Insulin Resistance Predicts Cognitive Decline: An 11-Year Follow-up of a Nationally Representative Adult Population Sample

Laura L. Ekblad,[1] Juha O. Rinne,[1,2] Pauli Puukka,[3] Hanna Laine,[4,5] Satu Ahtiluoto,[6] Raimo Sulkava,[6] Matti Viitanen,[4,7] and Antti Jula[3]

Diabetes Care 2017;40:751–758 | https://doi.org/10.2337/dc16-2001

OBJECTIVE

The aim of this study was to examine whether insulin resistance, assessed by HOMA of insulin resistance (HOMA-IR), is an independent predictor of cognitive decline.

RESEARCH DESIGN AND METHODS

The roles of HOMA-IR, fasting insulin and glucose, HbA_{1c}, and hs-CRP as predictors of cognitive performance and its change were evaluated in the Finnish nationwide, population-based Health 2000 Health Examination Survey and its 11-year follow-up, the Health 2011 study (*n* = 3,695, mean age at baseline 49.3 years, 55.5% women). Categorical verbal fluency, word-list learning, and word-list delayed recall were used as measures of cognitive function. Multivariate linear regression analysis was performed and adjusted for previously reported risk factors for cognitive decline.

RESULTS

Higher baseline HOMA-IR and fasting insulin levels were independent predictors of poorer verbal fluency performance (*P* = 0.0002 for both) and of a greater decline in verbal fluency during the follow-up time (*P* = 0.004 for both). Baseline HOMA-IR and insulin did not predict word-list learning or word-list delayed recall scores. There were no interactions between HOMA-IR and apolipoprotein E ε4 (*APOEε4*) genotype, hs-CRP, or type 2 diabetes on the cognitive tests. Fasting glucose and hs-CRP levels at baseline were not associated with cognitive functioning.

CONCLUSIONS

Our results show that higher serum fasting insulin and insulin resistance predict poorer verbal fluency and a steeper decline in verbal fluency during 11 years in a representative sample of an adult population. Prevention and treatment of insulin resistance might help reduce cognitive decline later in life.

Alzheimer disease, the most common type of dementia, has become a major public health concern in recent years. Targeting modifiable risk factors for cognitive decline in midlife could delay the onset of Alzheimer disease and thus help reduce the economic burden associated especially with the late stages of the disease (1). Diabetes is an acknowledged risk factor for Alzheimer disease and cognitive impairment (2–4). A recent review concluded that individuals with diabetes typically perform 0.3–0.5 SD units

[1]Turku PET Centre, University of Turku, Turku, Finland
[2]Division of Clinical Neurosciences, Turku University Hospital, Turku, Finland
[3]National Institute for Health and Welfare, Turku, Finland
[4]Turku City Hospital, University of Turku, Turku, Finland
[5]Department of Medicine, Turku University Hospital, University of Turku, Turku, Finland
[6]University of Eastern Finland, Kuopio, Finland
[7]Clinical Geriatrics, Karolinska Institutet, Karolinska University Hospital, Huddinge, Sweden

Corresponding author: Laura L. Ekblad, llekbl@utu.fi.

Received 17 September 2016 and accepted 8 March 2017.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-2001/-/DC1.

This article is featured in a podcast available at http://www.diabetesjournals.org/content/diabetes-core-update-podcasts.

lower on cognitive tests across all age-groups compared with the general population. The mechanisms underlying these subtle cognitive decrements, however, are not yet well established. These decrements most likely do not indicate early stages of dementia, but it is possible that they lower the threshold for developing clinical symptoms of dementia later in life (5).

Insulin resistance (IR) is closely associated with obesity, chronic low-grade inflammation, and low levels of physical activity and it can be seen as the hallmark of the metabolic syndrome and type 2 diabetes (DM2) (6). Epidemiological studies have shown that the metabolic syndrome in midlife increases the risk for cognitive decline (7,8). Recent evidence suggests that brain IR could be an important triggering factor in the development of Alzheimer disease neuropathology (9) and possibly a key link between the metabolic syndrome and cognitive decline (10). Treatment with intranasally administered insulin has been shown to improve memory in patients with Alzheimer disease and mild cognitive impairment (11). Previous studies indicate that the response to intranasal insulin varies according to the patients' sex and *APOEε4* genotype (12).

There are a number of cross-sectional studies linking IR with poorer cognitive performance (13–17). Only two previous longitudinal studies, to our knowledge, examined the effects of insulin or IR on cognitive decline over time. A study on 999 men showed that higher insulin levels at age 50 years predicted lower cognitive test scores 20 years later (18). The Atherosclerosis Risk in Communities (ARIC) cohort study (19) examined 7,148 individuals at baseline for fasting insulin and HOMA-IR. Cognitive performance was evaluated 3 and 9 years after baseline. The study concluded that both fasting insulin and HOMA-IR were associated with poorer cognition 3 years after baseline and with a decline in cognitive test scores during the 6-year follow-up for cognitive functioning.

The aim of this study was to assess whether IR is a risk factor for cognitive decline during 11 years. We hypothesized that IR, estimated with HOMA-IR, is an independent risk factor for cognitive decline and that, based on previous studies, *APOEε4* genotype (12,15) and sex (12,13,15) might influence this risk. Also, low-grade inflammation possibly modulates the risk of cognitive decline associated with the metabolic syndrome (20), which is why we hypothesized that even the association of IR and cognition could be modified by inflammation grade. To test these hypotheses, we studied 3,695 individuals who participated in the Finnish population-based Health 2000 and Health 2011 studies.

