biology is global in nature and not related to a single area of the brain, lending further support to an anti-inflammatory mechanism.

Strengths of this study are the relatively large sample size, examination of several cognitive domains, measures of cognitive change, inclusion of both sexes, and the availability of a wide spectrum of potential confounding variables. The study also has some limitations. Associations were based on fetuin-A values measured at a single time point, nonetheless we identified a strong signal for major decline in MMSE and Trails B over time that was robust to statistical adjustment for multiple covariates. Participants were predominantly Caucasian and middle to upper middle class. This limits generalizability, but is a strength to the extent that confounding by ethnicity, socioeconomic status and access to health care is minimized. The Rancho Bernardo population is relatively healthy and high functioning, which may have limited the robustness of our findings, but is unlikely to have caused them. The majority of participants were elderly men and women and our results may not generalize to younger adults.

The main limitation of this study is survival and participation bias, a characteristic of cohort studies of the elderly. The analysis of change in cognition is limited to participants who had the same cognitive function tests administered at two visits, 4 years apart. Individuals who did not return were older and less healthy (31% had died) than those who did and had lower baseline cognitive function scores, which might have obscured a stronger association with major cognitive decline, but is unlikely to account for the observed protective associations. Finally, although multiple cognitive domains were assessed, it is possible that untested domains may have yielded additional insights.

In summary, in community-dwelling individuals, higher plasma fetuin-A levels are independently associated with better cognitive function and reduced likelihood of major cognitive decline among older men and women. The protective association is universal for maintenance of executive function, but is only apparent in those without CVD for

maintenance of global cognitive function. These observations are consistent with the hypothesis that higher fetuin-A protects against cognitive decline in relatively high functioning older adults, although this may be less apparent in those with established vascular disease. Future studies with larger populations are required to determine if measurement of plasma fetuin-A will be useful as a tool for assessing risk of major cognitive decline and whether preventive therapies targeting fetuin-A are worthy of pursuit.

Acknowledgments

Sources of Funding:

This study was sponsored by a grant from the National Heart Lung and Blood Institute (R01HL096851) supporting Drs. Ix, Laughlin and Barrett-Connor. The Rancho Bernardo Study was funded by research grants AG028507 and AG018339 from the National Institute on Aging and grant DK31801 from the National Institute of Diabetes and Digestive and Kidney Diseases. Drs. Laughlin and Daniels were also supported by grants from the American Heart Association (Dallas, TX).

ABBREVIATIONS

CFT	cognitive function test
MMSE	Mini-Mental Status Exam
Trails B	Trails Making Test B
CVD	cardiovascular disease
eGFR	estimated glomerular filtration rate
HOMA-IR	homeostasis model assessment for insulin resistance
BMI	body mass index
BDI	Beck Depression Inventory
TNF	tumor necrosis factor

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Table 1

Baseline characteristics

	Baseline Sample (N=1382)	Follow-up Sample (N=855)
Demographics / Anthropomorphics		
Sex (% male)	39.1	38.0
Age (years)	74.9 (8.8)	73.4 (8.5)
College graduate (%)	39.0	39.1
Body mass index (kg/m^2)	25.3 (4.0)	25.4 (3.9)
Waist circumference (cm)	85.3 (12.6)	85.1 (12.4)
Vascular Risk Factors		
Systolic blood pressure (mmHg)	139 (22)	138 (21)
Diastolic blood pressure (mmHg)	75 (9)	76 (9)
Total cholesterol (mmol/L)	5.40 (0.95)	5.43 (0.95)
LDL cholesterol (mmol/L)	3.26 (0.85)	3.29 (0.85)
HDL cholesterol (mmol/L)[a]	1.45 (1.16, 1.78)	1.45 (1.18, 1.78)
Triglycerides (mmol/L)[a]	1.13 (0.87, 1.67)	1.14 (0.82, 1.64)
Fasting plasma glucose (mmol/L)	5.51 (1.32)	5.40 (1.16)
HOMA-IR	2.73 (2.27)	2.72 (2.40)
eGFR (ml/min/1.73m^2)	66.5 (16.5)	67.4 (16.3)
Health Status Markers		
Prevalent diabetes (%)	15.3	14.5
Prevalent CVD (%)	22.9	19.1
Number of comorbidities	1.6 (1.2)	1.5 (1.1)
Number of medications	1.2 (0.6)	1.2 (0.5)
Fair/poor self-assessed health (%)	10.3	6.9
Beck Depression Score	5.5 (4.4)	5.0 (4.0)
Lifestyle Parameters (%)		
Current smoker (yes)	6.8	4.8
Exercise (3+ times/week)	71.7	75.3
Daily alcohol (vs less or none)	34.7	36.7

HDL indicates high density lipoprotein; CVD, cardiovascular disease; LDL, low density lipoprotein; eGFR estimated glomerular filtration rate

Values are mean (SD) for continuous variables and proportions for categorical variables

