Hyperinsulinemia and Cognitive Decline in a Middle-Aged Cohort

SARA E. YOUNG, MD[1,2]
ARCH G. MAINOUS, III, PHD[1]
MARK CARNEMOLLA, BS[1]

OBJECTIVE — Determining modifiable risks factors for cognitive decline and dementia are a public health priority as we seek to prevent dementia. Type 2 diabetes and related disorders such as hyperinsulinemia increase with aging and are increasing in the U.S. population. Our objective was to determine whether hyperinsulinemia is associated with cognitive decline among middle-aged adults without type 2 diabetes, dementia, or stroke in the Atherosclerosis Risk in Communities (ARIC) cohort.

RESEARCH DESIGN AND METHODS — Middle-aged adults (aged 45–64 years at baseline) in the ARIC cohort had fasting insulin and glucose assessed between 1987 and 1989. Subjects with dementia, type 2 diabetes, or stroke at baseline were excluded from analysis. Three tests of cognitive function available at baseline and 6 years later were delayed word recall (DWR), digit symbol subtest (DSS), and first letter word fluency (WF). Cross-sectional comparisons and linear regression models were computed for cognitive tests at baseline and change in cognitive test scores to determine whether cognitive function was associated with two measures of insulin resistance, fasting insulin and homeostasis model assessment (HOMA). Linear regression models controlled for age, sex, race, marital status, education level, smoking status, alcohol use, depression, hypertension, and hyperlipidemia.

RESULTS — In unadjusted and adjusted analyses, hyperinsulinemia based on fasting insulin and HOMA at baseline was associated with significantly lower baseline DWR, DSS, and WF scores and a greater decline over 6 years in DWR and WF.

CONCLUSIONS — Insulin resistance is a potentially modifiable midlife risk factor for cognitive decline and dementia.

Diabetes Care 29:2688–2693, 2006

Determining modifiable risks factors for cognitive decline and dementia is a public health priority as we seek to prevent dementia, which affects at least 4 million individuals in the U.S. (1). Current therapies, such as cholinesterase inhibitors, may slow cognitive decline in some patients, although the absolute changes in disease trajectory are modest (2–4). Type 2 diabetes and related disorders such as hyperinsulinemia increase with aging and are increasing in the U.S. population (5,6). Previous studies have produced conflicting evidence linking diabetes, glucose intolerance, and hyperinsulinemia to cognitive decline and Alzheimer's dementia (7). Previous epidemiologic studies relate hyperinsulinemia or type 2 diabetes to Alzheimer's dementia cross-sectionally in older adults (8–12), whereas only a few studies have evaluated the longitudinal association between hyperinsulinemia and Alzheimer's dementia (13–15). None of these studies investigated an association between hyperinsulinemia and cognitive decline in middle-aged adults.

Insulin resistance is known to be associated with the development of age-related diseases including hypertension, coronary heart disease, stroke, cancer, and type 2 diabetes (16). People with insulin resistance are at an approximately fivefold risk for diabetes, but this risk can potentially be modified by modest weight loss and lifestyle modifications (17). It has been proposed that inflammation caused by oxidative stress is a common mechanism that exists for chronic progressive diseases including Alzheimer's dementia (18). The mechanisms that link type 2 diabetes and cognition are still debated (19). Insulin receptors are concentrated in the hippocampus, a brain region important in memory and learning (20). Animal and human models suggest that elevated insulin levels increase the amyloid β level (19), and accumulation of amyloid β has been implicated in development of Alzheimer's dementia.

The relationship of hyperinsulinemia to cognitive decline has not been previously examined in the Atherosclerosis Risk in Communities (ARIC) cohort (21,22). The primary aim of our current study was to determine whether hyperinsulinemia is associated with cognitive decline among middle-aged adult participants without type 2 diabetes, dementia, or stroke in the ARIC cohort.

RESEARCH DESIGN AND METHODS

Database

The ARIC cohort is a large, multiethnic, multisite longitudinal observational study of risk factors for vascular diseases that was initiated in 1987. This study is based on the publicly available ARIC dataset. Initially, 15,732 men and women aged 45–64 years were recruited from area sampling of four locations using population-wide lists for probability sampling (23). Four U.S. communities were sampled; three of the communities in the cohort were probability sampled. The fourth community (Jackson, MS) only sampled nonwhites.

