Association of Metabolic Dysregulation With Volumetric Brain Magnetic Resonance Imaging and Cognitive Markers of Subclinical Brain Aging in Middle-Aged Adults

The Framingham Offspring Study

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OBJECTIVE—Diabetic and prediabtic states, including insulin resistance, fasting hyperglycemia, and hyperinsulinemia, are associated with metabolic dysregulation. These components have been individually linked to increased risks of cognitive decline and Alzheimer's disease. We aimed to comprehensively relate all of the components of metabolic dysregulation to cognitive function and brain magnetic resonance imaging (MRI) in middle-aged adults.

RESEARCH DESIGN AND METHODS—Framingham Offspring participants who underwent volumetric MRI and detailed cognitive testing and were free of clinical stroke and dementia during examination 7 (1998–2001) constituted our study sample ($n = 2,439$; 1,311 women; age 61 ± 9 years). We related diabetes, homeostasis model assessment of insulin resistance (HOMA-IR), fasting insulin, and glycohemoglobin levels to cross-sectional MRI measures of total cerebral brain volume (TCBV) and hippocampal volume and to verbal and visuospatial memory and executive function. We serially adjusted for age, sex, and education alone (model A), additionally for other vascular risk factors (model B), and finally, with the inclusion of apolipoprotein E-ε4, plasma homocysteine, C-reactive protein, and interleukin-6 (model C).

RESULTS—We observed an inverse association between all indices of metabolic dysfunction and TCBV in all models ($P < 0.030$). The observed difference in TCBV between participants with and without diabetes was equivalent to approximately 6 years of chronologic aging. Diabetes and elevated glycohemoglobin, HOMA-IR, and fasting insulin were related to poorer executive function scores ($P < 0.038$), whereas only HOMA-IR and fasting insulin were inversely related to visuospatial memory ($P < 0.007$).

CONCLUSIONS—Metabolic dysregulation, especially insulin resistance, was associated with lower brain volumes and executive function in a large, relatively healthy, middle-aged, community-based cohort.

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Alzheimer's disease (AD) afflicts as many as 50% of people aged >85 years and is associated with significant health care and societal costs. With the rapid aging of the U.S. population, it is expected that, by the year 2050, the prevalence of AD will increase from the currently estimated 5 million to >11 million afflicted persons aged >65 years, unless effective prevention or treatment is found (1).

Because late-onset AD is a slowly progressive disease that affects people aged >65 years, some have argued that merely delaying its onset by several years would significantly decrease individual risk and the population burden of disease. The Framingham study estimated that a 5-year delay in the onset of AD would be equivalent to a reduction of lifetime risk by half, from 14 to 7% (2). Thus, although various disease-modifying agents are being investigated, a parallel search for modifiable risk factors that could delay the onset of AD would be a worthwhile endeavor.

Diabetes is a potentially modifiable risk factor that has been related in several population-based studies of older individuals to the risk of incident dementia and AD (3). However, the argument that it represents a causal factor would be strengthened if similar associations were demonstrable relating the entire spectrum of prediabetic and diabetic states with subclinical measures of subsequent AD risk in younger persons aged <65 years who are, as yet, free of clinical disease. Furthermore, examining insulin resistance (IR), hyperinsulinemia, and hyperglycemia, the three interwoven components of the diabetic and prediabetic states, could help clarify the relative importance of these elements in determining the risk of AD. To examine the possible association of midlife diabetic and prediabetic states with cognitive and brain magnetic resonance imaging (MRI) markers of

subsequent dementia and AD, we related diabetes, glycohemoglobin A_{1c} (HbA_{1c}), fasting serum insulin levels, and IR in the middle-aged, cognitively intact Framingham Offspring study population to measures of structural and functional brain aging.

