

Biomarkers for Insulin Resistance and Inflammation and the Risk for All-Cause Dementia and Alzheimer Disease

Results From the Framingham Heart Study

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Objective: To investigate the contribution of biomarkers of glucose homeostasis (adiponectin, glucose, glycated albumin, and insulin levels) and inflammation (high-sensitivity C-reactive protein and lipoprotein-associated phospholipase A₂ levels) to the risk of developing Alzheimer disease (AD) and all-cause dementia.

Design: Prospective cohort study.

Setting: Dementia-free Framingham Heart Study participants had sera measured for these biomarkers at the 19th biennial examination (1985-1988) and were followed up prospectively for the development of AD and all-cause dementia.

Participants: Eight hundred forty (541 women, median age of 76 years) subjects participated in the study.

Main Outcome Measures: We used sex-pooled and sex-specific multivariable Cox proportional hazards models adjusted for age, education, body mass index, recent change in weight, APOE ε4 allele status, and plasma docosahexaenoic acid levels to determine association of these

biomarkers with the development of all-cause dementia and AD.

Results: Over a mean follow-up period of 13 years, 159 persons developed dementia (including 125 with AD). After adjustment for other risk factors, only adiponectin in women was associated with an increased risk of all-cause dementia (hazard ratio [HR], 1.29; 95% confidence interval [CI], 1.00-1.66; *P* = .054) and AD (HR, 1.33; 95% CI, 1.00-1.76; *P* = .050) per 1-SD increase in adiponectin level. Women with baseline adiponectin values more than the median had a higher risk of all-cause dementia (HR, 1.63; 95% CI, 1.03-2.56; *P* = .04) and AD (HR, 1.87; 95% CI, 1.13-3.10; *P* = .01) as compared with those with values less than the median.

Conclusion: In women, increased plasma adiponectin levels are an independent risk factor for the development of both all-cause dementia and AD.

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DEMENTIA IS A PROGRESSIVE neurodegenerative disorder that is clinically characterized by loss of memory and cognitive decline. According to the World Alzheimer Report, currently about 36 million people worldwide are affected by dementia and it is estimated that this number will nearly double over the next 20 years. Of all forms of dementia, Alzheimer disease (AD) is the most common, comprising up to 80% in the elderly population.

In addition to the well-established risk factors for AD, ie, age, family history, and the presence of the APOE ε4 allele,¹⁻³ previously, a high plasma homocysteine level was found to be an independent risk fac-

tor for dementia,⁴ while high plasma levels of docosahexaenoic acid (DHA) significantly reduced the risk for developing dementia.⁵ Furthermore, data suggest that the management of cardiovascular risk factors, such as type 2 diabetes (T2D), high blood pressure, and obesity, may also reduce cognitive decline, although their impact on the risk of development of clinical AD is less certain.⁶

Insulin resistance and inflammation are important hallmarks of T2D and could provide a potential mechanism explaining the association between T2D and dementia.⁷ Although a central role for insulin in the pathology of AD and dementia has been suggested,^{8,9} and intervention trials using insulin-sensitizing drugs to

slow down cognitive decline are ongoing,¹⁰ there remains uncertainty regarding the role of insulin and glucose intolerance. Similarly, although the inflammatory marker lipoprotein-associated phospholipase A₂ (Lp-PLA₂) has been associated with the risk of incident dementia,¹¹ and there is evidence suggesting that C-reactive protein (CRP) is associated with cognitive decline¹²⁻¹⁵ and risk of dementia,¹⁶ other reports failed to find such an association.¹⁷⁻¹⁹ To our knowledge, no prior studies have simultaneously related measures of glucose homeostasis and markers of inflammation to the risk of incident dementia in a single elderly community-based cohort followed up for up to 2 decades.

