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Race and sex differences in the association between lifespan glycemic status and midlife cognitive function: the Bogalusa heart study

Kathryn L. Gwizdala [ID] [1]*, Lydia A. Bazzano[2],
Robert L. Newton Jr.[1†] and Owen T. Carmichael [ID] [3†]

[1]Physical Activity and Ethnic Minority Health Laboratory, Department of Population and Public Health Sciences, Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, LA, United States, [2]Tulane Center for Lifespan Epidemiology Research, Tulane University School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA, United States, [3]Biomedical Imaging Center, Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, LA, United States

Introduction: Glycemic markers throughout life are associated with increased risk of midlife cognitive decline, yet it is unclear whether these associations differ by race and sex.

Methods: This study used cross-sectional analysis of prospectively maintained cohort. 1,295 participants in the Bogalusa Heart Study, a biracial epidemiological cohort located in a micropolitan area core setting, provided fasting plasma insulin (FPI) and glucose (FPG) biannually from 1973 to 2016. Memory, executive function (EF), attention, working memory (WM), and global cognition (GC), collected 2013–2016. Glycemic markers (i.e., FPG, FPI, and HOMA-IR) averaged within lifespan epochs (≤20 years, childhood/adolescence (C/A); 21−40 years, early adulthood (EA); and 40−58 years, midlife). Linear regression models were analyzed for each epoch and separate models were analyzed with sex and race, education as a covariate.

Results: Sample was 59% women, 34% African American (AA). Among women, higher C/A FPG was associated with poorer memory and poorer GC. Higher EA FPG was associated with poorer WM. Among men, higher EA HOMA-IR was associated with worse attention. Higher C/A HOMA-IR and FPI were associated with *better* memory, as was higher EA FPI. Among AA, higher C/A FPG was associated with worse attention, EF, and GC. Higher EA HOMA-IR was associated with worse attention. Higher midlife FPI and C/A HOMA-IR were associated with worse WM and EF among White Americans (WAs).

Discussion: Markers indicative of hyperglycemia at different epochs were associated with worse midlife cognition in women, AAs, and WAs; but not in men. Differences in the relationship between lifespan glycemic exposures and midlife cognition could reflect broader health disparities.

1 Introduction

Type 2 diabetes is highly prevalent (1), and persons with diabetes (PWDs) have an increased risk of developing dementia and cognitive decline compared to those without the disease (2). An increased risk of dementia and cognitive decline may even extend to individuals exhibiting physiological precursors of diabetes including insulin resistance and hyperglycemia (3, 4). Yet, evidence that treating diabetes lowers the risk of dementia and cognitive decline is highly mixed (5–7), suggesting that our understanding of factors that influence the impact of diabetes-related metabolic processes on risk for dementia and cognitive decline is incomplete.

One such factor is race. Race is associated with differential health exposures that have the potential to influence the association between glycemic control and cognition. African Americans have twice the risk of developing cognitive impairment, and higher rates of diabetes and uncontrolled diabetes, in comparison to their White American counterparts (8). Socioeconomic factors including poorer access to healthcare and environmental stressors such as racial discrimination and neighborhood disadvantage exacerbate health disparities and are hypothesized to contribute to race disparities in cognitive outcomes (9, 10). Biological factors could also contribute to such race disparities: one study found that postmenopausal African American women had less of an increase in cardiorespiratory fitness following exercise training than white women did, for example (11). Older African Americans with diabetes exhibit a greater decline in circulating glucose levels prior to dementia diagnosis than corresponding White Americans with diabetes as well (12). In addition, at least one study has suggested that the relationship between diabetes and cognitive decline is stronger in African Americans compared to White Americans (8). Unfortunately, the evidence base supporting race differences, between African Americans and White Americans, in associations between glycemic control and cognition is small due to a long history of African American under-representation in health and aging research (13). For these reasons, it is imperative to assess if there are differences between African Americans and White Americans in the relationship between glycemic exposures and cognitive outcomes.

Sex is an additional factor that has the potential to influence the association between glycemic control and cognition. Women have higher risk for late life cognitive decline, dementia, AD, and vascular dementia than men (14, 15). However, a recent trial reported that women with diabetes had a *lower* risk for cognitive decline and dementia than corresponding men with diabetes (16), suggesting that sex differences in risk of cognitive outcomes may be modulated by glycemic control. Differences in endogenous sex hormones could also contribute to sex differences in glycemic-cognition relationships, as sex hormones have been found to modulate glycemic control and cognitive outcomes differently in men and women (17, 18). Finally, psychosocial and lifestyle factors that commonly differ by sex, such as education, occupation, or physical activity, may contribute to cognitive decline independently of, or interactively with, glycemic control (19). As a result, examining sex differences in relationships between glycemic exposures and cognitive outcomes is critically important to understand modifiers of the glycemic-cognitive relationship.

