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Metabolomic levels mediate the link between socioeconomic factors and changes in declarative memory in women with and without HIV

César Higgins Tejera [a,*], Raha Dastgheyb [a], Eran F. Shorer [a], Susie Lee [b], Deborah Gustafson [c], Anjali Sharma [b], Gypsyamber D'Souza [d], Kathleen M. Weber [e], Qibin Qi [b], Leah H. Rubin [a], Kathryn C. Fitzgerald [a,**]

[a] Johns Hopkins University, School of Medicine, Baltimore, MD, 21287, USA
[b] Albert Einstein College of Medicine, Bronx, NY, 10461, USA
[c] SUNY Downstate Health Sciences University, Brooklyn, NY, 11203, USA
[d] Johns Hopkins University, School of Public Health, Baltimore, MD, 21287, USA
[e] Rush University Medical College, Chicago, IL, 60612, USA

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STRUCTURED ABSTRACT

Introduction: Understanding metabolic pathways linking socioeconomic conditions and declarative memory (DM) may reveal interventional targets.
Methods: Using multivariable generalized estimating equation models in a subsample of the Women's Interagency HIV Study, we examined associations between peripheral metabolomic profiles and longitudinal performance on the Hopkins Verbal Learning Test-Revised (HVLT-R), a measure of DM in the overall sample and by serostatus. We also explored metabolite-mediated effects of income and employment on DM.
Results: In a sample of 324 women, 225 with HIV, average age 43.1 years, (65%) non-Hispanic Black. After false discovery rate [FDR]-correction, 15 metabolites were found to relate to learning and 16 to memory changes. Observed effect sizes were generally similar by serostatus. Top metabolites include serotonin, taurine, and niacinamide. In mediation analyses including all women, we found that 30% (95%CI: 4.4%-101.3%) of the effect of employment and 18.2% (95%CI: 2.1% to 72.3%) of the effect of income on learning was mediated through differences in metabolite levels.
Discussion: Metabolites mediate the effect of socioeconomic conditions on changes in DM in women.

1. Background

Cognitive decline is a feature of aging. However, progressive cognitive deterioration, which is characterized by multiple affected cognitive domains, including impairment in short and long-term memory and executive functioning, such that it interferes with activities of daily living. Collectively, these features may signal the preclinical stage of a neurological disorder (Elahi and Miller, 2017; Knopman et al., 2021; Masters et al., 2015; Jost and Kujach, 2025). Alzheimer's disease, a leading cause of morbidity and mortality in the US, generally manifests with rapid and disabling cognitive impairment (Alzheimer's disease facts and figures, 2019; Sloane et al., 1995). While women may have better cognitive reserve than men, they may experience faster declines in some domains including global cognition and executive functioning (Levine et al., 2021). Epidemiological evidence also suggests that women with HIV (WWH) experience lower performance in global cognition, and other domains such as declarative memory and motor function compared to men with HIV (Rubin et al., 2020), indicating similar patterns of cognitive deterioration in both WWH and women without HIV (WWoH). The high burden of cognitive deterioration among women may reflect sex-related differences in physiological responses to psychosocial stressors (abuse, violence, sexism), which are highly prevalent and frequently experienced through women's lifetime. Exposure to physical and sexual violence is linked to elevated cortisol levels independently on when the first act of violence occurred and the length of exposure (Lynch et al., 2022). Thus, stress related hormones may

* Corresponding author.
** Corresponding author. Johns Hopkins University, School of Medicine, Department of Neurology, 600 N. Wolfe Street, Pathology 627, Baltimore, MD, 21287, USA.
E-mail addresses: chiggi25@jh.edu (C.H. Tejera), fitzgerald@jhmi.edu (K.C. Fitzgerald).

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represent a potential mechanism for worse cognition among women (Salardini et al., 2025) a downstream consequence of gendered injustices in structural and socioeconomic factors (employment, income, poverty). (Krieger, 2024).

