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Adolescent fasting glucose and midlife brain health

High-normal adolescent fasting plasma glucose is associated with poorer midlife brain health: Bogalusa Heart Study

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Context: It is unclear how adolescent glycemic status relates to brain health in adulthood.
Objective: To assess the association between adolescent fasting plasma glucose (FPG) and MRI-based brain measures in midlife.
Design: Between 1973 and 1992, the Bogalusa Heart Study (BHS) collected FPG from children 3 to 18 years old, and followed up between 1992 and 2018. Cognitive tests and brain MRI were collected in 2013-2016 and 2018.
Setting: Observational longitudinal cohort study.
Participants: Of 1298 contacted BHS participants, 74 completed screening and 50 completed MRI.
Main Outcomes and Measures: Mean FPG per participant at ages less than 20, 20-40, and over 40 years old; brain white matter hyperintensity volume (WMH), gray matter volume (GM), and fMRI activation to a Stroop task; tests of logical and working memory, executive function, and semantic fluency.
Results: At MRI, participants were middle-aged (51.3 +/- 4.4 years) and predominantly female (74%) and Caucasian (74%). Mean FPG was impaired for 0, 2, and 9 participants in pre-20, 20-40, and over 40 periods. Pre-20 mean FPG above the pre-20 median value (*i.e.*, above 83.5 mg/dl) was associated with greater WMH (mean difference: 0.029 percent of total cranial volume, CI: [0.0059, 0.052], p=.015) and less fMRI activation (-1.41 units, [-2.78,-0.05] , p=.043) on midlife MRI, compared to below-median mean FPG. Controlling for over-40 mean FPG status did not substantially modify the associations. Cognitive scores did not differ by pre-20 mean FPG.

Conclusions: High-normal adolescent FPG may be associated with preclinical brain changes in midlife.

In this study, adolescent fasting plasma glucose in the high-normal range was associated with poorer brain structure and function in midlife irrespective of midlife fasting plasma glucose values.

Introduction

Type 2 diabetes mellitus (T2DM) is present in over 25% of US adults aged 65 years or older and prediabetes is present in more than 48%.[1,2] T2DM doubles the risk of cognitive impairment and dementia and greatly increases health care needs and costs. [3] Similarly, prediabetes increases risk for dementia [4]. However, it remains unclear whether improving glycemic control is a viable approach for reducing risk of cognitive impairment in prediabetes or T2DM [5-10 11-18].

One reason for inconsistencies in the relationship between cognitive outcomes and glycemic control is that lifespan exposures to the metabolic disturbances associated with T2DM, as well as clinically-silent brain injury, are rarely accounted for. The progression from cardiometabolic risk factors, to insulin resistance, to the beta cell dysfunction and hyperglycemia that characterize T2DM, develops insidiously over decades, starting as early as childhood [19,20]. Similarly, the brain changes that culminate in Alzheimer-related and vascular-related neuropathology develop insidiously over many years [21,22]. T2DM-related and cognitive-decline-related biological mechanisms may interact to impact the brain in complex ways during their progression [23-28 29,30]. Thus, it is possible that metabolic disturbances as early as childhood could influence brain health and cognitive functioning decades later, independent of metabolic status at that later time [31-35]. However, at this time it is not clear what effect, if any, metabolic exposures in childhood and young adulthood may have on brain health and cognitive function in midlife and old age.

One specific unknown is whether clinical thresholds for identifying prediabetes and T2DM are adequate to identify children and young adults at increased risk of adverse brain outcomes decades later. Fasting plasma glucose (FPG) thresholds for the clinical diagnosis of T2DM (≥ 126 mg/dl) and prediabetes (≥ 100 mg/dl) are based on an extensive evidence base linking these thresholds to risks of various adverse outcomes [36]. However, this evidence is based primarily on FPG exposures from midlife onward, and late-life cognitive decline was not considered when determining the thresholds. Among older adults, FPG at the high end of the normal range ("high-normal FPG") may be associated with reduced brain tissue volumes and increased rates of brain atrophy.[37,38] Among children, high-normal FPG may be associated with poorer beta cell function concurrently[39,40] and in the future [41]. But there is little data relating FPG to brain outcomes to determine whether current clinical thresholds are adequate to identify individuals at increased risk of cognitive decline.

