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GDF15 and its association with cognitive performance over time in a longitudinal study of middle-aged urban adults

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ABSTRACT

Serum GDF15 levels are correlated with multiple neurodegenerative diseases. Few studies have tested this marker's association with middle-aged cognitive performance over time, and whether race affects this association is unknown. We examined associations of initial serum GDF15 concentrations with longitudinal cognitive performance, spanning domains of global mental status, visual and verbal memory, attention, fluency, and executive function in a sub-sample of adults participating in the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study (n = 776, Age_{v1}:30-66y, 45.6 % male, 57.0 % African American, 43.0 % below poverty). This analysis consisted of mixed-effects regression models applied to the total selected sample, while also stratifying the analyses by race in the main analyses and further stratifying by sex, age group and poverty status in an exploratory analysis. Our main findings, which passed multiple testing and covariate-adjustment, indicated that GDF15 was associated with poorer baseline performance on several cognitive tests, including animal fluency [overall sample: (Model 1: $\gamma_0 \pm$ SE: -0.664 ± 0.208, $P < 0.001$; Model 2, $\gamma_0 \pm$ SE: -0.498 ± 0.217, $P < 0.05$)]. Among White adults, GDF15 was linked to poorer performance on a brief test of attention (Model 1: $\gamma_0 \pm$ SE: -0.426 ± 0.126, $P < 0.001$; Model 2, $\gamma_0 \pm$ SE: -0.281 ± 0.139, $P < 0.05$); and Trailmaking test, part B (Model 1: $\gamma_0 \pm$ SE: $+0.129 \pm 0.040$, $P < 0.001$; Model 2, $\gamma_0 \pm$ SE: $+0.089 \pm 0.041$, $P < 0.05$), the latter being also linked to higher GDF15 among individuals living below poverty. Among women, GDF15 was associated with poor global mental status (Normalized MMSE: Model 1: $\gamma_0 \pm$ SE: -2.617 ± 0.746, $P < 0.001$; Model 2: $\gamma_0 \pm$ SE: -1.729 ± 0.709, $P < 0.05$). GDF15 was not associated with decline on any of the 11 cognitive test scores considered in ~ 4 years of follow-up. In sum, we detected cross-sectional associations between GDF15 and cognition, although GDF15 did not predict rate of change in cognitive performance over time among a sample of middle-aged adults. More longitudinal studies are needed to address the clinical utility of this biomarker for early cognitive defects.

Abbreviations: AD, Alzheimer's disease; AF, Animal Fluency; APOE, Apolipoprotein E genotype; BVRT, Benton Visual Retention Test; BMI, Body Mass Index; BTA, Brief Test of Attention; CVLT-DFR, California Verbal Learning Test-Delayed Free Recall; CVLT-List A, California Verbal Learning Test-List A; CES-D, Center for Epidemiologic Studies-Depression; CSF, Cerebrospinal fluid; CDT, Clock Drawing Test; DS-B, Digits Span-Backward; DS-F, Digits Span-Forward; GDF15, Plasma growth/differentiation factor 15; HANDLS, Healthy Aging in Neighborhoods of Diversity across the Life Span; HEI-2010, Healthy Eating Index 2010 version; HS, High school; HIV, Human Immunodeficiency Virus; IMR, Inverse Mills Ratio; IRB, Institutional Review Board; MRI, Magnetic Resonance Imaging; MRV, Medical Research Vehicles; MMSE, Mini-Mental State Examination; OLS, Ordinary least squares; SD, Standard Deviation; SE, Standard Error; TRAILS A, Trailmaking Test Part A; TRAILS B, Trailmaking Test Part B; US, United States; WRAT-3, Wide Range Achievement Test 3rd revision.

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1. Introduction

Alzheimer's disease and related dementias (ADRD) is projected to affect 13.9 million individuals in the United States by 2060 (Matthews et al., 2019). Substantial race and ethnicity disparities exist for ADRD. For example, ADRD is most prevalent in African American adults over 65 and the disproportionate burden of ADRD in minority populations will be further exacerbated with the expected growth of the aging population (Matthews et al., 2019; Mayeda et al., 2016; Steenland et al., 2016). Therefore, it is important to develop non-invasive biomarkers that identify individuals at risk for ADRD earlier in their lifespan prior to cognitive decline.

Emerging evidence indicates that inflammation plays a role in cognitive decline and Alzheimer's Disease AD (Boyd et al., 2022). Therefore, there has been substantial interest in identifying inflammatory biomarkers that are associated with cognitive decline and dementia. Recent data has shown a link between the stress response protein growth differentiation factor 15 (GDF15), also known as MIC-1, and cognition (Fuchs et al., 2013; McGrath et al., 2020). GDF15 is a secreted protein originally described as a member of the TGF- β superfamily and has recently been shown to share functional homology with glial cell-derived neurotrophic factors (GDNFs) through binding with GDNF receptor α-like (GFRAL) (Emmerson et al., 2017; Hsu et al., 2017; Mullican et al., 2017; Yang et al., 2017). GDF15 is a pleiotropic factor that has a variety of functions both beneficial and deleterious depending on cellular context (Mullican and Rangwala, 2018). Circulating levels are elevated in response to stress, injury and inflammation and in homeostatic settings including energy and body-weight regulation in addition to pathological contexts such as cancer, cardiovascular disease and other age-associated diseases (Mullican and Rangwala, 2018; Tsai et al., 2018; Wang et al., 2021). Higher levels of GDF15 are also associated with all-cause mortality in community-dwelling white elderly populations (Daniels et al., 2011; Desmedt et al., 2019; Eggers et al., 2013; Wiklund et al., 2010; Xie et al., 2019) and also in diverse middle-aged populations (Freeman et al., 2020).

A few studies have shown a relationship between plasma/serum GDF15 and cognition. In a subset of the Sydney Memory and Aging Study (MAS) cohort of older White adults (mean age 78.5 yrs) containing cognitively normal participants and those with mild cognitive impairment (MCI), cross sectional analyses found that GDF15 was negatively associated with global cognition and cognitive domains at baseline and was associated with processing speed, memory, and executive function at a two-year follow-up. (Fuchs et al., 2013). Interestingly, participants with MCI at either timepoint had higher levels of GDF15. Prospective analysis revealed that higher GDF15 at baseline was significantly associated with a change in cognition from normal to MCI/dementia at follow-up. In a study in Singapore of older adults (mean age 72.8 yrs), GDF15 was associated with white matter hyperintensities and with individuals with both cerebrovascular disease and cognitive impairment no dementia and cerebrovascular disease and AD (Chai et al., 2016). In patients (mean age 61.8 yrs) admitted with acute decompensated heart failure, GDF15 was associated with cognitive impairment (Tung et al., 2022). GDF15 was associated with an MRI-based Alzheimer's disease score (AD-PS) in an older (mean age 76.4 yrs) cohort of cognitively normal, mild cognitive impairment, and dementia participants in the Atherosclerosis Risk in Communities (ARIC) study cohort (Casanova et al., 2022). GDF15 was also associated with the AD-PS score when the analysis was restricted only to cognitively normal individuals. Higher GDF15 was associated with an increased risk for all-cause and AD dementia in adults > 60 yrs in the Framingham Offspring cohort (McGrath et al., 2020). These studies indicate a potential relationship between circulating GDF15 levels and cognitive decline in older Asian or White cohorts. However, it is not known whether GDF15 is associated with cognition in younger middle-aged cohorts, which is a critical time to identify individuals at risk in preclinical stages prior to AD onset. In addition, little is known about GDF15 and cognition in the context of race, sex, or poverty status.

Thus, our study (i) Examined baseline GDF15 in relation to baseline and change in cognitive performance over time; (ii) Tested racial differentials in those main associations; as well as exploring those associations across sex, age group and poverty status.

2. Materials and methods

2.1. Database

In this study, we selected participants from the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study. HANDLS was initiated in 2004 and is a longitudinal, interdisciplinary, prospective study of socioeconomically diverse White and African American adults residing in Baltimore, MD. Baseline data (visit 1; v_1) were collected between 2004 and 2009 through home visits and physical examination including a cognitive test battery on the medical research vehicles (MRV). Participants visited the MRV for a follow-up in-person visit (v_2) between 2009 and 2013. All participants provided written informed consent. The Institutional Review Board of the National Institutes of Health, National Institute of Environmental Health Sciences approved the HANDLS study protocol.

2.2. Study sample

In our present study, up to two repeats on cognitive test scores were available from v_1 or v_2. Among the sub-set with complete v_2 follow-up data, mean ± SD follow-up time (n = 2,468 participants) was 4.66 ± 0.95y. Exposure data on plasma GDF15 concentrations were made available at v_1 for a sub-sample of White and African American HANDLS participants, after excluding those who did not survive beyond one year of follow-up from baseline. Fig. 1 depicts a study participant flowchart, with 3,720 HANDLS participants initially recruited, out of whom 1,036 had GDF15 concentration data at v_1. Of those participants, N = 776 had data on v_1 or v_2 for all 11 cognitive test scores, with an average number of observations/participant k = 1.6–1.8, indicating 10–20 % missingness on cognitive test performance outcomes at either visit. **Method S1** shows in detail how the sample was selected with respect to the GDF15 exposure. Compared to the initial sample with incomplete data for our analysis, the final sample was significantly older (Age_{v1}: 49.2 ± 0.33y vs 47.9 ± 0.17, P = 0.001), with no other differences detected by sex, race or poverty status.