Socioeconomic factors are structural forces that shape the distribution of health outcomes in a hierarchical manner, and it is well-documented that lower marginalized strata experience a higher burden of disease (Marmot, 2017; Krieger, 2001; Higgins Tejera et al., 2023, 2024). Among women, these inequities may reflect gendered injustices in the form of abuse, violence, and racism. Such injustices are rooted on a caste-based system of political marginalization, economic exploitation, and gender domination (Krieger, 2003, 2024; Higgins Tejera et al., 2024; Spanierman et al., 2009; Sharpe, 2012). It is well-established that income and employment disparities contribute to the generation and perpetuation of health inequities across the lifespan, particularly among women and women of color (Belle and Doucet, 2003; Kilbourne et al., 1994). However, to date there exist considerable gaps in understanding how these socioeconomic factors affect cellular and molecular pathways that modify individuals' susceptibility to cognitive decline. Mostly, prior research has focused on isolated biomarkers as mediators between sociodemographic factors (i.e., race) and cognitive outcomes (Higgins Tejera et al., 2023, 2024); but it is plausible that exposure to low income and lack of employment results in a myriad of altered biological processes that may lead to neurodegeneration, cognitive decline, and dementia risk. Testing large-scale biological mechanisms implicated in socioeconomic disparities in women is feasible through high-throughput metabolomic analysis (Fuller et al., 2023). Identifying the biological contributors of rapid cognitive decline associated with socioeconomic factors in adult women may offer key insights on structural contributors to Alzheimer's disease onset and progression, and reveal proximal biological targets for intervention prior to cognitive loss.

Metabolomics may be key to understanding a link between socioeconomic conditions and a variety of phenotypes (Fuller et al., 2023; Patti et al., 2012; Ramautar et al., 2013). Metabolites are small molecules detected in blood and other tissues that help regulate health and disease states. A person's metabolic phenotype reflects the interplay between genetics, environmental conditions (socioeconomic, life-stressful events), individual-level factors (diet, smoking, drinking), and their interactions (Patti et al., 2012; Ramautar et al., 2013; Fiehn, 2002). Multiple studies have identified metabolomic signatures associated with neurodegenerative diseases and Alzheimer's disease risk and outcomes (Fuller et al., 2023; Fitzgerald et al., 2021; Varma et al., 2018; Toledo et al., 2017a; Khan et al., 2022). However, few studies explore how socioeconomic factors such as employment and income alter biological systems to adversely affect cognitive trajectories (Robinson et al., 2021; He et al., 2022). This is particularly relevant for women, and especially those living with HIV, as the AIDS epidemic occurred at the intersection of multiple gendered injustices that placed women of color at high risk for HIV infection and subsequently cognitive decline (Edlin et al., 1994). In a subsample of the Women's Interagency HIV Study (WIHS), we aimed to characterize the metabolomic profile of cognitive deterioration in adult women and to identify metabolomic signatures associated with changes in declarative memory, as measured by verbal learning and verbal memory. In downstream analysis, we employ multiple mediation analysis to understand to what extent metabolite levels mediate the relationship between income and employment on changes in declarative memory.

2. Methods

We performed a longitudinal study with repeated measures of seven cognitive domains in a subsample of 324 adult WIHS women who underwent plasma metabolomic profiling in 2004-2006. The WIHS, now the MACS/WIHS Combined Cohort Study, started in 1994-1995 and is a prospective study of WWH and a comparison group of WWoH who share a similar distribution of demographic characteristics such as age, race, and income. WIHS participants underwent core interviews every six months to assess socio-demographic characteristics, medical history, health behaviors, medication use, and laboratory testing ($CD4^+$ cell counts and plasma HIV RNA viral load). Eligible participants for metabolomic analysis for this study were those older than 35 years, and without prior history of diabetes or carotid plaques (Bravo et al., 2020; Chai et al., 2019). Since 2009, all English-speaking participants received cognitive assessments every two years. We excluded participants with missing information in important covariates of interest. We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Vandenbroucke et al., 2007). The Johns Hopkins University Institutional Review Board approved this secondary data analysis. WIHS data is available through the Data Management and Analysis Center (WDMAC) (https://statepi.jhsph.edu/wihs/wordpress/?page_id=485).

2.1. Plasma metabolomic measures

We leveraged metabolomic data that were generated as a component to a prior study. This study applied untargeted metabolomic analysis to explore the role of peripheral metabolite species on cardiovascular dysfunction. A detailed description of this study, including metabolomics can be found elsewhere (Bravo et al., 2020). Briefly polar metabolites were measured in stored plasma specimens (10 μL) using liquid chromatography-tandem mass spectrometry at the Broad Institute Metabolomic Platform (Cambridge, Massachusetts). In the initial sample, a total of 155 polar metabolite species (i.e., amino acids and conjugates, acylcarnitines) were quantified. The current analysis includes a total of 131 polar metabolite species; after excluding those with more than 20% missing values.