RESEARCH DESIGN AND METHODS

Study Population

The data for this study were acquired from the Health 2000 Health Examination Survey and its 11-year follow-up survey, Health 2011. The surveys were conducted by the Finnish National Institute for Health and Welfare in 2000–2001 and 2011 (21,22). The Health 2000 survey was a nationwide, comprehensive, population-based examination survey representative of the Finnish adult population. A total of 8,028 individuals aged 30 years or older were randomly selected from the Finnish population register from 80 health service districts throughout Finland using a two-stage stratified cluster sampling procedure. Of the study population, 84% (n = 6,770) attended the health examination proper or the health examination at home (21).

In 2011 all the individuals alive who belonged to the Health 2000 study sample, who still lived in Finland and who had not refused to participate in the upcoming follow-up studies, were invited to the Health 2011 study (22).

Both studies were approved by the Ethics Committee for Epidemiology and Public Health in the hospital district of Helsinki and Uusimaa, Finland. All participants gave written informed consent for participating in the studies.

Altogether, 3,695 individuals who had attended the health examination proper in 2000 (n = 6,354) and who attended the health examination or the home health examination in 2011 and thus had been tested for cognition on both occasions were included in this study. Participants who, at baseline, had fasted for $<$4 h (n = 226); who had insulin treatment or unknown diabetes medication (n = 59); and who had not completed the cognitive tests (n = 127) or had missing HOMA-IR values (n = 4) were excluded. A total of 789 individuals had died or were lost to follow-up. A flowchart of the study population is provided in Supplementary Fig. 1.

In the analysis of low-grade inflammation and cognition, individuals with hs-CRP values $>$10 mg/L in 2000 (n = 105) were excluded to eliminate the confounding effects of an infectious disease.

The mean age in 2000 was 49.3 years (range 30–86), and 55.5% were women.

Measurements

Blood pressure was measured at baseline in a sitting position from the right arm with a standard mercury manometer (Mercuro 300; Speidel & Keller, Jungingen, Germany), and the average of two measurements was used for the analyses. Baseline fasting blood samples were drawn, the duration of fasting time was recorded, and the samples were stored at −70°C until analyzed.

Serum cholesterol, HDL cholesterol, triglycerides, glucose, hs-CRP, and insulin values were determined from the frozen samples. Cholesterol values were determined by a CHOD PAP test (Olympus System Reagent; OLYMPUS, Hamburg, Germany), HDL cholesterol values by a HDL-C Plus test (Roche Diagnostics, Mannheim, Germany), triglycerides by a GPO PAP test (Olympus System Reagent), and glucose values by a hexokinase test (Olympus System Reagent). Serum insulin was determined by a microparticle enzyme immunoassay (Abbott Laboratories Dainabot, Tokyo, Japan). HbA_{1c} was determined with an immunoturbidimetric method (Hemoglobin A1c assay; Abbott Laboratories). Serum hs-CRP was analyzed by an automated analyzer (Optima; Thermo Electron Oy, Vantaa, Finland) and an ultrasensitive immunoturbidimetric test (Ultrasensitive CRP; Orion Diagnostica, Espoo, Finland). The detection limit for quantitation of the CRP assay was 0.20 mg/L (23). Those who fell below this limit were given the value 0.2 mg/L divided by 2 = 0.1 mg/L. Non-HDL cholesterol was counted as total cholesterol minus HDL cholesterol. HOMA-IR was used as a measure of IR and counted by the equation fasting insulin (μU/mL) times fasting glucose (mmol/L) divided by 22.5 as previously described (24).

Cognitive Tests

The participants were tested at baseline and at follow-up for verbal fluency and encoding and retaining verbal material according to the Finnish version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) test battery (22,23,25,26). In the verbal fluency test, the participants were asked to list as

many animals as possible during 1 min. This categorical fluency test is considered to represent both language skills and executive functions. In the word-list learning test, 10 words were shown to the participants. The participants were asked to read the words aloud, to memorize them, and to repeat the words they remember within 90 s. In 2000, if the participant remembered all 10 words after one round, the result was counted as a full 30 points. In 2011, all three rounds were repeated for all participants, regardless of whether they remembered all 10 words after the first round or not. The word-list learning test was used to assess verbal learning and memory. After 5 min the participants were asked to recall as many words as possible from the previously presented word list (word-list delayed recall). The delayed recall test was used to evaluate verbal episodic memory. The change in cognitive test scores during the follow-up was counted as cognitive test score in 2000 minus cognitive test score in 2011.

Covariates

Previously reported risk factors for cognitive impairment (model 1: age, sex, years of education; model 2: also DM2, *APOEε4* genotype, BMI, systolic blood pressure, and levels of HDL and non-HDL cholesterol and triglycerides; and model 3: all previous covariates and Beck depression inventory [BDI] score [27], level of physical activity, smoking, and alcohol consumption), assessed at baseline, were used as covariates in the analyses. Sex, DM2, *APOEε4* genotype, physical activity score, smoking, and alcohol consumption were analyzed as categorical variables, and all other covariates were added to the model as continuous variables. Information on years of formal education, current smoking, alcohol consumption, and level of physical activity was addressed by a questionnaire. Excessive alcohol consumption was classified as >24/16 doses of alcohol (12 g alcohol/dose) per week (for men/women). Self-reported physical activity was assessed by asking the participants how often they exercised in their free time for at least 30 min vigorously enough to cause sweating and breathlessness to a mild extent. The results were classified as follows: 1 = a few times a year or more seldom, 2 = two to three times a month, 3 = once a week, four = two to three times a week, 5 = four to six times a week, and 6 = daily. Individuals using oral diabetes medication or who had fasting glucose values >7.0 mmol/L were classified as having DM2. *APOE* genotype was assessed in 3,469 individuals (93.8% of the study population) who gave their written consent for DNA sampling. *APOEε* genotyping was performed with the MassARRAY system (Sequenom, San Diego, California) with a modified protocol that has previously been described (28). *APOEε4* genotype was considered positive for subjects with one or two *ε4* alleles.