Finally, glycemic control-cognition relationships could be influenced by when in the lifespan glycemic control is measured. Most studies are cross-sectional or lack measurements from distal epochs of the lifespan, i.e., studies of middle aged and older adults generally lack measurements from youth and young adulthood. These studies generally suggest that poorer midlife to late life glycemic control is associated with a greater risk of late life cognitive decline (20, 21). A small number of cross sectional studies suggest that obese adolescents with type 2 diabetes have worse cognitive functioning and brain outcomes than corresponding metabolically healthy adolescents do (22, 23). Studies that relate early-life metabolic exposures to midlife cognitive outcomes are scarce, despite initial evidence that such exposures may affect the brain (24). This evidence suggests that relationships between midlife or late-life glycemic control and late-life cognitive function may be modified by glycemic control earlier in life, and therefore motivate further investigation of early life glycemic control and cognition later in life.

This study aimed to evaluate race and sex differences in the association between childhood to midlife glycemic markers and midlife cognitive function in a biracial population-based epidemiological cohort located in a micropolitan area core (25). The cohort was composed of individuals who self-identified as either White or African American. Within the framework of (26), we focused on Question 3: race and sex differences in the relationship between exposure (glycemic markers) and outcome (cognitive function). Together with a rigorous analysis of race and sex differences in the prevalences of poor glycemic control (Question 2) and low cognitive function (Question 1) in this cohort, our analysis could contribute to a better understanding of the possible impact that enhancing glycemic control within specific race and sex groups could theoretically have on disparities in cognitive function. We hypothesized that worse glycemic markers early in life would be associated with worse cognitive function in midlife, but that relationships between worse glycemic markers and worse cognitive function would be more severe among women and African Americans in comparison to men and White Americans.

2 Methods

2.1 Study design and population

Participants were enrolled in the Bogalusa Heart Study, a biracial population-based cohort of self-identified White and African Americans in Louisiana located in a micropolitan area core (25, 27). Individuals have been followed from childhood to adulthood on roughly a biannual basis for over 40 years. 1298 participants took part in the cognitive test visits between 2013 and 2016. Six individuals were removed from analysis for a total of 1,292 due to missing cognitive tests and education data (Shown in Figure 1). The Six excluded individuals were similar to the full sample ($n = 1,292$) which can be seen in the Supplementary Table 1.
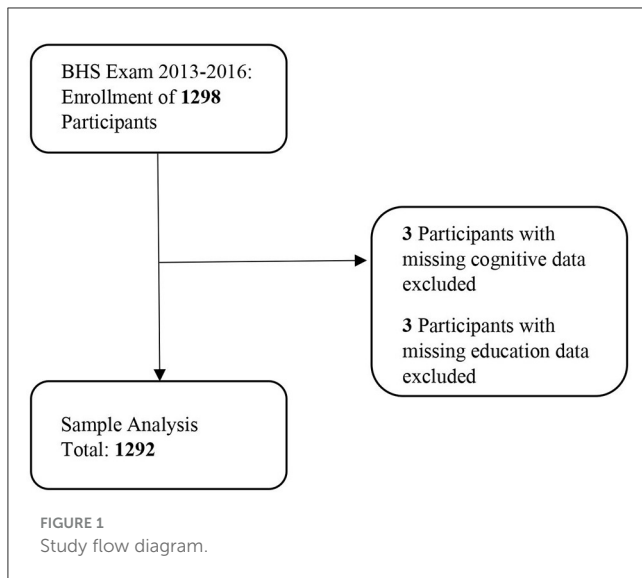
2.2 Standard protocol approvals, registrations, and patient consents

This study was approved by the Institutional Review Board at Tulane University and all participants provided informed consent.

2.3 Glycemic markers variables

Fasting plasma glucose (FPG) and insulin (FPI) collection, as well as processing procedures, have been described previously (28). Briefly, plasma insulin was analyzed using a radioimmunoassay procedure (Phadebas; Pharmacia Diagnostics, Piscataway, NJ) and plasma glucose was quantified via a Beckman glucose analyzer. Insulin and glucose measurements began during the 4th round of visits in 1976. Insulin resistance was characterized via the homeostasis model assessment of insulin resistance (HOMA-IR) utilizing the following formula: fasting insulin (μU/mL) x fasting glucose (mmol/L)/22.5 (29). Worse glycemic markers were considered to be higher levels of FPG, and FPI and higher HOMA-IR.

2.4 Cognition measures

The cognitive tests consisted of memory measures including logical memory I (narrative memory free recall), logical memory II (long term narrative memory free recall), and logical memory II R (long term memory recognition) from the Wechsler Memory Scale III (30); executive function measures including digit span backward and Trail Making B tests (31, 32), attention including Trail Making A test (32), and working memory including digit span forward (31); and a global cognition composite score created by averaging the z-scores of the domain tests (33).

2.5 Covariates

Race, sex, and years of education were included in analyses. Race was self-identified and included White Americans and African Americans. Data on ethnicity (Hispanic vs. non-Hispanic White Americans) was not reported historically by Bogalusa Heart Study participants. Sex was self-identified and included men and women. Years of education was self-reported.