2.3. Cognitive assessment

Trained clinical staff administered a series of cognitive tests, including: the Mini-Mental State Examination (MMSE), the California Verbal Learning Test (CVLT) immediate (List A) and Delayed Free Recall (DFR), the Benton Visual Retention Test (BVRT, # of errors), Brief Test of Attention (BTA), Animal Fluency test (AF), the Digit Span Forward and Backwards tests (DS-F and DS-B), the Clock Drawing Test (CDT), Trailmaking test parts A and B (TRAILS A and B, in seconds), (described in detail in **Method S2**). From these tests, a total of 11 cognitive tests scores were derived spanning the cognitive domains of global mental status, verbal memory, verbal fluency, attention, visual memory, visuospatial abilities and executive function, which includes working memory. Test scores with higher values reflected better cognitive performance with the exceptions of BVRT, Trails A, and Trails B.

2.4. Measurement of serum GDF15 protein levels

At visit 1, blood samples were collected in vials with no additives, centrifuged and serum was aliquoted and immediately frozen at −80 °C until use. The Quantikine ELISA kit (R&D Systems, Cat#SGD150, Minneapolis, MN) was used to quantify serum GDF15 (pg/mL) according to the manufacturer's instructions. Calibrator diluent RD5-20 was used to

dilute serum 1:4 and 50 μl was used for the assay. Pooled serum samples from 6 individuals were run in triplicate on each plate as controls. These triplicate pooled serum samples were used to calculate both the within plate (intra-assay) and between plates (inter-assay) coefficient of variation (CV). The intra-assay CV was 4.78 %. and the inter-assay CV was 9.95 %. GDF concentration was calculated based on internal standards. Assays were performed blind.

3. Covariates

We included additional covariates selected for their prior association with cognitive performance or decline. We included baseline measures of age (continuous, years), sex (male, female), race (White, African American), poverty status (below vs above 125 % the federal poverty line), educational attainment (less than high school, high school, more than high school), and literacy (Wide Range Achievement Test, third edition [WRAT-3]). We computed time between the first and second visits by subtracting age at v1 from age at v1. In addition, we included a wide range of health and behavioral characteristics including current smoking status (0 = No vs 1 = Yes), illicit drug use (0 = No vs 1 = Yes, using any of marijuana, opiates, and cocaine), body mass index (BMI, weight/height^2, kg.m^{-2}, continuous), self-rated health status categorized as 0 = poor/average (referent), 1 = good and 2 = very good/excellent, the Healthy Eating Index 2010 (HEI-2010) (Beydoun et al., 2020), measuring overall diet quality based on food and macronutrient-related guidelines for Americans, total energy intake (kcal/d), and depression symptomatology assessed using the 20-item CES-D. Finally, we included an index of morbidities which included hypertension, diabetes (0 = non-diabetic, 1 = pre-diabetic, 2 = diabetic), dyslipidemia or statin use, and self-reported history of any cardiovascular disease (atrial fibrillation, angina, coronary artery disease, congestive heart failure, and myocardial infarction) resulting in an unweighted index ranging from 0 to 5. Baseline use of anti-hypertensives, statins and diabetes medications were considered for a sensitivity analysis.

4. Statistical methods

All analyses were completed using Stata release 17 (STATA, 2019). First, we described the study sample's characteristics overall and across racial groups, comparing means and proportions with bivariate linear, logistic and multinomial logit models. Second, we adjusted those models by adding age, sex and poverty status to determine whether the net effect of race remained statistically significant at a type I error of 0.05. Third, to test our key hypotheses, we conducted several mixed-effects linear regression models (See **Method S3** for details). Main effect of GDF15 reflected the association of this exposure with baseline cognitive performance, while its interaction with time on study (i.e. GDF15 × *TIME*) could be interpreted as the adjusted effect of GDF15 on annualized rate of cognitive change. Those analyses were carried out separately on 11 cognitive test scores as outcomes, with main exposure being *z*-scores of GDF15 (Log_e transformed), and covariates entered in an incremental manner as follows: Model 1 or the reduced model: only socio-demographic variables (i.e. age at v1, sex, race and poverty status); Model 2, or the fully adjusted model: socio-demographics + all other lifestyle and health-related covariates. To preserve the sample size across those models, and given that covariates had individually < 5 % missing on average, we carried out multiple imputations (5 imputations, 10 iterations), by utilizing the chained equations method, with all covariates entered simultaneously in the estimation process as was done in previous studies(Beydoun et al., 2019; Beydoun et al., 2016a). In the mixed-effects linear regression models, and to allow for better interpretation of the intercept and time parameter, continuous covariates were centered at their means. Therefore, in our main analyses, **Models 1** and **2** were applied to 1 exposure (GDF15), 11 cognitive test scores with up to 2 repeats (i.e. effect of GDF15 on v_1 cognitive performance (CP_{v1}) and cognitive performance change over time (δCP)), one key stratifying variable (race), and 3 other stratifying variables that were explored (sex, age group and poverty status). GDF15 was Log_e transformed in all main analyses. Z-scoring of this exposure was carried out on the final eligible sample (N = 776), was done in previous studies (e.g.(Mielke et al., 2019)). Heterogeneity in the association between v1 exposure and v1 cognitive performance outcome by race was tested by adding the GDF15 × Race interaction term in separate models, while that of the relationship between GDF15 and cognitive change was tested with GDF15 × TIME × Race term included within the same model. In the unstratified models, those differences were also tested by age group, sex and poverty status in an exploratory analysis.

Furthermore, missingness in exposure and outcome data, resulting in

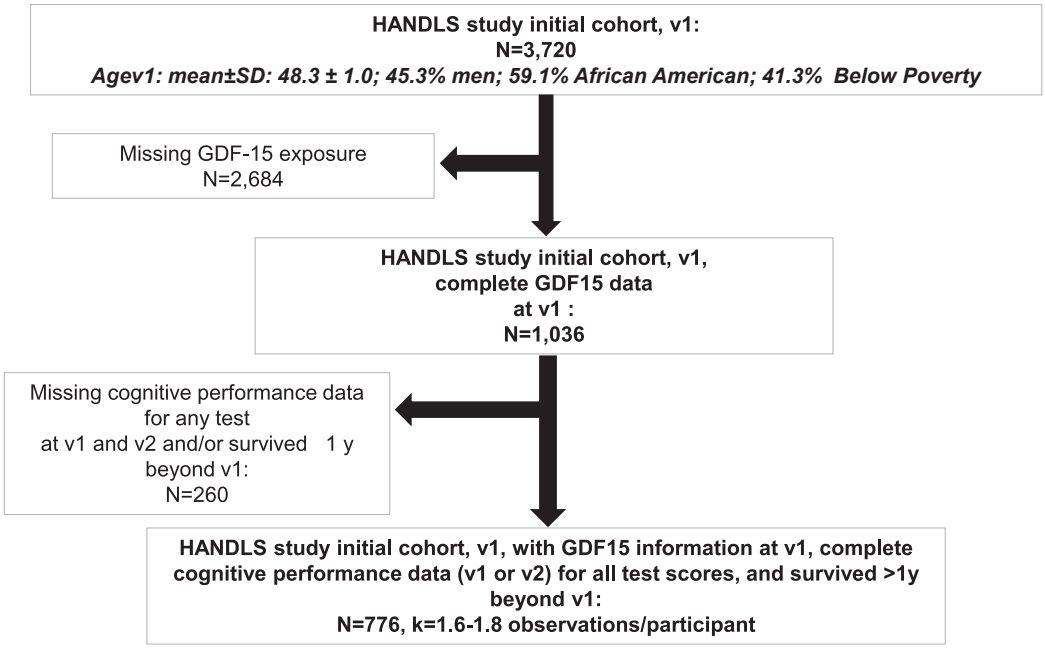


Fig. 1. Participant flowchart *Abbreviations*: GDF15 = Plasma growth/differentiation factor 15; HANDLS = Healthy Aging in Neighborhoods of Diversity across the Life Span; k=# of observations/participant; v_1 = Visit 1; v_2 = Visit 2.