The initial visit, occurring between 1987 and 1989, included comprehensive clinical and laboratory examination including insulin level in 15,027 subjects who fasted ≥8 h. Subsequent examina-

From the [1]Department of Family Medicine, Medical University of South Carolina, Charleston, South Carolina; and the [2]Department of Family Medicine, Medical College of Georgia, Augusta, Georgia.

Address correspondence and reprint requests to Sara E. Young, MD, Department of Family Medicine, Medical College of Georgia, HB-3032, Augusta, GA 30912-3500. E-mail: sayoung@mcg.edu.

Received for publication 4 May 2006 and accepted in revised form 17 September 2006.

Abbreviations: ARIC, Atherosclerosis Risk in Communities; DSS, digit symbol subtest; DWR, delayed word recall; HOMA, homeostasis model assessment; WF, first letter word fluency.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc06-0915

tions of the cohort have been every 3 years. At the second visit, occurring between 1990 and 1992, individuals underwent an initial cognitive evaluation. At the fourth visit, 6 years after initial cognitive evaluation, subjects had repeat cognitive evaluation.

Data abstraction

For most of the current analysis, 451 subjects were excluded because they gave a self-reported history of stroke or transient ischemic attack at visit 1, and 936 subjects were excluded because they had type 2 diabetes defined by fasting glucose of >126 mg/dl, nonfasting glucose of >200 mg/dl, a self-reported history of diabetes, or treatment for diabetes at visit 1. Ninety-three subjects with dementia, based on a delayed word recall (DWR) test score <3 when assessed at visit 2, were censored from analysis. A total of 1,409 individuals were excluded from further analysis based on dementia, stroke/transient ischemic attack, or type 2 diabetes. The 7,148 ARIC cohort subjects included in this analysis had information on fasting insulin and control variables at the first visit, control variables at the second visit, and cognitive test scores at the second and fourth visits. The full interview, laboratory, and examination methodology can be found on the ARIC Web site (http://www.cscc.unc.edu/aric/pubuse/).

Cognitive testing

Cognitive testing in the ARIC included serial assessments of the DWR test, the digit symbol subtest (DSS) of the Wechsler Adult Intelligence Scale-Revised, and the first letter word fluency (WF) test. The DWR is a test of verbal learning and recent memory in which the participant learns 10 common nouns by constructing sentences incorporating the words and then following a 5-min interval attempts to recall the nouns (24). With a cutoff of <3 for dementia and >3 for normal, the DWR test has an overall predictive accuracy of 95.2% for possible or probable Alzheimer's dementia and is not correlated with education or age in normal subjects (25). The DSS score is the number of correctly drawn symbols completed within the 90-s time limit. The DSS is considered a more sensitive measure of dementia than the often-used Mini-Mental State Exam. Components of cognitive functioning and psychomotor performance evaluated by the DSS include response speed, sustained attention, visual spatial skills, associative learning, and memory (24). The WF test measures mental agility in retrieving words starting with a particular letter; the score is based on the total number of words given by the participant. The WF test is particularly sensitive to damage to the frontal lobes of the brain (24).

Hyperinsulinemia

Hyperinsulinemia was defined by two clinical and two empirical measures of insulin resistance. Fasting insulin and homeostasis model assessment (HOMA) have been used to predict insulin resistance. HOMA is a measure of insulin sensitivity that compensates for potential fasting hyperglycemia; HOMA is calculated by dividing the product of fasting concentrations of glucose and insulin by a constant. The clinically relevant cutoffs defining hyperinsulinemia used in this current study are fasting insulin >12.2 mU/l and HOMA >2.6 (26). It is unclear what level of insulin resistance is associated with risk of cognitive decline or dementia; thus, we empirically defined hyperinsulinemia at the 75th percentile based on all subjects in the ARIC cohort who had fasting insulin measured at the initial visit. The 75th percentile was 14.0 mU/l for fasting insulin and 3.9 for HOMA.

Control variables

In an effort to determine the independent relationship between hyperinsulinemia and results of a test of cognitive function, control variables included age, sex, education level, marital status, smoking status, alcohol use, depression score, history of hypertension, and history of hyperlipidemia to control for factors that are known to have an impact on cognitive decline and dementia. Depressive symptom items from the Maastricht Questionnaire at visit 2 were used to determine the depression score (27). Hypertension was considered present if systolic blood pressure was ≥140 mmHg, if diastolic blood pressure was ≥90 mmHg, or if antihypertensive medications were being used at baseline. Hyperlipidemia was considered present if LDL was ≥140 mg/dl or if cholesterol-lowering agents were being used at baseline. To evaluate the potential effects of change in diabetes status and treatment status that may have occurred in subjects by the fourth visit, an additional control variable for later development of diabetes was defined by visit 4: fasting glucose ≥126 mg/dl, nonfasting glucose ≥200 mg/dl, self-reported history of diabetes, or treatment for diabetes at visit 4.

