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Brain Function and Structure and Risk for Incident Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Introduction—Diabetes is prospectively associated with cognitive decline. Whether lower cognitive function and worse brain structure is prospectively associated with incident diabetes is unclear.

Methods—We analyzed data for 10,133 individuals with cognitive function testing (1990–1992) and 1,212 individuals with brain magnetic resonance imaging (1993–1994) from the Atherosclerosis Risk in Communities cohort. We estimated hazard ratios (HR) for incident diabetes through 2014 after adjustment for traditional diabetes risk factors and cohort attrition.

Results—Higher level of baseline cognitive function was associated with lower risk for diabetes (per 1 standard deviation, HR: 0.94; 95% CI: 0.90, 0.98). This association did not persist after accounting for baseline glucose level, case ascertainment methods, and cohort attrition. No association was observed between any brain MRI measure and incident diabetes.

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Duality of interest

The authors report no conflicts of interest.

Author contributions

M.P.B. is the guarantor of this work, had full access to the data in this analysis, and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors had access to the data and participated in creating, editing, and reviewing this manuscript. M.P.B. researched data and wrote manuscript. A.A. contributed to discussion and reviewed/edited manuscript. RG. reviewed/edited manuscript. T.M. contributed discussion and reviewed/edited manuscript. E.S. contributed to discussion and reviewed/edited manuscript. J.S.P. contributed to discussion and reviewed/edited manuscript.

Discussion—This is one of the first studies to prospectively evaluate the association between both cognitive function and brain structure and the incidence of diabetes.

Keywords

cognitive function; brain magnetic resonance imaging; incident diabetes; epidemiology; prospective

1. Introduction

Diabetes is an established risk factor for cerebrovascular disease, [1] cognitive decline, [2] increased risk of dementia, [3] and greater burden of degenerative and vascular brain pathology. [4, 5] This suggests hyperglycemia precedes cognitive decline or structural changes to the brain. However, diabetes, dementia, and neurodegeneration share similar risk factors and may have long overlapping preclinical phases. [6–10] Diabetes is shown to have complex associations with other conditions of the brain; for example, diabetes and depression are shown to independently predict the incidence of the other. [10, 11] Mouse models of Alzheimer's disease suggest cerebral amyloidosis may produce subsequent metabolic dysfunction. [12] Therefore, it may be informative to investigate whether brain structure and cognitive function influence glucose metabolism over time.

Recent epidemiological evidence suggests an association between baseline level of cognitive function and subsequent development of impaired fasting glucose and diabetes. [13–15] However, determination of baseline brain health in these studies is limited to cognitive assessment only. Wechsler noted that factors not indicative of cognitive function per se, such as experience and familiarity with testing and socioeconomic structures, may influence performance on cognitive assessments. [16] Magnetic resonance imaging may provide a complementary method to characterize brain health where the method of measurement is less subject to these factors. Structural characterization of the health of the brain is needed to identify the underlying cerebral pathophysiology of this potential association and provides a biological anatomic marker for measurement and intervention. Investigation of this relationship may help clarify the natural history, changes in brain structure, and risk factors for cognitive dysfunction in diabetes. [17]

Our first aim (aim 1) was to assess the association between cognitive function in middle adulthood and the development of diabetes in later adulthood. The second aim (aim 2) was to evaluate the association between three structural measures obtained from brain imaging in middle adulthood and the development of diabetes in later adulthood. We hypothesized lower cognitive function and greater brain atrophy and white matter hyperintensity volume would be associated with an increased incidence of diabetes after taking into account traditional diabetes risk factors.

2. Methods

The ARIC study, initiated in 1987, used probability sampling to select, recruit, and enroll individuals drawn from four U.S. communities: Forsyth County, NC; the city of Jackson, MS; seven suburbs of Minneapolis, MN; and Washington County, MD.[18] Each field center

enrolled men and women aged 45–64 reflecting the racial/ethnic makeup of the community, with the exception of the Jackson cohort which only enrolled blacks, for a cohort total of 15,792 study participants in 1987–1989. Participants have been invited to participate in 5 clinic examinations in 1987–1989, 1990–1992, 1993–1995, 1996–1998, and 2011–2013 and receive annual follow-up telephone calls to update health-related developments occurring since the last contact. Participants gave written informed consent and the ARIC study procedures were reviewed and approved by each institution's review board.