Table 1
Study sample characteristics, overall and by race in final analytic sample with imputed covariates (N = 776), HANDLS 2004–2013.[a]

	Overall	White adults	African American adults
	(X ± SE), % **(N = 776)**	(X ± SE), % **(N = 334)**	(X ± SE), % **(N = 442)**
X ± SE or %±SE			
GDF15 at v_1, pg/mL			
Log_e transformed	+6.49 ± 0.020	+6.481 ± 0.035	+6.503 ± 0.032
Baseline socio-demographic, SES and health-related variables			
Sex, % male	45.6 ± 1.8	45.9 ± 2.7	45.5 ± 2.4
Age at v_1, yrs.	49.20 ± 0.33	49.2 ± 0.51	49.2 ± 0.44
African American, %	57.0 ± 1.8	0.00	100.0
Poverty status, % <125 % of the 2004 federal poverty guidelines	43.0 ± 1.8	36.5 ± 2.6***	48.0 ± 2.4
Education, Completed, %			
<HS	6.0 ± 0.9	8.9 ± 1.6***e	3.8 ± 1.0
HS	59.7 ± 1.8	53.4 ± 2.8	64.5 ± 2.3
>HS	34.3 ± 1.8	37.7 ± 2.7*	31.7 ± 2.2
Literacy, WRAT-3 score	42.6 ± 0.3	45.0 ± 0.4****e	40.8 ± 0.4
Baseline drug and tobacco use			
Any drug, current user, %	18.7 ± 1.4	12.5 ± 1.8	23.3 ± 2.1
Tobacco, current user, %	47.2 ± 1.8	40.1 ± 2.6	52.5 ± 2.4
BMI, kg/m^2	30.1 ± 0.3	30.3 ± 0.4	29.9 ± 0.4
Self-rated health, %			
Poor/Average,	28.9 ± 1.6	32.3 ± 2.6***e	26.2 ± 2.0
Good	38.0 ± 1.7	30.8 ± 2.5	43.3 ± 2.4
Very good/Excellent	33.2 ± 1.7	36.8 ± 2.6***,e	30.4 ± 2.2
HEI-2010 total score at v_1	42.4 ± 0.4	42.5 ± 0.7	42.2 ± 0.6
Total energy intake, kcal/day	2,014 ± 39.7	2,028 ± 55	2,003 ± 61.8
CES-D total score	15.5 ± 0.4	16.26 ± 0.70*,e	14.86 ± 0.52
Hypertension[b], %	48.4 ± 1.8	43.7 ± 2.8**e	51.8 ± 2.4
Diabetes[b], %			
No	62.9 ± 1.8	60.1 ± 2.7	65.1 ± 2.3
Pre-diabetic	18.7 ± 1.4	21.4 ± 2.3*	16.6 ± 1.8
Diabetic	18.4 ± 1.4	18.4 ± 2.1	18.3 ± 1.9
Dyslipidemia[b], %	28.8 ± 1.7	34.0 ± 2.7***,e	24.9 ± 2.1
Cardiovascular disease[b], %	20.3 ± 1.4	18.6 ± 2.2	21.6 ± 2.0
Co-morbidity index[b]	2.53 ± 0.05	2.56 ± 0.09	2.51 ± 0.07
Cognitive performance at v_1, unadjusted[c]			
MMSE, normalized	75.9 ± 0.6	79.7 ± 0.9****,e	73.0 ± 0.7
CVLT-List A	24.34 ± 0.25	25.7 ± 0.4****,e	23.4 ± 0.3
CVLT-DFR	7.09 ± 0.12	7.87 ± 0.19****,e	6.53 ± 0.15
BVRT	6.50 ± 0.18	6.32 ± 0.26	6.64 ± 0.25
BTA	6.57 ± 0.08	7.21 ± 0.12****,e	6.11 ± 0.11
AF	18.6 ± 0.20	19.65 ± 0.31****,e	17.89 ± 0.24
DS-F	7.28 ± 0.08	7.75 ± 0.13****,e	6.93 ± 0.10
DS-B	5.59 ± 0.08	6.23 ± 0.13****,e	5.11 ± 0.09
CDT	8.74 ± 0.04	8.90 ± 0.06***,e	8.63 ± 0.06
Log_e (TRAILS A)	3.51 ± 0.01	3.40 ± 0.02****,e	3.60 ± 0.02
Log_e(TRAILS B)	4.68 ± 0.03	4.41 ± 0.04****,e	4.87 ± 0.04
Annualized change in cognitive performance estimated between v_1 and v_2, unadjusted[c]			
MMSE, normalized	−0.32 ± 0.13†	−0.41 ± 0.20†	−0.20 ± 0.17
CVLT-List A	−1.46 ± 0.07†	−1.45 ± 0.10†	−1.46 ± 0.08†
CVLT-DFR	−0.47 ± 0.03†	−0.49 ± 0.05†	−0.46 ± 0.03†
BVRT	+0.50 ± 0.04†	+0.33 ± 0.05†,****e	+0.64 ± 0.06†
BTA	−0.085 ± 0.019†	−0.108 ± 0.031†	−0.065 ± 0.025†
AF	−0.030 ± 0.037	+0.001 ± 0.062	−0.038 ± 0.046
DS-F	−0.018 ± 0.016	+0.001 ± 0.027	−0.025 ± 0.020
DS-B	+0.025 ± 0.015	−0.015 ± 0.024	−0.025 ± 0.020
CDT	−0.010 ± 0.012	−0.021 ± 0.019	−0.001 ± 0.015
Log_e (TRAILS A)	+0.0098 ± 0.0041†	+0.0050 ± 0.0059	+0.011 ± 0.006
Log_e(TRAILS B)	+0.0237 ± 0.005†	+0.0255 ± 0.008†	+0.021 ± 0.007

Abbreviations: AF = Animal Fluency; BMI = Body Mass Index; BTA = Brief Test of Attention; BVRT = Benton Visual Retention Test; CDT = Clock Drawing Test; CES-D = Center for Epidemiologic Studies-Depression; CVLT-DFR = California Verbal Learning Test-Delayed Free Recall; CVLT-List A = California Verbal Learning Test-List A; DS-B = Digits Span-Backward; DS-F = Digits Span-Forward; GDF15 = Plasma growth/differentiation factor 15; HANDLS = Healthy Aging in Neighborhood of Diversity across the Lifespan; HEI-2010 = Healthy Eating Index, 2010 version; HS = High school; MMSE = Mini-Mental State Examination; SE = Standard Error; TRAILS A = Trailmaking Test, Part A; TRAILS B = Trailmaking Test, Part B; WRAT-3 = Wide Range Achievement Test, 3rd revision; X = mean.
*$p < 0.10$; ** $p < 0.05$; *** $p < 0.010$; ****$p < 0.001$, *t*-test for null hypothesis of no between-race differences.
[a]Values are means (X) ± SE for continuous variables and % for categorical variables. The sample selected has complete data on 11 cognitive test scores at visits 1 and/or 2 and complete data on GDF15 at visit 1. Other covariates were multiple imputed (5 imputations with 10 iterations), using chained equations. All cognitive test scores are in the direction of higher score → better performance with the exception of BVRT (# of errors) and TRAILS A and B (# of *sec*. to complete).
[b]The co-morbidity index was calculated as the sum of hypertension, diabetes and dyslipidemia (or statin use), and self-reported history of cardiovascular disease included atrial fibrillation, angina, coronary artery disease, congestive heart failure, or myocardial infarction, ranging from 0 to 5.
[c]Crude baseline cognitive test score. Sample sizes varied between 675 and 775 for overall sample.
[d]Crude estimated annual rate of change in cognitive performance based on mixed-effects linear regression model with TIME as the only covariate. Difference by race was determined by interacting *TIME* with race.
[e]$p < 0.05$ upon further adjustment for age, sex and poverty status in multiple linear, logistic, multinomial logit and mixed-effects linear regression models with race entered as the main predictor.
†$p < 0.05$, *t*-test for null hypothesis of $\gamma_1 = 0$ (fixed effects coefficient for *TIME*) in mixed-effects linear regression models with *TIME* as the only variable.

sample selectivity relative to the initially recruited sample, was addressed by using a two-stage Heckman selection strategy, as was done in other previous studies, through the inclusion of an inverse mills ratio into all mixed-effects linear regression models, both as a main effect and interacted with *TIME* (e.g. (Beydoun et al., 2013)).

Type I error rate for this study was set a priori for main and interactive effects before correcting for multiple testing to 0.05 and 0.10, respectively (Selvin, 2004). To correct for multiplicity in outcomes (i.e., 11 cognitive test scores), we used the familywise Bonferroni correction (Hochberg and Tamhane, 1987) approach, specifically for **Model 1**. Subsequent fully adjusted models (**Model 2**) for each outcome and in the stratified analyses were considered a sensitivity model that included both potentially confounding and mediating factors. Thus, for **Model 1**, significance levels were adjusted for main effects to $p < 0.00455$ (0.05/11), and for two-way interaction terms to $0.10/11 = 0.00910$, as done in previous work (Beydoun et al., 2016b). In our exploratory stratified analysis, all main hypotheses were tested across sex, age group (≤50y, >50y, with 50y approximating median age) and poverty status (above vs below poverty), separately, using the same modeling approach, applying the same type of familywise Bonferroni correction within stratum. Predictive margins (with 95 % CI) obtained from mixed models (both reduced and fully adjusted models), were used to illustrated key findings. A partial sensitivity analysis was carried out whereby mixed-effects linear regression models were extended for the overall sample by including baseline use of selected medication, namely statins, antihypertensive and diabetes drugs. Findings were compared with **Model 2**. The code used in data analyses can be available to readers, in part o or in full, and obtained directly from the corresponding author.