Statistical Analysis

The differences between individuals who did not attend the health examination proper or the home health examination in 2011 (n = 1,451) and those included in this study (n = 3,695) were analyzed by Student t test for continuous variables and x^2 test for categorical variables.

For the description of the characteristics of the study population, the study population was divided into three groups according to the baseline tertiles of HOMA-IR. The cutoff for the second tertile was 1.16 and for the third tertile 2.01. In all further analyses, HOMA-IR was analyzed as a continuous variable. Before the analyses, the skewed distributions of HOMA-IR, glucose, and insulin, HbA_{1c}, hs-CRP, triglycerides, and BDI score were corrected by a logarithmic transformation ($\log_e$). The age- and sex-adjusted differences among the tertiles of HOMA-IR for the characteristics were examined by ANCOVA for continuous variables and by logistic regression analysis for categorical variables.

Linear regression analysis was used to examine the associations of continuous, log-linear baseline HOMA-IR, glucose, insulin, HbA_{1c}, and hs-CRP and of the cognitive test scores in 2011 and the change in cognitive test scores from 2000 to 2011. First, the analyses were adjusted for age, sex, and education (model 1 [Table 2]). Model 1 was further adjusted for *APOEε4* genotype, DM2, BMI, systolic blood pressure, HDL and non-HDL cholesterol, and triglycerides (model 2 [Table 3]). The interactions of HOMA-IR × sex, HOMA-IR × hs-CRP, and HOMA-IR × *APOEε4* genotype and HOMA-IR × DM2 on cognitive test scores at follow-up and for the change in cognition from 2000 to 2011 were analyzed in model 2. Because of the variation in fasting times, the analyses for model 2 were performed additionally in the subpopulation who had fasted for 10 h or longer (35.8%, n = 1,321) prior to blood sampling.

In additional analyses model 2 was further adjusted for BDI score, physical activity, smoking, and alcohol consumption (model 3).

The analyses for change in cognition over 11 years were adjusted for baseline cognitive test scores in each model.

Statistical significance was set at $P < 0.05$ for all other tests except for interactions, where $P < 0.1$ was considered statistically significant.

There were no interactions for HOMA-IR × *APOEε4* genotype (all P values >0.26), HOMA-IR × hs-CRP (all P values >0.16), or HOMA-IR × DM2 (all P values >0.48) on any of the cognitive tests. The interaction for HOMA-IR × sex was significant for word-list delayed recall at follow-up (P = 0.06). Thus, sex-stratified analyses were performed only for HOMA-IR and this cognitive test. No other interactions were found for HOMA-IR × sex (all other P values >0.29).

The analyses were performed with JMP Pro 11.0 (SAS Institute, Cary, NC).

RESULTS

The characteristics of the study population according to the tertiles of HOMA-IR are shown in Table 1. Individuals with higher levels of HOMA-IR were older ($P_{trend} < 0.0001$), more often men than women ($P_{trend} < 0.0001$), had fewer years of education ($P_{trend} < 0.0001$), and were less often smokers ($P_{trend} < 0.009$) than those with lower levels of HOMA-IR (P_{trend} indicates age- and sex-adjusted differences among the tertiles of HOMA-IR). The mean cognitive test scores in 2000 and 2011, according to the tertiles of HOMA-IR and adjusted for age, sex, and years of education, are shown in Fig. 1.

The individuals who did not attend the health examination proper or the home health examination in 2011 were older ($P < 0.0001$) and had fewer years of formal education ($P < 0.0001$) than those included in this study. The proportion of women was similar in both groups (56.0% vs. 55.5%, P = 0.75) (data not shown).

Multivariate Correlates of Cognitive Performance

In the linear regression analyses adjusted for age, sex, and education (model 1), higher levels of HOMA-IR, glucose, and

Table 1—Characteristics of the study population at baseline and cognitive test scores at baseline and at follow-up according to the baseline tertiles of HOMA-IR