2.1. Assessment of cognitive function

Cognitive function was first assessed on all ARIC participants present at visit 2 (1990–1992). Cognitive function was measured with three neuropsychological tests: Delayed Word Recall (DWR), Digit Symbol Substitution Test (DSST), and first-letter Word Fluency Test (WFT). The DWR assesses memory and is composed of a set often common nouns presented to participants and asked to recall after a 5-minute interval. The test shows fair test re-test reliability over 6 months (r=0.75), with high specificity and sensitivity for dementia at a cut-off of 3 or more correct words recalled (specificity=0.98; sensitivity=0.89).[19] The DSST is a test requiring the subject to associate numbers with unique symbols, testing sustained attention and psychomotor speed. [16, 20] Test-retest reliability in middle-aged adults is 0.82. [20] The WFT requires participants to produce as many words as possible that begin with three different letters of the alphabet. [21] This test measures verbal function and mental agility in retrieving words, scored as the sum of all three trials. [22] Forms of this test have high test-retest reliability over 19–42 days in normal middle-aged adults (r=0.81 to 0.88).[23]

2.2. Brain magnetic resonance imaging

Basic details of MRI measurement and imaging analysis have been described previously. [24, 25] Briefly, during the first two years of the ARIC visit 3 wave (1993 and 1994), 1.5-Tesla MRI scanners (GE Signa or Picker) were used to capture brain images for selected participants at the MS and NC field centers. ARIC participants at the MS and NC field centers who were ≥55 years of age at the time of their visit 3 examination were eligible for the cerebral MRI examination. Participants were screened for the MRI evaluation and individuals with contraindications were ineligible for MRI. A total of 2,891 participants were screened for eligibility and after excluding ineligible participants and those who declined participation, 1,949 participants underwent cerebral MRI. [26]

Scans were interpreted and assigned a grade at the ARIC MRI Reading Center at Johns Hopkins Medical Institutions using a validated scoring protocol. [24, 25] Each image had a primary and secondary interpretation adjudicated by different board-certified radiologists, blinded to participant's characteristics. Brain MRI measures included ventricular size (VS), sulcal size (SS), and white matter hyperintensities (WMH). Each MRI measure was evaluated according to a semi-quantitative 10-point scale with visual pattern matching. For example, each image for VS was compared with a series of eight images of successively increasing VS ranging from "small and presumably normal" (grade 1) to "severe atrophy" (grade 8). Images with ventricles smaller than those in grade 1 received a grade of 0 and those worse than a grade 8 received grade 9. Images for SS were graded in a similar fashion.

WMH were estimated as the total volume of periventricular and subcortical white matter signal abnormality, similarly by visual comparison with eight images that successively increased from “barely detectable white matter changes” (grade 1) to “extensive, confluent changes” (grade 8). Images interpreted as no white matter change received grade 0 and those with changes more significant that grade 8 received grade 9. This grading system is shown to have high intra-reader reliability for VS (kappa=0.89) and WMH (kappa=0.81) and moderate reliability for SS (kappa=0.66).[27]

2.3. Determination of diabetes

Diabetes status was determined at each ARIC visit as fasting glucose ≥ 7.0 mmol/L, non-fasting glucose ≥ 6.5% (11.1 mmol/L), self-reported use of diabetes medication in the past 2 weeks, or self-report of a physician diagnosis, and at annual telephone follow-up calls by self-report of physician diagnosis or self-report of diabetes medication use. Percent glycated hemoglobin (HbAlc) was measured at ARIC visit 2 and values were used to exclude any additional potential undetected diabetes cases with HbAlc ≥ 48 mmol/mol that were not identified by the above criteria. Blood chemistries and measurements have been described previously. [18] Glucose was measured with the hexokinase/glucose-6-phosphate dehydrogenase method. HbAlc was measured in stored whole blood samples using high-performance liquid chromatography with instruments standardized to the Diabetes Control and Complications Trial assay (Tosoh Ale 2.2 Plus Glycohemoglobin Analyzer and Tosoh G7).[28]

2.4. Ascertainment of other characteristics

Interviewer-administered questionnaires were used to collect information on demographics, education, cigarette-years smoking and current smoking status, regular alcohol consumption, medication inventory, and medical and reproductive history. Sitting blood pressure was measured with a random-zero sphygmomanometer in triplicate with 5-minute rest intervals; the mean of the last two measurements was used for analysis. Self-reported hypertensive medication use was determined from the medication inventory as having taken a hypertensive medication in the past last two weeks. Body mass index (BMI) was calculated as the weight, in kilograms, divided by height, in meters, squared. Waist circumference was measured at the level of the umbilicus. Physical activity in the past year was assessed with a modified Baecke questionnaire determining physical activity in sports, leisure-time, and at work, and converted to sports index score ranging 1 to 5.[29] At visit 2, a 21-item Vital Exhaustion Questionnaire was administered to measure a state of exhaustion, which is shown to have high correlation with depressive symptoms (r= 0.62). [30]

