**SUPPLEMENTAL MATERIAL**

for the manuscript

AGING, DIABETES, OBESITY, AND COGNITIVE DECLINE:
A POPULATION-BASED STUDY

## Supplementary Text 1. Methods: Laboratory measures

Coefficients of variation (CVs) for laboratory assays were <3% unless otherwise noted. Serum glucose was determined enzymatically using reagents from Beckman-Coulter (Center Valley, PA), and insulin concentration was measured by radioimmunoassay (RIA) (Linco Research, St. Charles, MO). The intra- and inter-assay CVs for insulin were 4.8% and 10.5%, respectively. Insulin resistance was assessed by the homeostasis model assessment of insulin resistance (HOMA-IR) and was calculated as fasting insulin concentration (U/mL) x fasting glucose concentration (mmol/L)/22.5. HbA1c was measured in whole blood (EDTA) on an AU400 Chemistry Analyzer (Olympus Inc., Melville, NY) using reagents obtained from Pointe Scientific, Inc. (Canton, MI). C-reactive protein was measured using reagents from Beckman-Coulter (Brea, CA) and analyzed on the AU400.

Serum levels of total adiponectin were determined using RIA procedures developed by EMD Millipore (St Charles, MO). The intra- and inter-assay CVs were 8.2% and 11.8% for adiponectin. Resistin (EMD Millipore; St Charles, MO) and glucagon-like peptide-1 (GLP-1) (ALPCO; Salem, NH) were measured using ELISA procedures. The intra- and inter-assay CVs were 5.0% and 10.0% for resistin and 4.2% and 14.3% for GLP-1, respectively.

**Supplementary Table S1.**

**Unadjusted joint associations of metabolic indices with global cognitive decline slope, overall and stratified by WHR group**

| | Overall sample (n = 440) | | | Low WHR (n = 189) | | | High WHR (n = 189) | | |
|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **Coef** | **SE** | **p** | **Coef** | **SE** | **p** | **Coef** | **SE** | **p** |
| resistin | 0.004 | 0.050 | 0.932 | 0.000 | 0.077 | 0.999 | -0.023 | 0.050 | 0.643 |
| adiponectin | -0.137 | 0.051 | 0.008 | -0.096 | 0.077 | 0.213 | -0.067 | 0.055 | 0.224 |
| GLP-1 | -0.049 | 0.049 | 0.314 | -0.092 | 0.068 | 0.180 | -0.002 | 0.053 | 0.976 |
| HbA1c | -0.054 | 0.050 | 0.287 | -0.058 | 0.091 | 0.524 | -0.105 | 0.049 | 0.032 |
| | | | | | | | | | |

Note: Participants with missing data for any metabolic indices or covariates (see Table 1) were excluded. Laboratory assay variables (resistin, adiponectin, GLP-1, HbA1c) were first natural log-transformed; then these and global cognitive decline slope were standardized to have mean zero and unit standard deviation.

Abbreviations: Coef: coefficient, SE: standard error, HbA1c: hemoglobin A1c, GLP-1: glucagon-like peptide-1.

**Supplementary Table S2A.**

**Associations with global cognitive decline slope:**
**Low WHR group (n = 208)**

| | Unadjusted | | | | Adjusted for age, sex, education, *APOE*4*, mCES-D score, WHR, and SBP | | |
|---|---|---|---|---|---|---|---|
| **Variable** | **Coef** | **95% CI** | **p** | | **Coef** | **95% CI** | **p** |
| age | -0.371 | (-0.492, -0.249) | <0.001 | | n/a | | |
| female sex | 0.074 | (-0.205, 0.354) | 0.600 | | | | |
| education >HS | 0.349 | (0.090, 0.607) | 0.009 | | | | |
| *APOE*4* carriage | -0.482 | (-0.789, -0.175) | 0.002 | | | | |
| mCES-D score | -0.085 | (-0.266, 0.097) | 0.359 | | | | |
| BMI | 0.080 | (-0.047, 0.208) | 0.217 | | | | |
| WHR | -0.090 | (-0.263, 0.084) | 0.309 | | | | |
| SBP | -0.063 | (-0.189, 0.063) | 0.324 | | | | |
| CRP | 0.014 | (-0.121, 0.148) | 0.840 | | | | |
| glucose | -0.017 | (-0.166, 0.132) | 0.821 | | -0.033 | (-0.173, 0.106) | 0.636 |
| HbA1c | -0.050 | (-0.211, 0.111) | 0.539 | | -0.070 | (-0.222, 0.082) | 0.366 |
| insulin | 0.097 | (-0.040, 0.235) | 0.164 | | 0.053 | (-0.077, 0.183) | 0.424 |
| HOMA-IR | 0.082 | (-0.060, 0.225) | 0.257 | | 0.038 | (-0.096, 0.173) | 0.574 |
| resistin | 0.019 | (-0.118, 0.156) | 0.784 | | 0.022 | (-0.107, 0.151) | 0.740 |
| adiponectin | -0.090 | (-0.225, 0.046) | 0.194 | | -0.045 | (-0.179, 0.089) | 0.510 |
| GLP-1 | -0.101 | (-0.235, 0.032) | 0.135 | | -0.062 | (-0.186, 0.062) | 0.328 |