	Tertile of HOMA-IR			
	1st	2nd	3rd	P_{trend}
n (%)	1,246 (33.7)	1,221 (33.0)	1,228 (33.2)	
Female	784 (62.9)	677 (55.4)	589 (48.0)	<0.0001
Age (years)	47.0 ± 11.3	48.7 ± 11.8	52.1 ± 12.4	<0.0001
Years of education	12.5 ± 3.9	12.4 ± 4.0	11.2 ± 3.8	<0.0001
Fasting time (h:min)	8:41	9:12	9:42	<0.0001
HOMA-IR	0.83 ± 0.23	1.55 ± 0.24	3.56 ± 2.21	<0.0001
DM2	1 (0.0)	10 (0.8)	77 (6.3)	<0.0001
Fasting glucose (mmol/L)	5.1 ± 0.4	5.3 ± 0.4	5.8 ± 1.1	<0.0001
Fasting insulin (mU/L)	3.7 ± 1.0	6.6 ± 1.1	13.6 ± 6.2	<0.0001
HbA_{1c} % (mmol/mol)	5.1 ± 0.3 (32 ± 3.3)	5.2 ± 0.3 (33 ± 3.3)	5.5 ± 0.6 (37 ± 6.6)	<0.0001
hs-CRP (mg/L)	0.91 ± 1.43	1.18 ± 1.62	1.83 ± 2.07	<0.0001
Systolic blood pressure (mmHg)	125 ± 18	131 ± 19	139 ± 20	<0.0001
BMI (kg/m^2)	24.1 ± 3.1	26.3 ± 3.6	29.7 ± 4.6	<0.0001
HDL cholesterol (mmol/L)	1.51 ± 0.37	1.36 ± 0.35	1.19 ± 0.31	<0.0001
Non-HDL cholesterol (mmol/L)	4.25 ± 1.05	4.54 ± 1.05	4.91 ± 1.18	<0.0001
Triglycerides (mmol/L)	1.17 ± 0.56	1.37 ± 0.70	1.96 ± 1.20	<0.0001
*APOEε4**	391 (33.4)	368 (31.8)	361 (31.6)	0.73
BDI score	6.2 ± 6.4	6.3 ± 6.5	7.1 ± 6.7	0.04
Alcohol consumption >24/16 doses/week (for men/women)	71 (5.7)	79 (6.5)	85 (6.9)	0.84
Current smoking	277 (22.3)	226 (18.6)	196 (16.0)	0.009
Physical activity score	3.7 ± 1.4	3.7 ± 1.4	3.6 ± 1.4	0.0002
Verbal fluency in 2000	25.9 ± 7.0	25.2 ± 7.0	23.9 ± 6.9	<0.0001
Word-list learning in 2000†	22.1 ± 3.7	21.8 ± 4.0	20.9 ± 4.0	0.02
Word-list delayed recall in 2000‡	7.6 ± 1.8	7.5 ± 1.8	7.2 ± 1.8	0.52
Verbal fluency in 2011	25.4 ± 7.3	24.5 ± 7.6	22.7 ± 7.1	<0.0001
Word-list learning in 2011†	21.8 ± 4.3	21.5 ± 4.4	20.3 ± 4.6	0.02
Word-list delayed recall in 2011‡	7.5 ± 2.1	7.4 ± 2.1	6.9 ± 2.2	0.39

Data are mean ± SD or *n* (%), unless otherwise indicated. P_{trend} values for age- and sex-adjusted differences among the tertiles of HOMA-IR. The cutoff for the second tertile is 1.16 and for the third tertile 2.01. **APOEε4* genotype is considered positive for subjects with one or two ε4 alleles. †The maximum score for word-list learning is 30 points. ‡The maximum score for word-list delayed recall is 10 points.

insulin predicted a lower verbal fluency score (HOMA-IR $P < 0.0001$, glucose $P = 0.02$, and insulin $P < 0.0001$). Levels of HbA_{1c} ($P = 0.07$), or hs-CRP ($P = 0.17$) were not associated with verbal fluency scores 11 years later. None of these variables predicted performance on word-list learning (all *P* values >0.10) or word-list delayed recall tests (all *P* values >0.61) (Table 2). Higher baseline HOMA-IR ($P = 0.004$) and insulin ($P = 0.005$) levels were associated with a greater decline in verbal fluency from 2000 to 2011 but not with a decline in word-list learning ($P = 0.30$ and 0.44, respectively) or word-list delayed recall ($P = 0.90$ and 0.94, respectively) (Table 2).

In the linear regression model further adjusted for the previously recognized metabolic risk factors for cognitive decline and *APOEε4* genotype (model 2), higher levels of HOMA-IR and insulin were independent predictors of poorer verbal fluency at follow-up ($P = 0.0002$ for both). Baseline HOMA-IR or insulin levels were not associated with word-list learning ($P = 0.60$ and 0.69, respectively) or with word-list delayed recall ($P = 0.38$ and 0.37, respectively) at follow-up (Table 3). In sex-stratified analyses, HOMA-IR did not predict word-list learning performance in men ($P = 0.26$) or in women ($P = 0.99$) (data not shown).

Higher baseline HOMA-IR and insulin levels predicted a greater decline in verbal fluency ($P = 0.004$ for both) but not a decline in word-list learning ($P = 0.55$ and 0.66, respectively) or word-list delayed recall ($P = 0.96$ and 0.88) (Table 3).

Baseline glucose (all *P* values >0.12), HbA_{1c} levels (all *P* values >0.29), or hs-CRP levels (all *P* values >0.26) were not associated with any of the cognitive tests in 2011 or with the change in cognitive performance from 2000 to 2011 (glucose $P > 0.22$, HbA_{1c} $P > 0.44$, and hs-CRP $P > 0.15$) in model 2 (Table 3).

The results for the additional analyses of model 3 and the values of the covariates as determinants of cognitive performance are shown in Supplementary Tables 1 and 2. HOMA-IR ($P = 0.01$) and insulin ($P = 0.02$) were independent predictors of poorer verbal fluency at the 11-year follow-up. The results for a decline in verbal fluency from 2000 to 2011 were no longer statistically significant for HOMA-IR ($P = 0.051$) or insulin ($P = 0.056$, data not shown) in this additional model of adjustment.

The proportion of individuals who were examined after an overnight fast is shown in Supplementary Fig. 2. The results for the analyses of the individuals who had fasted for 10 h or longer ($n = 1,321$) are provided in Supplementary Table 3. In these participants, HOMA-IR ($P = 0.046$) and HbA_{1c} ($P = 0.01$) were independent predictors of poorer verbal fluency in 2011, and HOMA-IR ($P = 0.02$), insulin ($P = 0.02$), and HbA_{1c} ($P = 0.04$) predicted a greater decline in verbal fluency from 2000 to 2011.