2.2. Cognitive measures

Seven cognitive domains were evaluated prospectively and on average every two years after metabolomics measurements including: attention/working memory (Letter Number Sequencing), executive function (Trail Marking Test Part B, Stroop Color-Word Trial 3), declarative memory (Hopkins Verbal Learning Test-R total learning and delayed recall), verbal fluency (Controlled Oral Word Association Test and category fluency), processing speed (Symbol Digit Modalities Test, Stroop Color Naming Trial), and motor function (Grooved Pegboard). These cognitive assessments were transformed into seven demographically adjusted (age, years of education, and race/ethnicity) *T-scores* (mean ~ 50, and SD ~ 10), where higher scores represent better cognitive performance. In statistical analysis, we used cognitive domains in their continuous form and dichotomized (i.e., <1SD below the mean T-score) to denote domain-specific cognitive impairment.

2.3. Covariates

We identified a set of covariates as potential confounders between metabolite exposures and each cognitive domain. All covariates were measured at baseline (i.e., metabolomics measurement visit) and considered time-invariant. Although we acknowledge that some of these variables, in particular our exposures of interest (income, and employment status), some behavioral risk factors (drug use, smoking, drinking), and comorbid conditions (hypertension and diabetes) could change over time, our models assume they are fixed. Sociodemographic confounders included age (continuous, time-fixed); employment (unemployed or employed); income (≤$24K, >$24K & ≤$36K, >$36K); and race (i.e., non-Hispanic White; Hispanic/Other which includes White Hispanic, African American Hispanic, Other Hispanic, Asian Pacific Islander, Native American/Alaskan Native and Other; and non-Hispanic Black); health behaviors included body mass index (≤25 kg/m^2, >25 & ≤30 kg/m^2, >30 kg/m^2); drinking status (abstainer, >0-7 drinks/week, >7

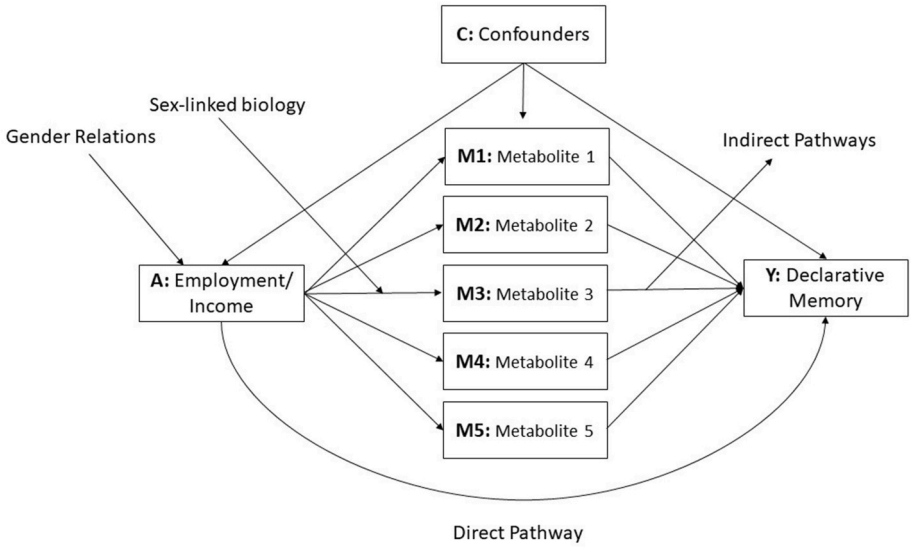

Fig. 1. Directed acyclic graph illustrating the relationship between employment and income, metabolite levels, and cognitive changes (measured through declarative memory or verbal learning and verbal memory) in a subsample of the WIHS. Caption:Exposure (A) represents structural health determinants such as employment or income, the exposure is influenced by gender relationships or injustices that placed women at socioeconomic disadvantage, these disadvantage influence a miriad of biological pathways that lead to cognitive changes. The exposure A influence multiple biological pathways (M1-M5) as indicated by the multiple arrows from exposure to metabolites. These metabolites also influence our outcome of interest (Y: declarative memory or verbal learning and memory). Sex-related hormones or sex-specific pathways influence the relationship between exposure and biological pathways, as represented by the arrow between sex-associated biology and metabolite levels. Lastly, the direct pathway represents all other pathways by which employment and income influence our outcome of interest that are not explicitly represented in the graph.

drinks/week); smoking status (currently smoking or not currently smoking); drug use (abstainer, any drug use); comorbid conditions included hypertension (systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg, self-reported, or use of anti-hypertension medication; yes or no), diabetes (if ever self-reported anti-diabetic medication or any fasting glucose$\geq$126 mg/dL or HbA1C $\geq$ 6.5% or any self-reported diabetes is confirmed; yes or no), hepatitis C (negative/solved infection or Ab+/active), and HIV-serostatus (WWH or WWoH). In mediation analysis, we used income as a binary variable ($\leq$\$24K versus >\$24K).