An additional potential factor that may contribute to the onset of AD and all-cause dementia is adiponectin. Adiponectin is a hormone derived from visceral fat, which sensitizes the body to insulin, has anti-inflammatory properties, and plays a role in the metabolism of glucose and lipids.²⁰ Higher levels of adiponectin have been shown to lower the risk for T2D,²¹ and there is widespread expression of the adiponectin receptor gene throughout the body, including in the brain.²² Despite the fact that increased adiponectin levels have been shown to have a beneficial effect on the signaling of insulin and the management of T2D, higher levels of adiponectin also have been related to an increased risk of all-cause mortality.^{23,24} Furthermore, visceral or central obesity has been linked to smaller brain volumes and a higher risk of AD.²⁵ Adiponectin levels are also inversely correlated with levels of leptin and brain-derived neurotrophic factor, both of which have been associated with a lower risk of incident dementia and AD.²⁶

We hypothesized that factors that underlie T2D (ie, insulin signaling and inflammation) may also contribute to the development of all-cause dementia and AD. Furthermore, based on the role adiponectin plays in insulin signaling and the presence of adiponectin receptors in neurological tissue, we hypothesized that adiponectin contributes to or serves as a risk marker for the development of all-cause dementia and AD. To investigate this hypothesis, we measured levels of plasma adiponectin, glucose, glycated albumin, and insulin (as measures of glucose homeostasis) and levels of plasma Lp-PLA₂ and CRP (as measures of inflammation) in a prospective cohort study in which the subjects were followed up for incident all-cause dementia and AD (the Framingham Heart Study).

METHODS

SUBJECTS AND THE DIAGNOSIS OF AD AND ALL-CAUSE DEMENTIA

The Framingham Heart Study is a longitudinal population-based study in which subjects have been examined every 2 years.²⁷ The dementia cohort consists of 3349 participants who were determined to be cognitively intact at examination cycle 14 when participants underwent a neuropsychological test battery (age range, 55-88 years).¹ At the 19th biennial examination (1985-1988), 2337 participants from this cohort were alive and free of dementia. Of these, 1370 (69.8%) underwent the 19th examination and had at least 1 year of follow-up data. Plasma adiponectin level was measured in 826 subjects (60.3% of those ex-

amined); 2 participants with moderate renal failure (serum creatinine level >2 mg/dL [to convert to micromoles per liter, multiply by 88.4]) were excluded. The study sample of 840 subjects consisted of 541 women and 299 men, with a mean age of 72 years. Seventy percent were high school graduates. Informed consent was obtained from all of the participants. The study was approved by the institutional review board for human research at the Boston University School of Medicine.

Members of the dementia cohort have been monitored for the development of stroke and dementia since their inclusion in the cohort. Participants were routinely administered a screening Mini-Mental State Examination at each biennial examination.²⁸ Persons who scored less than education-based cutoffs or who experienced a decline of 3 or more points on the Mini-Mental State Examination from the most recent previous examination were called back for a neurological and neuropsychological examination. For each case of possible dementia, a detailed case review was undertaken by a panel consisting of at least 1 neurologist (including P.A.W. and S.S.) and a neuropsychologist (R.A.). The panel determined the type of dementia and the date of diagnosis using serial neurological and neuropsychological assessments, a telephone interview with a family member or a caregiver, medical records, and imaging study results. The diagnosis of dementia was made according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.²⁹ Alzheimer disease was diagnosed when subjects met the criteria of the National Institute of Neurological Disorders and Stroke-Alzheimer's Disease and Related Disorders Association for definite, probable, or possible AD.³⁰ Subjects who had an interim stroke during the follow-up period were not excluded. All confirmed cases of dementia after the 19th biennial examination (through December 31, 2009) were included, providing longitudinal follow-up of up to 24 years.

LABORATORY ANALYSES

Blood was obtained in 0.1% EDTA at the 19th examination. Apolipoprotein E genotyping was performed using DNA isolated from blood cells and carried out as previously described.³ Total plasma homocysteine concentrations were determined with the use of high-performance liquid chromatography with fluorometric detection,⁴ and creatinine concentrations were estimated using the modified Jaffe method as described elsewhere.³¹ The DHA concentrations were measured as previously described.⁵ Insulin and glucose levels were measured as previously reported.^{32,33} Glycated albumin, Lp-PLA₂, high-sensitivity CRP (hsCRP), and adiponectin levels were measured in plasma on an Olympus AU400 with enzymatic reagents (Olympus America Inc) as reported elsewhere.³⁴⁻³⁶ Interassay coefficients of variation were less than 5% for all assays.