2.5. Statistical analysis

For aim 1, we assessed the association between cognitive function, determined at visit 2, and incidence of diabetes through 2014. We modeled cognitive function as a global cognitive function *z-score* and domain specific *z-scores* of the DWR, DSST, and WFT. For aim 2, we assessed the association between brain structure, determined at visit 3, and incidence of diabetes through 2014. Because the distribution of each MRI measure was right-skewed, 4 levels categorical variables were constructed. Ventricular size and sulcal size grade categories were defined as: grades 0–1 (reference), grade 2, grade 3, and grades ≥4. White

matter hyperintensities grade categories were defined as grade 0 (reference), grade 1, grade 2, and grades ≥3. These categories were chosen according to physiological interpretation and to ensure adequate numbers for events and comparison. An ordinal global score of brain structure was created by summing the score of each MRI measure, with a lower score indicating normal-healthy overall brain structure.

Individuals were excluded from the cognitive function and incident diabetes analysis (aim 1) if they were not present at the visit 2 examination. Individuals were excluded from the brain structure and incident diabetes analysis (aim 2) if they did not participate in the brain MRI at visit 3. We further excluded individuals who did not return after their index visit, were determined to have prevalent diabetes or self-reported prevalent stroke at their index visit, and individuals who were missing data on covariate information. Of the 14,348 individuals present at visit 2, we included 10,133 for analysis in aim 1 and 1,212 of the 1,934 individuals with adequate MRI data were included for analysis in aim 2. Categorical characteristics included race-field center (black-MS; black-NC; white-MD; white-MN; and white-NC), current smoking status (never; former; current), current alcohol consumption (zero; moderate: any up to 1 drink daily for females, up to 2 drinks daily for males; and heavy: greater than 1 drink daily for females, greater than 2 drinks daily for males), educational attainment (less than high school degree; high school graduate or vocational school; college degree or graduate school/professional school), parental history of diabetes (yes/no to maternal or paternal), and use of antihypertensive medication. All other characteristics were quantified and modeled continuously.

We used Cox proportional hazards to estimate hazard ratios (HR) for incident diabetes (and 95% confidence limits) with each individual's follow-up concluding with the date of exam or telephone call at which diabetes was first ascertained or administrative censoring on the date of their last contact. For analyses of aim 1, HRs for incident diabetes were calculated per 1 standard deviation unit increment in cognitive *z-score* after adjustment for age, sex, race-field center, educational attainment, smoking (cigarette-years and current status), alcohol consumption, physical activity sports index, BMI, waist circumference, fasting glucose, family history of diabetes, and depressive symptoms, systolic blood pressure and antihypertensive medication. For aim 1, all covariate data reflect ARIC visit 2 measurements except for education, cigarette-years smoking, paternal history of diabetes, and physical activity which were measured at visit 1. For aim 2, HRs for incident diabetes were calculated according to categorical grade for each MRI measure after adjustment for characteristics similar to aim 1. All covariates reflect those measured at visit 3, except for cigarette-years smoking, and family history of diabetes, which were measured at visit 1 and depressive symptoms, which were measured at visit 2. For each aim, we assessed effect modification by continuous age, sex, and race. We conducted multiple sensitivity analyses. We assessed results when diabetes ascertainment was limited to visit-based determination only. Individuals with lower baseline cognitive function and those who develop diabetes are more likely to be lost to follow-up, we used inverse probability of attrition weighting (IPAW) to examine the influence of selective attrition on our visit-based estimates. We used two logistic models to predict the probability of loss to follow-up due to dropout and loss to follow-up due to death at each exam at which diabetes was ascertained. [31] All IPAW models used the same predictor variables of age, a quadratic term for age centered, sex, race-

field center, education, smoking status, and cigarette-years, regular alcohol consumption, BMI, a quadratic term for BMI centered, fasting glucose, systolic blood pressure, hypertension status, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, physical activity sports index, neurocognitive test scores, family history of diabetes, health insurance status, and lipid-lowering and antihypertensive medication use. We stabilized these weights by re-running these models with a sub-set of covariates and multiplying the probabilities from the larger and reduced models. Second, we ran analyses stratified by normal glycemia, baseline fasting glucose <5.6 mmol/1 and HbAlc <5.7% (<39 mmol/mol), versus prediabetes levels of glycemia to identify if any observed association was consistent between individuals with normal glycemia and prediabetes. Lastly, we ran analyses excluding individuals scoring below sex- and race-specific 5th percentile for overall cognitive function to exclude potential prevalent cases of dementia at baseline. SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC) was used for statistical analysis.