CONCLUSIONS

Here, we show that higher levels of insulin and IR are independent predictors of poorer verbal fluency performance and

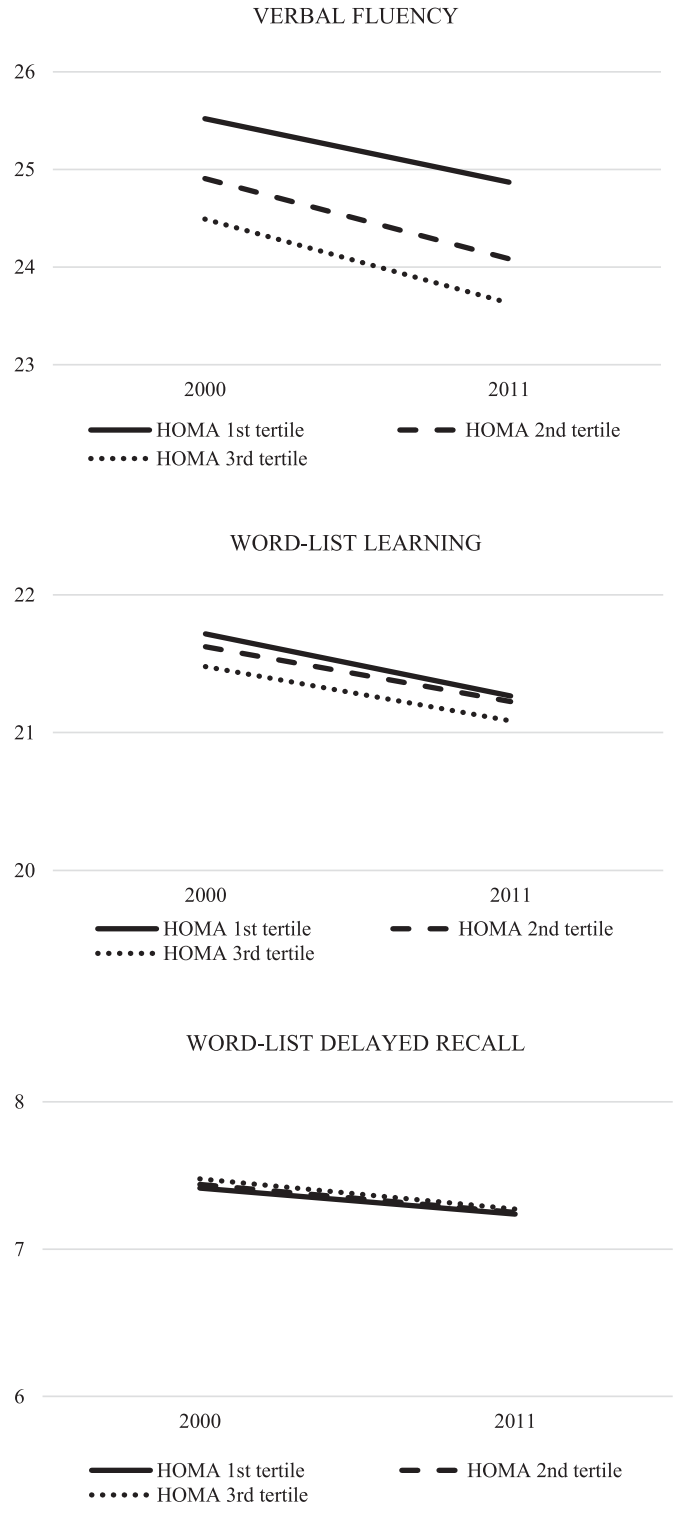

Figure 1—Change in mean cognitive test scores from 2000 to 2011, adjusted for age, sex, and years of education, according to the tertiles of HOMA-IR. *N* = 3,695. Range for verbal fluency, 0–54; word-list learning, 0–30; word-list delayed recall, 0–10.

of a greater decline in verbal fluency during 11 years. Insulin and IR were not associated with the word-list learning or word-list delayed recall tests, which were used as assessments of memory. Sex, *APOEε4* genotype, or hs-CRP levels did not modify these results. Baseline fasting glucose or hs-CRP levels did not predict cognitive test scores.

Our results are consistent with, and extend, the findings of the two previous longitudinal studies on insulin or IR and cognition (18,19). The follow-up study on 999 men showed that higher serum insulin concentrations at age 50 years were associated with lower cognitive *z* scores (based on Mini-Mental State Examination, Trail Making A, and Trail Making B tests) after 20 years, but this association was not statistically significant after adjustment for diastolic blood pressure. The longitudinal associations of IR and cognition were not reported (18). In the ARIC study IR was associated with a decline in delayed word recall and first-letter fluency (19). Compared with the ARIC study (19), the current study provides a longer follow-up period for cognitive decline, and unlike the ARIC study, adjustments were made for covariates closely associated with IR, such as BMI and level of physical inactivity, which have been reported to increase the risk for cognitive decline. In our study, IR did not predict word-list delayed recall after adjustment for age, sex, and education. Additional adjustments for metabolic covariates did not change our results. However, the delayed recall test that we used was slightly different from the test used in the ARIC study, which could be one possible explanation for the difference in the results regarding delayed recall. In both studies, the participants were asked to learn 10 nouns and to recall them after 5 minutes. In our study the words were repeated three times as a list, and in the ARIC study the words were incorporated in sentences. It is possible that the CERAD word-list delayed recall test that we used is not sensitive enough to assess a decline in delayed memory in middle-aged individuals.