RESEARCH DESIGN AND METHODS

Study population
The Framingham study's original cohort has been evaluated biennially since 1948 and screened prospectively for incident dementia since 1978. A sample drawn from the offspring (and spouses of the offspring) of the original participants (Framingham Offspring cohort) was enrolled in 1970–1972 and has been examined eight times during the past 37 years, approximately once every 4 years. Participants who attended offspring examination 7 (between 1998 and 2001) were invited to participate in brain MRI studies and a neuropsychologic assessment. The study population comprised 2,439 individuals (1,311 women), with a mean age of 62 ± 9 years who agreed to participate and were also free of clinical stroke, dementia, or other neurologic conditions such as a brain tumor that could alter MRI and cognitive performance.

Brain MRI study
Image acquisition. The methods followed for brain MRI have been described previously (4). In brief, subjects underwent neuroimaging on a Siemens Magnetom (Munich, Germany) 1-T or 1.5-T field strength machine using a double spin-echo coronal imaging sequence of 4-mm contiguous slices from nasion to occiput. Imaging data were transferred to a central location for processing and analyzed by operators who were blinded to the subject's identity, age, sex, exposure to stroke risk factors, and cognitive performance on neuropsychologic testing. Previously reported semiautomated analyses of pixel distributions based on mathematic modeling of MRI pixel intensity histograms for cerebrospinal fluid and white and gray brain matter were used to determine the optimal threshold of pixel intensity to best distinguish cerebrospinal fluid from brain matter (5). All analyses were performed using QUANTA 6.2, a custom-designed image analysis package, operating on an Ultra 5 workstation (Sun Microsystems, Santa Clara, CA).
Assessment of brain MRI measures. MRI measures assessed consisted of total

cerebral brain volume (TCBV), hippocampal volume (HV), and white matter hyperintensity volume. Brain volume was determined by manual outlining in coronal images of the intracranial vault above the tentorium to determine the total cranial volume as a measure of head size. Once the skull and other nonbrain tissues were removed from the image, mathematic modeling was performed to determine total parenchymal brain volume above the tentorium (cerebral). HV was estimated using operator-defined, manually traced boundaries. Because the medial wall of the temporal horn consists of the hippocampus, atrophy of the hippocampus will result in enlargement of the temporal horn volume. White matter hyperintensity volume was measured according to previously published methods (6), expressed as a proportion of the total intracranial volume, and log-transformed to normalize its distribution. We estimated the equivalency between the mean change in TCBV associated with chronologic aging and that associated with the presence of diabetes by dividing the regression coefficient for diabetes by the regression coefficient for age (7).

Cognitive evaluation
A comprehensive, well standardized, neuropsychologic test battery was administered to all participants and has been described previously (8). The neuropsychologic evaluation consisted of a 40-min test battery that included tests of verbal memory and abstract reasoning that were previously associated with an increased risk of developing AD in the original cohort (9). Also included were tests of frontal executive function that are sensitive in detecting cognitive impairment in persons with diabetes (10). The cognitive domains that we studied were verbal memory (Wechsler Memory Scale–Logical Memory), visual memory (Wechsler Memory Scale–Visual Reproduction), and executive function (Trail Making Tests A & B). The MRI and neuropsychologic testing were performed on the same day for most participants and, in all cases, by evaluators who were blind to the diabetes, HbA_{1c}, fasting insulin, and IR data.

Diabetic and prediabetic states
Fasting glucose, HbA_{1c}, and fasting insulin levels were estimated from blood samples drawn at the Offspring examination 7 after participants had fasted overnight for at least 8 h. Diabetes was determined by use of insulin or other diabetes medication or a fasting glucose concentration

≥126 mg/dL. Fasting glucose concentrations were measured in fresh specimens with a hexokinase reagent kit (A-gent Glucose Test; Abbott Laboratories, Inc., South Pasadena, CA); the intra-assay coefficient of variation (CV) was <3%.

HbA_{1c} was measured using high-performance liquid chromatography (HPLC) assays standardized to Diabetes Control and Complications Trial values by the National Glycohemoglobin Standardization Program (11). The HbA_{1c} assays have intra- and interassay CVs <3%. Assay drift in the HPLC method used in Framingham Offspring Study is prevented by the use of long-term stored reference samples.