5. Results

Table 1 describes the study sample characteristics in the selected sample and across racial groups. Overall, participants were on average ~ 48y old at visit 1 (v1), with proportion living below poverty being significantly greater among African American adults compared to White adults (48 % vs 36.5 %, P < 0.010). In contrast, a significantly higher proportion of White adults had < HS education (8.9 % vs 3.8 %, p < 0.010), compared with African American adults in the sample, with a marginally greater proportion having > HS education (37.7 % vs 31.7 %, p < 0.010). Importantly, mean literacy was significantly higher among White adults compared to their African American counterparts (WRAT-3 total score: 45.0 vs 40.8, p < 0.001). The main exposure, GDF15 did not differ across racial groups. However, most cognitive test scores measured at v1 indicated better cognitive performance among White adults compared to their African American counterparts. This difference was only marginally attenuated with the addition of age, sex, and poverty status in the linear model. In contrast, annual rate of change indicated a net decline in performance overall in several cognitive test scores including memory, attention and executive function. Nevertheless, only BVRT, a measure of visual memory, indicated differential decline over time across race, with faster decline observed among African American adults. Among other covariates of interest, both poor/average (32.3 % vs 26.2 %, p < 0.010) and very good/excellent (36.8 % vs 30.4 %, p < 0.010) self-rated health had a significantly greater proportion among White adults compared to African American adults. Hypertension was more prevalent at baseline among African American adults (51.8 % vs 43.7 %, p < 0.05), while the reverse was true for dyslipidemia (24.9 % vs 34.0 %, p < 0.010).

Time dependent cognitive performance outcomes were modeled against GDF15 serum concentration measured at the baseline visit, using a series of mixed-effects linear regression models (Tables 2, S1-S3). Main findings are depicted in Figs. 2-3 in the overall sample. GDF15 at v_1 was found to be associated with poorer baseline performance on tests reflecting attention (BTA), verbal fluency (AF) and executive function (Trailmaking test, part B). These associations passed correction for multiple testing in **Model 1**. However, only the association between

Table 2
Baseline (v_1) GDF15 and its association with cognitive performance at v_1 and change over time: overall and race-specific mixed-effects linear regression models: HANDLS 2004-2013.[a]

	GDF15, pg/mL, (v_1 Log_e transformed, z-scored)	
	Model 1	Model 2
	$\gamma \pm$ SE	$\gamma \pm$ SE
Overall	**(N = 776, k = 1.6–1.8)**	**(N = 776, k = 1.6–1.8)**
Outcome = Cognitive performance test score		
Normalized MMSE		
Exposure, γ_{0a}	**−1.28 ± 0.57****	−0.134 ± 0.540
Exposure × TIME, γ_{1a}	+0.26 ± 0.15*	+0.272 ± 0.160*
CVLT-List A		
Exposure, γ_{0a}	−0.40 ± 0.27	+0.134 ± 0.272
Exposure × TIME, γ_{1a}	+0.05 ± 0.08	+0.045 ± 0.084
CVLT-DFR		
Exposure, γ_{0a}	−0.16 ± 0.12	+0.094 ± 0.128
Exposure × TIME, γ_{1a}	+0.01 ± 0.03	+0.010 ± 0.035
BVRT		
Exposure, γ_{0a}	+0.12 ± 0.19	−0.242 ± 0.197
Exposure × TIME, γ_{1a}	−0.003 ± 0.051	−0.027 ± 0.054
BTA		
Exposure, γ_{0a}	**−0.296 ± 0.086******	−0.158 ± 0.090*
Exposure × TIME, γ_{1a}	+0.018 ± 0.023	+0.008 ± 0.025
AF		
Exposure, γ_{0a}	**−0.664 ± 0.208******	−0.498 ± 0.217**
Exposure × TIME, γ_{1a}	+0.063 ± 0.045	+0.049 ± 0.049
DS-F		
Exposure, γ_{0a}	−0.040 ± 0.085	−0.027 ± 0.009
Exposure × TIME, γ_{1a}	−0.002 ± 0.020[c]	+0.003 ± 0.021
DS-B		
Exposure, γ_{0a}	**−0.194 ± 0.083****	−0.087 ± 0.081
Exposure × TIME, γ_{1a}	+0.028 ± 0.032	+0.013 ± 0.020
CDT		
Exposure, γ_{0a}	+0.008 ± 0.050	+0.011 ± 0.053
Exposure × TIME, γ_{1a}	−0.011 ± 0.014	−0.008 ± 0.015
Log_e(TRAILS A)		
Exposure, γ_{0a}	+0.020 ± 0.016	−0.004 ± 0.017
Exposure × TIME, γ_{1a}	+0.0002 ± 0.0040	+0.0002 ± 0.0052
Log_e(TRAILS B)		
Exposure, γ_{0a}	**+0.085 ± 0.027*****	+0.038 ± 0.028
Exposure × TIME, γ_{1a}	−0.004 ± 0.006	−0.006 ± 0.007
White adults	**(N = 334, k = 1.6–1.8)**	**(N = 334, k = 1.6–1.8)**
Outcome = Cognitive performance test score		
Normalized MMSE		
Exposure, γ_{0a}	**−2.165 ± 0.915****	−0.676 ± 0.865
Exposure × TIME, γ_{1a}	**+0.534 ± 0.249****	**+0.644 ± 0.275****
CVLT-List A		
Exposure, γ_{0a}	−0.428 ± 0.443	−0.101 ± 0.463
Exposure × TIME, γ_{1a}	+0.014 ± 0.129	+0.083 ± 0.144
CVLT-DFR		
Exposure, γ_{0a}	−0.1159 ± 0.2019	+0.068 ± 0.219
Exposure × TIME, γ_{1a}	−0.0196 ± 0.0568	+0.031 ± 0.063
BVRT		
Exposure, γ_{0a}	0.3219 ± 0.2814	−0.279 ± 0.271
Exposure × TIME, γ_{1a}	−0.0295 ± 0.0642	−0.086 ± 0.072
BTA		
Exposure, γ_{0a}	**−0.426 ± 0.126******	−0.281 ± 0.139**
Exposure × TIME, γ_{1a}	+0.0093 ± 0.0397	+0.014 ± 0.045
AF		
Exposure, γ_{0a}	**−0.7927 ± 0.3357****	−0.4920 ± 0.3630
Exposure × TIME, γ_{1a}	+0.0849 ± 0.0783	+0.0420 ± 0.0890
DS-F		
Exposure, γ_{0a}	−0.1148 ± 0.1382	−0.005 ± 0.1360
Exposure × TIME, γ_{1a}	0.0202 ± 0.0353	+0.0230 ± 0.0400
DS-B		
Exposure, γ_{0a}	**−0.3589 ± 0.1413****	−0.237 ± 0.141*

(*continued on next page*)

Table 2 (*continued*)

	GDF15, pg/mL, (v_1 Log_e transformed, z-scored)	
	Model 1	Model 2
Exposure × TIME, γ_{1a}	+0.0349 ± 0.0306	+0.044 ± 0.035
CDT		
Exposure, γ_{0a}	−0.0290 ± 0.0753	+0.031 ± 0.081
Exposure × TIME, γ_{1a}	−0.0221 ± 0.0237	−0.011 ± 0.027
Log_e(TRAILS A)		
Exposure, γ_{0a}	**0.0533 ± 0.0224****	+0.0320 ± 0.0250
Exposure × TIME, γ_{1a}	−0.0021 ± 0.0073	−0.007 ± 0.009
Log_e(TRAILS B)		
Exposure, γ_{0a}	**+0.1291 ± 0.0396****	**+0.089 ± 0.041****
Exposure × TIME, γ_{1a}	+0.0263 ± 0.0136	-+0.019 ± 0.011*
African American adults	**(N = 442, k = 1.6–1.8)**	**(N = 442, k = 1.6–1.8)**
Outcome = Cognitive performance test score		
Normalized MMSE		
Exposure, γ_{0a}	−0.6277 ± 0.7425	−0.0820 ± 0.6980
Exposure × TIME, γ_{1a}	+0.0968 ± 0.2028	+0.1020 ± 0.2070
CVLT-List A		
Exposure, γ_{0a}	−0.4792 ± 0.3324	−0.0780 ± 0.3330
Exposure × TIME, γ_{1a}	+0.0849 ± 0.0995	+0.0550 ± 0.1060
CVLT-DFR		
Exposure, γ_{0a}	−0.2128 ± 0.1586	+0.0310 ± 0.1590
Exposure × TIME, γ_{1a}	+0.0239 ± 0.0406	−0.0050 ± 0.0430
BVRT		
Exposure, γ_{0a}	−0.0955 ± 0.2655	−0.3000 ± 0.2720
Exposure × TIME, γ_{1a}	0.0282 ± 0.0740	+0.0230 ± 0.0780
BTA		
Exposure, γ_{0a}	−0.2018 ± 0.1185*	−0.108 ± 0.122
Exposure × TIME, γ_{1a}	+0.0174 ± 0.0294	+0.005 ± 0.031
AF		
Exposure, γ_{0a}	**−0.6346 ± 0.2687****	**−0.625 ± 0.268****
Exposure × TIME, γ_{1a}	+0.0454 ± 0.0560	+0.032 ± 0.091
DS-F		
Exposure, γ_{0a}	+0.0291 ± 0.1102	−0.030 ± 0.111
Exposure × TIME, γ_{1a}	−0.0040 ± 0.0237	+0.003 ± 0.026
DS-B		
Exposure, γ_{0a}	−0.0723 ± 0.1011	−0.0120 ± 0.1000
Exposure × TIME, γ_{1a}	+0.0318 ± 0.0249	+0.0120 ± 0.0260
CDT		
Exposure, γ_{0a}	0.0291 ± 0.0684	−0.0120 ± 0.0710
Exposure × TIME, γ_{1a}	−0.00214 ± 0.0178	+0.004 ± 0.019
Log_e(TRAILS A)		
Exposure, γ_{0a}	−0.0073 ± 0.0220	−0.0270 ± 0.0220
Exposure × TIME, γ_{1a}	+0.0030 ± 0.0065	+0.002 ± 0.007
Log_e(TRAILS B)		
Exposure, γ_{0a}	+0.0505 ± 0.0380	+0.0140 ± 0.0380
Exposure × TIME, γ_{1a}	−0.0010 ± 0.0083	−0.0030 ± 0.0090