ADDITIONAL RISK FACTORS

Risk factors that could potentially confound the relation between the plasma markers and dementia or AD were defined based on data collected at the 19th biennial examination. Educational status was dichotomized at the level of high school completion. Diabetes mellitus was defined by a recorded casual blood glucose level of at least 200 mg/dL (to convert to millimoles per liter, multiply by 0.0555), a previous diagnosis of diabetes mellitus, or the use of a hypoglycemic agent or insulin. Systolic blood pressure and body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) were treated as continuous variables. Weight change was defined as change in weight from that recorded at 1 of the prior biennial examinations. This period averaged 4.3 years (range, 2-6 years) prior to examination 19.

STATISTICAL ANALYSIS

The population distributions of plasma adiponectin, insulin, glycated albumin, glucose, and hsCRP levels were positively skewed. The use of natural-log-transformed values provided the best-fitting model for analyses, in which these markers were treated as a continuous variable. Cox proportional hazards regression models were used to examine the relation between the study marker levels and the incidence of all-cause dementia and AD. The risk of dementia is more likely to change as a function of age than of time; we thus used age as the time scale, adjusting for left truncation at entry. Survival age was defined as age at di-

agnosis of dementia if the individual had dementia or age at death if the individual did not have dementia at death; the remaining participants were censored at the last age known to not have dementia. In analyses of AD, participants with incident non-AD dementia were censored at the date of diagnosis of dementia. Primary analyses were adjusted for age and sex. Supplementary analyses were additionally adjusted for BMI, weight change, APOE genotype (with or without an APOE $\epsilon 4$ allele), DHA concentrations, and educational level. An additional subset analysis was performed in 550 subjects who also had serum creatinine and plasma homocysteine measurements available. Plasma adiponectin levels were also evaluated with a median cutoff-based analysis. Testosterone selectively inhibits the secretion of adiponectin from adipocytes resulting in lower levels of circulating adiponectin in men. To take this into account, we investigated interactions by sex and additionally performed analyses stratified by sex. Subjects who had a stroke during the study period were not excluded, since such an event could lie along the causal pathway between elevated plasma levels of the study markers and the development of dementia. All statistical analyses were performed with the use of SAS software (SAS Institute).

Table 1. Baseline Subject Characteristics and Adiponectin Levels at Examination Cycle 19

Characteristic	Men	Women
Sample size	299	541
Age, y, mean (SD)	72 (4)	73 (4)
Adiponectin level, mg/L, mean (range)	10.6 (2.5-36.0)	16.5 (4.0-60.8)
Insulin level, μ U/mL, mean (range)	8.4 (0.4-167.6)	6.4 (0.8-137.6)
Glycated albumin level, %, mean (range)	14.7 (10.4-34.8)	14.7 (10.5-40.4)
Glucose level, mg/dL, mean (range)	96 (52-331)	92 (41-439)
Lp-PLA ₂ level, ng/mL, mean (SD)	269 (86)	267 (88)
hsCRP level, mg/L, mean (range)	2.9 (0.3-99.2)	2.7 (0.2-160.7)
Plasma homocysteine level, μ mol/L, mean (range) ^a	1.55 (0.62-9.02)	1.50 (0.47-8.73)
Plasma DHA level, % of total fatty acids, mean (SD)	3.5 (1.2)	3.6 (1.2)
BMI, mean (SD)	28 (4)	27 (5)
Waist to hip ratio, mean (SD)	1.0 (0.1)	0.8 (0.1)
Weight change over the past 4.3 y, lb, mean (SD)	-0.4 (11.7)	0.6 (10.8)
High school graduate, %	68	72
Diabetes mellitus, %	18	9
APOE genotype, %		
$\epsilon 2/\epsilon 2$ or $\epsilon 2/\epsilon 3$	11	10
$\epsilon 3/\epsilon 3$	70	69
$\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 4$, or $\epsilon 4/\epsilon 4$	19	21

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DHA, docosahexaenoic acid; hsCRP, high-sensitivity C-reactive protein; Lp-PLA₂, lipoprotein-associated phospholipase A₂.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; homocysteine to milligrams per liter, divide by 7.397; and insulin to picomoles per liter, multiply by 6.945.