We (15) and others (13) have discovered sex differences in the cross-sectional association of IR and cognition, suggesting that IR would be a risk factor for poorer cognitive performance in women but not in men. One longitudinal study on the metabolic syndrome and cognition, with a follow-up of 16 years, found that the metabolic syndrome was associated with cognitive decline only in women (29). These results could not be confirmed in the present longitudinal study. Men and women were both susceptible to the harmful effects of IR on cognition. Our previous cross-sectional study showed an interaction for *APOEε4* and IR on verbal fluency performance. In the stratified analyses the association of IR and poorer verbal fluency was evident only in noncarriers of *APOEε4* (15). Studies on intranasal

Table 2—Age-, sex-, and education-adjusted associations of baseline IR, fasting glucose and insulin, HbA_{1c}, and hs-CRP values with cognitive test scores at follow-up and with change in cognitive test scores from 2000 to 2011

	Verbal fluency		Word-list learning		Word-list delayed recall	
	β	SE	β	SE	β	SE
Cognitive test score, 2011†						
HOMA-IR	−0.81***	0.17	−0.14	0.09	0.01	0.05
Glucose	−2.40*	1.02	−0.91	0.56	−0.06	0.27
Insulin	−0.86***	0.19	−0.14	0.10	0.01	0.05
HbA_{1c}	−2.70	1.50	−0.86	0.81	−0.06	0.39
hs-CRP	−0.12	0.09	−0.04	0.05	−0.01	0.61
Change in cognition, 2000–2011‡						
HOMA-IR	0.41**	0.14	0.09	0.08	0.005	0.04
Glucose	1.37	0.8	0.91	0.49	0.37	0.24
Insulin	0.43**	0.15	0.07	0.09	−0.003	0.04
HbA_{1c}	1.29	1.22	0.67	0.71	0.21	0.34
hs-CRP	0.07	0.07	0.03	0.04	−0.007	0.02

N = 3,695, except for the analysis of hs-CRP and cognition, where n = 3,590. Estimates (β) and SEs are derived from linear regression analysis and adjusted for age, sex, and years of formal education. The analyses for change in cognition are adjusted even for baseline cognitive test scores. Logarithmic transformation is used for HOMA-IR, fasting glucose and insulin, HbA_{1c}, and hs-CRP to achieve a normal distribution. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. †Note that a negative estimate for cognitive test score in 2011 indicates a lower cognitive test score for those with higher levels of IR, fasting glucose, etc. ‡A positive estimate for the change in cognition from 2000 to 2011 indicates a greater decline in cognitive test score for those with higher levels of IR, fasting glucose, etc.

insulin and cognition suggest that possibly only noncarriers of *APOEε4* would benefit from treatment with intranasal insulin (12). The explanation for these sex and *APOEε4* differences, however, is still unclear. Here, the association of IR on cognition 11 years later was similar in noncarriers and carriers of *APOEε4*. The previous longitudinal studies (18,19) did not assess sex or *APOEε4* differences, and sex or *APOEε4* differences have not been investigated in most longitudinal studies on the metabolic syndrome and cognition. It is possible that the early effects of insulin or IR on cognition are different from their longitudinal effects. The possible modulating effect of sex and *APOEε4* genotype on the association of insulin or IR and cognition should be further explored in future studies, also by using sophisticated imaging techniques. A genetic and/or a sex difference in the association between IR and cognition would necessitate personalized preventive and therapeutic interventions to reduce the risk for cognitive decline.

Table 3—Multivariate correlations of baseline IR, fasting glucose and insulin levels, HbA_{1c}, and hs-CRP values with cognitive test scores at follow-up and with change in cognitive test scores from 2000 to 2011

	Verbal fluency		Word-list learning		Word-list delayed recall	
	β	SE	β	SE	β	SE
Cognitive test score, 2011†						
HOMA-IR	−0.86***	0.23	−0.07	0.13	0.05	0.06
Glucose	−1.93	1.25	−0.59	0.68	0.08	0.33
Insulin	−0.91***	0.25	−0.05	0.13	0.06	0.37
HbA_{1c}	−2.01	1.89	0.18	1.02	0.34	0.50
hs-CRP	−0.11	0.10	−0.01	0.05	0.01	0.03
Change in cognition, 2000–2011‡						
HOMA-IR	0.55**	0.19	0.07	0.11	0.002	0.05
Glucose	1.26	1.03	0.63	0.59	0.29	0.29
Insulin	0.58**	0.20	0.05	0.66	−0.01	0.06
HbA_{1c}	1.20	1.55	−0.05	0.90	0.11	0.44
hs-CRP	0.12	0.08	0.02	0.05	−0.001	0.02

N = 3,695, except for the analysis of hs-CRP and cognition, where n = 3,590. Estimates (β) and SEs are derived from linear regression analysis and adjusted for age, sex, years of education, *APOEε4* status, DM2, BMI, systolic blood pressure, HDL and non-HDL cholesterol, and triglycerides. The analyses for change in cognition are adjusted even for baseline cognitive test scores. Logarithmic transformation is used for HOMA-IR, fasting glucose and insulin, HbA_{1c}, hs-CRP, and triglycerides to achieve a normal distribution. **$P < 0.01$, ***$P < 0.001$. †Note that a negative estimate for cognitive test score in 2011 indicates a lower cognitive test score for those with higher levels of IR, fasting glucose, etc. ‡A positive estimate for the change in cognition from 2000 to 2011 indicates a greater decline in cognitive test score for those with higher levels of IR, fasting glucose, etc.