2.4. Statistical analysis

We examined the distribution of covariates at baseline using mean and SD for continuous variables and proportions for categorical variables. Metabolomics data are commonly skewed. As a result, we transformed all metabolites to the natural logarithmic scale, and standardized each prior to statistical analysis. We used multivariable Generalized Estimating Equation (GEE) models with an identity link, and an exchangeable correlation matrix to examine the longitudinal association between each of the 131 metabolite species and declarative memory (verbal learning and verbal memory) while adjusting for baseline covariates. Other cognitive domains were used as secondary endpoints. False discovery rate adjusted p-values were used to control for multiple comparisons (Benjamini and Hochberg, 1995). Metabolite species meeting the 5% FDR threshold were considered significantly associated with the outcome. In stratified models by serostatus, we explored these associations in WWH and WWoH. We also explored whether using domain-specific cognitive impairment (i.e., <1SD below the mean T-score) instead of domain-specific cognitive test scores led to the identification of common metabolite signatures. In these sensitivity models, we employed GEE Poisson models with a log-link function, and an exchangeable correlation matrix; the time elapsed between metabolomic assessment, and the last cognitive visit was used as an offset variable. We mapped FDR corrected significant metabolites to unique metabolomic pathways using the Human Metabolome Database (HMDB). In subsequent analysis, we employed fast metabolite-set enrichment analysis (akin to fast gene-set enrichment analysis) (Korotkevich et al., 2021; Subramanian et al., 2005) to identify functionally related metabolites to each cognitive domain using pathways defined by HMDB.

2.5. Mediation analysis

To test direct and indirect pathways by which income and employment affect cognitive trajectories in declarative memory (i.e., verbal learning and verbal memory), we performed causal mediation analysis. We used FDR-corrected metabolites associated with cognitive trajectories in verbal learning and memory from prior statistical analyses, and tested which ones were associated with income and employment to use in downstream mediation models as potential mediators. We used linear mixed effect models with a random intercept and a random slope, unstructured covariance matrix, and restricted maximum likelihood estimation to fit the model. These estimates were used to predict subject-specific declarative memory trajectories, and considered the final predicted value to reflect the average subject-specific response over time as our outcome of interest. We used income and employment as independent variables in separate mediation models and verbal learning and verbal memory as our outcomes of interest. We performed a series of multiple and single regression-based causal mediation models to calculate pure direct, and indirect effects, and estimated the mediated proportion, or the extent to which metabolite levels mediated the effect of income or employment on changes in declarative memory. Mediation models were adjusted for socioeconomic variables (age, race, and income if employment was treated as an exposure; or age, race, and employment if income was treated as an exposure), health behaviors (smoking status, drinking status, drug use, and body mass index), chronic conditions, hepatitis C status, and number of cognitive visits. These mediation models assume that our selected covariates account for all exposure-outcome, exposure-mediator, and mediator-outcome confounders, and that there are no mediator-outcome confounders affected by the exposure of interest. In our causal diagram (Fig. 1), the arrows from exposure to mediators, and from mediators to outcomes, represent the indirect pathways by which socioeconomic conditions affect changes

Table 1
Demographic characteristics and cognitive measures at baseline of a subsample of participants in the Women's Interagency HIV Study.