[a] Geometric mean (quartile 1, quartile 3)

Table 2

Association of fetuin-A levels with baseline cognitive function scores and impaired cognitive function

Cognitive Function Test	Baseline CFT Test Score	Fetuin-A association with CFT test score		Impaired Cognitive Function	Odds of Impaired Cognitive Function by Fetuin-A	
	Mean (SD)	β-coefficient*	p-value	Proportion (N)	OR (95% CI)*	p-value
MMSE	27.9 (2.3)	0.071	0.012	5.4 (74)	0.77 (0.58–1.02)	0.067
<age 75 (n=679)	28.5 (1.5)	0.003	0.94			
age 75+ (n=703)	27.4 (2.7)	0.117	0.004			
Trails B	134.6 (61.3)	−0.049	0.066	40.2 (556)	0.85 (0.74–0.96)	0.009
Category Fluency	17.3 (4.9)	0.004	0.89	15.8 (218)	0.93 (0.79–1.11)	0.44

*Standardized β-coefficients

*b*Adjusted for age, sex, education, and Beck Depression Inventory score

*c*Per standard deviation increase in fetuin-A

Table 3

Association of fetuin-A levels with 4-year change in cognitive function score and major cognitive decline

	4 Year Change			Major Cognitive Decline		
Cognitive Function Test	**Change Score**	**Fetuin-A association with Change Score**		**Cutpoint for Major Decline**	**Odds of Major Cognitive Decline by Fetuin-A**	
	Mean (SD)	**β-coefficient[a,b]**	**p-value**	**Change score**	**OR (95% CI)[b,c]**	**p-value**
MMSE	−1.21 (1.98)	−0.008	0.84	−3.63	0.73 (0.54–0.99)	0.048
No CVD (n=696)				−3.63	0.58 (0.40–0.84)	0.005
CVD (n=164)				−3.24	1.36 (0.73–2.54)	0.33
Trails B	5.46 (50.6)	−0.095	0.015	14.28	0.71 (0.56–0.91)	0.010
Category Fluency	−6.39 (4.27)	−0.010	0.79	−6.04	1.05 (0.80–1.38)	0.74

[a] Standardized β-coefficients

[b] Adjusted for age, sex, education, Beck Depression Inventory score, and mean of the baseline and follow-up score

[c] Per standard deviation increase in fetuin-A

Clin Endocrinol (Oxf). Author manuscript; available in PMC 2015 July 01.

Table 4

Multivariable odds ratios for major decline in MMSE score per SD higher baseline fetuin-A adjusting for, or excluding, potential covariates and effect modifiers

	No Prevalent CVD OR (95 % CI)	*P*-value	Prevalent CVD OR (95 % CI)	*P*-value
Cases /N	65/692		20/163	
Base model[a]	0.58 (0.40, 0.85)	0.005	1.24 (0.66, 2.33)	0.51
Base model[a] plus:				
Exercise, smoking, alcohol use	0.59 (0.40, 0.87)	0.007	1.14 (0.60, 2.16)	0.69
Classic CVD risk factors[b]	0.66 (0.45, 0.98)	0.033	1.20 (0.58, 2.49)	0.63
Kidney function (eGFR)	0.59 (0.40, 0.85)	0.005	1.24 (0.66, 2.35)	0.49
Insulin resistance (HOMA)	0.60 (0.41, 0.88)	0.008	1.16 (0.59, 2.28)	0.67
Health status markers[c]	0.59 (0.40, 0.86)	0.006	1.35 (0.70, 2.58)	0.37
Metabolic syndrome	0.60 (0.41, 0.88)	0.008	1.20 (0.63, 2.28)	0.57
Diabetes	0.57 (0.39, 0.84)	0.004	1.32 (0.70, 2.58)	0.37
Base model[a] excluding:				
Metabolic syndrome[d]	0.63 (0.43, 0.92)	0.017	1.61 (0.74, 3.50)	0.23
Diabetes[e]	0.52 (0.34, 0.81)	0.004	1.62 (0.78, 3.35)	0.20
Stroke history[f]	0.58 (0.40, 0.85)	0.005	1.03 (0.51, 2.07)	0.95

CVD indicates cardiovascular disease; OR, odds ratio; CI, confidence interval; HOMA, homeostasis model insulin resistance; eGFR, estimated glomerular filtration rate

[a] Base model adjusted for age, sex, education, Beck Depression Inventory score, and mean of the baseline and follow-up score

[b] Classic CVD risk factors includes BMI, waist, LDL, HDL, triglycerides, SBP, DBP, FPG

[c] Health status markers: number medications, number comorbidities, self-assessed health

[d] Cases/N = 59/577 for no prevalent CVD, 14/114 for prevalent CVD

[e] Cases/N = 57/601 for no prevalent CVD, 17/130 for prevalent CVD

[f] Cases/N = 65/692 for no prevalent CVD, 16/147 for prevalent CVD