In the current study a higher level of IR was associated with poorer performance on the categorical verbal fluency test, which represents the function of brain frontal and temporal lobe regions (30) and which can be considered as a measurement of language skills and executive function (31). In line with our findings, cross-sectional studies (13–17) on IR and cognition have shown associations between higher levels of IR and poorer executive function. There are several possible pathways to explain these findings, since the mechanisms between IR and cognitive decline are thought to be multifaceted. Cross-sectional brain positron emission tomography studies with ^{18}F-fluorodeoxyglucose show that, consistent with the localization of verbal fluency in the prefrontal and temporal cortices, higher levels of IR are associated with lower regional glucose metabolism in frontal, parietal, and temporal cortical areas in cognitively normal adults (32) and in adults at risk for Alzheimer disease (33). A similar pattern of ^{18}F-fluorodeoxyglucose–positron emission tomography reduction is seen in prodromal Alzheimer disease (34). Brain MRI studies show that IR is associated with lower temporal lobe gray matter volume (14,35) but also with lower volumes of wider areas, such as the prefrontal cortices and precuneus (35). In addition, brain white matter changes seen in MRI images are more common in individuals with the metabolic syndrome compared with those without (36), and these changes are associated with poorer verbal fluency in patients with prodromal Alzheimer disease (37).

The symptoms of Alzheimer disease typically begin with a decline in episodic memory, but this decline is only clinically evident close to the onset of the disease (38). We did not find any association

between IR and the CERAD word-list delayed recall test, a commonly used test of episodic memory to screen for Alzheimer disease. This could be due to our relatively young study population. Late-onset Alzheimer disease begins after 65 years of age, but neuropathological changes typical to the disease can be detected years or even decades before the onset of any cognitive symptoms. Typically, the accumulation of β-amyloid, the neuropathological hallmark of Alzheimer disease, can be detected first in the frontal and the temporal cortices of the brain (39). This is interesting, since categorical verbal fluency is subserved by these brain regions.

Our study has limitations. The golden standard for determining IR, the insulin clamp method, could not be used because of the large, comprehensive health examination nature of this epidemiological study. We could not control for all comorbid conditions associated with IR such as sleep apnea and nonalcoholic fatty liver disease, which have been associated with poorer cognitive performance. Also, we defined diabetes according to fasting glucose values and the use of oral antidiabetes drugs and, thus, individuals with normal fasting glucose but elevated postprandial values might have been falsely classified as not having diabetes. The word-list learning test was performed slightly differently in 2000 and 2011, and this might have affected the scores of both word-list learning and word-list delayed recall. However, only 17 participants had received a full 30 points on the word-list learning test, and excluding these individuals did not change our results. In the word-list delayed recall, the delayed recall section only lasted for 5 min. This test is designed to screen for Alzheimer disease, and it may be that in this middle-aged population a test with a longer delay would have been more sensitive to detect delayed memory decline. The fasting times of our study volunteers varied, which might have resulted in falsely higher HOMA-IR values for those with a shorter fasting time. However, the baseline HOMA-IR values were not higher for participants who had fasted for 4–10 h compared with those who had fasted for >10 h. Thus, we are confident that including participants who had fasted for 4–10 h did not give false positive associations between HOMA-IR and cognitive performance. To confirm this, we provide additional analyses for the subpopulation who had fasted for 10 h or longer. The strength of our study is the large, population-based study cohort, based on a nationally representative sample of the Finnish adult population. The long follow-up time allows us to examine the decline in cognition associated with IR.

In conclusion, we show that IR is an independent risk factor for cognitive decline and, more specifically, a decline in verbal fluency. Although the differences between the tertiles of IR in verbal fluency performance are small, and not of clinical significance at the individual level, these subtle changes in cognition associated with IR could lower the threshold for more severe changes in cognition over time. Longitudinal studies involving more detailed neuropsychological assessment and brain anatomical and functional imaging are needed to explore the different cognitive domains and the neuroanatomical and neuropathologic changes associated with IR. Targeting therapeutic strategies, such as lifestyle interventions, at people with IR in midlife could potentially reduce the incidence of cognitive decline later in life.

Acknowledgments. The authors sincerely thank all the volunteers who participated in the Health 2000 and the Health 2011 surveys for their generous contribution. The authors thank Kaisa Silander, Mari Kaunisto, and the staff of the Technology Centre, Institute for Molecular Medicine Finland (FIMM), University of Helsinki, for the *APOE* genotyping work.

Funding. This study was supported by personal grants from the foundation of Yrjö Jahnsson (L.L.E.), the Finnish Brain Foundation (Suomen Aivosäätiö) (L.L.E.), the Paulo Foundation (L.L.E.), and Finnish Governmental Research Funding for Turku University Hospital and Turku City Hospital.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. L.L.E. analyzed data and wrote the manuscript. L.L.E., J.O.R., P.P., H.L., S.A., R.S., M.V., and A.J. planned this study. J.O.R., P.P., H.L., S.A., R.S., M.V., and A.J. critically revised and edited the manuscript for important intellectual content. P.P. helped with the statistical analysis of data. S.A., R.S., and A.J. took part in designing the Health 2000 and Health 2011 surveys. All authors approved the final version of the manuscript to be published. L.L.E. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the Alzheimer's Association International Conference, Toronto, Ontario, Canada, 24–28 July 2016.