Statistical methods

Descriptive statistics and Student's *t* tests to compare mean baseline cognitive test scores and cognitive test change scores between those with and without hyperinsulinemia were computed. Change scores for cognitive tests were calculated as visit 4 minus visit 2 values for each subject. SAS statistical software (SAS Institute, Cary, NC) was used; results were considered statistically significant if $P < 0.05$.

Multiple variable linear regression models with the dependent variable of baseline cognitive test score or cognitive test change score were computed to evaluate associations with measures of hyperinsulinemia. Control variables, as described above, were used in all linear regressions to adjust for potential confounders. In these forced inclusion models, the dependent variable of either baseline cognitive test score or cognitive test change score was a continuous variable. Age, alcohol use, and depression score were treated as continuous variables in linear regressions. Additional multiple linear regression models included the control variables as described above as well as a control variable for later development of diabetes to assess the effects of change over time in diabetes status and treatment status.

RESULTS — The corresponding percentiles for the clinically informed cutoffs of fasting insulin >12.2 mU/l and HOMA >2.6 were 68.2 and 56.8, respectively, in all subjects in the ARIC cohort who had fasting insulin measured. Characteristics of ARIC participants without type 2 diabetes, dementia, or stroke/transient ischemic attack at baseline are presented in Table 1. DWR at baseline, available in the 7,148 individuals included in subsequent analyses, was 6.78 ± 1.43 (means ± SD). Minimum baseline DWR was 3, and maximum DWR was 10. The greatest decline in DWR score at 6-year follow-up was −7, and 5 was the greatest improvement. At follow-up cognitive testing, 72 participants had developed DWR scores <3. DWR change score, available in 7,008 individuals, was −0.153 ± 1.54. DSS at baseline, available in the 7,136 individuals included in subsequent analyses, was 46.9 ± 13.4. Minimum baseline DSS was 0, and maximum DSS was 93. The greatest decline in DSS score at the 6-year fol-

Table 1—*Characteristics of participants in the ARIC study who did not have diabetes, dementia, or stroke at baseline*

Characteristics	*n*	Percent
Demographics		
Age (years)	7,148	53.7 (mean)
Sex		
Male	3,173	44.39
Female	3,975	55.61
Race		
White	5,729	80.15
Nonwhite	1,419	19.85
Marital status		
Married	5,819	81.41
Divorced	572	8.00
Widowed	449	6.28
Separated	174	2.43
Never married	134	1.87
Education level		
Basic education (0–11 years)	1,184	16.58
Intermediate education (12–16 years)	3,057	42.80
Advanced education (17–21 years)	2,902	40.63
Diseases and expenses		
Hypertension	2,878	40.26
No hypertension	4,270	59.74
Hyperlipidemia	3,811	53.32
No hyperlipidemia	3,337	46.68
Depression score	7,147	2.18 (mean)
Cigarette smoking status		
Never smoked	3,228	45.18
Former smoker	2,424	33.93
Current smoker	193	20.90
Alcohol use status		
No alcohol use	4,243	59.36
Alcohol use	2,894	40.49
Measures of insulin resistance		
Baseline fasting insulin >12.2 mU/l	1,908	26.69
Baseline fasting insulin <12.2 mU/l	5,240	73.30
Baseline HOMA >2.6	2,600	36.37
Baseline HOMA <2.6	4,548	63.63

low-up was −59, and 63 was the greatest improvement. DSS change score, available in 6,986 individuals, had a mean of −2.55 ± 6.94. WF at baseline, available in the 7,142 individuals included in subsequent analyses, was 34.6 ± 12.2. Minimum baseline WF was 0, and maximum WF was 86. The greatest decline in WF score at the 6-year follow-up was −44, and 66 was the greatest improvement. WF change score, available in 6,991 individuals, was −0.657 ± 7.91.