Note: Laboratory assay variables (CRP, glucose, HbA1c, insulin, HOMA-IR, resistin, adiponectin, GLP-1) were first natural log-transformed; then these and other quantitative variables (age, mCES-D score, BMI, WHR, SBP, global cognitive decline slope) were standardized (using the entire sample of n=478) to have mean zero and unit standard deviation.

Abbreviations: Coef: coefficient, CI: confidence interval, HS: high school, mCES-D: Modified Center for Epidemiology Depression Scale, BMI: body mass index, WHR: waist-hip ratio, SBP: systolic blood pressure, CRP: C-reactive protein, HbA1c: hemoglobin A1c, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, GLP-1: glucagon-like peptide-1.

**Supplementary Table S2B.**

**Associations with global cognitive decline slope:**
**High WHR group (n = 203)**

| | Unadjusted | | | | Adjusted for age, sex, education, *APOE*4*, mCES-D score, WHR, and SBP | | |
|---|---|---|---|---|---|---|---|
| **Variable** | **Coef** | **95% CI** | **p** | | **Coef** | **95% CI** | **p** |
| age | -0.186 | (-0.282, -0.091) | <0.001 | | n/a | | |
| female sex | 0.044 | (-0.160, 0.248) | 0.674 | | | | |
| education >HS | 0.069 | (-0.124, 0.261) | 0.482 | | | | |
| *APOE*4* carriage | 0.216 | (-0.075, 0.508) | 0.145 | | | | |
| mCES-D score | -0.044 | (-0.184, 0.096) | 0.539 | | | | |
| BMI | 0.041 | (-0.061, 0.143) | 0.428 | | | | |
| WHR | 0.000 | (-0.119, 0.118) | 0.995 | | | | |
| SBP | -0.032 | (-0.136, 0.072) | 0.547 | | | | |
| CRP | -0.011 | (-0.108, 0.086) | 0.824 | | | | |
| glucose | -0.098 | (-0.194, -0.003) | 0.044 | | -0.102 | (-0.202, -0.001) | 0.047 |
| HbA1c | -0.094 | (-0.183, -0.004) | 0.042 | | -0.130 | (-0.226, -0.035) | 0.008 |
| insulin | 0.004 | (-0.092, 0.100) | 0.938 | | -0.055 | (-0.161, 0.050) | 0.303 |
| HOMA-IR | -0.030 | (-0.127, 0.066) | 0.536 | | -0.083 | (-0.187, 0.021) | 0.118 |
| resistin | -0.046 | (-0.141, 0.050) | 0.347 | | -0.034 | (-0.133, 0.065) | 0.499 |
| adiponectin | -0.011 | (-0.108, 0.085) | 0.816 | | 0.016 | (-0.085, 0.118) | 0.751 |
| GLP-1 | 0.004 | (-0.100, 0.109) | 0.934 | | 0.000 | (-0.109, 0.110) | 0.994 |

Note: Laboratory assay variables (CRP, glucose, HbA1c, insulin, HOMA-IR, resistin, adiponectin, GLP-1) were first natural log-transformed; then these and other quantitative variables (age, mCES-D score, BMI, WHR, SBP, global cognitive decline slope) were standardized (using the entire sample of n=478) to have mean zero and unit standard deviation.