This study assesses the associations between FPG at different stages of the lifespan and cognition-relevant MRI markers of midlife brain health[21,22,42,43], and assesses the adequacy of current clinical thresholds to identify individuals whose glycemic status is associated with an increased risk of adverse brain outcomes, using data from the Bogalusa Heart Study (BHS).

Materials and Methods

Study sample.

The BHS began in 1973 as a community-based cohort study of atherosclerosis and risk factors for cardiovascular disease in a bi-racial population of children in a semi-rural town in southeastern Louisiana [44]. Most participants enrolled as children, and many attended regular follow-up visits through adulthood. Between 2013 and 2016, cognitive tests were administered

for the first time to 1,298 participants. Inclusion criteria for this study included prior participation in BHS, completion of cognitive testing, lack of MRI contraindications, and right handedness (to prevent confounding effects of handedness on completion of fMRI tasks). A CONSORT diagram is shown in Figure 1. Briefly, the 1298 individuals who completed cognitive testing previously were contacted about this project via mailed flyers. From that group, 74 individuals completed screening procedures and 9 were deemed ineligible due to MRI contraindication or left-handedness. Of the remaining 65 individuals, 50 completed the required MRI; 2 failed to arrive for the MRI; 1 had to halt the MRI early due to claustrophobia; and 12 were ready to be scheduled for MRI at the time the study reached its target of 50 completers. Participants in this study provided informed consent. The study was overseen by the Institutional Review Board of Pennington Biomedical Research Center.

Physiological measures.
Measurement of FPG and insulin have been described previously[45-47]. Both were measured following a standardized protocol at a centralized laboratory. FPG were analyzed by an enzymatic method using the Beckman glucose analyzer[48]. Plasma insulin concentrations were measured using a radioimmunoassay procedure (Phadebas; Pharmacia Diagnostics, Piscataway, NJ).

MRI acquisition.
Brain MRI scans were performed on a GE Discovery 3T scanner at Pennington Biomedical Research Center. A 32-channel phased array head coil was used. Sequences included: 1. T1-weighted 3D BRAVO (voxel size, .94 x .94 x 1.2 mm^3; voxel array, 256 x 256 x 140; flip angle, 12 degrees; NEX, 2; TI, 450; bandwidth, 31.25; total run time, 6:41); 2. Axial 2D FLAIR (voxel size, 1.07 x 1.07 x 2 mm^3; voxel array, 224 x 224 x 69; flip angle, 160 degrees; TE, 95 ms; TR, 9000 ms; TI, 2250 ms; NEX, 1; bandwidth, 31.25; total run time, 4:58); 3. Axial 2D gradient echo EPI BOLD (voxel size, 3x3x3 mm^3; voxel array, 64x64x43; flip angle, 90 degrees; TE, 35 ms; TR, 2500 ms; NEX, 1). Participants wore a respiratory monitoring belt and pulse oxygenation sensor to model respiratory and cardiac effects on the BOLD signal [49].

Cognitive tests.
Cognitive testing included Logical Memory I and II tests of verbal memory [14], Digit Span Forwards and Backwards tests of attention and concentration [14], Trail Making Test (TMT), part A, and the Digit Coding test.[14] The Letter and Word reading tests, from the Wide Range Achievement Test (WRAT), measure participants' ability to decode and offer a general level of academic achievement. Measurement of participant current vocabulary was used to further reflect achieved education.[15]

fMRI task.
Our Stroop task tested inhibitory control in the context of negative feedback and time-pressured responses [50]. In each trial, for 400-5000 ms participants saw one probe word and four target words that were names of colors. The task was to identify the target word whose color matched that of the probe. In the congruent (incongruent) condition, word meaning matched (did not match) the color it was printed in. Correct (incorrect) responses on 3 consecutive incongruent trials prompted a 300 ms reduction (increase) in stimulus duration. Four 52-60 second incongruent trial blocks were interleaved with 4 congruent trial blocks, each of which had the same number of trials as the previous incongruent block. The inter-block interval was 10-17 seconds. Stroop task performance was summarized in terms of task accuracy (*i.e.*, percent of trials answered correctly), mean reaction times to congruent and incongruent trials, and the so-

called interference effect (*i.e.*, the difference in mean reaction times between incongruent and congruent conditions).

