Insulin resistance predicts cognitive decline – an 11-year follow-up of a nationally representative adult population sample

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Abstract

Objective: The aim of is this study was to examine if insulin resistance, assessed by the Homeostatic model assessment 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 high sensitive C-reactive protein (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*=3695, 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´s 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´s 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´s disease and cognitive impairment (2–4). A recent review concluded that individuals with diabetes typically perform 0.3–0.5 SD units lower on cognitive tests across all age groups, when compared to 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 (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´s 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´s 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 predicted lower cognitive test scores 20 years later (18). The Atherosclerosis Risk in

Communities (ARIC) cohort study (19) examined 7148 individuals at baseline for fasting insulin and HOMA-IR. Cognitive performance was evaluated three and nine years after baseline. The study concluded that both fasting insulin and HOMA-IR were associated with poorer cognition three years after baseline, and with a decline in cognitive test scores during the six-year follow-up for cognitive functioning.

The aim of this study was to assess if 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 3695 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 was 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. 8028 individuals aged 30 years or more were randomly selected from the Finnish population register from 80 health service districts throughout Finland using a two-stage stratified cluster sampling procedure. 84 % (*n*=6770) of the study population 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 3695 individuals who had attended the health examination proper in 2000 (*n*=6354) 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 less than 4 hours (*n*=226), who had insulin treatment or unknown diabetes medication (*n*=59), who had not completed the cognitive tests (*n*=127) or had missing HOMA-IR values (*n*=4) were excluded. 789 individuals had died or were lost to follow-up. A flow-chart of the study population is provided in Supplementary Figure S1.

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 years), and 55.5 percent 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, Hamburg, Germany), HDL-cholesterol by a HDL-C Plus test (Roche Diagnostics GmbH, Mannheim, Germany), triglycerides by a GPO PAP test (Olympus System Reagent, Germany), and glucose by a hexokinase test (Olympus System Reagent, Germany). 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 high sensitive 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 CERAD test battery (The Consortium to Establish a Registry for Alzheimer´s Disease) (22, 23, 25, 26). In the verbal fluency test, the participants were asked to list as many animals as possible during one minute. This categorical fluency test is considered to represent both language skills and executive

functions. In the word-list learning test, ten 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 seconds. In 2000, if the participant remembered all ten words after one round, the result was counted as full 30 points. In 2011, all three rounds were repeated for all participants, regardless of whether they remembered all ten words after the first round or not. The word-list learning test was used to assess verbal learning and memory. After five minutes 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 type 2 diabetes [DM2], *APOEε4* genotype, BMI, systolic blood pressure, level of HDL and non-HDL cholesterol and triglycerides; Model 3: all previous covariates and Beck´s 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 were addressed by a questionnaire. Excessive alcohol consumption was classified as > 24/16 doses of alcohol (12 g of alcohol per 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 minutes vigorously enough to cause sweating and breathlessness to a mild extent. The results were classified as: 1=a few times a year or more seldom, 2=2–3

times a month, 3=once a week, 4=2–3 times a week, 5=4–6 times a week, 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 3469 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 which is described elsewhere (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*=1451) and those included in this study (*n*=3695) were analyzed by Student´s *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 cut-off 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 analysis of covariance 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}, hs-CRP and 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 hours or longer (35.8 %, n=1321) 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 for '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 SAS JMP Pro 11.0 (SAS Institute, Cary, NC, USA).

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}-values for age and sex adjusted differences). 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 Figure 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 insulin predicted a lower verbal fluency score (HOMA-IR: p<0.0001, glucose: p=0.02, 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, nor with the change in cognitive performance from 2000 to 2011 (p-values: glucose p>0.22; HbA_{1c} p>044; hs-CRP p>0.15) in Model 2. (Table 3.)