2.6 Statistical analysis

The groups of interest were men, women, White Americans, and African Americans. The glycemic marker predictors of interest included FPI, FPG, and HOMA-IR averaged within one epoch of the lifespan. The epochs covered birth to 20 years of age (childhood/adolescence), 21- 40 years of age (early adulthood), and 40–58 years of age (midlife). The cognitive outcomes included logical memory I, logical memory II, logical memory II R, digit span forward and backward, Trail Making A and B tests, and global cognition. The z-scores of the individual tests were utilized for analyses.

Separate linear regression models were run, each of which included one sex or race group of interest, had one glycemic marker predictor of interest, had one cognitive outcome of interest, and had years of education as a covariate (with sex as a covariate for models grouped by race and race as a covariate for models grouped by sex). Modeling sex and race groups separately allows for the relationship between glycemic markers and cognitive outcomes to have different estimates (slopes), whereas controlling for these variables pools the estimate of these two groups (i.e., men/women or African American/White American) together and only allows the intercept to be different. R pseudocode for an example model is as follows: lm (formula = Global Cognition ~ Mean Glucose [early adulthood epoch] + Race + Years of Education). We considered including household income as a proxy measure of socioeconomic status into these models, but co-linearity between income and education was high enough to warrant concern about model stability. Models that included income instead of education as a covariate provided similar parameter estimates and goodness of fit compared to those that included education (data not shown). Models that included education are shown in the Results section because that variable was available from a larger sample of individuals. Each model was evaluated with an F test for model fit and a double-sided p-value threshold of 0.05.

Outliers among the cognitive and glycemic variables (i.e., outliers were above the 75th or below the 25th percentile by a factor of 3 times the interquartile range) were identified and removed. Outliers were removed from the glycemic variables in each lifespan epoch: childhood/adolescence (31 insulin, 20 glucose, 36 HOMA-IR outliers removed), early adulthood (39 insulin, 41 glucose, 47 HOMA-IR outliers), and midlife (12 insulin, 72 glucose, 15 HOMA-IR outliers). No outliers removed for the global cognition composite score, logical memory I and II, and digit span backwards. There were 4 outliers removed for logical memory II recognition, 1 outlier

TABLE 1 Participant characteristics: demographic and metabolic.

Measure	Overall	Men	Women	p-value, 95% CI	White American	African American	p-value, 95% CI
Sample size	1292	530	762	-	848	444	-
Sex (% Women)	59%	-	-	-	57%	63%	-
Race (% African American)	34%	31%	37%	-	-	-	-
Education	13.32 ± 2.48	13.09 ± 2.44	13.47 ± 2.5	**p < 0.01, (−0.65, −0.11)**	13.67 ± 2.6	12.64 ± 2.09	**p < 0.001, (0.77, 1.3)**
Childhood/Adolescence Epoch ($\leq$20 years)							
Glucose (mg/dL)	84.57 ± 7.01 n = 1,229	86.66 ± 7.05 n = 504	83.11 ± 6.6 n = 725	**p < 0.001, (2.76, 4.33)**	85.09 ± 6.53 n = 797	83.6 ± 7.73 n = 432	**p < 0.001, (0.64, 2.36)**
Insulin (mg/dL)	13.31 ± 9.28 n = 938	12.9 ± 8.78 n = 364	13.57 ± 9.58 n = 574	p > 0.05, (−1.86, 0.53)	12.49 ± 7.95 n = 596	14.73 ± 11.09 n = 342	**p < 0.01, (−3.58, −0.90)**
HOMA-IR	2.79 ± 2.18 n = 938	2.76 ± 1.98 n = 364	2.81 ± 2.3 n = 574	p > 0.05, (−0.33, 0.23)	2.63 ± 1.88 n = 596	3.07 ± 2.61 n = 342	**p < 0.01, (−0.75, −0.12)**
Early adulthood Epoch (21−40 years)							
Glucose (mg/dL)	85.87 ± 18.06 n = 1,108	89.03 ± 19.09 n = 437	83.81 ± 17.07 n = 671	**p < 0.001, (3.01, 7.43)**	84.24 ± 13.06 n = 733	89.05 ± 24.83 n = 375	**p < 0.001, (−7.50, −2.12)**
Insulin (mg/dL)	12.44 ± 9.7 n = 1,071	11.9 ± 9.23 n = 417	12.79 ± 9.98 n = 654	p > 0.05, (−2.06, 0.28)	11.18 ± 6.44 n = 722	15.05 ±13.9 n = 349	**p < 0.001, (−5.41, −2.34)**
HOMA-IR	2.77 ± 3.07 n = 1,057	2.78 ± 3.43 n = 407	2.76 ± 2.83 n = 650	p > 0.05, (−0.38, 0.42)	2.39 ± 1.82 n = 710	3.55 ± 4.6 n = 347	**p < 0.001, (−1.67, −0.66)**
Midlife (>40 years)							
Glucose (mg/dL)	103.37 ± 34.89 n = 1,173	105.35 ± 31.9 n = 477	102.01 ± 36.75 n = 696	p > 0.05, (−0.62, 7.30)	102.44 ± 31.58 n = 785	105.24 ± 40.75 n = 388	p > 0.05, (−7.43, 1.83)
Insulin (mg/dL)	12.93 ± 9.99 n = 472	13.15 ± 9.74 n = 187	12.78 ± 10.17 n = 285	p > 0.05, (−1.47, 2.20)	12.31 ± 9.67 n = 324	14.29 ±10.58 n = 148	p = 0.05, (−4, 0.03)
HOMA-IR	3.21 ± 3 n = 470	3.27 ± 2.77 n = 187	3.17 ± 3.15 n = 283	p > 0.05, (−0.44, 0.64)	2.97 ± 2.79 n = 324	3.74 ± 3.37 n = 146	**p < 0.05, (−1.40, −0.15)**