3. Results

The summary statistics for the 10,133 individuals analyzed for aim 1 are presented in Table 1. At ARIC visit 2, female sex, white race, greater educational attainment, greater physical activity level, and moderate alcohol intake were associated with higher *z-scores* of global cognitive function. Older age, current smoking, higher BMI, waist circumference, and systolic blood pressure, and greater cigarette-years of smoking and depressive responses were associated with lower *z-scores* of global cognitive function. In regard to aim 2, only older age, male sex, higher systolic blood pressure, and greater cigarette-years of smoking were consistently associated with worse grade for each MRI measure at visit 3. Supplementary tables 1 – 3 present summary statistics according grade category for each MRI measure. A majority of participants were graded as having slightly abnormal imaging for each MRI measure. The ordinal global score of brain structure ranged from 0 to 19. The global brain structure score had a mean of 5.8 (standard deviation 2.2) and median of 6.0.

3.1. Cognitive function and incident diabetes

For aim 1, during a median follow-up time of 19.1 years, there were 2,999 newly identified cases of diabetes (19 cases/1,000 person-years). After adjustment for age, sex, and race-field center, a 1-SD unit increment in global cognitive function z-score was significantly associated with lower risk for incident diabetes (Table 2; HR=0.85 and 95% CI=0.82, 0.89). After final adjustment, cognitive function remained inversely associated with incidence of diabetes, although the association was attenuated (HR=0.94; 95% CI=0.90, 0.98). Of the individual factors, adjustment for field center and education resulted in the greatest attenuation of HR estimates. Of the three neurocognitive tests, only the WFT was associated with incidence of diabetes after final adjustment (HR=0.94; 95% Q=0.90, 0.99). When stratified by baseline glycemic status, global cognitive function was inversely associated with incidence of diabetes for individuals with prediabetes (HR=0.92; 95% 0=0.87, 0.97), while global cognitive function was not associated with incident diabetes for individuals with normal glucose at baseline. However, the test of interaction was not statistically significant (p = 0.24). In a sensitivity analysis when incident diabetes was determined at

ARIC study visits only (n events=l,723; n sample=9,925), global cognitive function was not associated with incident diabetes, with or without IPAW, after full adjustment (Table 2). Supplementary table 4 presents results when excluding individuals who scored below the 5th percentile for each race and sex in overall cognitive function. Hazard estimates when excluding these individuals were not materially different from the full sample. We did not find evidence of a quadratic association between any measure of cognitive function and incidence of diabetes. Tests for effect modification by continuous age, sex, and race were not significant (all p>0.10).

3.2. Brain MRI measures and incident diabetes

Median follow-up time for aim 2 was 14.3 years, during which 334 new cases of diabetes were identified (21 cases/1,000 person-years). Table 3 presents hazard ratio estimates for the association between the ordinal score of global brain structure and each of the individual scores and incident diabetes. A 1-unit increment in global brain structure score was associated with a 6% increase in hazard for incident diabetes after adjustment for age, sex, race-field center (95% CI 1.00, 1.12). This association was not significant after full adjustment. In our fully adjusted model, we observed a slightly stronger association per a 1-unit increment in global brain structure and the incidence of diabetes for individuals determined not to have elevated fasting glucose at baseline, but we did not find evidence for a statistical interaction by baseline glucose level (p=0.12). We did not find an association between global brain structure score and incidence of diabetes when diabetes was determined as visit-based diabetes cases or when using IPAW to account for cohort attrition.

After adjustment for age, sex, and race-field center, the group with the highest WMH grade (≥ 3) had 59% greater risk of developing diabetes (95% CI=1.03, 2.45) relative to those with a WMH grade of 0. Individuals in the intermediate WMH groups were not at significantly greater risk for developing diabetes compared to those with a grade of 0. These HR estimates were slightly attenuated after full adjustment, with the 95% CI including 1. We did not find evidence for a statistical interaction (p>0.10 for all MRI measures) by baseline fasting glucose for any association, however, qualitatively, we observed differences in MRI grade and incidence of diabetes by baseline glucose status for both WMH and VS (Table 3). By contrast, sulcal size was not associated with incidence of diabetes in overall models, or when stratified by baseline fasting glucose. HR estimates were substantially lower in sensitivity analyses using visit-based incident diabetes cases only (n cases=169; n sample=l, 190), and no associations were statistically significant (Table 3). Results were similar with and without IPAW. Tests for effect modification by age, sex and race were not significant (all p>0.10).