Structural MRI data analysis.
Post-processing of structural MRI data follows techniques described previously [51-53]. Key FLAIR processing steps include manual removal of non-brain elements from the FLAIR image by operator guided tracing of the dura mater within the cranial vault, resulting in delineation of a total cranial volume (TCV) region; MRI non-uniformity correction of the TCV [54]; thresholding of TCV into brain and non-brain tissues [55]; fitting a single Gaussian distribution to the brain tissue intensity distribution and labeling of all voxels with intensity greater than 3.5 standard deviations above the mean as WMH [56]. Key T1-weighted image processing steps include MRI non-uniformity correction [57]; and segmentation of gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) by a Bayesian maximum-likelihood expectation-maximization algorithm [58]. The primary measures of interest in subsequent analysis were volumes of WMH, GM, and WM, each expressed as a percentage of TCV.

fMRI data preprocessing.
Preprocessing of fMRI included slice timing correction, head motion correction, smoothing, co-registration to the T1-weighted image, and warping T1-weighted data to a standard coordinate frame (using Statistical Parametric Mapping 12). Cardiac and respiratory time series were regressed out of the data using RETROICOR [49]. Time points with excess head rotation (>1.5 degrees) or translation (1.5 mm) were removed from analysis. Voxel time series were entered into a first-level general linear model, where the experimental design was modeled as boxcar functions convolved with the canonical hemodynamic response function.

fMRI activation analysis.
The *inhibitory control* contrast was measured between congruent and incongruent blocks in the Stroop task. Data from incorrect, missing, or pre-attentive (i.e., < 200 ms) responses were removed from analysis. The 3D coordinates of ROIs that repeatably show fMRI signal differences in this version of the Stroop task under the inhibitory control contrast (covering occipital, fusiform, angular, middle frontal, inferior frontal, superior frontal, cingulate, and middle temporal gyri; and within the cerebellum, precuneus, insula, lentiform nucleus, thalamus) were identified from a published report [50]. The mean beta value for the inhibitory control contrast among all voxels in an 3-mm-radius sphere centered at each ROI location was calculated. Principal components analysis (PCA) was then applied to the set of all ROI means. PCA is a dimension reduction technique that reduces a given large set of measurements (in this case the ROI means) to a smaller number of numbers (the PCA *coefficients*) that, together, explain the greatest amount of variability in the measurements. We reduced each set of ROI means to a single PCA coefficient that provided a univariate summary of the overall level of activation of all ROIs under the inhibitory control contrast (referred to hereafter as “Stroop activation”).

Statistical analysis.
Statistical analysis focused on summarizing FPG within different epochs of the lifespan, and relating FPG within those epochs to MRI outcome measures. We separated all FPG measurements into three epochs: those collected before age 20 (“pre-20”), between ages 20 and 40 (“20-40”), and after age 40 (“over-40”). For each individual, the mean FPG within each epoch was calculated. The median pre-20 mean FPG was then calculated, and mean FPG values were categorized in terms of whether they were below this threshold (“low-normal”) or above it. The range of mean FPG values above the threshold is referred to as “high-normal” in the pre-20

epoch since no values were in the impaired range in this epoch; and as "high-normal or impaired" in the 20-40 epoch since 2 individuals had values in the impaired range in this epoch. To assess possible legacy effects of adolescent mean FPG levels on midlife MRI measures, ANOVA models were used to identify differences in MRI and cognitive measures between individuals with low-normal and high-normal mean FPG during the pre-20 epoch. Similar ANOVA models were used to identify differences in MRI and cognitive measures between individuals with low-normal and high-normal or impaired mean FPG during the 20-40 epoch. Each of these models included the mean FPG category in that epoch as the primary covariate of interest, and sex, race, and age at the time of MRI as nuisance covariates. In addition, we added mean FPG category in the over-40 epoch as a nuisance covariate, to assess whether associations between FPG status earlier in life and midlife MRI variables was independent of midlife FPG status.

