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Glycemia, diabetes status, and cognition in middle aged Hispanics

José A. Luchsinger, MD[1,2], **Rafi Cabral, MD**[1], **Joseph P. Eimicke, MPH**[3], **Jennifer J. Manly, PhD**[4], and **Jeanne Teresi, PhD**[2]

[1]Department of Medicine, Columbia University Medical Center, New York, NY

[2]Department of Epidemiology, Columbia University Medical Center, New York, NY

[3]Research Division, Hebrew Home for the Aged in Riverdale, Bronx, NY

[4]Gertrude H. Sergievsky Center, Columbia University Medical Center, New York, NY

Abstract

Objective—To examine the association of glycemia and diabetes status with cognition among 600 Hispanics aged 55 to 64 years from Northern Manhattan.

Methods—Diabetes was ascertained by history or Hemoglobin A1c (HbA1c). Normal glucose tolerance (NGT) and pre-diabetes were ascertained with HbA1c. Memory was assessed with the Selective Reminding Test (SRT). Executive abilities were assessed using the Color trails 1 and 2, and verbal fluency test. The cross-sectional association of glycemia and diabetes status with cognitive performance was examined using linear regression.

Results—Participants were a mean age of 59.2 ± 2.9 years old, 76.7% were women, and more than 65% had pre-diabetes or diabetes. HbA1C ($\beta = -0.97$; $p < 0.001$) and diabetes ($\beta = -2.06$; $p = 0.001$) were related with lower SRT total recall after adjustment for demographics, education, and vascular risk factors. Pre-diabetes was associated with worse performance in color trails 2 ($\beta = -6.45$ $p = 0.022$) after full adjustment.

Conclusions—Higher glycemia and diabetes are related to worse memory and executive abilities in late middle age, while pre-diabetes is related only to worse executive abilities. Longitudinal follow-up is needed to understand the order and progression of these deficits.

Keywords

Glycemia; pre-diabetes; diabetes; cognition; middle age

Corresponding author: José A. Luchsinger, 630 West 168th Street, PH9 Center, room 210, New York, NY 10032, Jal94@cumc.columbia.edu, Tel: 212-3054730, Fax: 212-3059349.

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INTRODUCTION

According to the 2014 Alzheimer's Disease facts and figures report from the Alzheimer's association(1) 11% of people aged 65 years and older, and a third of people 85 years and older dementia (AD), the most extreme common form of cognitive impairment, characterized by loss of the ability to live independently. The most common cause of dementia is Alzheimer's disease, which accounts for 60 to 80 % of dementias, followed by vascular dementia, although half of all dementias may have a cerebrovascular component (1). Given the longer life expectancy of the population, the cases of dementia in persons 65 years and older is expected to increase by 40% by 2025 from current numbers (1). In addition, over a fifth of persons over the age of 70 have non-dementia cognitive impairment (2). There are currently no known curative or preventive measures dementia or the cognitive impairment that precedes it.(3) Thus, there has been great interest in the search for modifiable dementia risk factors.(4) One of the strongest risk factors to emerge to date is type 2 diabetes (referred to as diabetes in the rest of this manuscript)(5).

Diabetes is an abnormal elevation of glucose levels that has significant implications for health, including cardiovascular disease, end-stage renal disease, mobility limitations, limb loss, visual impairment, cognitive impairment, and premature mortality, (6–8) generally requiring medical treatment. Pre-diabetes is a less severe glucose elevation that is also related to adverse outcomes and puts persons at a high risk of diabetes(9). Over 100 million adults in the US have diabetes or pre-diabetes, 25 million have diabetes, and 79 million have pre-diabetes (10), comprising a third of the U.S. population.

There have been numerous studies showing an association of diabetes a higher risk of dementia, including Alzheimer's and vascular dementia (8, 11–14), amnestic and non-amnestic mild cognitive impairment (MCI) (15), and cognitive impairment without dementia,(16, 17) with memory and global cognitive decline (18). Moreover, persons with MCI and diabetes are more likely to advance to dementia (19, 20).

Although diabetes in older age is related to a higher risk of categories of cognitive impairment, when cognitive performance is examined as an outcome in persons aged 65 years and older, diabetes status is related to lower cognitive performance but not to steeper cognitive decline,(21, 22) suggesting that the onset of cognitive impairment related to diabetes begins before the age of 65. However, most cognition studies enroll elderly participants with a mean age around 75 years of age (23), and many studies that relate middle age risk factors such as diabetes to dementia in older age do not have concurrent midlife cognitive data(24–26). Furthermore, most studies examining the association between diabetes and cognitive impairment do not ascertain pre-diabetes, thus classifying persons with pre-diabetes as normal, which can underestimate the risk of cognitive impairment associated with diabetes.