^aHomocysteine was measured in a subset of 550 individuals.

RESULTS

The cohort was followed up for a median of 13 years. One hundred fifty-nine subjects developed dementia during the follow-up period (including 125 cases of AD). The baseline characteristics of the sample (at the 19th biennial examination) are shown in **Table 1**.

Age- and sex-adjusted hazard ratios (HRs) for all-cause dementia and AD for every 1-SD increase in adiponectin, insulin, glycated albumin, glucose, Lp-PLA₂, and hsCRP concentrations are presented in **Table 2**. Baseline levels of adiponectin, insulin, glycated albumin, glucose, and Lp-PLA₂ were not associated with all-cause dementia or AD in a model adjusted for age and sex. A high plasma hsCRP level, however, was associated with a reduced risk for both all-cause dementia (HR, 0.78; 95% confidence interval [CI], 0.66-0.93; $P = .004$) and AD (HR, 0.79; 95% CI, 0.65-0.95; $P = .01$).

Multivariate-adjusted HRs for a 1-SD increase in hsCRP concentrations are presented in **Table 3**. A high plasma hsCRP level remained protective against all-cause dementia and AD after adjusting for BMI and weight changes (HR, 0.78; 95% CI, 0.65-0.93; $P = .006$ and HR, 0.82; 95% CI, 0.67-1.00; $P = .048$, respectively). However, the associations were no longer statistically significant after adjustments were made for

Table 2. Age- and Sex-Adjusted HRs for Alzheimer Disease and All-Cause Dementia by 1-SD Increase in Concentrations

Measurement	All-Cause Dementia			Alzheimer Disease		
	No./Total No.	HR (95% CI)	P Value	No./Total No.	HR (95% CI)	P Value
Adiponectin	159/840	1.14 (0.97-1.34) ^a	.13	125/840	1.19 (0.98-1.43) ^a	.08
Insulin	153/812	0.94 (0.80-1.10)	.44	122/812	0.90 (0.75-1.07)	.24
Glycated albumin	159/840	1.12 (0.93-1.35)	.23	125/840	1.04 (0.83-1.30)	.75
Glycated albumin >16.5%	159/840	1.34 (0.91-1.98)	.14	125/840	1.23 (0.79-1.93)	.36
Blood glucose	158/837	1.04 (0.87-1.25)	.67	125/837	0.97 (0.78-1.20)	.75
Lp-PLA ₂	159/838	0.98 (0.84-1.15)	.80	125/838	0.98 (0.82-1.18)	.86
hsCRP	159/838	0.78 (0.66-0.93)	.004	125/838	0.79 (0.65-0.95)	.01

Abbreviations: CI, confidence interval; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; Lp-PLA₂, lipoprotein-associated phospholipase A₂.

^aTest for interaction with sex: $P < .05$.

Table 3. Multivariate-Adjusted HRs for Alzheimer Disease and All-Cause Dementia by 1-SD Increase in hsCRP Concentrations

	All-Cause Dementia			Alzheimer Disease		
	No./Total No.	HR (95% CI)	P Value	No./Total No.	HR (95% CI)	P Value
Model 1 ^a	159/838	0.78 (0.66-0.93)	.004	125/838	0.79 (0.65-0.95)	.01
Model 2 ^b	153/805	0.78 (0.65-0.93)	.006	121/805	0.82 (0.67-1.00)	.048
Model 3 ^c	116/634	0.83 (0.67-1.03)	.09	92/634	0.86 (0.68-1.10)	.23

Abbreviations: CI, confidence interval; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein.

^aAdjusted for age.

^bAdjusted for age, body mass index, and weight change.