Abbreviations: AF = Animal Fluency; BTA = Brief Test of Attention; BVRT = Benton Visual Retention Test; CDT = Clock Drawing Test; CES-D = Center for Epidemiologic Studies-Depression; CVLT-DFR = California Verbal Learning Test-Delayed Free Recall; CVLT-List A = California Verbal Learning Test-List A; DS-B = Digits Span-Backward; DS-F = Digits Span-Forward; GDF15 = Plasma growth/differentiation factor 15; HANDLS = Healthy Aging in Neighborhood of Diversity across the Lifespan; HEI-2010 = Healthy Eating Index, 2010 version; k = number of observations/participant; MMSE = Mini-Mental State Examination; SD = Standard Deviation; SE = Standard Error; TRAILS A = Trailmaking Test, Part A; TRAILS B = Trailmaking Test, Part B; WRAT-3 = Wide Range Achievement Test, 3rd revision; X = mean.

*$p < 0.10$; ** $p < 0.05$; *** $p < 0.010$; ****$p < 0.001$, test for null hypothesis of $\gamma = 0$. Shaded values passed $q < 0.05$ correction for multiple testing in Model 1.

[a] Models 1A.1–1 K.2 included GDF15 (Log_e transformed, z-scored) as the main predictor for v1 cognitive performance and cognitive change over time (11 test scores), using a series of mixed-effects linear regression models, carried out in the overall population, and stratified by race. These models adjusted only for age, sex, race, poverty status, and the inverse mills ratio. Models 2A.1–2 K.2 followed a similar approach but adjusted further for selected socio-demographic, lifestyle and health-related factors, namely educational attainment, the WRAT-3 score, current drug use, current tobacco use, body mass index, self-rated health, co-morbidity index, HEI-2010, total energy intake, and the CES-D total score. 1 SD of baseline Log_e(GDF15) is estimated at 0.70; Mean = 6.55.

[b] $p < 0.05$ for Race × GDF15 in models that are unstratified by race to which this 2-way interaction was included.

[c] $p < 0.05$ for Race × GDF15 × *TIME* in models that are unstratified by race to which this 3-way interaction was included.

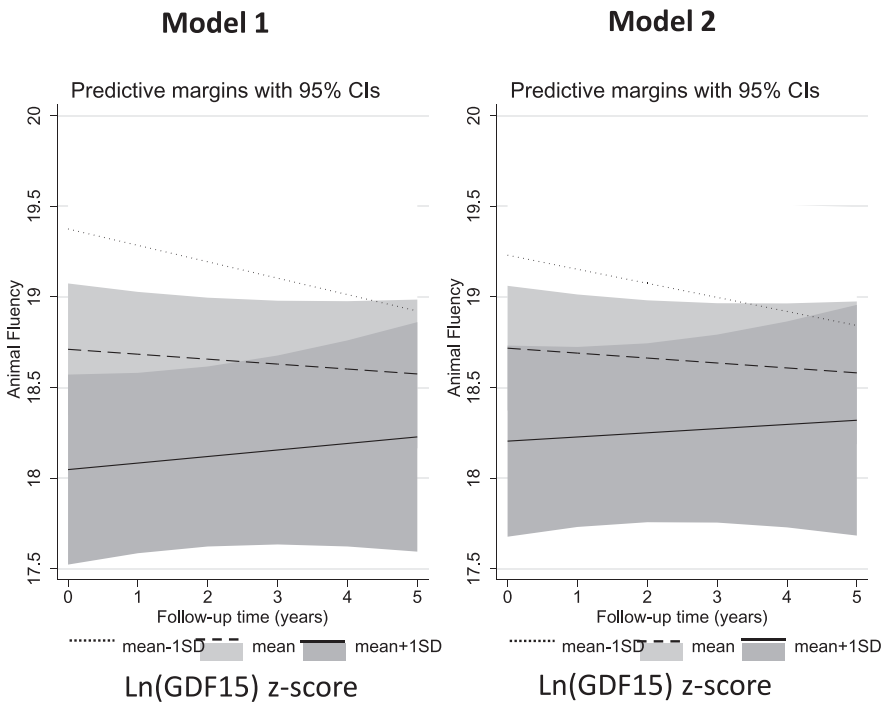
GDF15 and AF remained statistically significant after further adjustment for other socio-demographic, lifestyle and health-related factors (Model 1: $\gamma_{06} \pm$ SE: −0.664 ± 0.208, P < 0.001; Model 2, $\gamma_{06} \pm$ SE: −0.498 ± 0.217, P < 0.05), including literacy and educational attainment. Extension of **Model 2** with the addition of select medication use at baseline did not alter this finding.

In models stratified by race, several additional findings emerged. Among White adults, a higher GDF15 concentration was linked to poorer performance in the domain of Attention (BTA), an association that passed correction for multiple testing and remained statistically significant at a type I error of 0.05 in the fully adjusted model (Model 1: $\gamma_{05} \pm$ SE: −0.426 ± 0.126, P < 0.001; Model 2, $\gamma_{05} \pm$ SE: −0.281 ± 0.139, P < 0.05), despite marked attenuation. This pattern of poorer performance at baseline with higher GDF15 was also observed among White adults for the executive function domain as represented by Trailmaking test B, measured in seconds, Log_e transformed (Model 1: $\gamma_{011} \pm$ SE: +0.129 ± 0.040, P < 0.001; Model 2, $\gamma_{011} \pm$ SE: +0.089 ± 0.041, P < 0.05). In other exploratory analyses, stratified separately by sex, age group and poverty status, we found that, upon correction for multiple testing in model 1 and further covariate adjustment in model 2, GDF15 was associated with poorer baseline performance among women in the case of global mental status (Normalized MMSE: Model 1: $\gamma_{01} \pm$ SE: −2.617 ± 0.746, P < 0.001; Model 2: $\gamma_{01} \pm$ SE: −1.729 ± 0.709, P < 0.05), and among participants living below poverty in the case of BTA (Model 1: $\gamma_{05} \pm$ SE: −0.399 ± 0.128, P < 0.001; Model 2, $\gamma_{05} \pm$ SE: −0.319 ± 0.134, P < 0.05). All other findings did not satisfy both conditions. Nevertheless, most of these findings suggested homogeneous effects of GDF15 across race, sex, age group and poverty status on both baseline performance and annualized rate of changes, with only few exceptions. The key results in the overall sample are depicted in Figs. 2 and 3. Fig. 2 shows the main baseline performance finding with AF and GDF15, while Fig. 3 shows all the results in the overall sample, indicating that most of these findings involved baseline GDF15 vs poorer performance on several cognitive performance tests at baseline. In fact, GDF15 was not associated with cognitive decline over time, particularly upon correction for multiple testing.

6. Discussion

6.1. Main findings

This study is one of just a few to investigate serum GDF15 baseline concentration in relation to cognitive performance over time, among middle-aged adults. It is also the first to do so in a bi-racial urban cohort of middle-aged men and women. Cognitive performance was measured up to two times over a period of 4.3 years, with an average of 85 % having complete data on both visits. The cognitive tests reflected global mental status, as well as domains of visual and verbal memory, attention, and executive function. Our main findings indicated that higher GDF15 was associated with poorer baseline performance on several cognitive tests, including animal fluency (overall sample and women), a brief test of attention (among White adults, women, and individuals living below poverty), and Trailmaking test, part B (among White adults and women), and global mental status in women, upon correction for multiple testing and further adjustment for key covariates. We did not detect an association between GDF15 and decline in cognitive performance over time in this sample of middle-aged adults.