4. Discussion

In this prospective population-based study of adults, we found a weak association between higher overall cognitive function and lower risk for developing diabetes. These findings were predominantly found in individuals with prediabetes at baseline, but not in individuals with normal glucose levels, possibly a result of reverse-causation. In contrast, we did not find an association between worsening white matter hyperintensities, sulcal size, or ventricular size

with increased risk for developing diabetes in our full sample, after adjustment. In general, associations were weaker when diabetes ascertainment was restricted to only those cases determined at ARIC study visits.

The results from our first aim expand on the body of research from two cohorts previously assessing the association between cognitive function and glucose metabolism. [13–15] Investigators from the Metabolic, Lifestyle and Nutrition Assessment in Young Adults (MELANY) study observed that, among young Israeli adults, those with the lowest level of cognitive function had two-fold increased risk for developing diabetes or impaired fasting glucose, compared to individuals with the highest level of cognitive function after adjustment for diabetes risk factors. [14, 15] Data from Elderly Nutrition and Health Survey in Taiwan (NAHSIT Elderly) showed older women with cognitive impairment had a significant 2.4-fold greater risk for developing diabetes compared to those without cognitive impairment, while in elderly men this association was more modest and not statistically significant.[13] Several factors may have contributed to our finding that cognitive function was not associated with incident diabetes in the same magnitude as previously reported. The MELANY cohort is considerably younger than the ARIC population. The factors that lead to onset of diabetes in early adulthood may differ in their strength of association with developing diabetes in older age. [32] The difference in findings between ARIC and NAHSIT could be due to adjustment schemes or reverse-causation. The results reported in NAHSIT data are not simultaneously adjusted for SES or education, mental health, physical activity, BMI, and fasting glucose and individuals had, on average, fasting glucose levels reflecting prediabetes. [13]

Findings from second aim are novel, previous research on this topic has been unable to incorporate measurement of brain structure; the longitudinal relationship between brain structure and diabetes incidence is unclear. In the current study, we found white matter hyperintensities, ventricular size, and sulcal size in middle adulthood were not associated with developing diabetes. Previous investigation in ARIC has shown diabetes to be associated with worsening sulcal size and incident vascular infarcts, but not with changes to ventricular size or development of white matter hyperintensities. [5] It has been hypothesized that with regard to the temporal order of abnormalities of the brain becoming clinically apparent, structural abnormalities present clinically before cognitive function. [33] Our sample was relatively young (mean age 57) and healthy at baseline and differences in brain tissue volumes may not be clinically apparent. In a population of healthy white men and women from the U.S., age-associated brain tissue volume did not begin to show marked differences until 55 years of age. [34] Individuals who were included in the cognitive function and incident diabetes analysis who were not included in the brain structure and incident diabetes analysis were younger and had greater BMI and waist circumference. The samples were otherwise similar in sex, education, smoking, physical activity, blood pressure, and fasting glucose. If the brain health is associated with the development of diabetes it is unclear why we would not observe an association between both cognitive function and brain structure and incident diabetes. We observed attenuation of our hazard estimates for the association of cognitive function and incident diabetes after adjustment for educational attainment and educational attainment was positively associated with cognitive function at baseline. Therefore, we may observe an association between higher cognitive function and

lower risk for diabetes because our measurement of cognitive function signals greater educational attainment that is not reflected in our measurement of education.

There are several other potential mechanisms that may explain an association between cognitive function and brain structure and incidence of diabetes. The brain is highly dependent on glucose to function and home to a large concentration of insulin receptors which play various roles in glucose transport within the central nervous system and regulation of the body's homeostatic controls. [35, 36] Relatedly, the hypothalamic-pituitary-adrenal (HPA) axis also works to counteract threats to homeostasis of the body's systems and stress-induced activation of the HPA axis is associated with less favorable levels of cardiovascular and diabetes risk factors. [37] This suggests chronic dysfunction or abnormalities to the hypothalamus or HPA axis could have an impact on metabolic homeostasis. Insulin resistance in the cerebral tissues may also explain our results. Brains of patients with Alzheimer's disease show impaired insulin signaling and reduced expression of genes encoding insulin signaling compared to controls. [38] This brain-limited form of impaired insulin signaling and insulin resistance as been proposed as a neuroendocrine condition similar to, yet unique from, type 2 diabetes mellitus, termed "Type 3 diabetes". [38, 39] In addition to insulin resistance, diabetes and Alzheimer's disease share other risk factors. This may suggest that a common antecedent is responsible for the association between diabetes and neurodegeneration. The idea that diseases previously thought distinct spring from a "common soil" is not unique. [40]