Abbreviations: Coef: coefficient, CI: confidence interval, HS: high school, mCES-D: Modified Center for Epidemiology Depression Scale, BMI: body mass index, WHR: waist-hip ratio, SBP: systolic blood pressure, CRP: C-reactive protein, HbA1c: hemoglobin A1c, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, GLP-1: glucagon-like peptide-1.

**Supplementary Text 2.**

**Multiple imputation and inverse probability weighting methods**

We used inverse probability weighting (IPW) to generalize results to the entire MYHAT cohort of 1982 participants. With logistic regression, we modeled the probability of being in the subsample of n = 478 that provided the fasting blood samples, using the baseline variables listed in Supplementary Table S3 as predictors. Since some participants had missing data for these baseline variables, we first performed multiple imputation using the R package mice[1]. The imputation model included all variables in Supplementary Table S3, as well as an indicator variable encoding which participants were in the fasting blood subsample. Number of multiple imputations was set to 5, and the predictive mean matching method was used.

[1] Stef van Buuren, Karin Groothuis-Oudshoorn (2011). mice: Multivariate Imputation by Chained Equations in R. Journal of Statistical Software, 45(3), 1-67. URL https://www.jstatsoft.org/v45/i03/).

**Supplementary Table S3.**

**Baseline variables used in Inverse Probability Weighting (IPW) logistic regression model (n = 1982)**

| Variable | Number missing n (%) |
|---|---|
| age at baseline | 0 (0) |
| sex | 0 (0) |
| race (white vs nonwhite) | 0 (0) |
| education (high school (HS) or less vs more than HS) | 0 (0) |
| systolic blood pressure (SBP) | 13 (0.7) |
| diastolic blood pressure (DBP) | 15 (0.8) |
| waist:hip ratio (WHR) | 119 (6.0) |
| diabetes diagnosis (DM) | 3 (0.2) |

The 5 imputed datasets were used to fit the logistic regression model of being in the fasting blood sample group (using the pool() function in mice). Results are shown in Supplementary Table S4.

**Supplementary Table S4.**

**Estimates for logistic regression model of being in the fasting blood sample group (n = 1982)**

| Coefficient | Estimate | SE | statistic | df | p-value |
|---|---|---|---|---|---|
| intercept | 4.660 | 1.132 | 4.115 | 922.487 | <0.001 |
| age | -0.075 | 0.008 | -9.329 | 1969.242 | <0.001 |
| female sex | 0.481 | 0.142 | 3.376 | 1219.746 | 0.001 |
| education > HS | 0.291 | 0.112 | 2.610 | 1970.796 | 0.009 |
| nonwhite race | -0.759 | 0.286 | -2.653 | 1970.671 | 0.008 |
| SBP | -0.006 | 0.004 | -1.540 | 1932.345 | 0.124 |
| DBP | -0.004 | 0.007 | -0.622 | 1836.627 | 0.534 |
| WHR | 0.801 | 0.785 | 1.020 | 337.424 | 0.308 |
| DM | -0.085 | 0.135 | -0.629 | 1965.614 | 0.530 |

Note: Model was estimated using data from all 1982 MYHAT participants.

Predictions on the logit scale for each individual in the lab sample were generated using the 5 imputed datasets and their respective estimated logistic regression coefficients. Then these predicted values were averaged for each individual and transformed to a probability using the inverse logit function. Inverse probability weights were formed by calculating the reciprocal of the probabilities.

In order to fit the inverse probability weighted fully-adjusted multivariable regression models assessing the joint associations of metabolic predictors with cognitive decline slope to the 478 participants in the fasting blood subsample (Supplementary Table S6), we carried out multiple imputation a second time to fill in missing data in the predictor variables (Supplementary Table S5). In addition to all variables listed in Supplementary Table S5, global cognitive decline slope and inverse probability weights were also included in the imputation model. Number of multiple imputations was set to 5, and the predictive mean matching method was used.

**Supplementary Table S5.**

**Variables used in IPW multivariable regression models assessing the joint associations of metabolic predictors with cognitive decline slope (n = 478)**

| Variable | Number missing n (%) |
|---|---|
| age at time of fasting blood draw | 0 (0) |
| sex | 0 (0) |
| education (high school (HS) or less vs more than HS) | 0 (0) |
| *APOE*4* carriage | 22 (4.6) |
| mCES-D score at assessment closest to blood draw date | 1 (0.2) |
| WHR at assessment closest to blood draw date | 67 (14.0) |
| SBP at assessment closest to blood draw date | 13 (2.7) |
| resistin | 3 (0.6) |
| adiponectin | 1 (0.2) |
| GLP-1 | 37 (7.7) |
| HbA1c | 11 (2.3) |

For WHR-stratified models, we averaged WHR from the 5 imputed datasets and used sex-specific medians (median WHR = 0.97 for men and 0.86 for women) to assign participants to the low (n = 244) or high (n = 234) WHR groups.