^cModel 2 with additional adjustment for *APOE* ϵ 4 allele, plasma docosahexaenoic acid concentration, and educational level.

Table 4. Age- and Sex-Adjusted HRs for Alzheimer Disease and All-Cause Dementia by 1-SD Increase in Adiponectin Concentrations

	All-Cause Dementia			Alzheimer Disease		
	No./Total No.	HR (95% CI)	P Value	No./Total No.	HR (95% CI)	P Value
All	159/840	1.14 (0.97-1.34)	.13	125/840	1.19 (0.98-1.43)	.08
Men	46/299	0.84 (0.62-1.12)	.23	32/299	0.89 (0.63-1.27)	.52
Women	113/541	1.31 (1.07-1.61)	.009	93/541	1.32 (1.06-1.65)	.02

Abbreviations: CI, confidence interval; HR, hazard ratio.

the other risk factors (HR, 0.83; 95% CI, 0.67-1.03; $P = .09$ for all-cause dementia and HR, 0.86; 95% CI, 0.86-1.10; $P = .23$ for AD).

Significant sex interactions were observed for adiponectin ($P < .05$) (Table 2) and further analyses in men and women revealed that among women, higher baseline adiponectin levels significantly predicted higher risk for all-cause dementia and AD (HR, 1.31; 95% CI, 1.07-1.61; $P = .009$ and HR, 1.32; 95% CI, 1.06-1.65; $P = .02$, respectively) (Table 4).

Age-adjusted correlations of adiponectin level with measures of body composition and weight loss are presented in Table 5. There was an inverse association between plasma adiponectin levels, BMI, and waist to hip ratio in both men and women. These associations were mainly due to a strong correlation observed in women ($r = -0.36$ and $r = -0.37$; $P < .001$ for BMI and waist to hip ratio, respectively). The correlation between plasma adiponectin levels and weight change was weaker and only significant in women ($r = -0.11$; $P < .01$).

Results of subsequent analyses regarding adiponectin level performed on women only are given in Table 6 and Table 7. Although adjustments for BMI and weight change did have a small effect on the HR, plasma adiponectin level remained a marginally significant risk factor for both all-cause dementia and AD in the fully adjusted model (HR, 1.29; 95% CI, 1.00-1.66; $P = .054$ and HR, 1.33; 95% CI, 1.00-1.76; $P = .050$, respectively). Among women with nonmissing creatinine and plasma homocysteine concentrations, additional adjustment for these variables did not alter the HRs, indicating that there was no confounding by creatinine or plasma homocysteine level (data not shown). Results of quartile analyses of adiponectin level in women showed a threshold at the median. Women with a baseline adiponectin concentration more than the (sex-specific) median had a significantly higher risk of all-cause dementia and AD even in the fully adjusted model (HR, 1.63; 95% CI, 1.03-

Table 5. Age-Adjusted Correlations of Adiponectin With Measures of Weight Loss and Body Composition at Examination Cycle 19^a

	All	Men	Women
BMI	-0.30 ^b	-0.15 ^c	-0.36 ^b
WHR	-0.47 ^b	-0.15 ^d	-0.37 ^b
Weight change	-0.08 ^d	-0.09	-0.11 ^c

Abbreviations: BMI, body mass index; WHR, waist to hip ratio.

^aCorrelations were adjusted for age and sex.

^b $P < .001$.

^c $P < .01$.

^d $P < .05$.

2.56; $P = .04$ and HR, 1.87; 95% CI, 1.13-3.10; $P = .01$, respectively) (Table 7).

To determine if survival bias played in our analysis, we did additional analysis stratified by median age (72 years) for the association of dementia with a 1-SD increase in hsCRP or adiponectin concentrations (eTable 1 and eTable 2, <http://www.archneurology.com>). The direction of the effect estimates were the same for both age groups for both hsCRP and adiponectin levels. This was also true for the analysis comparing women with an adiponectin concentration more than and less than the median value (eTable 3).