There are several limitations to our study that warrant consideration. First, the technology used in the brain MRIs and the visual pattern matching methods used to determine and assign pathology are dated compared to current methods, which may lead to greater misclassification of brain structure, attenuation of association, and fail to detect an effect that is present known as type II error. Second, it is possible that reverse-causation may explain our results; it has been shown diabetes is associated with subsequent cognitive decline and brain pathology and these are two disease processes with long concurrent preclinical phases. We performed analyses stratified by baseline glucose status in an attempt to mitigate this phenomenon, however these results should be interpreted with caution due to fewer number of diabetes events within glucose strata. Third, MRI was only performed on a select group of individuals at the North Carolina and Mississippi field centers; these findings may not generalize to other geographic and socioeconomic populations with different risk factor profiles. Lastly, it is possible that unmeasured confounding is present. Our study also has some notable strengths, including long follow-up and standardized assessment of potential confounders in a large biracial cohort. In view of the limitations and strengths of this work the results should be interpreted cautiously.

In conclusion, for individuals in middle adulthood, higher overall cognitive function may be associated with lower risk for developing diabetes. However, these associations were weak in magnitude and of marginal significance. In contrast, we did not observe an association between differences in brain structure and incidence of diabetes. Cognitive differences in middle adulthood associated with subsequent incidence of diabetes may be the result of underlying risk for both due to incipient dysglycemia, or reverse-causation. Validation of

these results in different cohorts is warranted, including standardized evaluation and characterization of baseline brain structure and function and metabolic health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ARIC	Atherosclerosis Risk in Communities
DSST	Digit Symbol Substitution Test
DWR	Delayed Word Recall
HPA	Hypothalamic-pituitary-adrenal
IPAW	Inverse probability of attrition weighting
MELANY	Metabolic, Lifestyle and Nutrition Assessment in Young Adults
NAHSIT Elderly	Elderly Nutrition and Health Survey in Taiwan
SS	Sulcal size
VS	Ventricular size
WFT	Word Fluency Test
WMH	White matter hyperintensities

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1. Systematic review: We used PubMed to identify observational studies assessing the prospective association between cognitive function or brain structure and future risk for developing diabetes in humans.
2. Interpretation: If better cognitive function in middle adulthood is associated with reduced risk for developing diabetes in later adulthood, the strength of this association is weak and likely influenced by baseline glucose status, cohort attrition, and diabetes ascertainment methods. Cognitive function and brain structure in middle adulthood do not appear to be meaningful predictors of future diabetes.
3. Future directions: Our findings highlight the potential role of reverse-causation in previous studies in this area and that future study of this association be on young adults at the start of follow-up, before the onset of cognitive decline and impaired metabolism. Subsequent investigation of this association should include accurate and contemporary methods of evaluation for cognitive function, brain structure, and metabolic health.

Table 1

Participant characteristics according to quartile of global cognitive function *z-score* at visit 2 (1990–1992)

		Global Cognitive Function Quartiles, *z-score*				
Characteristic	***z-score* range**	**Q1 (−4.8,−0.64)**	**Q2 (−0.65, 0.04)**	**Q3 (0.05, 0.68)**	**Q4 (0.69,3.1)**	**Overall (−4.8,3.1)**
n		2532	2532	2533	2534	10,133
Age, years		58.2 ± 5.7	56.9 ± 5.6	56.3 ± 5.6	55.0 ± 5.3	56.6 ± 5.7
Women, %		44	53	60	68	56
Race, white, %		60	82	88	93	81
Education, ≥ some college[a], %		16	35	48	61	40
Current smoking, %		26	21	19	16	20
Cigarette-years smoking[a]		347 ± 450	296 ± 405	263 ± 375	230 ± 344	284 ± 398
Alcohol, none daily, %		73	65	60	56	64
Alcohol, moderate daily, %		22	27	32	34	28
Sports index (range 1–5)[a]		2.3 ± 0.7	2.5 ± 0.8	2.6 ± 0.8	2.6 ± 0.8	2.5 ± 0.8
Systolic blood pressure, mm Hg		123 ± 19	119 ± 17	119 ± 17	117 ± 17	119 ± 18
Antihypertensive medication use, %		35	28	25	21	27
BMI, kg/m^2		28.4 ± 5.5	27.4 ± 4.9	27.1 ± 4.7	26.6 ± 4.8	27.3 ± 5.0
Waist circumference, cm		99 ± 13	97 ± 13	95 ± 13	93 ± 14	96 ± 14
Fasting glucose, mmol/L		5.7 ± 0.5	5.6 ± 0.5	5.6 ± 0.5	5.6 ± 0.5	5.6 ± 0.5
Parental history of diabetes[a], %		24	23	21	20	22
Depressive symptoms (range 0–42; higher: depressive)		11 ± 9	10 ± 8	9 ± 8	9 ± 8	10 ± 8
Delayed word recall, total words (range 0–10)		5.4 ± 1.3	6.5 ± 1.1	7.2 ± 1.0	8.0 ± 1.1	6.8 ± 1.5
Digit symbol substitution, correct symbols (no upper limit)		32.1 ± 10.3	44.5 ± 8.2	51.1 ± 8.0	59.7 ± 8.7	46.9 ± 13.3
Word fluency test, words listed (no upper limit)		22.6 ±8.6	31.2 ± 8.0	37.1 ± 8.3	46.4 ± 9.7	34.3 ± 12.2