Plasma insulin concentrations were measured using the Coat-A-Count ^{125}I–labeled radioimmunoassay (Diagnostic Products, Los Angeles, CA); this assay has a cross-reactivity with proinsulin at the midcurve of 40%; the intra- and interassay CVs were 5 to 10%.

IR was estimated using a standardized measure of insulin sensitivity: the homeostasis model assessment of IR (HOMA-IR). The HOMA-IR (mmol/L × μU/mL) formula is defined as fasting insulin (μU/mL) times fasting glucose (mmol/L)/22.5.

Statistical analyses
We related presence or absence of diabetes and levels of HbA_{1c}, fasting insulin, and HOMA-IR to the MRI and cognitive outcomes listed in RESEARCH DESIGN AND METHODS. Data for participants receiving insulin treatment were excluded in the analyses involving insulin levels. We constructed linear regression models adjusted for covariates previously shown to affect brain volume and cognitive function in the Framingham cohort including:

- Model A: age, sex, education (for cognitive measures) only;
- Model B: the above with inclusion of nondiabetes cardiovascular risk factors at examination 7: systolic blood pressure, smoking, prevalent cardiovascular disease;
- Model C: additional adjustment for factors previously associated with risk of dementia in the Framingham original cohort, namely, apolipoprotein E (apoE)-ε4 genotype, and serum homocysteine levels, C-reactive protein (CRP), and interleukin-6 (IL-6) at examination 7.

We also adjusted for the time interval between examination 7 and MRI or cognitive testing in all analyses.

In secondary analyses, we excluded subjects with clinical diabetes and looked at the effect of the duration of diabetes on the relationship between diabetes and MRI measures by stratifying the subjects into three categories: *1*) nondiabetic as determined at Offspring examination 7 and at the earlier examination 5 (1991–1995) using the same criteria described earlier (referent); *2*) nondiabetic at examination 5 and diabetic at examination 7; *3*) diabetic at examinations 5 and 7.

RESULTS—The characteristics of the study population at examination 7 (1998–2001) are presented in Table 1. We observed an inverse association between all indices (diabetes, HbA_{1c}, HOMA-IR, fasting insulin level) of metabolic dysfunction evaluated at examination 7 and TCBV in all models (Table 2). Adjustment for covariates (models B and C; Table 2) did not appreciably alter these associations. The observed difference in TCBV of 1.24% between participants with and without diabetes was equivalent to the effect of approximately 6 years of chronologic aging. Of note, the association of IR and hyperinsulinemia with TCBV remained significant when the analysis was restricted to subjects who had not yet developed clinical diabetes (Table 3). In contrast, none of the metabolic indices were associated with HV.

Considering the cognitive measures, we found that examination 7 diabetes and HbA_{1c}, HOMA-IR and fasting insulin were each related to poorer executive function. This inverse relationship between executive function and HbA_{1c}, HOMA-IR, and fasting insulin persisted even after adjustment for covariates (Table 2) and the exclusion of participants with clinical diabetes from the analysis (Table 3). HOMA-IR and fasting insulin, but not clinical diabetes or HbA_{1c}, were inversely related to visuospatial memory (Table 2). These associations remained significant after adjustment for covariates (models B and C; Table 2).

A surprising finding was an apparent association between diabetes and better performance in verbal memory tasks, although this effect was attenuated after adjustment for all covariates. There was an interaction with insulin levels, so that this apparent beneficial effect was only seen in subjects who also had elevated plasma insulin levels and was not seen in the subsample of participants who were not receiving insulin.

Stratifying participants according to their diabetes status at examination cycles 5 and 7 revealed that the cross-sectional association between diabetes and TCBV was present only in those participants who had diabetes at both examination cycles (diabetes duration ≥ 4 years; $P < 0.001$) and not in those who developed diabetes only at examination 7 ($P = 0.113$). No such differential patterns according to length of time with clinical diabetes were observed for the other indices of metabolic dysfunction and measures of brain aging (Supplementary Table 1A).