Model 1: γ_0±SE: -0.664±0.208, P<0.001
Model 2, γ_0±SE: -0.498±0.217, P<0.05

Fig. 2. Predictive margins of GDF15 vs cognitive performance over time, Animal Fluency, overall [a] $GDF15v_1$ values are Log_e transformed and z-scored. Levels of exposure are −1: mean – 1SD; 0: at mean; +1: mean + 1SD. 1 SD of baseline Log_e(GDF15) is estimated at 0.70; Mean = 6.55. All test scores presented in these figures are coded in the direction of higher score → better performance. *Abbreviations*: AF = Animal Fluency; $GDF15_{v1}$ = Plasma GDF15 levels, Log_e transformed, z-scored at v_1.

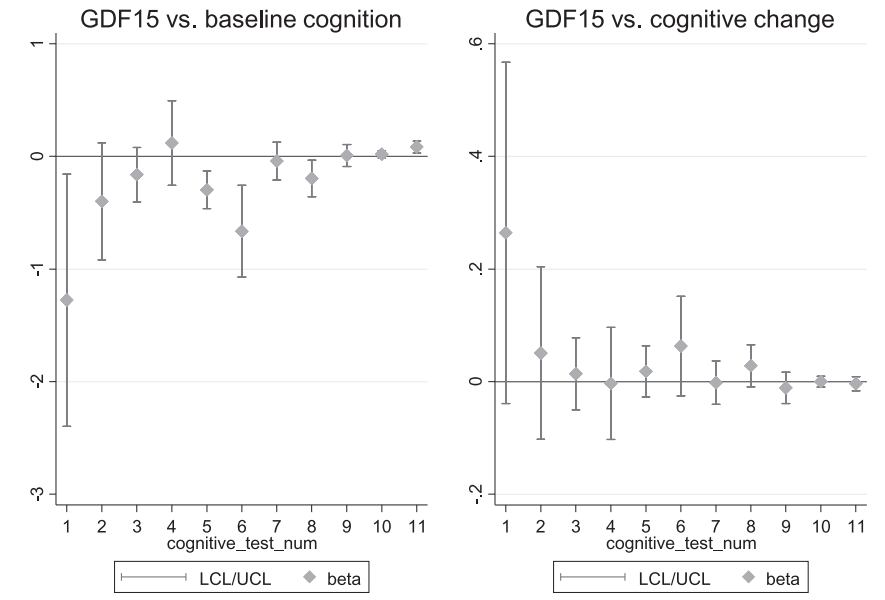


Fig. 3. Summary of mixed-effect linear regression models, reduced model (i.e. Model 1), overall *Abbreviations*: AF = Animal Fluency; BTA = Brief Test of Attention; BVRT = Benton Visual Retention Test; CDT = Clock Drawing Test; CVLT-DFR = California Verbal Learning Test-Delayed Free Recall; CVLT-List A = California Verbal Learning Test-List A; DS-B = Digits Span-Backward; DS-F = Digits Span-Forward; FC = Follow-up cognition; $GDF15_{v1}$ = Plasma GDF15 levels, Log_e transformed, z-scored at v_1; TRAILS A = Trailmaking Test, Part A; TRAILS B = Trailmaking Test, part B. [a] 1 SD of baseline Log_e(GDF15) is estimated at 0.70; Mean = 6.55.. BVRT, TRAILS A and B are coded in the direction of higher score → poorer performance. All other test scores are in the direction of higher score → better performance. [b]Cognitive tests were: 1. Normalized MMSE; 2.CVLT-List A; 3.CVLT-DFR;4.BVRT;5.BTA;6.AF;7.DS-F;8.DS-B;9.CDT;10. TRAILS A;11.TRAILS B.

6.2. Previous studies and biological mechanisms

Our baseline findings agree with a previous study that reported in a cross-sectional analysis that GDF15 was associated with cognition at Wave 1 and processing speed, memory, and executive function in cross-sectional analyses at Wave 2 (Fuchs et al., 2013). In this previous study, participants were White, older (mean age 78.5) and were both cognitively normal and diagnosed with MCI (Fuchs et al., 2013). The longitudinal analyses from this cohort were consistent with our longitudinal analysis in finding only a trend in higher GDF15 at baseline with global cognition, executive function, and processing speed. However, a comparison of the extreme tertiles of GDF15 from the previous study revealed that participants in the GDF15 upper tertile had lower memory and executive function compared to participants in the lower tertile. Importantly, Fuchs *et al.* showed participants with MCI, as well as those who declined cognitively over 2 years from normal to MCI, had elevated

levels of circulating GDF15. As this earlier cohort was older (mean age 78.5 at Wave 1) this data shows that GDF15 may have predictive value for future cognitive decline in older at-risk adults. Concordantly, higher GDF15 was recently reported to be associated with an elevated risk for all-cause and AD dementia after a ~ 12 year follow up in older > 60 yrs adults in the Framingham Offspring cohort (McGrath et al., 2020).

GDF15 plays a role in a variety of normal physiologic and pathologic processes, however, the association of GDF15 and brain health is still unclear. Circulating levels of GDF15 increase with age (Tanaka et al., 2018), may be indicative of brain aging (Casanova et al., 2022), and are associated with all-cause mortality (Desmedt et al., 2019; Xie et al., 2019). Therefore, it may be that GDF15 orchestrates systemic age-related inflammation, or is involved in a compensatory response in the setting of tissue injury and cellular stress. Several lines of evidence indicate that GDF15 may reflect subclinical brain injury or damage. For example, GDF15 levels are associated with white matter hyperintensities (WMH) in the Framingham Offspring cohort (Andersson et al., 2015; McGrath et al., 2020), and was a marker of cognitive impairment and AD in patients with WMH (Chai et al., 2016). GDF15 and 6 other inflammatory markers were used to make an inflammatory compositive score, which was found in the MarkVCID cohort of cognitively normal and MCI participants to be associated with WMH (Altendahl et al., 2020). However, GDF15 was not associated with WMH in the MAS study (Jiang et al., 2015a) but was associated with atrophy in subcortical and cortical gray matter (Jiang et al., 2015b). Higher GDF15 was also related to lower total brain and hippocampal volumes in another study of adults > 60 yrs (McGrath et al., 2020). Therefore, it may be that elevated GDF15 reflects subclinical brain injury or damage, but more studies are warranted to fully understand.

Studies in rodents point to a beneficial role of GDF15 in promoting brain health, which may reflect its recent discovery as a ligand of the putative neuroprotective receptor GFRAL (Emmerson et al., 2017). Specifically, GDF15 knock-out mice have defects in migration and proliferation of hippocampal precursor cells and progressive loss of motoneurons (Carrillo-Garcia et al., 2014; Strelau et al., 2009). GDF15 has also been posited to be a protective factor against neuronal injury, promote regeneration of neurons and axonal elongation (Jiang et al., 2021; Schindowski et al., 2011; Strelau et al., 2009). Recently, it was reported GDF15 can enhance the ability of microglial cells to clear amyloid beta both *in vitro* in cultured microglial cells and *in vivo* in an AD mouse model (Kim et al., 2018). Collectively, these data point to a pivotal and complex neuroprotective role for GDF15. Yet, we still do not fully understand if higher systemic levels of GDF15 may reflect a causative or compensatory response in the setting of neurodegenerative disorders. Nevertheless, it is important to examine the relationship between GDF15 and cognition at midlife since quantifying GDF15 may be an attractive non-invasive biomarker of cognitive decline. This would aid in identifying individuals at risk for AD, ADRD and other neurodegenerative diseases.

A recent review suggests that in rodent models elevated GDF15 has a net effect of reducing food intake and BMI, by binding to GFRAL and recruitment of the RET tyrosine kinase receptor in the hindbrain (Wang et al., 2021). The association of GDF15 with BMI was shown to be independent of appetite-regulating hormones, such as leptin and ghrelin, making it an important target for human obesity and many associated metabolic disorders (Wang et al., 2021). The association of BMI with age-related cognitive decline has been shown to be a complex relationship as well, depending on the age group of individuals who are followed up over time. At mid-life, obesity is generally shown to be directly related to cognitive impairment with age, while at older ages, underweight is shown to predict future risk of cognitive impairment, including incidence of dementia (Beydoun et al., 2008; Beydoun and Kivimaki, 2020). Thus, the role of GDF15 in cognition may be modulated by baseline BMI. In our present study, we have accounted for BMI, which was weakly and inversely related to GDF15 (Pearson's r = -0.06 between Log_e transformed GDF15 and BMI, p = 0.07). Nevertheless, it is worth noting that the average BMI in our study sample is markedly greater than the mean BMI observed in other national studies of middle-aged adults, including the more recent National Health and Nutrition Examination Surveys (Wang et al., 2020). Therefore, our results may only be generalizable to similar populations of ethnically and socioeconomically diverse urban adults.