We sought to overcome the limitations of previous studies with elderly cohorts and incomplete ascertainment of diabetes status by recruiting a community based cohort of Hispanics from New York City aged 55 to 64 years with a high prevalence of diabetes and pre-diabetes and with detailed concurrent ascertainment of diabetes status and cognitive

performance. Here we present the first cross-sectional analyses of this cohort based on its baseline assessment data.

METHODS

Participants

The current study is a cross-sectional analysis from the baseline visit of the 600 participants in the Northern Manhattan Study of Metabolism and Mind (NOMEM), recruited in the community of Northern Manhattan in New York City, the catchment area of Columbia University Medical Center (CUMC), where this study is based. Northern Manhattan is comprised of Washington Heights-Inwood and Central Harlem. Washington Heights begins at 155th Street, and extends northward to the tip of Manhattan Island. Washington Heights is bounded on the west by the Hudson River and on the east by the East River. Central-Harlem spans East-West from the Harlem River to Morningside Avenue, and North and South from 155th Street to 110th Street in Manhattan. NOMEM participants completed their baseline examination between 01/01/2012 and 12/31/2013. The explicit goal of NOMEM was to study the relation of diabetes and pre-diabetes with mental health outcomes, including cognition, in middle-aged Hispanics. We focused on Hispanics because they are the predominating ethnic group in Washington Heights, the immediate area surrounding CUMC (27). NOMEM is currently approved by the Institutional Review Board of Columbia University Medical Center (IRB AAAI5156). All study participants provided written informed consent. The inclusion criteria for NOMEM were: self-identified Hispanic (any Hispanic subgroup); man or woman; and age between 55 and 64 years in the recruitment period between 01/01/2012 and 12/31/2013, and living in Northern Manhattan. Exclusion criteria included: history of cancer other than non-melanoma skin cancer that could preclude long-term follow-up; presence of a clinical diagnosis of dementia (unlikely in this age group); Visual, hearing, or physical impairment that could preclude participation in the study due to inability to complete study questionnaires; and the inability or unwillingness to undergo phlebotomy. Our main recruitment method was the distribution of study flyers in English and Spanish in Northern Manhattan with details of the inclusion and exclusion criteria. A total of 747 persons demonstrated interest in participating and were screened, and 147 were excluded. The reasons for exclusion were, younger than 55 years (n=52, 35.3%), living outside of Northern Manhattan (n= 48, 32.6%), older than 64 years (n= 16, 10.8%), not Hispanic (n=10, 6.8%), changed their mind about participation (n = 17, 11.5%), and were unwilling or unable to undergo Phlebotomy (n = 4, 2.7%)

Measures

Exposures—Our exposures of interest were glycemia ascertained by hemoglobin A1c (HbA1c) and diabetes categories. HbA1c is a stable measure of 3-month glycemia (28). HbA1c was measured by boronate affinity chromatography with the Primus CLC 385 (Primus, Kansas City, MO). Hemoglobin A1c (HbA1c) was used for the ascertainment of normal glucose tolerance (NGT), pre-diabetes, and undiagnosed diabetes.. Diabetes was defined by clinical history or by HbA1c ≥ 6.5%, following 2010 American Diabetes Association (ADA) criteria(29). Pre-diabetes was determined following ADA 2010 criteria (HbA1c between 5.7 to 6.4%). We focused on diabetes and pre-diabetes as exposures

because diabetes is a clinical entity treated by physicians with pharmacological and non-pharmacological interventions, and pre-diabetes is increasingly acknowledged for interventions to prevent diabetes.

Covariates—We chose covariates that have been reported to predict cognitive performance and are also related to diabetes. We collected date of birth, sex, years of education, racial group, and country of origin (following the 2010 census format for Hispanics) (30). We ascertained adiposity because it is a predictor and correlate of diabetes(31) that also predicts cognitive impairment (32). Body Mass Index (BMI) was calculated using weight and height (BMI = weight in kg/height in m^2). Standing height was measured using a stadiometer calibrated in cm. Body weight was measured using a balance beam scale calibrated in kg. With the participant standing, measurements were taken to the nearest 0.1 kg of weight with a balance scale and height without shoes to nearest 0.5 cm. Waist circumference (WC) was measured at the level of the umbilicus. Hip circumference was measured at the level of maximal protrusion of the gluteal muscles. Waist-hip ratio (WHR) was calculated as the ratio of waist circumference to hip circumference. Depressive symptoms were collected as a covariate because it is a correlate of cognitive impairment(33) and diabetes(34). We measured depressive symptoms using the Patient Health Questionnaire-9 (PHQ-9) (35). High Sensitivity C-reactive protein (hsCRP) is a marker of inflammation and a predictor of cardiovascular disease(36) and memory impairment (37) that is elevated in diabetes and pre-diabetes (36). Thus, it was examined as a covariate and potential vascular mediator. It was measured using ELISA (Diagnostic Systems Laboratories, Inc, Webster, Texas).