For continuous measures, mean ± standard deviation is shown, as are the p values for t tests comparing men and women; and t tests comparing White Americans and African Americans. 95% confidence intervals for the men mean value minus women mean value, and White American mean value minus African American mean value, are also shown. Bold values indicate p-values and 95% CIs of the statistically significant t-tests conducted.

removed for digit span forward, 12 outliers removed for Trail Making Test A and 16 outliers removed for Trail Making Test B.

Reported model estimates are interpreted as 1 unit of glycemic predictor change corresponding to the reported units of change in the cognitive score (e.g., a reported estimate of −0.5 would mean 1 unit of glycemic predictor change corresponds to −0.5 units of cognitive score change). Additional analyses were run utilizing models containing both childhood/adolescence and early adulthood glycemic marker epochs to clarify whether they each have an independent influence on midlife cognitive function. These analyses followed the same structure as the primary analyses above with the exception that instead of having one time epoch in the model, there were two-time epochs. An example model is as follows, lm (formula = Global Cognition ∼ Mean Glucose [20 and under years old Epoch] + Mean Glucose [21 to 40 years old Epoch] + Race + Years of Education). To adjust for multiple comparisons, false discovery rate was computed based on all models that showed initial significance (34). R version 4.0.3 for Windows was used to estimate all statistical models, with stats, jtools, psych, and ggplot packages used to calculate model summaries and for graphing.

2.7 Data availability

These data are available upon request to the BHS Steering Committee via the Center for Lifespan Epidemiology. Data request and sharing procedures are available on the website www.clersite.org. Part of these data are archived at the NHLBI BioLINCC data repository and may also be requested there.

3 Results

3.1 Participants

Characteristics of the sample are summarized in Tables 1, 2 (cognitive outcomes only). The mean age at the time of cognitive testing was 48.2 ± 5.24 years. 59% of the sample was women, and 34 and 66% were African American and White Americans, respectively.

3.2 Sex stratified analyses

Model estimates and p-values for statistically significant effects in the sex-specific models are reported in Table 3.

TABLE 2 Participant characteristics: cognitive outcomes.

Measure	Overall	Men	Women	p-value, 95% CI	White American	African American	p-value, 95% CI
Global cognitive function	0.01 ± 5.36	−0.75 ± 5.12	0.53 +/- 5.47	**p < 0.001, (−1.87, −0.70)**	1.27 ± 4.97	−2.41 ± 5.26	**p < 0.001, (3.08, 4.28)**
Logical memory I	0 ± 1	−0.08 ± 1	0.06 +/- 0.99	**p < 0.05, (−0.25, −0.03)**	0.18 ± 0.99	−0.34 ± 0.93	**p < 0.001, (0.41, 0.63)**
Logical memory II	0 ±1	−0.11 ± 1	0.08 +/- 0.99	**p < 0.001, (−0.31, −0.08)**	0.19 ± 0.99	−0.36 ± 0.91	**p < 0.001, (0.44, 0.66)**
Logical memory II r	0 ± 0.99	−0.11 ± 1.05	0.09 +/- 0.95	**p < 0.001, (−0.31, −0.09)**	0.17 ± 0.92	−0.31 ± 1.06	**p < 0.001, (0.36, 0.60)**
Digit span forward	0 ± 1	0.02 ± 0.99	−0.01 +/- 1.01	p > 0.05, (−0.08, 0.14)	0.12 ± 0.96	−0.24 ± 1.03	**p < 0.001, (0.25, 0.48)**
Digit span backward	0 ± 1	−0.04 ±1.02	0.03 ± 0.99	p > 0.05, (−0.19, 0.036)	0.2 ± 1	−0.38 ± 0.88	**p < 0.001, (0.48, 0.70)**
Trail making A	0 ± 1	0.08 ± 0.93	−0.06 ± 1.03	**p < 0.05, (0.023, 0.24)**	−0.12 ± 0.82	0.22 ± 1.24	**p < 0.001, (−0.47, −0.21)**
Trail making B	0 ± 1	0.07 ± 0.96	−0.05 ± 1.02	**p < 0.05, (0.005, 0.23)**	−0.17 ± 0.87	0.32 ± 1.14	**p < 0.001, (−0.61, −0.40)**

For continuous measures, mean ± standard deviation is shown, as are the p values for t tests comparing men and women; and t tests comparing White Americans and African Americans. 95% confidence intervals for the men mean value minus women mean value, and White American mean value minus African American mean value, are also shown. Bold values indicate p-values and 95% CIs of the statistically significant t-tests conducted.