COMMENT

Risk factors for AD and all-cause dementia exhibit overlap with those for cardiovascular disease. One of the important risk factors for cardiovascular disease is T2D and our purpose was to investigate the contribution of markers of glucose homeostasis and inflammation to the development of AD and all-cause dementia. We did not find indications that plasma insulin, glucose, and glycated albumin levels were associated with AD or all-cause de-

Table 6. Multivariate-Adjusted HRs for Alzheimer Disease and All-Cause Dementia by 1-SD Increase in Adiponectin Concentrations in Women

	All-Cause Dementia			Alzheimer Disease		
	No./Total No.	HR (95% CI)	P Value	No./Total No.	HR (95% CI)	P Value
Model 1 ^a	113/541	1.31 (1.07-1.61)	.009	93/541	1.32 (1.06-1.65)	.02
Model 2 ^b	109/521	1.22 (0.98-1.51)	.08	91/521	1.22 (0.96-1.54)	.11
Model 3 ^c	85/419	1.29 (1.00-1.66)	.054	71/419	1.33 (1.00-1.76)	.050

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aAdjusted for age.

^bAdjusted for age, body mass index, and weight change.

^cModel 2 with additional adjustment for *APOE* ϵ 4 allele, plasma docosahexaenoic acid concentration, and educational level.

Table 7. Multivariate-Adjusted HRs for Alzheimer Disease and All-Cause Dementia More Than vs Less Than Median Adiponectin Concentrations in Women

	All-Cause Dementia			Alzheimer Disease		
	No./Total No.	HR (95% CI)	P Value	No./Total No.	HR (95% CI)	P Value
Model 1 ^a	113/541	1.56 (1.07-2.28)	.02	93/541	1.84 (1.21-2.80)	.005
Model 2 ^b	109/521	1.44 (0.97-2.13)	.07	91/521	1.62 (1.05-2.50)	.03
Model 3 ^c	85/419	1.63 (1.03-2.56)	.04	71/419	1.87 (1.13-3.10)	.01

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aAdjusted for age.

^bAdjusted for age, body mass index, and weight change.

^cModel 2 with additional adjustment for *APOE* ϵ 4 allele, plasma docosahexaenoic acid concentration, and educational level.

mentia. In addition, the inflammatory marker Lp-PLA₂ was not associated with AD or all-cause dementia. Higher plasma levels of hsCRP, the other inflammatory marker under investigation, initially appeared to be associated with a lower risk for AD and all-cause dementia. This association, however, was no longer significant after adjusting for the additional risk factors, including the presence of the *APOE* ϵ 4 allele. The latter finding is in line with a previous report suggesting that in *APOE* ϵ 4 carriers, the elevated plasma levels of CRP reflect a better immune function and are associated with a decreased risk for AD and dementia.³⁷ Alternatively, persons with elevated levels of CRP and *APOE* ϵ 4 may have died of alternative causes before the examination round of this study and were therefore not included.

Our data indicated that adiponectin level was an independent risk factor for all-cause dementia and AD in women. One of the main features of adiponectin is that it has been shown to play a role in the sensitization of insulin and therefore may become a therapeutic target for the treatment of T2D. Surprisingly, a higher adiponectin level was found to be a predictor of all-cause and vascular mortality.^{23,24} In concurrence with the mortality findings, the current investigation shows that an elevated adiponectin level is also an independent predictor for all-cause dementia and AD in women. A recent cross-sectional study from Japan also found that high adiponectin levels were associated with mild cognitive impairment and AD.³⁸

To clarify the positive association of adiponectin with mortality, a number of possibilities have been raised, including the known elevation of plasma adiponectin levels with impaired renal function and weight loss.³⁹ This latter concept may be especially relevant in our study since

weight loss is a significant risk factor for mortality in elderly individuals.^{40,41} In addition, patients with dementia usually have prodromal and subsequent weight loss that would be predicted to increase adiponectin levels. In our study population, we also found a significant correlation between age-adjusted correlation of adiponectin level and weight change in women. However, it did not impact the significance of adiponectin level as a risk factor for AD in women.