Dyslipidemia is present in diabetes and pre-diabetes(38) and is a predictor of cognitive impairment. We ascertained dyslipidemia with high density lipoprotein (HDL) and non-HDL cholesterol (total cholesterol – HDL) because these measures are superior to low density lipoprotein as predictors (39) and do not require fasting. Total cholesterol and HDL were measured using enzymatic colorimetric methods (Vitros; Johnson & Johnson, Brunswick, NJ) and were used as covariates and potential mediators. Hypertension is a correlate of diabetes(40) and a risk factor for dementia in middle age(41). Thus, we collected resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) as a covariate and potential mediator. We calculated mean arterial pressure (MAP) using the formula MAP = (2 × DBP + SBP)/3. We also defined hypertension as a self-reported history of hypertension, taking medications for hypertension, or having a systolic BP > 140 mmHg or a diastolic BP > 90. Using an automated oscillometric device, 3 measurements were obtained at 1-minute intervals in a seated position after 5 minutes of rest. The average of the 2^{nd} and 3^{rd} measurements were recorded. History and medications were ascertained from questionnaires. This included self- reported vascular disease, cancer, smoking, and all medications. We classified diabetes medications as metformin, sulfonylureas, thiazolidenidiones, insulin, and other medications including glucagon peptide agonists.

Outcomes—A bilingual tester administered the neuropsychological battery. Participants were asked the language of their preference (English, Spanish), and this language was used for the neuropsychological examination. A committee of Spanish speakers from Cuba,

Puerto Rico, Spain, and the Dominican Republic translated all interview questions, test instructions, and stimuli into Spanish, and then back translated to ensure accuracy. When necessary, scoring criteria were modified so that credit is given for responses reflecting regional idioms. The neuropsychological battery was designed to capture executive functioning and memory, the 2 main cognitive domains affected by diabetes(15). Executive functioning is affected early in cerebrovascular disease and is thought to be the main domain affected in vascular cognitive impairment (42). Memory impairment is thought to be the earliest domain affected in Alzheimer's dementia(43). The tests used to assess executive functioning were the Color Trails Test (44) and verbal fluency. Color Trails 1 is a test of sustained visual attention, psychomotor speed, and simple sequencing that involves connecting circles containing the numbers 1 through 25 in order as quickly as possible. Color Trails 2 also involves connecting circles containing the numbers 1 through 25 in order as quickly as possible, but the examinee must shift between pink and yellow colored circles. Like Part 1, Color Trails 2 assesses visual attention and psychomotor speed but also requires a higher level of executive functioning skills. For the verbal fluency test, the patient is given 1 minute to name as many words beginning with a particular letter as possible. Normative data and frequency counts exist for this test in Spanish as well as English(45). Three categories, Animals, Food, and Clothing are administered to assess category fluency. These tests are scored such that a higher value reflects better performance.

Memory was assessed with the Selective Reminding Test (SRT) (46). The SRT is a standard tool in the assessment of verbal memory and dementia and has been used as a sensitive longitudinal measure of changes in memory function. Several studies attest to its predictive value for dementia(47–49). We have translated this test into Spanish using words of similar frequency to those in the standard test versions. Participants are given 6 trials to learn a list of 12 unrelated words. After each attempt at recalling the list, the participant is reminded only of the words that were not recalled and then must attempt to recall the entire list. To assess short-term memory we used total recall (maximum score=72 words). To assess long-term recall, delayed recall was assessed 15 minutes after completing the 6 trials of immediate recall (maximum score = 12 words); recognition of words not recalled is then tested using multiple-choice arrays (maximum score = 12). Scores reflect words recalled and higher scores reflect better performance.

Statistical analysis

General cohort characteristics were compared across diabetes categories using ANOVA for continuous variables and Likelihood ratio chi-square tests used for categorical variables. First we conducted an omnibus test for all groups, and if statistically significant, we compared pre-diabetes and diabetes with the reference group (NGT) separately. The distributions of the outcomes were examined and found to be normal or close enough to normal to not warrant transformation, with the exception of SRT Recognition, where the majority of the participants received the maximum score of 12 (recognized all words). Analyses of this test required an exact test. Colinearity diagnostics were examined and found to be adequate.