CONCLUSIONS—In the middle-aged community sample of stroke- and dementia-free Framingham Offspring participants, we observed that clinical diabetes and various metabolic indices associated with diabetic and prediabetic states were associated with the subclinical changes of smaller brain volumes and poorer cognitive performance, especially on tests of executive function and visual memory. These findings were observed even among participants who did not have clinical diabetes, and the most consistent association was with IR, which is important in the evolution of clinical type 2 diabetes.

The relationship between diabetes and cognition was reported >85 years ago, when Miles and Root (12) observed that patients with diabetes did not perform as well as control subjects in tests of memory, mental arithmetic, and psychomotor efficiency. Multiple studies since then have shown an adverse effect of baseline diabetes status on concomitant cognitive function and cognitive decline on follow-up. Diabetes has been associated with cognitive changes that affect learning and memory, mental speed, and mental flexibility (13), and population-based studies have also related diabetes to the risk of incident dementia and AD (3). The Memory in Diabetes (MIND) substudy of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed an inverse relationship between glycohemoglobin levels and performance on cognitive tests; whereas, fasting plasma glucose, a measure with greater day-to-day variability, was not associated with test performance (14). The cognitive impairment associated with diabetes may begin even before the appearance of clinical disease; compared with women with normal glucose, women with impaired fasting glucose levels had worse baseline cognitive scores and an almost twofold risk of developing cognitive impairment over a 4-year period (15).

The pathophysiologic mechanisms underlying the purported relationship between diabetes, prediabetes, and dementia, thus far, remains unclear but could involve direct effects on AD neuropathology or indirectly via diabetic vasculopathy, leading to cerebrovascular brain injury. Hyperglycemia can be harmful by promoting oxidative stress, the formation of toxic advanced glycation end products, and induction for receptors for advanced glycation end products. A direct effect of insulin on cognition is supported by observations that insulin readily crosses the

Table 1—*Characteristics of subjects at examination cycle 7 (1998–2001)*

Characteristic	Women	Men
n	1,311	1,128
Age (years)	61 ± 9	61 ± 9
High-school degree	97.3	95.5
Current cigarette smoking	12.8	11.9
Systolic blood pressure	125 ± 20	127 ± 17
ApoE4	22.8	22.6
Plasma homocysteine (μmol/L)	7.7 ± 2.5	9.1 ± 4.1
CRP (mg/L)	4.5 ± 5.4	3.7 ± 6.8
IL-6 (pg/mL)	3.8 ± 4.5	4.0 ± 5.8
Diabetes	7.2	13.3
Fasting glucose (mg/dL)	99 ± 22	108 ± 29
HbA_{1c} (%)	5.6 ± 0.8	5.7 ± 1.1
HOMA-IR (mmol/L × μU/mL)	3.9 ± 3.7	5.0 ± 4.2
Fasting insulin (μU/mL)	15.6 ± 12.5	18.7 ± 14.2
Time interval (years)		
Examination 7 to MRI	0.8 ± 0.8	0.8 ± 0.9
Examination 7 to cognitive test	0.8 ± 0.9	0.8 ± 0.9

Continuous data are presented as mean ± SD; categoric data as percentages.

Table 2—*Association between metabolic dysregulation measures and markers of brain aging*