References

1. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. Alzheimers Dement 2007;3:186–191
2. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam Study. Neurology 1999;53:1937–1942
3. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 2006;5:64–74
4. Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. Intern Med J 2012;42:484–491
5. Biessels GJ, Strachan MW, Visseren FL, Kappelle LJ, Whitmer RA. Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions. Lancet Diabetes Endocrinol 2014;2:246–255
6. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595–1607
7. Yates KF, Sweat V, Yau PL, Turchiano MM, Convit A. Impact of metabolic syndrome on cognition and brain: a selected review of the literature. Arterioscler Thromb Vasc Biol 2012;32:2060–2067
8. Siervo M, Harrison SL, Jagger C, Robinson L, Stephan BC. Metabolic syndrome and longitudinal changes in cognitive function: a systematic review and meta-analysis. J Alzheimers Dis 2014;41:151–161
9. Correia SC, Santos RX, Perry G, Zhu X, Moreira PI, Smith MA. Insulin-resistant brain state: the culprit in sporadic Alzheimer's disease? Ageing Res Rev 2011;10:264–273
10. Kim B, Feldman EL. Insulin resistance as a key link for the increased risk of cognitive impairment in the metabolic syndrome. Exp Mol Med 2015;47:e149
11. Craft S, Baker LD, Montine TJ, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Arch Neurol 2012;69:29–38
12. Claxton A, Baker LD, Wilkinson CW, et al. Sex and ApoE genotype differences in treatment response to two doses of intranasal insulin in adults with mild cognitive impairment or Alzheimer's disease. J Alzheimers Dis 2013;35:789–797
13. Schuur M, Henneman P, van Swieten JC, et al. Insulin-resistance and metabolic syndrome are related to executive function in women in a large family-based study. Eur J Epidemiol 2010;25:561–568
14. Benedict C, Brooks SJ, Kullberg J, et al. Impaired insulin sensitivity as indexed by the HOMA score is associated with deficits in verbal fluency and temporal lobe gray matter volume in the elderly. Diabetes Care 2012;35:488–494
15. Ekblad LL, Rinne JO, Puukka PJ, et al. Insulin resistance is associated with poorer verbal fluency performance in women. Diabetologia 2015;58:2545–2553
16. Abbatecola AM, Paolisso G, Lamponi M, et al. Insulin resistance and executive dysfunction in older persons. J Am Geriatr Soc 2004;52:1713–1718
17. Geroldi C, Frisoni GB, Paolisso G, et al. Insulin resistance in cognitive impairment: the InCHIANTI study. Arch Neurol 2005;62:1067–1072
18. Kilander L, Nyman H, Boberg M, Hansson L, Lithell H. Hypertension is related to cognitive

impairment: a 20-year follow-up of 999 men. Hypertension 1998;31:780–786
19. Young SE, Mainous AG 3rd, Carnemolla M. Hyperinsulinemia and cognitive decline in a middle-aged cohort. Diabetes Care 2006;29:2688–2693
20. Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA 2004;292:2237–2242
21. Aromaa A, Koskinen S. Health and functional capacity in Finland. Baseline results of the Health 2000 health examination survey [Internet], 2004. Helsinki, Finland, National Public Health Institute. Available from http://urn.fi/URN:NBN:fi-fe201204193452. Accessed 1 June 2016
22. Lundqvist A, Mäki-Opas T, Eds. Health 2011 survey – methods [Internet], 2016. Tampere, Finland, Finnish National Institute for Health and Welfare. Available from http://urn.fi/URN:ISBN:978-952-302-669-8. Accessed 1 September 2016
23. Heistaro S, Ed. Methodology report. Health 2000 survey [Internet], 2008. Helsinki, Finland, National Public Health Institute. Available from http://urn.fi/URN:NBN:fi-fe201204193320. Accessed 1 June 2016
24. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–419
25. Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology 1989;39:1159–1165
26. Hänninen T, Pulliainen V, Salo J, et al. ja Suomen muistitutkimusyksiköiden asiantuntijaryhmä. Kognitiiviset testit muistihäiriöiden ja alkavan dementian varhaisdiagnostiikassa: CERAD-tehtäväsarja. Suom Laakaril 1999;54:1967–1975
27. Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory-II. San Antonio, TX, Psychological Corporation, 1996
28. Jänis MT, Siggins S, Tahvanainen E, et al. Active and low-active forms of serum phospholipid transfer protein in a normal Finnish population sample. J Lipid Res 2004;45:2303–2309
29. McEvoy LK, Laughlin GA, Barrett-Connor E, et al. Metabolic syndrome and 16-year cognitive decline in community-dwelling older adults. Ann Epidemiol 2012;22:310–317
30. Gourovitch ML, Kirkby BS, Goldberg TE, et al. A comparison of rCBF patterns during letter and semantic fluency. Neuropsychology 2000;14:353–360
31. Shao Z, Janse E, Visser K, Meyer AS. What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. Front Psychol 2014;5:772
32. Baker LD, Cross DJ, Minoshima S, Belongia D, Watson GS, Craft S. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. Arch Neurol 2011;68:51–57
33. Willette AA, Bendlin BB, Starks EJ, et al. Association of insulin resistance with cerebral glucose uptake in late middle-aged adults at risk for Alzheimer disease. JAMA Neurol 2015;72:1013–1020
34. Langbaum JB, Chen K, Lee W, et al.; Alzheimer's Disease Neuroimaging Initiative. Categorical and correlational analyses of baseline fluorodeoxyglucose positron emission tomography images from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Neuroimage 2009;45:1107–1116
35. Willette AA, Xu G, Johnson SC, et al. Insulin resistance, brain atrophy, and cognitive performance in late middle-aged adults. Diabetes Care 2013;36:443–449
36. Segura B, Jurado MA, Freixenet N, Falcón C, Junqué C, Arboix A. Microstructural white matter changes in metabolic syndrome: a diffusion tensor imaging study. Neurology 2009;73:438–444
37. Makino T, Umegaki H, Suzuki Y, et al. Relationship between small cerebral white matter lesions and cognitive function in patients with Alzheimer's disease and amnestic mild cognitive impairment. Geriatr Gerontol Int 2014;14:819–826
38. Twamley EW, Ropacki SA, Bondi MW. Neuropsychological and neuroimaging changes in preclinical Alzheimer's disease. J Int Neuropsychol Soc 2006;12:707–735
39. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging 1997;18:351–357