Generalized Linear Models were used to relate HbA1c as a continuous variable and diabetes categories to cognitive performance. For analyses examining hbA1c as a continuous variable. we explored non-linear associations with quadratic and cubic terms. We conducted analyses examining HbA1c in the whole cohort, and also excluding persons on diabetes treatment because diabetes medications reduce HbA1c, and thus, HbA1c in these persons may not reflect chronic glycemia exposure. For analyses examining diabetes status as the exposure, the NGT group was the reference group in all analyses. Three models were examined for each outcome. Model 1 adjusted for age and gender. Model 2 additionally adjusted for education and Hispanic subgroup (Dominican origin). Model 3 additionally adjusted for components of the metabolic syndrome that accompany pre-diabetes and diabetes(50). The rationale for models 1 and 2 were to adjust for potential confounders. The rationale for model 3 was to examine associations between diabetes status and cognitive performance that were independent of elements of the metabolic syndrome that accompany pre-diabetes and diabetes(50). Including adiposity, hypertension, dyslipidemia, and inflammation, and may act as potential mediators. If there was one more than one variable for each of these constructs (e.g. adiposity), we chose the variable that was most strongly associated with diabetes status to represent the construct (see Table 1). For example, BMI was more strongly associated with diabetes status than WC or WHR, and thus, we chose BMI as the measure of adiposity. Following this principle, the variables that represented each construct in model 3 were as follows: BMI for adiposity, HDL for dyslipidemia, systolic BP for hypertension, and hsCRP for inflammation. Lastly we conducted secondary analyses calculating composite cognitive scores using Z scores. Z scores for each test were estimated using the formula Z = (test score – mean test score)/standard deviation. Three composites were estimated adding the Z scores: a memory composite that including total recall, delayed recall, and recognition of the SRT; an executive composite that included the scores of the color trails 1 and 2, and the category fluency test; and a total composite score including all test z scores. We also examined whether cognitive performance varied by diabetes treatment. All analyses were performed using IBM SPSS Statistics version 21.

RESULTS

Overall, the sample had a mean age of 59.2 ± 2.9 years, included 76.7% women, and had an average of 9.8 ± 4.2 years of education (see Table 1). Nearly all of the participants spoke Spanish (97.8%) with the majority identifying themselves as Dominican (86.3%). The prevalence of NGT, pre-diabetes, and diabetes were 34.6%, 34.5% and 30.8% respectively.

As expected, persons with pre-diabetes and diabetes had a less favorable educational and metabolic and vascular profile compared with persons with NGT (Table 1). Compared with persons with NGT, persons with pre-diabetes and diabetes were less educated, more likely to be of Dominican origin, had a higher BMI, lower HDL cholesterol, and higher HsCRP. Persons with diabetes, but not persons with pre-diabetes, also had higher WC, WHR, and systolic BP, There were no significant differences between the NGT, pre-diabetes, and diabetes groups in regards to age, sex, diastolic BP, MAP, non-HDL cholesterol, and depressive symptoms. Eighty of the 185 persons with diabetes reported using a diabetes medication (43%). The most commonly reported medication was metformin (n=70, 87.5%

of all persons taking diabetes medications), followed by sulfonylureas (n= 11, 13.7%), thiazolidenidiones (n= 8, 10%), and insulin (n = 7, 8.7%).

Unadjusted bivariate analyses relating diabetes status with cognitive performance (Table 1) demonstrated that compared with persons with NGT, persons with diabetes had worse performance in the SRT total recall and delayed recall, and the verbal fluency test, while persons with pre-diabetes had worse performance in the color trails 2 test. We conducted multivariate analyses relating HbA1c examined continuously and diabetes categories to the tests of memory (Table 2) and executive function (Table 3). HbA1c was inversely related to performance in total recall of the SRT even in the full model and after exclusion of person on diabetes medications (Table 2). HbA1c was also inversely related to performance in delayed recall of the SRT after full adjustment and after exclusion of persons reporting use of diabetes medications. There was no association of HbA1c examined continuously or diabetes categories with recognition of the SRT. Examination of quadratic and cubic terms for HbA1c in relation to all subtests of the SRT did not reveal non-linear associations.

Diabetes, but not pre-diabetes, was associated with worse performance in total recall of the SRT even after full adjustment including vascular and metabolic risk factors. Diabetes, but not pre-diabetes, was associated with worse performance in delayed recall of the SRT, but this association was attenuated and became non-significant in the model adjusting for education and Hispanic subgroup.

In terms of tests of executive function, HbA1c examined continuously was only inversely related to performance in verbal fluency after adjustment for age and sex. These associations were present including and excluding persons on diabetes medications, but became non-significant after adjustment for components of the metabolic syndrome, suggesting that these components mediate the association between HbA1c and executive function performance. Examination of quadratic and cubic terms for HbA1c in relation to all tests of executive function did not reveal non-linear associations.

Pre-diabetes, but not diabetes, was associated with worse performance in the color trails 1 and 2. The association for the color trails 1 was attenuated and became non-significant after adjustment for education and Hispanic subgroup, while the association with the color trails 2 was robust even after adjustment for components of the metabolic syndrome.