In unadjusted analyses, utilizing both clinical cutoffs and highest quartiles of both fasting insulin and HOMA, hyperinsulinemia at baseline was associated with significantly lower baseline DWR, DSS, and WF scores. DWR change scores for participants with hyperinsulinemia based on highest quartile fasting insulin, highest quartile HOMA, and HOMA with a cutoff of 2.6 had significantly greater decline than those without hyperinsulinemia (Table 2). WF change scores for participants with hyperinsulinemia based on highest quartile fasting insulin, fasting insulin with a cutoff of 12.2 mU/l, and highest quartile HOMA had significantly greater decline than those without hyperinsulinemia. DSS change scores were not significantly different between those with and without hyperinsulinemia. Variables for age, sex, race, and education level were statistically significant in most of the fully adjusted multiple linear regression models and explained a majority of the variance in cognitive test scores and change scores. R^2 values for the linear regression models of baseline cognitive function tests with all control variables, but before addition of any hyperinsulinemia variable, were 0.125 for DWR, 0.492 for DSS, and 0.224 for WF. Multiple variable linear regression models adjusted for potential confounders showed lower baseline DWR scores for those with hyperinsulinemia, although only in the model utilizing fasting insulin with 12.2 mU/l as the cutoff was the hyperinsulinemia variable statistically significant (Table 3). Similarly, adjusted models showed lower baseline DSS scores for those with hyperinsulinemia, although the hyperinsulinemia variable was statistically significant only when utilizing highest quartile fasting insulin or highest quartile HOMA. Adjusted multiple variable linear regression models showed lower baseline WF scores using both empirical and both clinical cutoffs for hyperinsulinemia, and all hyperinsulinemia variables were statistically significant in their models of baseline WF scores.

In adjusted multiple variable linear regression models, greater decline in DWR over 6 years was found in those with hyperinsulinemia, although only in the model utilizing the highest HOMA quartile as the cutoff was the hyperinsulinemia variable statistically significant. Adjusted models showed greater decline in WF change scores for those with hyperinsulinemia, although only in the model utilizing the highest fasting insulin quartile as the cutoff was the hyperinsulinemia variable statistically significant. In adjusted models for DSS change scores, none of the hyperinsulinemia variables were statistically significantly.

In terms of the strength of the relationship of hyperinsulinemia and cognitive tests in addition to the statistical significance previously shown, we conducted several additional analyses. The Spearman's rank correlation coefficient, summarizing the strength of the relationship between hyperinsulinemia by highest quartile fasting insulin and cognitive testing, was $r = 0.144$ ($P < 0.0001$) for baseline DSS score, $r = 0.070$ ($P < 0.0001$) for baseline DWR, and $r = 0.084$ ($P < 0.0001$) for baseline WF. Following adjustment for control variables in linear regression analyses of cognitive tests, the relationships remained significant; however, there was an indication of substantial shared variance with some of the control variables. For example, the partial correlation between baseline DSS score and hyperinsulinemia by highest quartile

Table 2—*Mean baseline cognitive test scores and mean cognitive test change scores compared between those with and without hyperinsulinemia at baseline*

	With hyperinsulinemia	Without hyperinsulinemia	*P* value
Fasting insulin (cutoff 75th percentile)			
Baseline DWR	6.58 ± 1.42	6.83 ± 1.42	<0.0001*
DWR change score	−0.254 ± 1.53	−0.129 ± 1.54	0.0074*
Baseline DSS	43.0 ± 13.7	47.9 ± 13.1	<0.0001*
DSS change score	−2.74 ± 7.30	−2.51 ± 6.85	0.2954
Baseline WF	32.5 ± 12.3	35.1 ± 12.1	<0.0001*
WF change score	−1.19 ± 7.86	−0.532 ± 7.92	0.0064*
Fasting insulin (cutoff 12.2 mU/l)			
Baseline DWR	6.59 ± 1.40	6.85 ± 1.43	<0.0001*
DWR change score	−0.205 ± 1.57	−0.134 ± 1.55	0.0906
Baseline DSS	43.7 ± 13.7	48.1 ± 13.1	<0.0001*
DSS change score	−2.66 ± 7.14	−2.51 ± 6.86	0.4348
Baseline WF	32.7 ± 12.2	35.3 ± 12.1	<0.0001*
WF change score	−1.035 ± 7.83	−0.520 ± 7.94	0.0164*
HOMA (cutoff 75th percentile)			
Baseline DWR	6.56 ± 1.41	6.82 ± 1.43	<0.0001*
DWR change score	−0.277 ± 1.52	−0.128 ± 1.54	0.0025*
Baseline DSS	42.8 ± 13.8	47.8 ± 13.2	<0.0001*
DSS change score	−2.74 ± 7.26	−2.51 ± 6.87	0.3152
Baseline WF	32.3 ± 12.4	35.0 ± 12.1	<0.0001*
WF change score	−1.08 ± 7.84	−0.570 ± 7.93	0.0423*
HOMA (cutoff 2.6)			
Baseline DWR	6.64 ± 1.41	6.86 ± 1.43	<0.0001*
DWR change score	−0.211 ± 1.54	−0.120 ± 1.54	0.0171*
Baseline DSS	44.4 ± 13.7	48.4 ± 13.0	<0.0001*
DSS change score	−2.57 ± 7.00	−2.54 ± 6.91	0.8335
Baseline WF	33.1 ± 12.1	35.5 ± 12.2	<0.0001*
WF change score	−0.88 ± 7.84	−0.53 ± 7.96	0.0799