6.3. Strengths and limitations

There are several notable strengths to our study. First, GDF15 was measured in relation to cognition in a community-based population and was among the first to do so in a cohort of middle-aged adults. In addition, serum GDF15 was detected and quantified in non-demented individuals, most studies thus far have examined GDF15 in cognitively normal and patients with MCI. Therefore, our data add value to utilizing this biomarker as an early marker to monitor cognitive decline over time. Second, we included in our analysis an extensive battery of cognitive tests that spanned many aspects of cognition as well as measuring global mental status. Additionally, we had access to test scores at up to two visits, approximately 4 years apart. Third, the well-balanced sampling of HANDLS allowed for stratification of our analyses by race, sex, and poverty status. Fourth, we used advanced statistical techniques, including mixed-effects linear regression models, multiple imputation, and 2-stage Heckman selection to test our key hypotheses, while reducing confounding and selection biases. Both a strength and limitation to our study is that our sample is younger compared to previous studies that examined these questions in older adults. In our younger cohort cognitive decline was limited and was only evident above the age of 50y. This may have reduced our ability to detect an association between GDF15 at v_1 and change in cognitive function in the overall population. The short follow-up in this younger cohort and the small number of repeats, may also have reduced the ability to utilize GDF15 as a predictor of cognitive decline in this cohort. However, our results do indicate that GDF15 may correlate with decreased cognitive performance at a single point in time, indicating a potential acute association with performance rather than an effect on change over time. A larger number of repeats may have yielded a different result with respect to the association between GDF15 and cognitive change in this study population. Finally, residual confounding in an observational study such as ours is a major limitation, especially that we were unable to control for physical exercise, which was not measured at the baseline HANDLS visit. In fact, previous studies have shown that physical exercise tended to increase circulating GDF15 concentrations, while markedly reducing the rate of age-related cognitive decline (Beydoun et al., 2014; Kleinert et al., 2018). Other factors such as psychotropic medications were also not readily available at the baseline visit, while still others including supplement use were only made available at the follow-up visit.

7. Conclusions

In sum, we detected cross-sectional associations between higher GDF15 and poorer cognition. In a short-term follow-up (~4 yrs), GDF15 did not predict rate of change in cognitive performance over time among a sample of middle-aged adults. More longitudinal studies with longer follow-up times are needed to address the clinical utility of this biomarker for early cognitive defects.

CRediT authorship contribution statement

May A. Beydoun: Conceptualization, Data curation, Formal analysis, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Nicole Noren Hooten:** Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. **Jordan Weiss:** Methodology, Visualization, Writing – original draft, Writing – review & editing. **Hind A. Beydoun:** Methodology, Writing – original draft,

Writing – review & editing. **Michael Georgescu:** Writing – original draft, Writing – review & editing. **David W. Freeman:** Investigation, Validation, Writing – original draft, Writing – review & editing. **Michele K. Evans:** Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Alan B. Zonderman:** Conceptualization, Data curation, Methodology, Validation, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2022.12.015.

References

Altendahl, M., Maillard, P., Harvey, D., Cotter, D., Walters, S., Wolf, A., Singh, B., Kakarla, V., Azizkhanian, I., Sheth, S.A., Xiao, G., Fox, E., You, M., Leng, M., Elashoff, D., Kramer, J.H., Decarli, C., Elahi, F., Hinman, J.D., 2020. An IL-18-centered inflammatory network as a biomarker for cerebral white matter injury. PLoS One 15, e0227835.

Andersson, C., Preis, S.R., Beiser, A., DeCarli, C., Wollert, K.C., Wang, T.J., Januzzi Jr., J. L., Vasan, R.S., Seshadri, S., 2015. Associations of Circulating Growth Differentiation Factor-15 and ST2 Concentrations With Subclinical Vascular Brain Injury and Incident Stroke. Stroke 46, 2568–2575.

Beydoun, M.A., Beydoun, H.A., Wang, Y., 2008. Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. Obes. Rev. 9, 204–218.

Beydoun, M.A., Beydoun, H.A., Kitner-Triolo, M.H., Kaufman, J.S., Evans, M.K., Zonderman, A.B., 2013. Thyroid hormones are associated with cognitive function: moderation by sex, race, and depressive symptoms. J. Clin. Endocrinol. Metab. 98, 3470–3481.

Beydoun, M.A., Beydoun, H.A., Gamaldo, A.A., Teel, A., Zonderman, A.B., Wang, Y., 2014. Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis. BMC Public Health 14, 643.

Beydoun, M.A., Beydoun, H.A., Mode, N., Dore, G.A., Canas, J.A., Eid, S.M., Zonderman, A.B., 2016a. Racial disparities in adult all-cause and cause-specific mortality among us adults: mediating and moderating factors. BMC Public Health 16, 1113.

Beydoun, M.A., Canas, J.A., Dore, G.A., Beydoun, H.A., Rostant, O.S., Fanelli-Kuczmarski, M.T., Evans, M.K., Zonderman, A.B., 2016b. Serum Uric Acid and Its Association with Longitudinal Cognitive Change Among Urban Adults. J. Alzheimers Dis. 52, 1415–1430.

Beydoun, M.A., Hossain, S., Beydoun, H.A., Shaked, D., Weiss, J., Evans, M.K., Zonderman, A.B., 2020. Red Cell Distribution Width Is Directly Associated with Poor Cognitive Performance among Nonanemic, Middle-Aged, Urban Adults. J. Nutr. 150, 128–139.

Beydoun, H.A., Huang, S., Beydoun, M.A., Hossain, S., Zonderman, A.B., 2019. Mediating-Moderating Effect of Allostatic Load on the Association between Dietary Approaches to Stop Hypertension Diet and All-Cause and Cause-Specific Mortality: 2001–2010 National Health and Nutrition Examination Surveys. Nutrients 11.

Beydoun, M.A., Kivimaki, M., 2020. Midlife obesity, related behavioral factors, and the risk of dementia in later life. Neurology 94, 53–54.

Boyd, R.J., Avramopoulos, D., Jantzie, L.L., McCallion, A.S., 2022. Neuroinflammation represents a common theme amongst genetic and environmental risk factors for Alzheimer and Parkinson diseases. J. Neuroinflammation 19, 223.

Carrillo-Garcia, C., Prochnow, S., Simeonova, I.K., Strelau, J., Holzl-Wenig, G., Mandl, C., Unsicker, K., von Bohlen Und Halbach, O., Ciccolini, F., 2014. Growth/differentiation factor 15 promotes EGFR signalling, and regulates proliferation and migration in the hippocampus of neonatal and young adult mice. Development 141, 773-783.

Casanova, R., Anderson, A.M., Barnard, R.T., Justice, J.N., Kucharska-Newton, A., Windham, B.G., Palta, P., Gottesman, R.F., Mosley, T.H., Hughes, T.M., Wagenknecht, L.E., Kritchevsky, S.B., 2022. Is an MRI-derived anatomical measure of dementia risk also a measure of brain aging? Geroscience.

Chai, Y.L., Hilal, S., Chong, J.P.C., Ng, Y.X., Liew, O.W., Xu, X., Ikram, M.K., Venketasubramanian, N., Richards, A.M., Lai, M.K.P., Chen, C.P., 2016. Growth differentiation factor-15 and white matter hyperintensities in cognitive impairment and dementia. Medicine (Baltimore) 95, e4566.

Daniels, L.B., Clopton, P., Laughlin, G.A., Maisel, A.S., Barrett-Connor, E., 2011. Growth-differentiation factor-15 is a robust, independent predictor of 11-year mortality risk in community-dwelling older adults: the Rancho Bernardo Study. Circulation 123, 2101–2110.

Desmedt, S., Desmedt, V., De Vos, L., Delanghe, J.R., Speeckaert, R., Speeckaert, M.M., 2019. Growth differentiation factor 15: A novel biomarker with high clinical potential. Crit. Rev. Clin. Lab. Sci. 56, 333–350.

Eggers, K.M., Kempf, T., Wallentin, L., Wollert, K.C., Lind, L., 2013. Change in growth differentiation factor 15 concentrations over time independently predicts mortality in community-dwelling elderly individuals. Clin. Chem. 59, 1091–1098.

Emmerson, P.J., Wang, F., Du, Y., Liu, Q., Pickard, R.T., Gonciarz, M.D., Coskun, T., Hamang, M.J., Sindelar, D.K., Ballman, K.K., Foltz, L.A., Muppidi, A., Alsina-Fernandez, J., Barnard, G.C., Tang, J.X., Liu, X., Mao, X., Siegel, R., Sloan, J.H., Mitchell, P.J., Zhang, B.B., Gimeno, R.E., Shan, B., Wu, X., 2017. The metabolic effects of GDF15 are mediated by the orphan receptor GFRAL. Nat. Med. 23, 1215–1219.