The results for the additional analyses of Model 3 and the value of the covariates as determinants of cognitive performance are shown in Supplementary tables S1 and S2. 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 the Supplemental Figure S2. The results for the analyses of the individuals who had fasted for 10 hours or longer (n=1321) are provided in the Supplemental Table S3. 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.

Discussion

Here, we show that higher levels of insulin and IR are independent predictors of poorer verbal fluency performance and 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 were associated with lower cognitive *z*-scores (based on MMSE, Trail making A and Trail making B tests) after 20 years, but this association was not statistically significant after adjusting 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 to the ARIC study (19), the present 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 adjusting for age, sex and education. Additional adjustments for metabolic covariates did not change our results. However, the delayed recall test 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 ten nouns and to recall them after five 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 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 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 non-carriers of *APOEε4* (15). Studies on intranasal insulin and cognition suggest that possibly only non-carriers 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 non-carriers and carriers of *APOEε4*. The previous longitudinal studies (18, 19) did not assess sex or *APOEε4* differences, nor have sex or *APOEε4* differences 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.

In the present 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 (PET) studies with ^{18}F-fluorodeoxyglucose (FDG) 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´s disease (33). A similar pattern of FDG-PET reduction is seen in prodromal Alzheimer´s disease (34). Brain MRI studies show that IR is associated with lower temporal lobe grey 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 when compared to those without (36), and these changes are associated with poorer verbal fluency in patients with prodromal Alzheimer´s disease (37).

The symptoms of Alzheimer´s 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´s disease. This could be due to our relatively young study population. Late-onset Alzheimer´s 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 beta-amyloid, the

neuropathological hallmark of Alzheimer´s 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 non-alcoholic 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 antidiabetic drugs and thus, individuals with normal fasting glucose, but elevated post-prandial 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 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 five minutes. This test is designed to screen for Alzheimer's 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 hours, when compared to those who had fasted for longer than 10 hours. Thus, we are confident that including participants who had fasted for 4–10 hours did not give as false positive associations between HOMA-IR and cognitive performance. To confirm this, we provide additional analyses for the subpopulation who had fasted for 10 hours 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 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 life-style interventions, at people with IR in midlife could potentially reduce the incidence of cognitive decline later in life.

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LLE analyzed the data and wrote the manuscript. PP helped with the statistical analysis of the data. SA, RS, and AJ took part in designing the Health 2000 and 2011 surveys. LLE, JOR, PP, HL, SA, RS, MV and AJ planned this study. JOR, PP, HL, SA, RS, MV and AJ critically revised and edited the manuscript for important intellectual content. All authors approved the final version of the manuscript to be published. LLE 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.