Data are means ± SD. *Significant *P* values of *t* test.

fasting insulin, net of the influence of the other control variables, was significant but had dropped to $r = 0.029$ ($P = 0.0154$). With the addition of a variable controlling for later development of diabetes to the previously described multiple linear regression models exploring change in cognitive function scores, none of the previously described statistically significant hyperinsulinemia variables became nonsignificant. The variable controlling for later development of diabetes was not statistically significant in any of the additional models.

CONCLUSIONS — Cognitive decline and dementia are typically considered diseases of the elderly, although prevention of cognitive decline may require intercession earlier in midlife. We have described the relationship between hyperinsulinemia and change in cognitive function over time independent of diabetes over 6 years in a middle-aged cohort. This study provides evidence that decline in cognitive function in a middle-aged adult cohort without preexisting dementia, stroke/transient ischemic attack, or type 2 diabetes was greater in participants with higher measures of insulin resistance.

With such a large cohort, there is often more than sufficient power to detect significant differences between groups. More relevant to future interpretation is the minimum detectable difference between each group's mean cognitive changes and whether these differences are clinically significant. These performance decrements were small and probably not clinically significant to participants but offer evidence for initiation of cognitive impairment and cognitive decline associated with insulin resistance in midlife. In considering clinical significance, a previous study (22) using the ARIC cohort showed that diabetic subjects did not have a significant decline in DWR compared with nondiabetic subjects, though diabetic subjects had a greater decline in two other tests of cognitive function. This current study does not address the mechanisms by which hyperinsulinemia causes impaired cognition and cognitive decline. Given our findings of significant differences in decline in DWR and WF between those with and without hyperinsulinemia (excluding individuals with type 2 diabetes and after controlling for later development of diabetes), insulin resistance may increase risk of dementia and progression of dementia by mechanisms discrete to insulin resistance independent of the pathogenic course of type 2 diabetes. Assessing what incremental predictive value novel risk markers add to existing models of risk has been a challenge even in research of coronary heart disease prevention (28,29). The utility of this strategy in dementia prevention, particularly with assessment of potentially modifiable risk factors to identify individuals at risk for dementia toward providing preventive action, is in its infancy, and further exploration of the predictive utility of novel risk factors that have modest though independent statistical associations with cognitive decline is warranted.

The strengths of this study include its large, population-based, multiethnic, longitudinal nature with repeat cognitive testing and its younger subject age than studies that have previously investigated longitudinal associations between hyperinsulinemia and dementia (14,15). Additional strengths are the use of two measures of insulin resistance, which we explored at both empirical and clinical cutoff levels.

Use of the ARIC cohort allowed for examination of the relationship between insulin and cognitive function in both men and women and allowed for assessment of potentially preclinical cognitive decline, unlike the study by Okereke et al. (15), which included only older women in the Nurses' Health Study, and Peila et al. (14), which included only elderly Japanese-American men. A limitation of this study is that we were unable to directly link time to development of decline; instead, we were limited to using a 6-year time frame. While some decline may have happened earlier, this time frame for an intermediate indicator of dementia seems like a reasonable assessment.