Results

Description of sample.

A summary of participant characteristics is shown in Table 1. Participants were in middle age at the time of their MRI (mean age: 51.3), predominantly female (74%), and were Caucasian (74%) or African American (26%). The average participant provided FPG measurements covering a span from early adolescence (12.1 years) to middle age (50.4 years). The number of FPG measurements per participant was approximately 2 to 3 per epoch on average (an average of 2.9, 3.8, and 2.4 measurements in the pre-20, 20-40, and over-40 epochs). Distributions of gray matter, white matter, and WMH volumes were similar to those of a similar, nominally-healthy epidemiological cohort of similar age [62]. Demographic variables, cardiometabolic variables, and cognitive measurements were largely similar in this group compared to the broader set of BHS participants they were sampled from (Table 1). The current group displayed higher scores on the Digit Coding test than the broader sample did, and had provided a relatively larger number of FPG measurements during the 20-40 epoch. The current group had relatively lower representation of male participants and African American participants than the broader sample did.

Glycemic trajectories.

Trajectories of FPG over time for each participant are plotted in Figure 2, along with boundaries between epochs, accepted thresholds for the diagnosis of prediabetes (≥ 100 mg/dl) and T2DM (≥ 126 mg/dl), and the median pre-20 mean FPG value used to define the low-normal group. The data shows a general trend of greater FPG variability in later epochs, with some individuals increasing significantly in the over-40 years. The number of individuals with mean FPG values in the prediabetes or T2DM range differed by epoch (pre-20: 0; 20-40: 2; over-40: 9). Of the 9 individuals with mean FPG values in the prediabetes or T2DM range in the over-40 epoch, 2 had mean FPG values in the prediabetes or T2DM range, and 2 had mean FPG values in the high-normal range, in the 20-40 epoch. Of those 9 individuals, 4 had mean FPG values in the high-normal range in the pre-20 epoch. Other cardiometabolic indicators during each epoch are shown in Table 2.

Mean pre-20 FPG and MRI measures.

High-normal pre-20 mean FPG was associated with significantly greater WMH volume as a percentage of TCV (mean difference: 0.029 percent, CI: [0.0059, 0.052], p=.015) and significantly less Stroop activation (mean difference, -1.41 units, 95% CI [-2.78,-0.05], p=.043), compared to low-normal pre-20 mean FPG (see Figure 3). Differences in GM, WM, and CSF

volumes between those with high-normal and low-normal pre-20 mean FPG were not statistically significant. Correcting the MRI measures for TCV did not substantially modify these associations. When over-40 mean FPG was added to these models, the significant effects of mean FPG category on WMH volume (p=.021) and Stroop activation (p=.045) remained statistically significant, with minimal attenuation of significance.

Mean 20-40 FPG and MRI measures.
High-normal or impaired mean FPG in the 20-40 epoch was associated with significantly greater WMH volume (mean difference .029 percent, CI [0.0004, 0.058], p=.047), less GM volume (mean difference -0.97 percent, CI [-1.91, -0.033], p=.043), and a trend toward less Stroop activation (mean difference -1.57 units, CI [-3.27, 0.13], p=.070), compared to low-normal 20-40 mean FPG. Differences in WM and CSF volumes between those with high-normal or impaired and low-normal 20-40 mean FPG were not statistically significant. Correcting the MRI measures for TCV did not substantially modify these associations. When over-40 mean FPG was added to these models, the significant effects of mean FPG category on WMH and GM volumes were no longer statistically significant.

Stroop task performance and cognitive tests.
Stroop task accuracy (mean 69% +/- standard deviation 9.1%) was similar to that seen in one prior study utilizing the same, adaptive version of the task [50,63]. Mean reaction time (1645 +/- 617 ms) was also in line with that of a prior publication [63]. None of the performance measures were associated with mean FPG status in the pre-20 or 20-40 epochs, in models that controlled for sex, race, and age at the time of MRI scan (all p>.05). Scores on none of the cognitive tests were associated with mean FPG status in any epoch (all p>.05).