Values are means ± standard deviations for continuous and percentages for categorical.

[a]Data measured at ARIC visit 1, 1987–1989

Table 2

HRs (95% CI) for incident diabetes according to domain of cognitive function *z*-score from 1990–1992 through 2014

	HR (95% CI) per 1 SD cognitive function *z*-score			
Model Adjustments	**Global**	**DWR**	**DSST**	**WFT**
Model 1[a]	0.85 (0.82, 0.89)	0.94(0.91,0.98)	0.86 (0.82,0.90)	0.87(0.84,0.91)
Model 2[b]	0.92 (0.88, 0.97)	0.98 (0.94, 1.02)	0.94 (0.89,0.99)	0.93 (0.89,0.97)
Model 3[c]	0.94 (0.90, 0.98)	0.98 (0.94, 1.02)	0.97 (0.92,1.02)	0.94 (0.90,0.98)
Model 3[c] Stratified				
Glucose < 5.6 mmol/l and HbAlc < 39 mmol/mol[e]	0.98 (0.90, 1.08)	1.01 (0.94, 1.09)	1.00(0.90,1.10)	0.96 (0.89,1.04)
Glucose ≥ 5.6 mmol/l or HbAlc ≥ 39 mmol/mol[e]	0.92 (0.87, 0.97)	0.97 (0.93, 1.02)	0.96 (0.90,1.02)	0.92 (0.88,0.97)
P for interaction[d]	0.24	0.36	0.50	0.36
Visit-based diabetes cases only				
Number of cases/ n total	1723/9925			
Model 3[c]	0.98 (0.92, 1.04)	0.96 (0.92, 1.02)	1.02(0.95,1.09)	0.99 (0.94,1.05)
Model 3[c] with IPAW	0.99 (0.93, 1.06)	0.99 (0.94, 1.04)	1.02(0.95,1.09)	0.99 (0.93,1.05)

[a] Adjusted for visit 2 covariate values (unless noted) for age, sex, and race-field center

[b] As for the model described above, with the addition of education (visit 1), current smoking status, cigarette-years (visit 1), regular alcohol consumption, and physical activity sports index (visit 1)

[c] As for model b described above, with the addition of BMI, waist circumference, fasting glucose, parental history of diabetes (visit 1), depressive symptoms, systolic blood pressure and antihypertensive medication use

[d] P for interaction is a test of heterogeneity of effects by glucose stratum

[e] HbAlc of 39 mmol/mol is equivalent to HbAlc of 5.7%

Table 3

HRs (95% CI) for incident diabetes for overall brain structure and according to category of white matter hyperintensities, ventricular size, and sulcal size from 1993–1994 through 2014

	HR (95% CI) per 1-unit increment in Overall Brain Structure Score				
Number of cases/ n total	334/1212				
Model 1[a]	1.06(1.00, 1.12)				
Model 2[b]	1.06(1.00, 1.12)				
Model 3[c]	1.05(0.99, 1.12)				
Model 3[c] Stratified					
Glucose < 5.6 mmol/1	1.14(1.04, 1.26)				
Glucose ≥ 5.6 mmol/1	1.01 (0.93, 1.09)				
P for interaction[d]	0.12				
Visit-based cases only, n=l190					
Number of cases/ n total	169/1190				
Model 3[c]	1.04(0.95, 1.13)				
Model 3[c] with IPAW	1.01(0.92, 1.12)				
	White Matter Hyperintensities grade, range 0 – 9				
	0	1	2	≥3	p trend[e]
Number of cases/ n total	56/180	166/638	76/281	36/113	
Model 1[a]	Ref.	0.88(0.65, 1.20)	1.14(0.80, 1.64)	1.59(1.03,2.45)	0.02
Model 2[b]	Ref.	0.85(0.63, 1.16)	1.06(0.73, 1.53)	1.47 (0.95, 2.28)	0.05
Model 3[c]	Ref.	0.88(0.64, 1.20)	1.01 (0.69, 1.48)	1.53 (0.97, 2.41)	0.08
Model 3[c] Stratified					
Glucose < 5.6 mmol/l	Ref.	0.87(0.52, 1.47)	1.28 (0.70, 2.35)	2.02 (1.00, 4.06)	0.02
Glucose ≥ 5.6 mmol/l	Ref.	0.86(0.58, 1.29)	0.87(0.53, 1.45)	1.37 (0.73, 2.54)	0.55
P for interaction[d]	0.20				
Visit-based cases only, n=1190					
Number of cases/ n total	32/177	92/622	36/281	9/110	