For the overall sample of 478 and the WHR-stratified subgroups, the 5 imputed datasets were used to fit the multiple regression models (using the pool() function in mice). Results are shown in Supplementary Table S6.

**Supplementary Table S6.**

**Joint associations of metabolic predictors with cognitive decline slope, overall and stratified by WHR group, with imputation for missing data and inverse probability weighting to generalize to the entire MYHAT cohort**

| | Overall sample (n = 478) | | | | Low WHR (n = 244) | | | | High WHR (n = 234) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **Coef** | **SE** | **p** | | **Coef** | **SE** | **p** | | **Coef** | **SE** | **p** |
| resistin | 0.046 | 0.051 | 0.367 | | 0.068 | 0.084 | 0.415 | | 0.004 | 0.050 | 0.930 |
| adiponectin | -0.040 | 0.052 | 0.444 | | -0.070 | 0.089 | 0.435 | | 0.002 | 0.049 | 0.968 |
| GLP-1 | -0.027 | 0.049 | 0.582 | | -0.028 | 0.080 | 0.726 | | 0.008 | 0.052 | 0.876 |
| HbA1c | -0.060 | 0.052 | 0.249 | | -0.039 | 0.094 | 0.677 | | -0.095 | 0.048 | 0.048 |

Note: Models are adjusted for age, sex, education, *APOE*4* carriage, mCES-D score, WHR, and SBP

Abbreviations: Coef: coefficient, SE: standard error, HbA1c: hemoglobin A1c, GLP-1: glucagon-like peptide-1.

## Supplementary Table S7.

**Interaction between WHR group (high vs. low) and predictors with cognitive decline**

| | Unadjusted | | | | Adjusted for age, sex, education, *APOE*4*, mCES-D score, and SBP | | | |
|---|---|---|---|---|---|---|---|---|
| **Variable** | **Coef** | **95% CI** | **P** | **n** | **Coef** | **95% CI** | **p** | **n** |
| glucose | -0.081 | (-0.256, 0.093) | 0.360 | 410 | -0.057 | (-0.226, 0.112) | 0.510 | 389 |
| HbA1c | -0.043 | (-0.221, 0.134) | 0.630 | 400 | -0.046 | (-0.222, 0.130) | 0.606 | 379 |
| insulin | -0.094 | (-0.260, 0.073) | 0.269 | 402 | -0.120 | (-0.287, 0.047) | 0.159 | 381 |
| HOMA-IR | -0.113 | (-0.283, 0.058) | 0.194 | 402 | -0.127 | (-0.296, 0.043) | 0.142 | 381 |
| resistin | -0.065 | (-0.231, 0.101) | 0.444 | 408 | -0.055 | (-0.218, 0.108) | 0.506 | 387 |
| adiponectin | 0.078 | (-0.087, 0.244) | 0.353 | 410 | 0.079 | (-0.082, 0.240) | 0.334 | 389 |
| GLP-1 | 0.106 | (-0.065, 0.277) | 0.224 | 379 | 0.068 | (-0.100, 0.236) | 0.428 | 360 |

Note: Laboratory assay variables (CRP, glucose, HbA1c, insulin, HOMA-IR, resistin, adiponectin, GLP-1) were first natural log-transformed; then these and other quantitative variables (age, mCES-D score, SBP, global cognitive decline slope) were standardized (using the entire sample of n=478) to have mean zero and unit standard deviation. Reference level for WHR group is low WHR, so coefficients represent the additional effect of the predictor for those in the high WHR group.

Abbreviations: Coef: coefficient, CI: confidence interval, mCES-D: Modified Center for Epidemiology Depression Scale, WHR: waist-hip ratio, SBP: systolic blood pressure, HbA1c: hemoglobin A1c, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, GLP-1: glucagon-like peptide-1.

**Supplementary Figure S1. CART cross-validation results**