Lastly, we examined the association of HbA1c and diabetes categories with composite Z scores of memory, executive function, and global cognitive function (Table 4). HbA1c examined continuously was robustly associated with worse performance in the memory score and global Z scores even after adjustment for components of the metabolic syndrome and exclusion of person reporting use of diabetes medications. HbA1c was also associated with worse performance in the executive Z score after adjustment for age, sex, education, and Hispanic subgroup, but this association was attenuated after adjustment for components of the metabolic syndrome. Pre-diabetes was associated with worse performance in the executive z score even after adjustment for components of the metabolic syndrome, but was not associated with the memory score or the global score. Diabetes was associated with all scores after adjustment for age and sex, but these associations became non-significant after

adjustment for education and Hispanic subgroup for the memory and executive scores, and after adjustment for components of the metabolic syndrome for the global score.

Lastly, we conducted secondary analyses comparing cognitive performance between the 105 persons with diabetes not reporting diabetes medication use and the 80 reporting diabetes medication use. There were no significant differences between these 2 groups in performance in any of the tests.

DISCUSSION

We found in a sample of middle aged Hispanics with a high prevalence of pre-diabetes and diabetes that higher glycemia and diabetes were strongly associated with worse performance in memory and more weakly with executive function, while pre-diabetes was associated with worse performance in executive function.

Most studies examining the association between diabetes and cognitive impairment have been conducted in older cohorts and focus on cognitive diagnoses such as dementia and MCI. Studies of older adults have shown that diabetes is associated with worse cognitive performance but not accelerated cognitive decline(51–54). Neuroimaging studies show that diabetes is associated with lower brain volumes but not decreases in brain volumes (55), paralleling the findings for cognitive performance. Although several studies suggest that the cognitive trajectories of most older adults with diabetes do not substantially differ from those seen in normal aging (56), other studies have shown accelerated cognitive aging in diabetes (57–61). Collectively, these studies prompt the question of the critical period when decrements associated with diabetes begin. Our study is cross sectional, but our results suggest that decrements in memory related to diabetes and increased glycemia are already detectable in late middle age, and that deficits in executive function are most strongly related to pre-diabetes. Studies in middle-aged adults diagnosed with diabetes suggest that cognitive decrements likely begin during the pre-diabetic stages and progress slowly(53, 62–64). One view proposes that there are two crucial periods of life during which diabetes-related cognitive decrements occur: early in life during brain development and later in life when age-related neurodegenerative changes occur, often at age 65 or older(65). However, middle age may also be a critical time point, when the prevalence of diabetes and prediabetes increases along with the brain's susceptibility to cognitive impairment (65).

The mechanisms underlying the association between diabetes and cognitive impairment remain uncertain. It is well known that diabetes (66) and pre-diabetes (67,68) are risk factors for clinical stroke and higher cerebrovascular disease on brain imaging (69). It is increasingly accepted that cerebrovascular disease interacts with Alzheimer's pathology to increase the risk of dementia(70). However, diabetes, pre-diabetes, and related insulin resistance may be linked to increased accumulation (71, 72) or impaired clearance (73–76) of brain amyloid, the putative culprit of Alzheimer's dementia(77). The greatest gaps in knowledge in the relation of diabetes and related conditions with dementia to date seem to be the lack of establishment of a causal association, and whether diabetes can affect the amyloid cascade in addition to acting as a cerebrovascular risk factor(78). Diabetes clearly increases the risk of cerebral infarcts(79, 80), but its association with Alzheimer's

neuropathology is less clear and studies are conflicting(79–83). Evidence from autopsy studies suggests that vascular and Alzheimer pathologies may have an additive effect on cognitive impairment (84, 85) raising the possibility that those with diabetes who may be at risk for vascular pathologies require less Alzheimer's pathology to reach a threshold where cognitive impairment manifests itself clinically. We do not have neuroimaging data or biomarkers of Alzheimer's disease, but can address mechanisms indirectly. Traditionally, impairment in executive function has been attributed to cerebrovascular disease and disruption of frontal subcortical networks (42, 86–88). Our results showing lower performance in executive functions related to pre-diabetes and diabetes indirectly suggests an underlying cerebrovascular mechanism. Deficits in memory are usually thought to be the earliest maker of Alzheimer's pathology. In particular, deficits in recognition are considered to be a surrogate marker of hippocampal dysfunction, one of the earliest injuries in Alzheimer's disease (43, 89). Deficits in memory demonstrated by lower total recall and delayed recall with normal recognition may be due to cerebrovascular mechanisms and disruption of the frontal-subcortical pathways that also underlie executive impairment. Our study showed that diabetes status was related to lower total recall and delayed recall, but there were no differences in recognition, suggesting a retrieval deficit related to frontal-subcortical damage rather that a consolidation deficit related to hippocampal damage. Thus, deficits in both memory and executive function in our sample could be explained by cerebrovascular damage. However, it is also possible that deficits in recognition are not yet evident in this relatively young cohort because of ceiling effects. The relationship between diabetes and lower memory performance changed only modestly after adjusting for vascular risk factors, indirectly suggesting that this association may be independent of cerebrovascular mechanisms. Surprisingly, we found that pre-diabetes, but not diabetes, was associated with worse performance in the color trails 2, a test of executive function. Since diabetes is a more severe and advanced form of hyperglycemia than pre-diabetes, the expectation was that deficits in all domains would be more severe in diabetes, as was found for memory. We do not have an explanation for this finding. Longitudinal observation will allow us to determine the trajectories of cognitive change in all domains and may yield additional information on this observation.

