SUPPLEMENTARY DATA

**Supplementary 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.

SUPPLEMENTARY DATA

**Supplementary 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.

SUPPLEMENTARY DATA

**Supplementary 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.

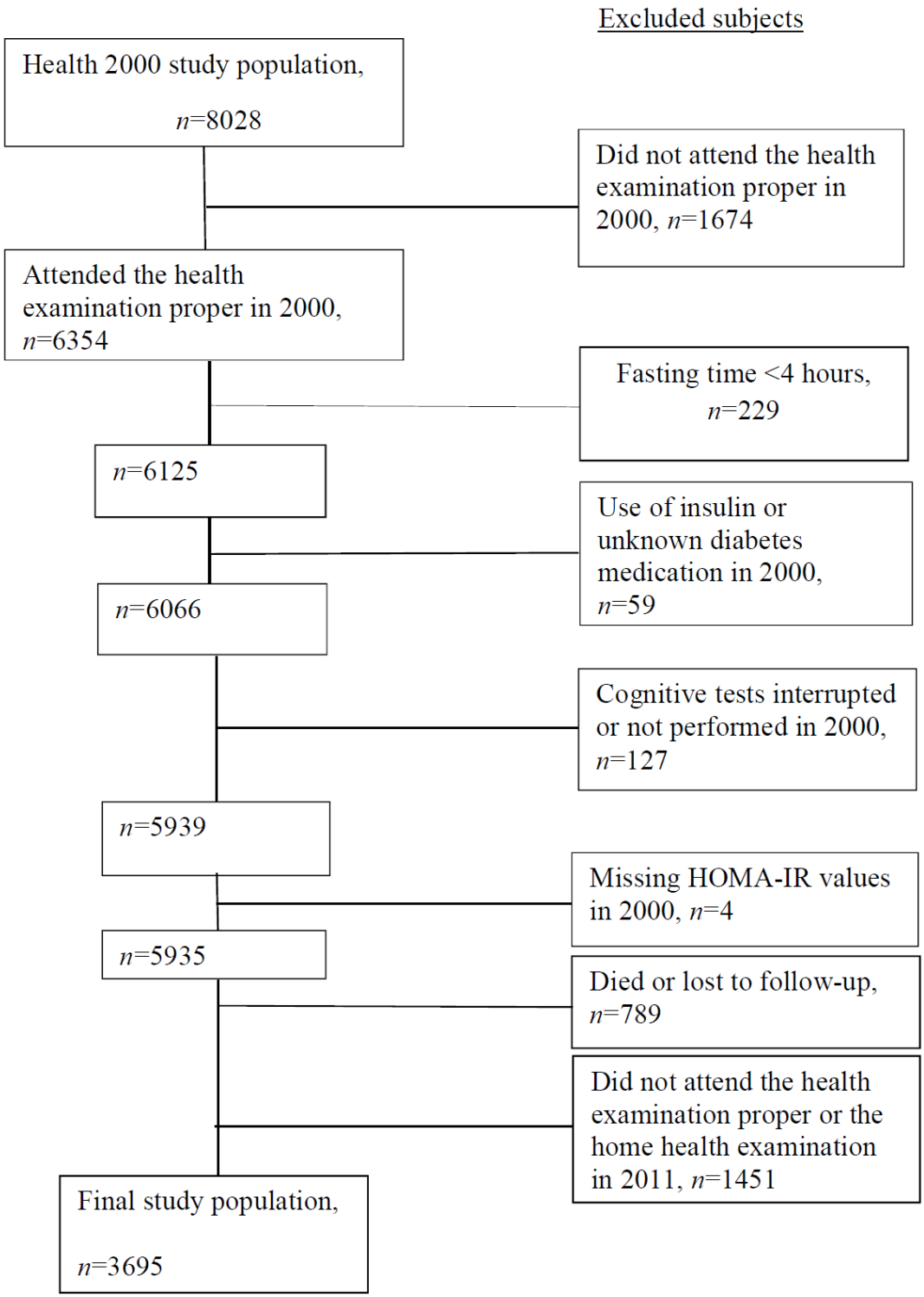
*P*-values: **P*<0.05, ***P*<0.01, ****P*<0.001.

[†] 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.

SUPPLEMENTARY DATA

**Supplementary Figure S1.** The study selection process



SUPPLEMENTARY DATA

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