TABLE 3 Sex stratified analyses: glycemic marker cognition estimates.

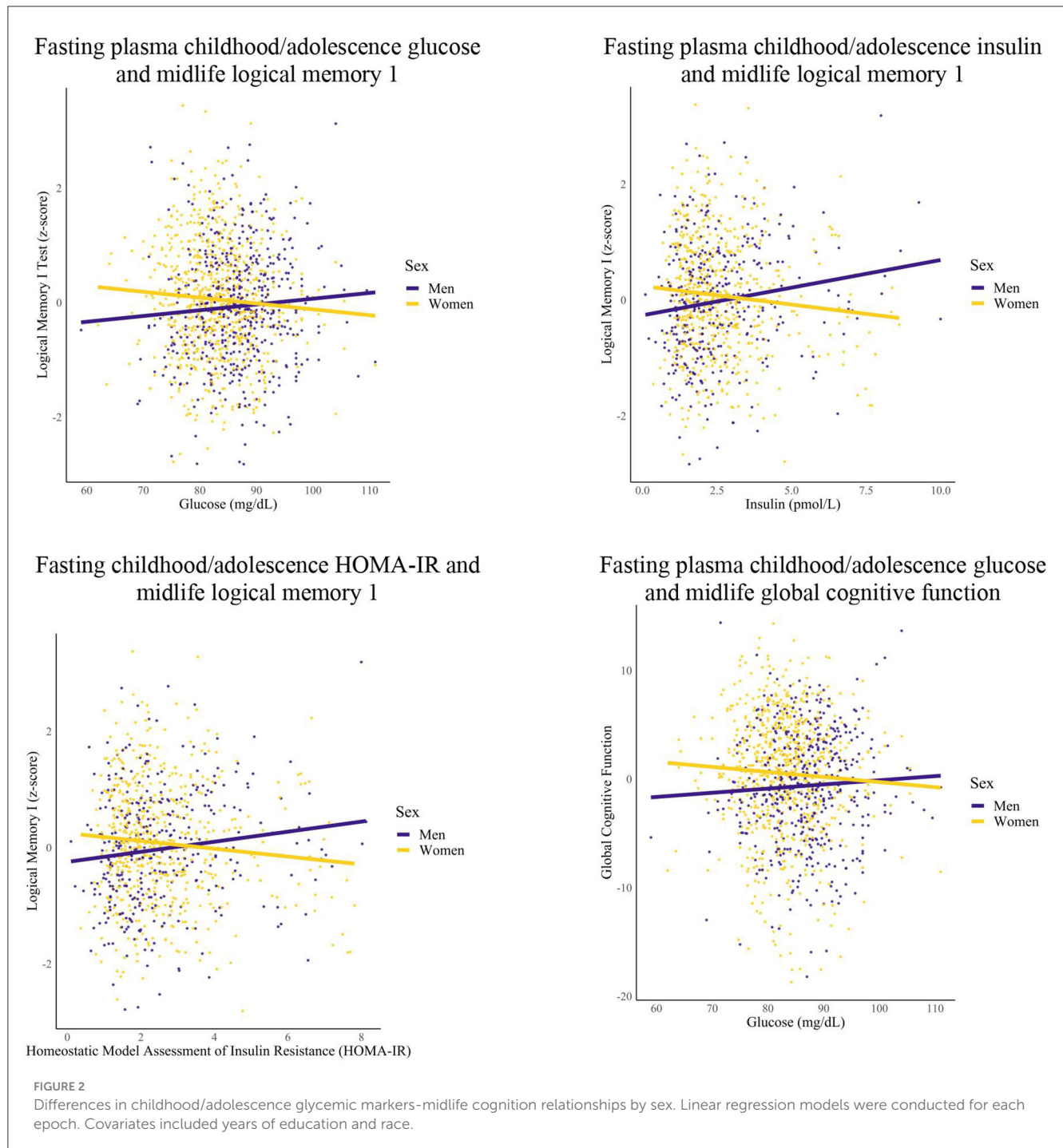| Group of interest	Model components[a]			Results	
Sex	Glycemic time epoch[b]	Glycemic predictor	Cognitive outcome task	Model estimate	p-value
Women	Childhood/adolescence	FPG[c]	Logical memory 1	−0.01	0.024
	Childhood/adolescence	FPG	Logical memory 2 recognition	−0.01	0.0413
	Childhood/adolescence	FPG	Global cognition	−0.07	0.024
	Early adulthood	FPG	Digit span forward	−0.01	0.0378
Men	Childhood/adolescence	HOMA-IR	Logical memory 1	0.09	0.024
	Childhood/adolescence	FPI[d]	Logical memory 1	0.02	0.024
	Childhood/adolescence	HOMA-IR	Logical memory 2	0.08	0.0378
	Childhood/adolescence	FPI	Logical memory 2	0.02	0.0366
	Early adulthood	FPI	Logical memory 2	0.02	0.0416
	Early adulthood	HOMA-IR	Trail making test A	−0.08	0.024

[a]Linear regression models were conducted for each epoch. Covariates included years of education, sex for models grouped by race and race for models grouped by sex. [b]Glycemic time epoch indicates what time point in the lifespan the glycemic predictor was collected in for that reported model estimate. [c]FPG, Fasting plasma glucose. [d]FPI, Fasting plasma insulin.