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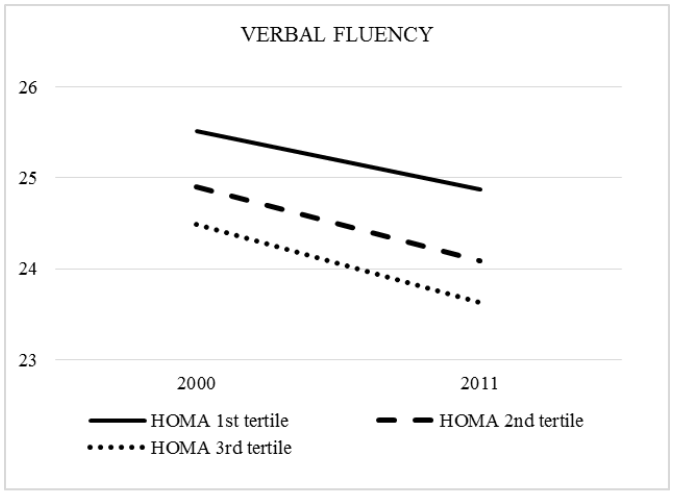
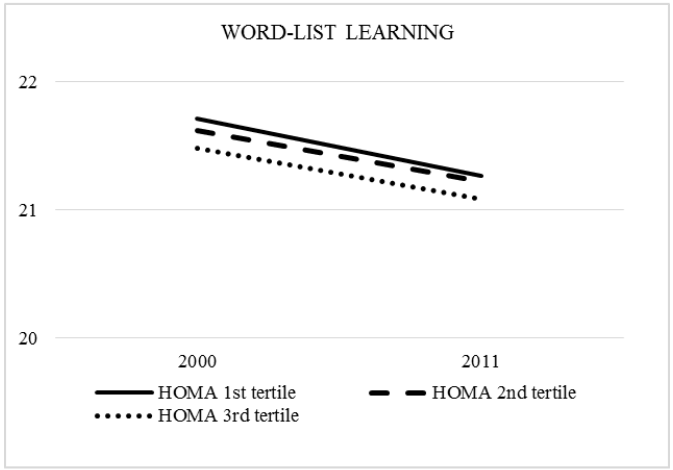
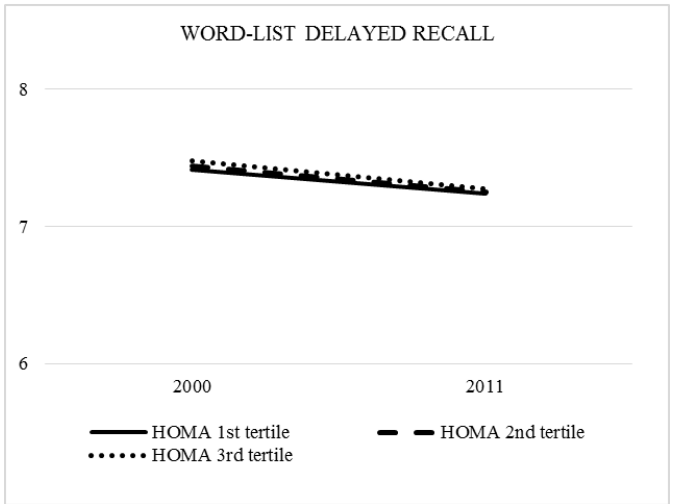
Figure 1 – Change in mean cognitive test scores from 2000 to 2011, adjusted for age, sex and years of education, according to the tertiles of HOMA-IR. *N*=3695.







Range for verbal fluency: 0–54; word-list learning: 0–30, word-list delayed recall: 0–10.

Table 1 – Characteristics of the study population according to the baseline tertiles of HOMA-IR.

Characteristics				
Tertiles of HOMA-IR	**1st**	**2nd**	**3rd**	p_{trend}
***n* (%)**	1246 (33.7)	1221 (33.0)	1228 (33.2)	
Female (*n*/%)	784 (62.9)	677 (55.4)	589 (48.0)	<0.0001
Age	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
Type 2 diabetes (n/%)	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 (*n*/%)*	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 per week (men/women) (*n*/%)	71 (5.7)	79 (6.5)	85 (6.9)	0.84
Current smoking (*n*/%)	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

The characteristics are presented as mean±SD, unless otherwise stated. P_{trend}-values for age and sex adjusted differences among the tertiles of HOMA. The cut-off 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 epsilon 4 alleles.

† The maximum score for word-list learning is 30 points.

‡ The maximum score for word-list delayed recall is 10 points.

Table 2 – Age, sex and education adjusted associations of baseline insulin resistance, fasting glucose and insulin, HbA1c, and high sensitive CRP values with cognitive test scores at follow-up and with change in cognitive test scores from 2000 to 2011. *N*=3695, except for the analysis of CRP and cognition, where *n*=3590.

Cognitive test score in 2011[†]						
	Verbal fluency		**Word-list learning**		**Word-list delayed recall**	
	β	**SE**	**β**	**SE**	**β**	**SE**
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 from 2000 to 2011[‡]						
	Verbal fluency		**Word-list learning**		**Word-list delayed recall**	
	β	**SE**	**β**	**SE**	**β**	**SE**
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

Estimates (β) and standard errors (SE) 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.