The results of this study lead us to propose that insulin resistance is a potentially modifiable midlife risk factor for dementia. Hopefully, the results of this study will lead to assessments and interventions in middle age that can prevent or reduce the burden of dementia in the ag-

Table 3—*Linear regression models for cognitive test scores and cognitive test change scores with hyperinsulinemia variables*

	β Coefficient of hyperinsulinemia variable	*P* value
Baseline DWR		
Fasting insulin (cutoff 75th percentile)	−0.0687	0.0962
Fasting insulin (cutoff 12.2 mU/l)	−0.0779	0.0351*
HOMA (cutoff 75th percentile)	−0.0677	0.1154
HOMA (cutoff 2.6)	−0.0315	0.3583
DWR change scores		
Fasting insulin (cutoff 75th percentile)	−0.0929	0.0527
Fasting insulin (cutoff 12.2 mU/l)	−0.0335	0.4351
HOMA (cutoff 75th percentile)	−0.1135	0.0245*
HOMA (cutoff 2.6)	−0.0563	0.1604
Baseline DSS		
Fasting insulin (cutoff 75th percentile)	−0.7665	0.0092*
Fasting insulin (cutoff 12.2 mU/l)	−0.4598	0.0834
HOMA (cutoff 75th percentile)	−0.7009	0.0218*
HOMA (cutoff 2.6)	−0.3405	0.1634
DSS change scores		
Fasting insulin (cutoff 75th percentile)	−0.4039	0.0727
Fasting insulin (cutoff 12.2 mU/l)	−0.2931	0.1370
HOMA (cutoff 75th percentile)	−0.3753	0.1119
HOMA (cutoff 2.6)	−0.1140	0.5262
Baseline WF		
Fasting insulin (cutoff 75th percentile)	−0.6618	0.0447*
Fasting insulin (cutoff 12.2 mU/l)	−0.7098	0.0161*
HOMA (cutoff 75th percentile)	−0.6867	0.0471*
HOMA (cutoff 2.6)	−0.6918	0.0115*
WF change scores		
Fasting insulin (cutoff 75th percentile)	−0.5634	0.0226*
Fasting insulin (cutoff 12.2 mU/l)	−0.4105	0.0626
HOMA (cutoff 75th percentile)	−0.3952	0.1256
HOMA (cutoff 2.6)	−0.2296	0.2617

Reference levels being those without hyperinsulinemia at baseline. All regressions adjusted for age, sex, race, marital status, education level, smoking status, alcohol use, depression score, history of hypertension, and history of hyperlipidemia. *Significant *P* values of Wald *F* test for hyperinsulinemia variables.

ing population. Middle-aged subjects without dementia, type 2 diabetes, or stroke at baseline who have hyperinsulinemia have a greater decline in performance on tests of cognitive function over a 6-year period compared with subjects without hyperinsulinemia.

Acknowledgments— This study was supported in part by grants 1D12HP00023 and 1D14HP00161 from the Health Resources and Services Administration and grant 1PS0AG021677 from the National Institute of Aging.