Variable	Model	HOMA-IR (mmol/L × μU/mL)	P	Fasting insulin (μU/mL)	P	HbA$_{1c}$ (%)	P	Diabetes	P
TCBV	A	**−0.07 ± 0.02**	**<0.001**	**−0.02 ± 0.01**	**<0.001**	**−0.31 ± 0.07**	**<0.001**	**−1.24 ± 0.20**	**<0.001**
	B	**−0.06 ± 0.02**	**<0.001**	**−0.02 ± 0.01**	**<0.001**	**−0.27 ± 0.07**	**<0.001**	**−1.08 ± 0.20**	**<0.001**
	C	**−0.04 ± 0.02**	**0.003**	−0.01 ± 0.01	0.050	**−0.23 ± 0.07**	**0.002**	**−0.97 ± 0.21**	**<0.001**
HV	A	−0.000 ± 0.000	0.428	−0.000 ± 0.000	0.731	−0.001 ± 0.001	0.476	−0.003 ± 0.004	0.380
	B	−0.000 ± 0.000	0.461	−0.000 ± 0.000	0.746	−0.001 ± 0.001	0.510	−0.003 ± 0.004	0.436
	C	−0.000 ± 0.000	0.521	−0.000 ± 0.000	0.891	−0.001 ± 0.001	0.423	−0.003 ± 0.004	0.522
Verbal memory	A	0.007 ± 0.006	0.287	0.001 ± 0.002	0.781	0.02 ± 0.02	0.406	**0.15 ± 0.07**	**0.031**
	B	0.007 ± 0.006	0.295	0.001 ± 0.002	0.744	0.02 ± 0.02	0.515	**0.14 ± 0.07**	**0.039**
	C	0.005 ± 0.007	0.503	−0.000 ± 0.002	0.808	0.02 ± 0.02	0.495	0.14 ± 0.07	0.059
Visual memory	A	**−0.02 ± 0.01**	**0.003**	**−0.005 ± 0.002**	**0.005**	−0.04 ± 0.02	0.114	−0.10 ± 0.07	0.169
	B	**−0.02 ± 0.01**	**0.004**	**−0.005 ± 0.002**	**0.007**	−0.03 ± 0.02	0.274	−0.08 ± 0.07	0.280
	C	**−0.02 ± 0.01**	**0.003**	**−0.005 ± 0.002**	**0.006**	−0.02 ± 0.02	0.385	−0.08 ± 0.07	0.262
Executive function	A	**−0.03 ± 0.01**	**<0.001**	**−0.007 ± 0.002**	**<0.001**	**−0.07 ± 0.02**	**0.002**	**−0.15 ± 0.07**	**0.031**
	B	**−0.03 ± 0.01**	**<0.001**	**−0.007 ± 0.002**	**<0.001**	**−0.06 ± 0.02**	**0.009**	−0.13 ± 0.07	0.064
	C	**−0.03 ± 0.01**	**<0.001**	**−0.007 ± 0.002**	**<0.001**	**−0.06 ± 0.02**	**0.022**	**−0.15 ± 0.07**	**0.038**

Model A: Adjusted for age, sex, education. Model B: Adjusted for age, sex, education, systolic blood pressure, smoking, history of cardiovascular disease. Model C: Adjusted for age, sex, education, systolic blood pressure, smoking, history of cardiovascular disease, apoE-ε4 genotype, serum homocysteine levels, CRP, IL-6. Statistically significant relationships are in boldface.

blood-brain barrier and the high concentration of insulin receptors on the hippocampus and medial temporal cortex (16), areas of the brain that are primarily involved in memory and affected by AD neuropathology. At excessively high or low levels, insulin has been shown in vitro to downregulate choline acetyltransferase (17), the enzyme that catalyzes the production of the neurotransmitter acetylcholine, which is deficient in AD. Furthermore, insulin has been implicated in τ phosphorylation and amyloid deposition, the pathophysiologic mechanisms for AD (18).

Diabetes is an established risk factor for stroke and other vascular disorders, leading to an alternate hypothesis that the link between diabetes and dementia is indirect, mediated by vascular pathology (19). In the Rotterdam Study, however, diabetes was associated with MRI markers of AD risk, including smaller hippocampus and amygdala volumes, even after accounting for vascular pathology (20).