P-values: **P*<0.05, ***P*<0.01, ****P*<0.001.

Logarithmic transformation is used of HOMA-IR, fasting glucose and insulin, HbA_{1c}, and hs-CRP to achieve a normal distribution.

[†] Note that a negative estimate for cognitive test score in 2011 indicates a lower cognitive test score for those with higher levels of insulin resistance, 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 insulin resistance, fasting glucose etc.

Table 3 – Multivariate correlations of baseline insulin resistance, fasting glucose and insulin levels, HbA_{1c} and high sensitivity CRP values with cognitive test scores at follow-up and with change in cognitive test scores from 2000 to 2011. *N*=3695, except for the analysis of CRP and cognition, where *n*=3590.

Cognitive test score in 2011†						
	Verbal fluency		**Word-list learning**		**Word-list delayed recall**	
	β	**SE**	**β**	**SE**	**β**	**SE**
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 from 2000 to 2011‡						
	Verbal fluency		**Word-list learning**		**Word-list delayed recall**	
	β	**SE**	**β**	**SE**	**β**	**SE**
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
HbA1c	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

Estimates (β) and standard errors (SE) are derived from linear regression analysis and adjusted for age, sex, years of education, *APOEε4* status, Type 2 diabetes, 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 of HOMA-IR, fasting glucose and insulin, HbA_{1c}, CRP and triglycerides to achieve a normal distribution.

P-values: **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 insulin resistance, 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 insulin resistance, fasting glucose etc.

On-line only Supplemental Material

Supplemental Table S1 – Multivariate regression analysis of different cardiovascular and cognitive risk factors as independent predictors of cognitive performance after 11 years. *N*=3965.

Cognitive test score in 2011						
	Verbal fluency		**Word-list learning**		**Word-list delayed recall**	
	β	**SE**	**β**	**SE**	**β**	**SE**
HOMA-IR	-0.62*	0.25	-0.01	0.14	0.06	0.07
age	-0.14***	0.01	-0.14***	0.01	-0.07***	0.004
education	0.51***	0.04	0.32***	0.02	0.14***	0.01
sex	0.32	0.27	1.66***	0.15	0.66***	0.07
Type 2 DM	-0.74	0.83	-0.70	0.46	-0.27	0.22
systolic BP	-0.02**	0.01	-0.005	0.004	-0.004*	0.002
BMI	0.04	0.03	0.001	0.02	0.002	0.009
triglycerides	0.19	0.37	-0.16	0.20	-0.02	0.10
HDL-C	0.60	0.43	0.13	0.23	0.02	0.11
non-HDL-C	0.01	0.13	0.05	0.07	-0.006	0.04
BDI score	-0.22	0.14	-0.19*	0.08	-0.08*	0.04
smoking	-0.22	0.33	-0.62***	0.18	-0.24**	0.09
alcohol	0.97	0.50	-0.13	0.27	-0.14	0.13
APOEε4	-0.30	0.26	-0.16	0.14	-0.16*	0.07
Physical activity	0.13	0.09	0.03	0.05	0.006	0.02
Adjusted R^2	21.9		36.9		33.4	

Estimates (β) and standard errors (SE) are derived from linear regression analysis adjusted for all variables shown in the table. Logarithmic transformation is used of HOMA-IR, triglycerides and BDI (Beck´s depression inventory) score to achieve a normal distribution.

P-values: **P*<0.05, ***P*<0.01, ****P*<0.001.

Supplemental Table S2 – Multivariate regression analysis of different cardiovascular and cognitive risk factors as independent predictors of cognitive decline during 11 years. *N*=3965.