Qualitative descriptions of those results are described here. Selected associations from these analyses are represented visually in Figure 2. Note that Trails A and B have been transformed so that higher scores indicate better performance.

Among women, greater FPG within the childhood/adolescence epoch was associated with worse memory (1 unit increase FPG, 0.01 unit decrease logical memory 1 and logical memory 2 recognition) and global cognition performance (1 unit increase FPG, 0.07 unit decrease global cognition) in midlife. Additionally, women had greater FPG within the early adulthood epoch that was associated with worse midlife Digit Span Forward performance (1 unit increase FPG, 0.01 unit decrease digit span forward performance).

Among men, greater HOMA-IR and FPI levels within the childhood/adolescence epochs were associated with greater memory performance (1 unit increase HOMA-IR, 0.09 unit increase logical memory 1 and 0.08 unit increase logical memory 2; 1 unit increase FPI, 0.02 unit increase logical memory 1 and 2 performance). Furthermore, men had greater early adulthood FPI that was associated with greater midlife memory performance (1 unit increase FPI, 0.02 unit increase logical memory 2), but higher HOMA-IR in early adulthood was associated with worse Trail Making Test A performance (1 unit increase HOMA-IR, 0.08 unit decrease Trail Making Test A performance). After additional analyses, the significant association between early adulthood FPI and midlife memory performance was attenuated for men.

FIGURE 2
Differences in childhood/adolescence glycemic markers-midlife cognition relationships by sex. Linear regression models were conducted for each epoch. Covariates included years of education and race.

For women, no significant relationships were found for the childhood/adolescence and early adulthood epochs for FPI and HOMA-IR (data not shown) with select significant relationships for FPG (as reported in this section). For men, no significant relationships were found for the childhood/adolescence and early adulthood epochs for FPG (data not shown) with select significant relationships found for FPI and HOMA-IR (as reported in this section). For both groups, no significant relationships were found for any of the metabolic markers within the midlife epoch.

3.3 Race stratified analyses

Model estimates and *p*-values for statistically significant effects in the race-specific models are reported in Table 4. Qualitative descriptions of those results are described here. Selected associations from these analyses are represented visually in Figure 3. As above, Trails A and B have been transformed so that higher scores indicate better performance.

Among African Americans, greater FPG within the childhood/adolescent epoch was associated with worse Digit

TABLE 4 Race stratified analyses: glycemic marker cognition estimates.

Group of Interest	Model components[a]			Results	
Race	Glycemic time epoch[b]	Glycemic predictor	Cognitive outcome task	Model estimate	p-value
African Americans	Childhood/adolescence	FPG[c]	Digit span backward	−0.01	0.0416
	Childhood/adolescence	FPG	Trail making test A	−0.01	0.0378
	Childhood/adolescence	FPG	Global cognition	−0.06	0.049
	Early adulthood	HOMA-IR	Trail making test A	−0.07	0.0378
White Americans	Midlife	FPI[d]	Digit span forward	−0.01	0.0416
	Childhood/adolescence	HOMA-IR	Digit span backward	−0.08	0.024

[a]Linear regression models were conducted for each epoch. Covariates included years of education, sex for models grouped by race and race for models grouped by sex. [b]Glycemic time epoch indicates what time point in the lifespan the glycemic predictor was collected in for that reported model estimate. [c]FPG, Fasting plasma glucose. [d]FPI, Fasting plasma insulin.

Span Backward (1 unit increase FPG, 0.01 unit decrease Digit Span Backward performance), Trail Making Test A (1 unit increase FPG, 0.01 unit decrease Trail Making A performance), and global cognition scores (1 unit increase FPG, 0.06 unit decrease global cognition). Additionally, African Americans had greater HOMA-IR within the early adulthood epoch that was associated with worse Trail Making Test A scores (1 unit increase HOMA-IR, 0.07 unit decrease Trail Making A performance).

Among White Americans, greater levels of FPI during midlife was associated with worse Digit Span Forward scores (1 unit increase of FPI, 0.01 unit decrease Digit Span Forward performance). Furthermore, White Americans had greater HOMA-IR within the childhood/adolescent epoch that was associated with worse Digit Span Backward scores (1 unit increase HOMA-IR, 0.08 unit decrease Digit Span Backward performance).