Another important consideration is that individuals with diabetes have lower educational attainment, and this may be related to lower cognitive reserve(90). Lower cognitive reserve may decrease resilience to Alzheimer's and cerebrovascular pathology. However, educational attainment is commonly treated as a confounder and potential source of bias in cognitive testing. The interpretation of the models adjusting for education is difficult because attenuation of effect estimates and statistical significance may be due mediation by cognitive reserve rather than confounding by education. The strengths of our study include a unique age group seldom recruited in studies of aging and cognition, a comprehensive cognitive battery that demonstrated to be sensitive to differences in cognitive performance at a relatively young age, and the ascertainment of prediabetes and NGT status using HbA1c.

Limitations of our study include the cross-sectional nature of the analysis, the lack of neuroimaging data, and the lack of APOE-ε4 genotype, a strong genetic risk factor for cognitive impairment and a modifier of the effects of diabetes on cognition(80, 91, 92). These limitations will be overcome in the future with the completion of the ongoing follow-

up assessments with 24 month intervals, the planned acquisition of brain imaging to ascertain cerebrovascular disease and brain volumes with Magnetic Resonance Imaging, and biomarkers of AD such as amyloid PET and CSF amyloid and Tau, and APOE-ε4 genotyping. Although our neuropsychological battery was comprehensive, it could have benefitted from complementary tests such as those from the NIH toolbox (93). It is possible that having a more comprehensive battery could have helped us detect relationships of glycemia and diabetes status with cognitive performance that were not possible with the available battery. Another potential limitation is the use of HbA1c for the ascertainment of diabetes categories. The boundaries for pre-diabetes and diabetes using HbA1c by ADA criteria were chosen because they correlate with fasting glucose or 2-hour oral glucose tolerance test definitions of pre-diabetes and diabetes (94). However, there have been reported discrepancies between these 2 methods and concerns that use of HbA1c criteria are not as good at oral glucose tolerance test, particularly in ethnic minorities (95). Another concern is that our community-based sample of volunteers is not representative of the community at large or the population of the United States, particularly given the high proportion of pre-diabetes and diabetes that we found. The National Health and Nutrition Examination Survey (NHANES) (96) reported that the standardized prevalence of pre-diabetes in the Unites States population in 2005–2006 was 34.5% in persons aged 40 to 59 years and 37.4% in those aged 60 to 74 years, and the prevalence of diabetes was 12.4% for persons aged 40 to 59 years, and 30% for persons aged 60 to 74 years. The NHANES data was not reported for the age range in our study or for Caribbean-Hispanics, who comprise the majority of our sample. However, it seems reasonable to say that the prevalences in our sample are at least comparable to the National Average, and could be expected to be higher in 2012–2013 given that the projected lifetime risk of diabetes is approximately 40%(97) and a large proportion of this trend is accounted for by non-Hispanic Blacks and Hispanics(98, 99), who have twice the prevalence of diabetes compared to non-Hispanic Whites (98). Lastly, we did not have information on duration of diabetes and on whether it was type 1 or type 2. This may have implications for the types and severity of cognitive impairment found in relation to diabetes.

Our study shows that cognitive deficits related to diabetes and pre-diabetes are apparent in late middle age, emphasizing the necessity of a lifespan approach to the study of the cognitive effects of diabetes. These findings are important from a public heath standpoint because a third of the US population suffers from either diabetes and pre-diabetes, and as shown in our sample, this proportion is alarmingly higher in late middle aged Hispanics in New York City. It Is important to determine the causality of the association between diabetes and cognitive impairment, the underlying mechanisms, and whether the prevention or reversion of pre-diabetes and diabetes can reverse its associated cognitive impairment.