Change in cognition from 2000 to 2011						
	Verbal fluency		**Word-list learning**		**Word-list delayed recall**	
	β	**SE**	**β**	**SE**	**β**	**SE**
HOMA-IR	0.40	0.21	0.02	0.12	-0.002	0.06
age	0.13***	0.01	0.10***	0.01	0.05***	0.003
education	-0.19***	0.03	-0.17***	0.02	-0.08***	0.01
sex	-0.17	0.23	-0.84***	0.14	-0.36***	0.06
Type 2 DM	0.88	0.69	0.73	0.40	0.17	0.20
systolic BP	0.01	0.01	0.002	0.004	0.002	0.002
BMI	-0.05	0.03	-0.02	0.02	-0.01	0.01
triglycerides	-0.12	0.30	0.13	0.18	0.004	0.09
HDL-C	-0.24	0.35	-0.11	0.21	-0.01	0.10
non-HDL-C	0.07	0.11	-0.01	0.06	0.03	0.03
BDI score	0.11	0.12	0.07	0.07	0.03	0.03
smoking	0.14	0.27	0.48**	0.16	0.21**	0.08
alcohol	-0.49	0.42	0.24	0.24	0.16	0.12
APOEε4	0.41	0.22	0.04	0.13	0.10	0.06
Physical activity	-0.12	0.08	-0.03	0.04	-0.005	0.02
Baseline cognition	0.43***	0.02	0.49	0.02	0.47***	0.02
Adjusted R^2	24.9		24.2		22.6	

Estimates (β) and standard errors (SE) are derived from linear regression analysis adjusted for all variables shown in the table. Logarithmic transformation is used of HOMA-IR, triglycerides and BDI (Beck´s depression inventory) score to achieve a normal distribution.

P-values: **P*<0.05, ***P*<0.01, ****P*<0.001.

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 insulin resistance, fasting glucose etc.

Supplemental Table S3 – Multivariate correlations on baseline insulin resistance, fasting glucose and insulin levels, HbA_{1c} and high sensitivity CRP values with cognitive test scores at follow-up and with change in cognitive test scores from 2000 to 2011 of the subset of the study population (35.8 %) who had fasted for 10 hours or longer prior to blood sampling. *N*=1321, except for the analysis of CRP and cognition, where *n*=1159.

Cognitive test score in 2011†						
	Verbal fluency		**Word-list learning**		**Word-list delayed recall**	
	β	**SE**	**β**	**SE**	**β**	**SE**
HOMA-IR	-0.79*	0.40	-0.12	0.22	0.07	0.11
Glucose	-3.38	2.10	-0.87	1.18	-0.10	0.56
Insulin	-0.77	0.43	-0.10	0.24	0.08	0.11
HbA_{1c}	-7.62*	3.09	-1.56	1.74	-0.34	0.82
hs-CRP	-0.06	0.17	0.04	0.10	0.05	0.05

Change in cognition from 2000 to 2011‡						
	Verbal fluency		**Word-list learning**		**Word-list delayed recall**	
	β	**SE**	**β**	**SE**	**β**	**SE**
HOMA-IR	0.80*	0.33	0.13	0.20	0.03	0.09
Glucose	2.16	1.75	1.04	1.05	0.03	0.09
Insulin	0.83*	0.36	0.11	0.21	0.003	0.10
HbA1c	5.20*	2.58	1.25	1.55	0.39	0.73
hs-CRP	0.16	0.14	-0.02	0.09	-0.04	0.04

Estimates (β) and standard errors (SE) are derived from linear regression analysis and adjusted for age, sex, years of education, *APOEε4* status, Type 2 diabetes, 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