Although we did not have data on the entire sample for plasma creatinine or homocysteine levels, we studied these variables in a subset ($n = 550$) of study participants and found no direct evidence for confounding. Furthermore, adiponectin level remained a significant risk factor for all-cause dementia and AD in women when taking into account the established risk factors, ie, *APOE* ϵ 4 allele, plasma DHA level, and level of education, suggesting that at least in women, adiponectin level is an independent risk factor or risk marker for all-cause dementia and AD.

A previous study from the Framingham population using samples from examination 22 has shown that elevated levels of leptin were associated with a reduced incidence of dementia and AD and with higher total cerebral brain volumes in asymptomatic older adults.²⁶ To see if selection bias explained the results, we compared the characteristics of the study subjects included in that study with subjects in our study. The flowchart showing all inclusion and exclusion criteria along with subject numbers of the 2 studies is shown in the eFigure. The characteristics of the subjects included in the 2 studies were similar (eTable 4). In addition, the majority of the subjects were included in both studies (56.5%; 479 of 848). Therefore,

it is unlikely that selection bias would explain our findings. Furthermore, additional analysis stratified by median age also showed that a high adiponectin level was associated with an increased risk of dementia in both age groups. Although the significant differences were found only in the age group 72 years and older, this could be explained by low numbers of subjects with dementia in the age group younger than 72 years. These findings would exclude the survival bias as well.

It is well established that insulin signaling is dysfunctional in the brains of patients with AD,⁶ and since adiponectin enhances insulin sensitivity, one would also expect beneficial actions protecting against cognitive decline. Our data, however, indicate that elevated adiponectin level was associated with an increased risk of dementia and AD in women. Alternatively, adiponectin levels may have risen as a (protective) response to vascular damage or changes in brain morphology that had not yet been identified at the time of enrollment into the study. To distinguish between these 2 possibilities, studies reporting the correlation between multiple measures of adiponectin and cognitive decline over time, and in addition, mendelian randomization studies linking genetic variation in the adiponectin gene to plasma adiponectin levels and cognitive decline, will be of great interest. To our knowledge, to date, there are no data relating baseline adiponectin levels to changes in cognition. Furthermore, although polymorphisms in the promoter region of the adiponectin gene with direct effects on adiponectin levels have been identified,^{42,43} no study that we know of has investigated the role of these genetic variants in relation to cognitive end points.

To our knowledge, this is the first prospective study to report that adiponectin level is an independent risk factor for all-cause dementia and AD in women. The strengths of our investigation include its prospective design, the large community-based sample, and the long follow-up period. Some limitations are the predominantly white nature of our study sample; hence, our results require verification in other racial and ethnic samples. Furthermore, the lack of an association between some of the circulating biomarkers tested (such as Lp-PLA₂ and insulin levels) and the risk of dementia or AD could be a reflection of the age at which these markers were tested and of our relatively limited sample size. In addition, circulating levels of these markers might not reflect concentrations in the brain parenchyma or in the cerebrospinal fluid. We have not corrected for multiple testing and would consider our results exploratory, requiring confirmation in other samples. Finally, a limitation of our study is the limited number of male cases; therefore, we cannot rule out the possibility that the absence of an association between adiponectin levels and the risk of dementia in men might reflect inadequate power to detect an effect. On the other hand, animal models have shown that testosterone downregulates adiponectin release from fat cells, and in human population studies, including the current study, women have higher plasma adiponectin levels than men.^{44,45}

The fact that in women we find a threshold effect above which adiponectin level becomes a risk factor

for dementia suggests that in men the absence of an effect of adiponectin could reflect that men have adiponectin levels less than a threshold value for increasing the risk of dementia. Thus, the sex dimorphism with regard to adiponectin levels might partially explain the lower risk of AD observed among men in another study.⁴⁶

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Online-Only Material: The eTables and eFigure are available at <http://www.archneurol.com>.

Additional Information: The Framingham Dementia Study was planned and is being carried out by Drs Wolf, Au, Beiser, and Seshadri. The selection of the assays for this were made by Dr Schaefer, and the assays for this study were measured by Dr Ai and Ms Otokoza.

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