Discussion

In this study, middle-aged, Deep Southern, semi-rural individuals who during early adolescence had exhibited mean FPG in the high-normal range (*i.e.*, above a low-normal threshold, but still below the accepted cutoff for prediabetes) showed signs of poorer MRI-based markers of brain health in midlife, even after controlling for midlife FPG, suggesting a persistent legacy effect of pre-20 glycemic status as a risk marker. There are two key implications of this finding. First, it reinforces the importance of elevated early-life FPG as a risk marker by identifying poorer midlife brain health as another possible outcome of it [64,65 66]. Second, it suggests that established clinical thresholds for T2DM (FPG ≥ 126 mg/dl) and prediabetes (≥ 100 mg/dl) may be inadequate to identify adolescents with an increased risk of poorer midlife brain health.

The finding that early-life FPG may be associated with brain health decades later adds to a growing literature suggesting that early life experiences influence health outcomes later in life[31-34]. This literature points to critical periods during which exposure to environmental or physiologic stimuli induces "programming" of a fixed future aspect of organ function [35]. Differing brain regions grow at different paces during the first three decades of life [67], and complex hormonal signaling events modulate those trajectories [68-71]. Because insulin- and glucose-related signaling molecules are involved in brain growth and maturation [72-76], it is plausible that metabolic disturbances associated with elevated FPG could result in consequences for brain development proximally as well as years into the future. Testing this hypothesis will require longitudinal series of brain and metabolic measures collected throughout adolescence, young adulthood, and midlife.

A striking aspect of our findings is that no early-life mean FPG values were in the prediabetes or T2DM range. Individuals who had "high-normal" mean FPG values in that epoch (greater than 83.5 mg/dl, less than 100 mg/dl) had greater WMH volume and less brain activation to a cognitive task. Increased risks of poorer outcomes among those with high-normal FPG has been reported previously, [37,3839-41], although large-scale epidemiological data including adolescent and midlife data is highly limited. Our study was too small to determine whether midlife brain outcomes scaled continuously and linearly with adolescent mean FPG across the entire normal range, or whether there is a critical threshold value above which poorer brain outcomes are especially probable. Large-scale studies of these questions are needed, because an association between high-normal adolescent FPG and adverse midlife outcomes could in the long run trigger a shift in clinical practice toward identifying such individuals and intervening early to lower FPG.

Associations between mean FPG and midlife brain outcomes were similar within adolescent and early adulthood epochs, with two notable differences. First, midlife gray matter volume was associated with FPG status only in young adulthood. Prior studies suggest that gray matter deficits, representing cell death, represent a final common pathway that can follow multiple modes of cell distress, including lesion formation (represented by WMHs) and neuronal dysfunction (represented by fMRI) [21,77-79]. Thus, if the young adults high-normal or impaired mean FPG were exposed to a greater duration or severity of brain injury processes than corresponding adolescents, we would expect gray matter deficits to appear only in the young adults. Second, while associations between high-normal mean FPG in the adolescent epoch and poorer midlife brain outcomes remained significant after controlling for midlife FPG status, the same was not true of high-normal or impaired mean FPG in the young adulthood epoch. This suggests that the young adults with high-normal or impaired mean FPG may simply be ones who go on to have elevated FPG in midlife and thus might have poorer brain health due to midlife status alone. A larger study is needed to determine the degree to which both epochs of the lifespan are independently associated with midlife brain outcomes.

The key strength of this study is its utilization of lifespan data from a large, community-based, bi-racial, Deep Southern, semi-rural epidemiological cohort. The key limitation is its lack of brain MRI concurrent with early-life FPG. This limitation was unavoidable—functional MRI did not become available until roughly 20 years after the first FPG measurement. Our small sample size and lack of other glycemic measures such as hemoglobin A1C (which also was not widely utilized until long after cohort initiation) are additional limitations.

In conclusion, individuals with mean FPG at the high end of the normal range during adolescence went on to exhibit more WMHs and less fMRI activation during a cognitive task at midlife, independent of midlife mean FPG. The results could have implications for identification of youth at risk of poorer midlife brain health.

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Figure 1: CONSORT diagram for the current study.