References

1. Haan MN, Wallace R: Can dementia be prevented? Brain aging in a population-based context. *Annu Rev Public Health* 25: 1–24, 2004
2. Xiong G, Doraiswamy PM: Combination drug therapy for Alzheimer's disease: what is evidence-based, and what is not? *Geriatrics* 60:22–26, 2005
3. Schmitt B, Bernhardt T, Moeller H, Heuser I, Frolich L: Combination therapy in Alzheimer's disease: a review of current evidence. *CNS Drugs* 18:827–844, 2004
4. Schulz V: Ginkgo extract or cholinesterase inhibitors in patients with dementia: what clinical trials and guidelines fail to consider. *Phytomedicine* 10:74–79, 2003
5. Cowie CC, Rust KF, Byrd-Holt D, Eberhardt MS, Saydah S, Geiss LS, Engelgau MM, Ford ES, Gregg EW: Prevalence of diabetes and impaired fasting glucose in adults: United States, 1999–2000. *MMWR* 52:833–837, 2003
6. Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, , Wiedmeyer HM, Byrd-Holt DD: Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults: the Third National Health and Nutritional Examination Survey, 1988–1994. *Diabetes Care* 21:518–524, 1998
7. Areosa Sastre A, Grimley Evans J: Effect of the treatment of type II diabetes mellitus on the development of cognitive impairment and dementia. *Cochrane Database* CD003804, 2003
8. Abbatecola AM, Paolisso G, Lamponi M, Bandinelli S, Lauretani F, Launer L, Ferrucci L: Insulin resistance and executive dysfunction in older persons. *J Am Geriatr Soc* 52:1713–1718, 2004
9. Kuusisto J, Koivisto K, Mykkanen L, Helkala EL, Vanhanen M, Hanninen T, Kervinen K, Kesaniemi YA, Riekkinen PJ, Laakso M: Association between the features of the insulin resistance syndrome and Alzheimer's disease independently of apolipoprotein E4 phenotype: cross sectional population based study. *BMJ* 315: 1045–1049, 1997
10. Kalmijn S, Feskens EJM, Launer LJ, Stijnen T, Kromhout D: Glucose intolerance, hyperinsulinaemia and cognitive function in a general population of elderly men. *Diabetologia* 38:1096–1102, 1995
11. Ott A, Stolk RP, Hofman A, Vanharskamp F, Grobbee DE, Breteler MMB: Association of diabetes mellitus and dementia: the Rotterdam Study. *Diabetologia* 39: 1392–1397,1996
12. Vanhanen M, Koivisto K, Kuusisto J, Mykänen L, Helkala EL, Hänninen T, Riekkinen P, Soininen H, Laakso M: Cognitive function in an elderly population with persistent impaired glucose tolerance. *Diabetes Care* 21:398–402, 1998
13. Luchsinger J, Tang M, Shea S, Mayeux R: Hyperinsulinemia and risk of Alzheimer disease. *Neurology* 63:1187–1192, 2004
14. Peila R, Rodriguez BL, White LR, Launer LJ: Fasting insulin and incident dementia in an elderly population of Japanese-American men. *Neurology* 63:228–233, 2004
15. Okereke O, Hankinson SE, Hu FB, Grodstein F: Plasma C peptide level and cognitive function among older women without diabetes mellitus. *Arch Intern Med* 165:1651–1656, 2005
16. Facchini FS, Hua N, Abbasi F, Reaven GM: Insulin resistance as a predictor of age-related diseases. *Clin Endocrinol Metab* 86:3574–3578, 2001
17. Harris MI, Klein R, Welborn TA, Kniman MW: Onset of NIDDM occurs at least 4–7 yr before clinical diagnosis. *Diabetes Care* 15:815–819, 1992
18. Forrester JS: Common ancestors: chronic progressive diseases have the same pathogenesis. *Clin Cardiol* 27:186–190, 2004
19. de la Monte SM, Wands JR: Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: relevance to

Alzheimer's disease. *J Alzheimers Dis* 7: 45–61, 2005
20. Wickelgren I: Tracking insulin to the mind. *Science* 280:517, 1998
21. Cerhan JR, Folsom AR, Mortimer JA, Shahar E, Knopman DS, McGovern PG, Hays MA, Crum LD, Heiss G: Correlates of cognitive function in middle-aged adults. *Gerontology* 44:95–105, 1998
22. Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M, McGovern P, Folsom AR: Cardiovascular risk factors and cognitive decline in middle aged adults. *Neurology* 56:42–48, 2001
23. ARIC Investigators: The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. *Am J Epidemiol* 129: 687–702, 1989
24. Lezak MD: *Neuropsychological Assessment*. 3rd ed. New York, Oxford University Press, 1995
25. Knopman DS, Ryberg S: A verbal memory test with high predictive accuracy for dementia of the Alzheimer type. *Arch Neurol* 46:141–145, 1989
26. McAuley KA, Williams SM, Mann JI, Waler RJ, Lewis-Barned NJ, Temple LA, Duncan AW: Diagnosing insulin resistance in the general population. *Diabetes Care* 24:460–464, 2001
27. McGowan L, Dickens C, Percival C, Douglas J, Tomenson B, Creed F: The relationship between vital exhaustion, depression and comorbid illnesses in patients following first myocardial infarction. *J Psychosom Res* 57:183–188, 2004
28. Folsom AR, Chambless LE, Ballantyne CM, Coresh J, Heiss G, Wu KK, Boerwinkle E, Mosley TH, Sorlie P, Diao G, Sharrett AR: An assessment of incremental coronary risk prediction using c-reactive protein and other novel risk markers: the Atherosclerosis Risk in Communities Study. *Arch Intern Med*166:1368–1373, 2006
29. Llyod-Jones DM, Tian L: Predicting cardiovascular risk: so what do we do now? *Arch Intern Med* 166:1342–1344, 2006