For White Americans, no significant relationships were found for the childhood/adolescence epoch for FPG (data not shown) with one significant relationship found for HOMA-IR (as reported in this section), and for the midlife epoch, no significant relationships were found for HOMA-IR and FPG (data not shown) with one significant relationship found for FPI (as reported in this section). Additionally for White Americans, there were no significant relationships found for any metabolic marker for the early adulthood epoch. For African Americans, no significant relationships were found for the childhood/adolescence epoch for HOMA-IR (data not shown) with select significant relationships found for FPG (as reported in this section), and for the early adulthood epoch, no significant relationships were found for FPI and FPG (data not shown) with one significant relationship found for HOMA-IR (as reported in this section). Additionally for African Americans, no significant relationships were found for any of the metabolic markers within the midlife epoch. For both groups, no significant relationships were found for the childhood/adolescence epoch for FPI.
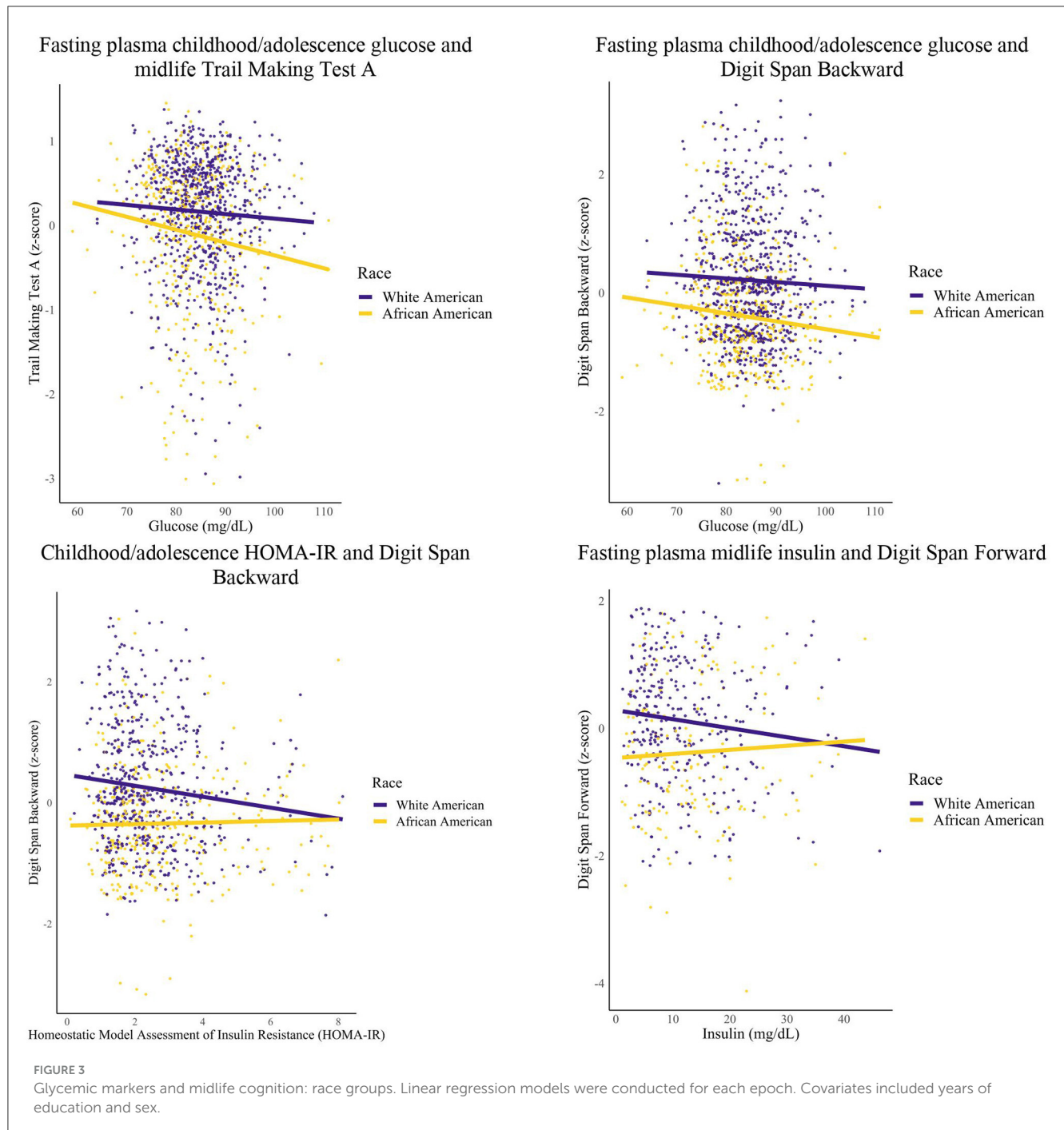
4 Discussion

In support of our hypotheses, poorer glycemic markers in childhood/adolescence and early adulthood were associated with worse midlife cognitive function in certain groups (i.e., women,

African Americans, and White Americans). In addition, poorer midlife fasting plasma insulin was associated with worse working memory among White Americans. However, contradicting our hypotheses, poorer glycemic markers in childhood/adolescence and early adulthood were associated with *better* cognitive functioning among men. Overall, the pattern of findings suggests that cognitive outcomes associated with glycemic dysfunction differ significantly by sex and that childhood/adolescence is a key time period for glycemic markers.