Figure 2: Real trajectories of fasting plasma glucose in study participants are shown. Mean fasting plasma glucose values were calculated during the pre-20, 20-40, and over-40 periods of the lifespan. Individuals were categorized according to whether the mean fasting plasma glucose value was above, vs. below, the pre-20 sample median value of 83.5 mg/dl.

Figure 3: White mater hyperintensity (WMH) volume at a midlife MRI was significantly elevated (left) and fMRI activation to a Stroop task was significantly less (right), among those who had mean FPG above the median value during the pre-20 period.

Table 1: Demographic, cardiometabolic, and neurocognitive characteristics of participants in the current study as well as participants in the most recent Bogaulsa Heart Study cognitive assessment, from which current study participants were sampled. P values for t tests that assess differences between the two groups are provided in the third column.

	This study	Most recent BHS cognitive assessment	p-value
N	**50**	**1298**	
Sex (% male)	**26**	**41.1**	
Race (% African American)	**26**	**34.5**	
Age at first FPG (years)	**12.9 +/- 4.8**	**12.4+/-6.0**	**0.5606**
Age at most recent FPG (years)	**48.8 +/- 4.7**	**48.1+/-5.2**	**0.3488**
Number of FPG measurements pre-20	**2.5 +/- 1.3**	**2.6+/-1.2**	**0.5644**
Number of FPG measurements 20-40	**3.6 +/- 1.2**	**2.7+/-1.3**	**<0.001**
Number of FPG measurements over 40	**2.1 +/- 1.2**	**1.8+/-1.2**	**0.083**
BMI (kg/m^2)	**30.9 +/- 7.4**	**31.4 +/- 7.8**	**0.656**
SBP (mm Hg)	**121.3 +/- 15.4**	**123.6 +/- 17.3**	**0.3546**
DBP (mm Hg)	**76.3 +/- 9.3**	**78.8 +/-11.7**	**0.1358**
Total cholesterol (mg/dl)	**186.6 +/- 34.3**	**192.7 +/- 40.4**	**0.2925**
Digit Coding	**65.6 +/- 16.4**	**58.8 +/- 17.7**	**0.0076**
Logical Memory 2 Total Score	**17.2 +/- 6.9**	**16.0+/-7.3**	**0.2533**
Digit Span Backward	**7.7 +/- 2.2**	**7.7+/-2.5**	**1**
Trails Making Test Part B (seconds)	**57.4 +/- 28.8**	**62.3+/-30.1**	**0.2581**
Age at MRI (years)	**51.3 +/- 4.4**	**NA**	
Gray matter volume on MRI (% of TCV)	**41 +/- 1.4**	**NA**	
White matter volume on MRI (% of TCV)	**34 +/- 1.6**	**NA**	
WMH volume on MRI (% of TCV)	**.03 +/- .04**	**NA**	

Table 2: Metabolic markers measured at clinical visits within the three time periods (mean +/- standard deviation). Values are broken down by the mean FPG measured at clinical visits within that time period. * Significantly different from corresponding low-normal mean FPG group by two-tailed T tests.

	Below age 20		Ages 20-40		Above age 40	
	Low-normal mean FPG	High-normal mean FPG	Low-normal mean FPG	High-normal or impaired mean FPG	Low-normal mean FPG	High-normal or impaired mean FPG
N	22	26	37	12	6	42
Mean fasting glucose	79.0+/-3.3	87.2+/-3.93*	77.8+/-3.85	89.3+/-7.2*	79.3+/-3.13	97.4+/-12.9*
Mean BMI	18.2+/-2.4	22.1+/-5.5*	27.9+/-6.5	33.8+/-7.7	26.0+/-3.1	31.6+/-6.6*
Mean HOMA	2.3+/-1.1	2.83+/-1.2	1.75+/-.91	4.19+/-4.0	.97+/-.25	3.8+/-2.1*
Mean SBP	101.8+/-8.0	106.4+/-8.0	108.8+/-8.9	118.3+/-13.3*	124.5+/-22.9	120.6+/-13.8
Mean DBP	64.0+/-6.4	66.5+/-6.4	72.1+/-5.2	75.5+/-7.68	78.4+/-13.5	78.0+/-7.9