HR (95% CI) per 1-unit increment in Overall Brain Structure Score					
Model 3[c]	Ref.	0.84(0.56, 1.28)	0.98 (0.57, 1.66)	0.56 (0.25, 1.24)	0.34
Model 3[c] with IPAW	Ref.	0.84(0.55, 1.30)	0.87(0.50, 1.50)	0.40(0.16, 1.01)	0.13
	Sulcal Size grade, range 0–9				
	0–1	2	3	≥4	p trend[e]
Number of cases/ n total	75 / 289	181 / 614	61 / 238	17 / 71	
Model 1[a]	Ref.	1.09(0.83, 1.43)	0.94 (0.67, 1.33)	0.99 (0.58, 1.70)	0.74
Model 2[b]	Ref.	1.06(0.81, 1.40)	0.99(0.70, 1.41)	1.01 (0.59, 1.74)	0.96
Model 3[c]	Ref.	1.08(0.82, 1.43)	1.05 (0.74, 1.49)	0.93 (0.54, 1.60)	0.94
Model 3[c] Stratified					
Glucose < 5.6 mmol/l	Ref.	1.56 (0.97, 2.52)	1.46(0.81,2.66)	1.97(0.75,5.17)	0.12
Glucose ≥ 5.6 mmol/l	Ref.	0.92 (0.64, 1.33)	0.89(0.57, 1.41)	0.62(0.31, 1.23)	0.23
P for interaction[d]	0.21				
Visit-based cases only, n=l 190					
Number of cases/ n total	41/281	89/606	28/233	11/70	
Model 3[c]	Ref.	1.06(0.72, 1.58)	1.24 (0.74, 2.08)	1.58 (0.77, 3.25)	0.20
Model 3[c] with IPAW	Ref.	1.11(0.73, 1.68)	1.18(0.68,2.03)	1.65 (0.75, 3.63)	0.27
	Ventricular Size grade, range 0–9				
	0 – 1	2	3	≥4	p trend[e]
Number of cases/ n total	49/209	150/536	89/301	46/166	
Model 1[a]	Ref.	1.16(0.84, 1.61)	1.34 (0.94, 1.92)	1.40(0.92,2.13)	0.06
Model 2[b]	Ref.	1.19(0.86, 1.65)	1.32(0.92, 1.89)	1.44(0.95,2.19)	0.07
Model 3[c]	Ref.	1.20(0.86, 1.67)	1.28(0.88, 1.86)	1.47 (0.96, 2.25)	0.08
Model 3[c] Stratified					
Glucose < 5.6 mmol/l	Ref.	1.71 (0.99, 2.96)	2.13(1.15,3.97)	1.84(0.90,3.78)	0.06
Glucose ≥ 5.6 mmol/l	Ref.	1.07 (0.69, 1.66)	1.04 (0.64, 1.69)	1.41 (0.82, 2.45)	0.30
P for interaction[d]	0.74				

	HR (95% CI) per 1-unit increment in Overall Brain Structure Score				
Visit-based cases only, n=l 190					
Number of cases/ n total	28/201	84/530	40/296	17/163	
Model 3[c]	Ref.	1.02 (0.65, 1.62)	1.11(0.66, 1.87)	1.26 (0.65, 2.44)	0.45
Model 3[c] with IPAW	Ref.	0.97 (0.60, 1.54)	0.96(0.55, 1.65)	1.16(0.59,2.28)	0.77

[a] Adjusted for visit 3 covariate values (unless noted), for age, sex, and race-field center

[b] As for the model described above, with the addition of education (visit 1), current smoking status, cigarette-years (visit 1), regular alcohol consumption, and physical activity sports index (visit 1)

[c] As for model b described above, with the addition of BMI, waist circumference, fasting glucose, parental history of diabetes (visit 1), depressive symptoms (visit 2), systolic blood pressure and antihypertensive medication use

[d] P for interaction is a test of heterogeneity of effects by glucose stratum

[e] P trend is testing for linear trend in HR across categories