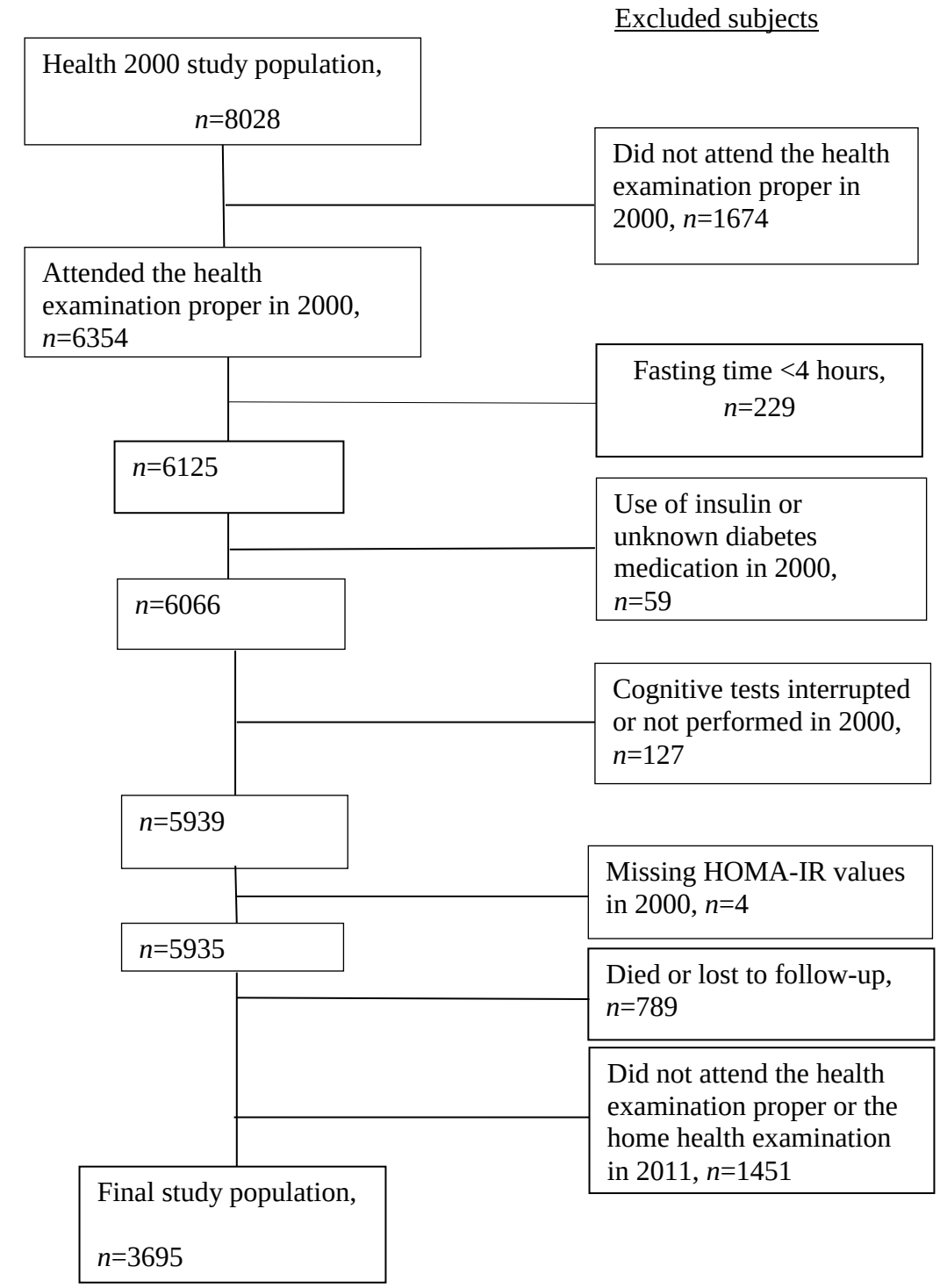
Logarithmic transformation is used of HOMA-IR, fasting glucose and insulin, HbA_{1c}, CRP and triglycerides to achieve a normal distribution.

P-values: **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 insulin resistance, 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 insulin resistance, fasting glucose etc.

Supplemental Figure S1 – The study selection process



Supplemental Figure S2 – Variation of fasting times and hour of blood sampling in the study population. *N*=3695.