Abbreviations

BMI	body mass index
DBP	diastolic blood pressure
HbA1c	Hemoglobin A1c

HDL	high density lipoprotein
hsCRP	high sensitivity C-Reactive Protein
MAP	mean arterial pressure
NHANES	National Health and Nutrition Examination Survey
NGT	Normal Glucose Tolerance
NOMEM	Northern Manhattan Study of Metabolism and Mind
SBP	systolic blood pressure
SRT	Selective Reminding test
WC	Waist circumference

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Table 1

General characteristics of the cohort and comparison among participants with normal glucose tolerance (NGT), pre-diabetes, and diabetes.

	Entire sample (n=600)	NGT (n=208)	Pre-Diabetes (n=207)	Diabetes (n=185)
Age in years	59.3 ± 2.9	59.1 ± 2.9	59.3 ± 2.8	59.4 ± 3.0
Women	460 (76.7)	152 (72.9)	167 (80.8)	141 (76.2)
Education in years	9.8 ± 4.2	10.6 ± 4.1	9.6 ± 3.9*	9.2 ± 4.5**
Dominican origin	519 (86.5)	171 (82.3)	188 (90.6)*	160 (86.7)*
Body Mass Index (BMI) (kg/m^2)	29.2 ± 5.2	28.0 ± 4.8	29.0 ± 5.3**	30.7 ± 5.2***
Waist circumference (cms)	93.8 ± 24.8	96.5 ± 11.7	97.3 ± 10.1	102.7 ± 16.2***
Waist to hip ratio	0.93 ± 0.08	0.92 ± 0.08	0.92 ± 0.07	0.95 ± 0.08**
Systolic blood pressure (mmHg)	132.6 ± 17.0	131.4 ± 15.9	131.0 ± 14.4	135.9 ± 20.4*
Diastolic blood pressure (mmHg)	78.9 ± 13.9	80.0 ± 12.4	79.0 ± 13.5	77.4 ± 15.8
MAP	96.0 ± 16.5	96.8 ± 14.5	95.8 ± 15.4	95.5 ± 19.6
% Hypertension	212 (35.4)	67(32.1)	69 (33.3)	77 (41.9)*
HbA1c	6.2 ± 1.2	5.4 ± 0.2	5.9 ± 0.2***	7.5 ± 1.6 ***
HDL cholesterol (mg/dL)	52.0 ± 16.2	56.2 ± 18.8	50.2 ± 14.0*	49.4 ± 14.3***
Non-HDL cholesterol (mg/dL)	147.4 ± 39.4	148.7 ± 40.1	149.7 ± 35.8	143.3 ± 42.3
hsCRP (mg/L)	4.56 ± 9.2	3.4 ± 3.9	4.9 ± 12.2*	5.5 ± 9.3*
PHQ-9 Score	2.1 ± 3.5	1.9 ± 3.6	1.9 ± 3.2	2.4 ± 3.6
Tests of memory (words)				
SRT Total Recall	40.7 ± 8.3	41.7 ± 8.3	41.2 ± 7.8	39.0 ± 8.7**
SRT Delayed Recall	5.8 ± 2.1	6.0 ± 2.1	5.8 ± 2.0	5.5 ± 2.2*
SRT Recognition	11.5 ± 1.3	11.5 ± 1.4	11.5 ± 1.1	11.5 ± 1.4
Test of executive abilities (scores)				
Color Trials 1	22.8 ± 21.4	25.2 ± 23.0	20.7 ± 20.0	22.3 ± 20.8
Color Trials 2	27.6 ± 23.9	31.1 ± 26.5	25.0 ± 21.3*	26.6 ± 23.4
Verbal Fluency	33.6 ± 9.9	35.0± 10.6	33.4 ± 8.3	32.4 ± 10.5*

ANOVA was used to compare means across diabetes categories for continuous variables and Likelihood ratio chi-square tests used for categorical variables. First an omnibus test was conducted, and if significant, diabetes and pre-diabetes were compared with NGT. Continuous variables are presented as means ± standard deviations. Categorical outcomes are presented as frequencies (percentages). Significance levels are presented as follows for pairwise comparisons:

* < 0.05

** <0.01

*** < 0.001

Table 2

Relation of glycemia and diabetes status with performance in memory. Diabetes status was defined as normal glucose tolerance (NGT), pre-diabetes, and diabetes.