Freeman, D.W., Noren Hooten, N., Kim, Y., Mode, N.A., Ejiogu, N., Zonderman, A.B., Evans, M.K., 2020. Association between GDF15, poverty and mortality in urban middle-aged African American and white adults. PLoS One 15, e0237059.

Fuchs, T., Trollor, J.N., Crawford, J., Brown, D.A., Baune, B.T., Samaras, K., Campbell, L., Breit, S.N., Brodaty, H., Sachdev, P., Smith, E., 2013. Macrophage inhibitory cytokine-1 is associated with cognitive impairment and predicts cognitive decline - the Sydney Memory and Aging Study. Aging Cell 12, 882–889.

Hochberg, Y., Tamhane, A.C., 1987. Multiple comparison procedures. Wiley, New York.

Hsu, J.Y., Crawley, S., Chen, M., Ayupova, D.A., Lindhout, D.A., Higbee, J., Kutach, A., Joo, W., Gao, Z., Fu, D., To, C., Mondal, K., Li, B., Kekatpure, A., Wang, M., Laird, T., Horner, G., Chan, J., McEntee, M., Lopez, M., Lakshminarasimhan, D., White, A., Wang, S.P., Yao, J., Yie, J., Matern, H., Solloway, M., Haldankar, R., Parsons, T., Tang, J., Shen, W.D., Alice Chen, Y., Tian, H., Allan, B.B., 2017. Non-homeostatic body weight regulation through a brainstem-restricted receptor for GDF15. Nature 550, 255–259.

Jiang, J., Trollor, J.N., Brown, D.A., Crawford, J.D., Thalamuthu, A., Smith, E., Breit, S. N., Liu, T., Brodaty, H., Baune, B.T., Sachdev, P.S., Wen, W., 2015a. An inverse relationship between serum macrophage inhibitory cytokine-1 levels and brain white matter integrity in community-dwelling older individuals. Psychoneuroendocrinology 62, 80–88.

Jiang, J., Wen, W., Brown, D.A., Crawford, J., Thalamuthu, A., Smith, E., Breit, S.N., Liu, T., Zhu, W., Brodaty, H., Baune, B.T., Trollor, J.N., Sachdev, P.S., 2015b. The relationship of serum macrophage inhibitory cytokine-1 levels with gray matter volumes in community-dwelling older individuals. PLoS One 10, e0123399.

Jiang, W.W., Zhang, Z.Z., He, P.P., Jiang, L.P., Chen, J.Z., Zhang, X.T., Hu, M., Zhang, Y. K., Ouyang, X.P., 2021. Emerging roles of growth differentiation factor-15 in brain disorders (Review). Exp. Ther. Med. 22, 1270.

Kim, Y., Noren Hooten, N., Evans, M.K., 2018. CRP Stimulates GDF15 Expression in Endothelial Cells through p53. Mediators Inflamm. 2018, 8278039.

Kleinert, M., Clemmensen, C., Sjoberg, K.A., Carl, C.S., Jeppesen, J.F., Wojtaszewski, J.F. P., Kiens, B., Richter, E.A., 2018. Exercise increases circulating GDF15 in humans. Mol. Metab. 9, 187–191.

Matthews, K.A., Xu, W., Gaglioti, A.H., Holt, J.B., Croft, J.B., Mack, D., McGuire, L.C., 2019. Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015–2060) in adults aged >/=65 years. Alzheimers Dement. 15, 17–24.

Mayeda, E.R., Glymour, M.M., Quesenberry, C.P., Whitmer, R.A., 2016. Inequalities in dementia incidence between six racial and ethnic groups over 14 years. Alzheimers Dement. 12, 216–224.

McGrath, E.R., Himali, J.J., Levy, D., Conner, S.C., DeCarli, C., Pase, M.P., Ninomiya, T., Ohara, T., Courchesne, P., Satizabal, C.L., Vasan, R.S., Beiser, A.S., Seshadri, S., 2020. Growth Differentiation Factor 15 and NT-proBNP as Blood-Based Markers of Vascular Brain Injury and Dementia. J. Am. Heart Assoc. 9, e014659.

Mielke, M.M., Syrjanen, J.A., Blennow, K., Zetterberg, H., Vemuri, P., Skoog, I., Machulda, M.M., Kremers, W.K., Knopman, D.S., Jack, C., Jr., Petersen, R.C., Kern, S., 2019. Plasma and CSF neurofilament light: Relation to longitudinal neuroimaging and cognitive measures. Neurology 93, e252-e260.

Mullican, S.E., Lin-Schmidt, X., Chin, C.N., Chavez, J.A., Furman, J.L., Armstrong, A.A., Beck, S.C., South, V.J., Dinh, T.Q., Cash-Mason, T.D., Cavanaugh, C.R., Nelson, S., Huang, C., Hunter, M.J., Rangwala, S.M., 2017. GFRAL is the receptor for GDF15 and the ligand promotes weight loss in mice and nonhuman primates. Nat. Med. 23, 1150–1157.

Mullican, S.E., Rangwala, S.M., 2018. Uniting GDF15 and GFRAL: Therapeutic Opportunities in Obesity and Beyond. Trends Endocrinol Metab 29, 560–570.

Schindowski, K., von Bohlen und Halbach, O., Strelau, J., Ridder, D.A., Herrmann, O., Schober, A., Schwaninger, M., Unsicker, K., 2011. Regulation of GDF-15, a distant TGF-beta superfamily member, in a mouse model of cerebral ischemia. Cell Tissue Res 343, 399-409.

Selvin, S., 2004. Statistical Analysis of Epidemiologic Data. Oxford University Press.

Stata, 2019. Statistics/Data Analysis: Release 17.0. Stata Corporation, Texas.

Steenland, K., Goldstein, F.C., Levey, A., Wharton, W., 2016. A Meta-Analysis of Alzheimer's Disease Incidence and Prevalence Comparing African-Americans and Caucasians. J. Alzheimers Dis. 50, 71–76.

Strelau, J., Strzelczyk, A., Rusu, P., Bendner, G., Wiese, S., Diella, F., Altick, A.L., von Bartheld, C.S., Klein, R., Sendtner, M., Unsicker, K., 2009. Progressive postnatal motoneuron loss in mice lacking GDF-15. J. Neurosci. 29, 13640–13648.

Tanaka, T., Biancotto, A., Moaddel, R., Moore, A.Z., Gonzalez-Freire, M., Aon, M.A., Candia, J., Zhang, P., Cheung, F., Fantoni, G., consortium, C.H.I., Semba, R.D., Ferrucci, L., 2018. Plasma proteomic signature of age in healthy humans. Aging Cell 17, e12799.

Tsai, V.W.W., Husaini, Y., Sainsbury, A., Brown, D.A., Breit, S.N., 2018. The MIC-1/GDF15-GFRAL Pathway in Energy Homeostasis: Implications for Obesity, Cachexia, and Other Associated Diseases. Cell Metab. 28, 353–368.

Tung, Y.C., Hsiao, F.C., Lin, C.P., Hsu, W.C., Chu, P.H., 2022. Cognitive impairment and its association with circulating biomarkers in patients with acute decompensated heart failure. J. Geriatr. Cardiol. 19, 227–237.

Wang, Y., Beydoun, M.A., Min, J., Xue, H., Kaminsky, L.A., Cheskin, L.J., 2020. Has the prevalence of overweight, obesity and central obesity levelled off in the United States? Trends, patterns, disparities, and future projections for the obesity epidemic. Int. J. Epidemiol. 49, 810–823.

Wang, D., Day, E.A., Townsend, L.K., Djordjevic, D., Jorgensen, S.B., Steinberg, G.R., 2021. GDF15: emerging biology and therapeutic applications for obesity and cardiometabolic disease. Nat. Rev. Endocrinol. 17, 592–607.

Wiklund, F.E., Bennet, A.M., Magnusson, P.K., Eriksson, U.K., Lindmark, F., Wu, L., Yaghoutyfam, N., Marquis, C.P., Stattin, P., Pedersen, N.L., Adami, H.O., Gronberg, H., Breit, S.N., Brown, D.A., 2010. Macrophage inhibitory cytokine-1 (MIC-1/GDF15): a new marker of all-cause mortality. Aging Cell 9, 1057–1064.

Xie, S., Lu, L., Liu, L., 2019. Growth differentiation factor-15 and the risk of cardiovascular diseases and all-cause mortality: A meta-analysis of prospective studies. Clin. Cardiol. 42, 513–523.

Yang, L., Chang, C.C., Sun, Z., Madsen, D., Zhu, H., Padkjaer, S.B., Wu, X., Huang, T., Hultman, K., Paulsen, S.J., Wang, J., Bugge, A., Frantzen, J.B., Norgaard, P., Jeppesen, J.F., Yang, Z., Secher, A., Chen, H., Li, X., John, L.M., Shan, B., He, Z., Gao, X., Su, J., Hansen, K.T., Yang, W., Jorgensen, S.B., 2017. GFRAL is the receptor for GDF15 and is required for the anti-obesity effects of the ligand. Nat. Med. 23, 1158–1166.