The finding that better glycemic markers are associated with better cognitive function in certain groups is consistent with several prior observational and interventional studies (20, 21, 35). The finding is also consistent with a prior finding from this cohort that better glycemic markers are associated with better brain outcomes (24). Conversely, the opposite association observed in other subgroups in this study—better glycemic markers being associated with *worse* cognition—has also been supported in prior studies (36, 37). In addition, this same relationship between glycemic markers and cognitive function within certain subgroups has been reported to be null in some studies (35) and U-shaped in others (38). Together, these findings suggest that the relationship between glycemic markers and cognitive functioning is complex with more longitudinal investigations exploring the nuances of different subgroups needed to fully understand the nature of it.

Sex differences in the relationship between glycemic markers and cognitive function could be driven by sex differences in behavioral and biological contributors to glycemic markers and cognitive function. Women exhibit more physical inactivity than men in multiple parts of the lifespan, and men have traditionally exhibited higher levels of physical activity due to greater engagement in physically demanding jobs (39, 40). This greater level of physical activity attainment may have buffered the brains of the male participants against the negative effects of poorer glycemic markers (41). Alternatively, differing temporal patterns of endogenous sex hormone levels between sexes, including during puberty (42), could modify these associations, as sex hormone levels are believed to affect glycemic markers and diabetes risk (17) as well as possibly dementia risk (43). This difference in timing could fail to safeguard the brains of women, in comparison to men, from the effects of glycemic markers on cognition. Future work is needed to better understand the biological basis of observed

FIGURE 3
Glycemic markers and midlife cognition: race groups. Linear regression models were conducted for each epoch. Covariates included years of education and sex.

sex differences in relationships between lifespan glycemic markers and cognition.

We did not find any prominent differences between African Americans and White Americans for the glycemic marker cognition relationships as the corresponding effects were similar and going in the same direction despite significant vs. non-significant relationships varying between races. This contrasts with our hypothesis that cognitive effects of poorer glycemic markers would be especially prominent among African Americans due to differences in biological factors (e.g., APOE genotype), intervention responses (e.g., poorer aerobic outcomes) and environmental stressors (e.g., structural racism, poorer access to healthcare, poorer

air quality, etc.) in comparison to White Americans, each of which could confer a greater risk of poor cognitive outcomes (9, 11, 44, 45). The finding also contrasts with prior data that addressed a similar question (8). Within the current small literature, there is one study that also observed no differences in glycemic-cognition relationships between race groups (46). Our lack of such race differences may be due in part to our inclusion of education as a covariate in statistical models, as education may have served as a proxy for some of the aforementioned environmental stressors. Indeed, prior studies have suggested that controlling for education can attenuate race differences in cognition poverty level (47, 48). Due to the nuances of the glycemic-cognition relationship, more

longitudinal investigations of race differences in matched samples of AA and WA are warranted.

We found that glycemic markers in earlier epochs of the lifespan was associated with cognitive function in midlife. This aligns with previous findings in this same cohort showing that higher FPG in early life was associated with poorer brain health in midlife (24). The finding also aligns with previous studies of youth with Type 1 Diabetes (T1D) who went on to have worse cognitive function as young adults (an average of 5.5 years and 12 years later respectively) than youth without T1D did (49, 50). The results could be driven by the sensitivity of the brain during childhood and adolescence years to stressors such as impaired glucose markers (51). Future studies should utilize cognitive measures at multiple times points across the lifespan to provide a more complete picture of the dynamic effects that fluctuations in glycemic markers have on cognitive function throughout the lifespan. Furthermore, this study's findings also suggest that early life is a key time for future interventions on glycemic markers.

This study has notable strengths. The participants provided glycemic data covering approximately 40 years of the lifespan, thus enabling novel assessment of epoch-dependent relationships with cognition. The racial and socioeconomic diversity of the cohort is an additional strength, although generalization of results outside of this micropolitan area core setting should be approached with caution. One weakness is that glycemic marker measures did not include modern measures such as Hemoglobin A1c (Hba1c), which had not been developed until after the initiation of the cohort.

5 Conclusions

The findings from the current study are one of the first to suggest that early life glycemic markers are important determinants of future cognitive outcomes in this semi-rural, biracial cohort. Other important findings indicate that the relationship between glycemic markers and cognitive outcomes was similar across racial groups and in the expected direction, however these differed by sex group. Our results point to future directions which should include measures of brain function (e.g., functional MRI), glucose metabolism (e.g., fluorodeoxyglucose positron emission tomography or FDG-PET), and neurodegenerative disease (e.g., amyloid PET) to clarify mechanisms underlying sex and race differences in glycemic markers effects on the brain across the lifespan. Improving this understanding could provide insight into how to individually tailor glycemic marker interventions so that they lessen adverse brain consequences.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of Tulane University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

KG drafting and revision of the manuscript for content, including medical writing for content, study concept or design, and analysis or interpretation of data. LB drafting and revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data. RN and OC drafting and revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1200415/full#supplementary-material

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