	Model 1: Adjusted for age and gender		**Model 2: also adjusted for education and Dominican origin.**		**Model 3: also adjusted for BMI, HDL cholesterol, Systolic BP, and hsCRP**	
	Estimate	**p-value**	**Estimate**	**p-value**	**Estimate**	**p-value**
Selective Reminding Test Total recall						
HbA1c (n=600)	−1.07	<.001	−0.80	.004	−0.971	0.002
HbA1c (n=520)*	−1.38	<.001	−1.04	.002	−1.41	<0.001
NGT	0	-	0	-	0	-
Pre-diabetes	−0.59	.46	−0.08	0.91	−0.46	0.59
Diabetes	−2.65	.001	−1.93	.012	−2.06	0.025
Selective Reminding Test Delayed recall						
HbA1c (n=600)	−0.21	.003	−0.16	0.033	−0.23	0.005
HbA1c (n=520)*	−0.27	.002	−0.21	0.024	−0.32	0.004
NGT	0	-	0	-	0	-
Pre-diabetes	−0.19	.33	−0.12	0.55	−0.08	0.71
Diabetes	−0.53	.010	−.40	0.065	−0.40	0.10
Selective Reminding Test Recognition						
HbA1c (n=600)	−0.09	.063	−0.05	0.28	−0.08	0.14
HbA1c (n=520)*	−0.08	.14	−0.04	0.49	−0.09	0.19
NGT	0	-	0	-	0	-
Pre-diabetes	−0.019	.88	−.01	0.90	−0.04	0.75
Diabetes	−0.020	.88	.07	0.60	0.01	0.90

Generalized Linear Models were used to compare the pre-diabetes and diabetes groups to the NGT

*denotes exclusion of 80 persons with diabetes who reported diabetes treatment.

Table 3

Relation of glycemia and diabetes status with performance in executive abilities. Diabetes status was defined as normal glucose tolerance (NGT), pre-diabetes, and diabetes.

	Model 1: Adjusted for age and gender		Model 2: also adjusted for education and Dominican origin.		Model 3: also adjusted for BMI, HDL cholesterol, Systolic BP, and hsCRP	
	Estimate	**p-value**	**Estimate**	**p-value**	**Estimate**	**p-value**
Color trails 1						
HbA1c (n=600)	−1.17	.15	−1.11	.17	−1.12	.64
HbA1c (n=520)*	−0.82	.44	−0.99	.35	−0.75	.55
NGT	0	-	0	-	0	-
Pre-diabetes	−4.58	.043	−4.01	.073	−4.27	.084
Diabetes	−2.98	.20	−2.07	.38	−1.46	.58
Color trails 2						
HbA1c (n=600)	−1.05	.25	−1.01	.27	−0.80	.43
HbA1c (n=520)*	−1.45	.23	−1.68	.17	−1.15	.43
NGT	0	-	0	-	0	-
Pre-diabetes	−6.20	.011	−5.53	.034	−6.45	.022
Diabetes	−4.55	.083	−3.68	.17	−2.97	.31
Verbal fluency						
HbA1c (n=600)	−0.85	.010	−0.58	.07	−0.58	.12
HbA1c (n=520)*	−1.10	.007	−0.79	.050	−0.77	.11
NGT	0	-	0	-	0	-
Pre-diabetes	−1.55	.11	−0.90	0.34	−0.62	.54
Diabetes	−2.58	.012	−1.62	.091	−1.32	.22

Generalized Linear Models were used to compare the pre-diabetes and diabetes groups to the NGT

*denotes exclusion of 80 persons with diabetes who reported diabetes treatment.

Table 4

Relation of glycemia and diabetes status with performance composite measures of memory, executive abilities, and global cognition, ascertained as Z scores. Diabetes status was defined as normal glucose tolerance (NGT), pre-diabetes, and diabetes

	Model 1: Adjusted for age and gender		Model 2: also adjusted for education and Dominican origin.		Model 3: also adjusted for BMI, HDL cholesterol, Systolic BP, and hsCRP	
	Estimate	p-value	Estimate	p-value	Estimate	p-value
Memory Z score						
HbA1c (n=600)	−0.29	<.001	−0.21	.010	−0.28	.002
HbA1c (n=520)*	−0.35	<.001	−0.25	.011	−0.39	.001
NGT	0	-	0	-	0	-
Pre-diabetes	−0.15	.50	−0.07	.74	−0.13	.60
Diabetes	−0.55	.024	−0.33	.16	−0.41	.13
Executive Z score						
HbA1c (n=600)	−0.18	.021	−0.16	.043	−0.15	.081
HbA1c (n=520)*	−0.20	.061	−0.20	.052	−0.17	.17
NGT	0	-	0	-	0	-
Pre-diabetes	−0.56	.014	−0.44	.050	−0.51	.041
Diabetes	−0.51	.031	−0.38	.12	−0.31	.23
Global z score						
HbA1c (n=600)	−0.43	.001	−0.37	.005	−0.43	.004
HbA1c (n=520)*	−0.46	.009	−0.45	.009	−0.54	.009
NGT	0	-	0	-	0	-
Pre-diabetes	−0.70	.063	−0.50	0.18	−0.58	.15
Diabetes	−1.06	.009	−0.79	.044	−0.77	.082

Generalized Linear Models were used to compare the pre-diabetes and diabetes groups to the NGT

*denotes exclusion of 80 persons with diabetes who reported diabetes treatment.