We found that, in this late adult population with a mean age of 62 years, clinical diabetes and each of the metabolic dysfunction markers of IR, hyperinsulinemia, and hyperglycemia (elevated HbA$_{1c}$) were associated with signs of accelerated brain aging, as measured by MRI TCBV, and by poorer performance on tests of executive function. The association with IR and hyperinsulinemia, which are early markers of a compensated prediabetic state, were also observed in a subsample without clinical diabetes.

In addition, we found that there appear to be different patterns of association between markers of a hyperglycemic state versus measures of IR when each is related to cognitive markers of aging. Measures of IR (HOMA-IR and fasting insulin levels) were inversely associated with visual memory and executive function, whereas glycemic indices (diabetes and HbA$_{1c}$) were inversely associated only with performance on executive function. We also found a marginally significant

direct association between diabetes and verbal memory, which disappeared after adjusting for all covariates. This finding is contrary to previously published studies and may be a chance artifact given our cohort's younger average age compared with previous studies. Because it was restricted to persons on insulin supplementation, it could reflect a beneficial effect of exogenous insulin on memory (21).

Our data strengthen earlier findings relating diabetes status to cognitive function, even in stroke- and dementia-free community-dwelling middle-aged men and women. Taken together, these findings suggest that the insulin resistant states seen in prediabetes and diabetes, as well as hyperglycemia, accelerate brain structural and cognitive aging, albeit in slightly different patterns, with the most robust associations being with IR.

In contrast to investigations into the association between glycemia and cognition, fewer studies have explored the possible links between insulin levels and

Table 3—*Association between metabolic dysregulation measures and markers of brain aging after exclusion of participants with clinical diabetes**

Variable	HOMA-IR (mmol/L × μU/mL)	P	Fasting insulin (μU/mL)	P	HbA$_{1c}$ (%)	P
TCBV	**−0.10 ± 0.03**	**<0.001**	**−0.03 ± 0.01**	**<0.001**	0.02 ± 0.12	0.859
HV	0.000 ± 0.001	0.784	0.000 ± 0.000	0.543	0.000 ± 0.002	0.999
Verbal memory	0.008 ± 0.009	0.405	0.001 ± 0.002	0.574	−0.035 ± 0.043	0.404
Visual memory	−0.011 ± 0.009	0.193	−0.004 ± 0.002	0.132	0.000 ± 0.043	1.000
Executive function	**−0.026 ± 0.009**	**0.003**	**−0.007 ± 0.002**	**0.002**	**−0.102 ± 0.042**	**0.016**

Values in boldface type are significant. *Adjusted for age, sex, and education (for cognitive measures).

IR, and brain structure and cognitive performance. Although hyperinsulinemia has been directly linked (22) to AD risk, there is also accumulating evidence linking insulin levels and cognitive performance in individuals without dementia. Hyperinsulinemia has been associated with lower scores on the Mini-Mental State Examination in individuals without dementia (23). Furthermore, IR, as measured by the HOMA-IR, has likewise been associated with poorer cognition and, more recently, with diffusely decreased cortical glucose uptake on fluorodeoxyglucose-positron emission tomography scans (24,25). Our findings of inverse relationships between fasting insulin levels, HOMA-IR, and brain volume and cognitive performance—even after controlling for vascular risk factors— appear to support these findings.

One limitation of our study is that we only examined a cross-sectional association but did not examine the association of these measures with change. Another limitation is the primarily white ethnicity of the Framingham study sample; hence, these associations need to be examined among community-dwelling individuals of other ethnicities. Our results do support ongoing studies to examine whether early detection and management of diabetes and metabolic dysfunction, particularly IR, would be able to delay the clinical onset of cognitive disorders.

Diabetic and prediabetic states characterized by IR, hyperinsulinemia, and hyperglycemia, when present in late middle age, are related to decreased brain volume and lower cognitive performance on executive function and memory tasks. These results extend the body of evidence linking metabolic dysfunction to the risk of dementia and AD in late life. These results suggest that clinical trials attempting to delay cognitive and structural brain loss by controlling metabolic dysfunction, even in individuals free of clinical diabetes and as early as the 7th decade, might be warranted.

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