Characteristic	n	M (SD)
Attention/Working Memory	305	49.21 (9.77)
Executive Function	324	50.61 (9.84)
Verbal Learning	314	49.32 (10.19)
Verbal Memory	314	49.54 (10.38)
Verbal Fluency	309	49.35 (8.58)
Processing Speed	324	50.21 (9.92)
Motor Function	308	49.29 (11.21)
Age (years)		43.14 (5.90)
Follow-up Time (years)		11.91 (3.19)
Employment, n (%)		
Unemployed		205 (63%)
Employed		119 (37%)
Income		
<24K		246 (76%)
>24K to <36K		40 (12%)
>36K		38 (12%)
Race		
Non-Hispanic White		21 (6.5%)
Hispanic/Other		91 (28%)
Non-Hispanic Black		212 (65%)
Body Mass Index		
<25 kg/m^2		96 (30%)
>25 to <30 kg/m^2		105 (32%)
>30 kg/m^2		123 (38%)
Drinking Status		
Abstainer		167 (52%)
1-7 Drinks/Week		122 (38%)
>7 Drinks/Week		35 (11%)
Smoking Status		
Not Currently Smoking		152 (47%)
Currently Smoking		172 (53%)
Drug Use		
Abstainer		242 (75%)
Any Drug Use		82 (25%)
Hypertension		
No		245 (76%)
Yes		79 (24%)
Diabetes		
No		309 (95%)
Yes		15 (4.6%)
HIV Status		
Women without HIV		99 (31%)
Women with HIV		225 (69%)
Hepatitis C		
Negative/Solved		244 (75%)
Ab Positive/Active		80 (25%)

[1]n (%); Mean (SD).

in declarative memory. These indirect pathways may be affected by sex-associated biological processes such as sex-related hormones or sex-specific metabolomic pathways associated to the stress response (Krieger, 2003, 2024; Qiao et al., 2025; Wang et al., 2025). Additionally, the arrows from exposure to mediators are influenced by gender relationships and gender-related injustices. In this sense, gender-related inequities in employment and income are conceived as rooted in sexism (i.e., unequal gender relationships), and their connection with multiple metabolites represent the myriad of biological expressions of gender-related injustices (Krieger, 2003). Lastly, the direct pathway represents all potential pathways not illustrated in the directed acyclic graph (DAG) by which employment and income affect cognitive changes.

3. Results

In a sample of 324 women (WWH = 225, WWoH = 99), the average age at baseline was 43.1 years (5.9), 63% were unemployed, 76% had annual income less than $24K, 65% were non-Hispanic Black (Table 1). WWH were similar to WWoH in age, follow-up time, income, race, body mass index, drinking status and cognitive test scores except for verbal learning, where WWoH scored on average 2.9 points higher than WWH at baseline. Additionally, WWH were more likely to be unemployed, less likely to be smokers, report drug use, or have diabetes than WWoH (Supplemental Table 1). Over an average follow-up time of 11.9 years (SD = 3.2), participants had 4.9 verbal learning and memory visits; 3.6 attention/working memory visits; 8.3 executive functioning visits; 4.0 verbal fluency visits, 8.4 processing speed visits; and 4.0 motor function visits.

In multivariable GEE models and among 131 metabolites species, we identified 45 metabolites were associated with total learning on the HVLT-R (learning), but only 15 after FDR correction; 38 metabolites associated with delayed recall on the HVLT-R (memory) of which 16 met the FDR threshold of statistical significance. In secondary analyses including other cognitive domains, we found that 14 metabolites were associated with motor function using a nominal p-value threshold of 0.05, Only 2 were associated with worse motor function over time after FDR correction: cotinine ($\beta = -2.73$; 95%CI: 4.41, −1.06; FDR p-value = 0.04) and hydroxyproline ($\beta = -1.6$; 95%CI: 2.51, −0.7; FDR p-value = 0.02). We found 15 metabolites associated with attention/working memory; 6 with executive function; 9 with processing speed; and 6 with verbal fluency. But none of these species were significant after FDR correction (Fig. 2, Supplemental Fig. 1, Supplemental Table 2). Among the seven cognitive domains, learning and memory shared 22 metabolites species; the top five metabolites associated with higher scores in verbal learning and memory were serotonin, taurine, adenosine, niacinamide, and alpha glycerophosphocholine (Figs. 2 and 3). On average, 1-SD above the mean serotonin levels was associated with higher verbal learning ($\beta = 2.21$; 95%CI: 1.41,3.01; FDR p-value <0.001) and higher verbal memory ($\beta = 2.55$; 95%CI: 1.73,3.38; FDR p-value <0.001) scores over time (Supplemental Table 2). Similar associations were observed for taurine (verbal learning $\beta = 1.95$; 95%CI: 1.16,2.74; FDR p-value <0.001 & verbal memory $\beta = 2.23$; 95%CI: 1.36,3.10; FDR p-value <0.001), adenosine (verbal learning $\beta = 1.89$; 95%CI: 1.04,2.74; FDR p-value 0.001 & verbal memory $\beta = 1.84$; 95% CI: 0.90,2.78; FDR p-value 0.008), niacinamide (verbal learning $\beta = 1.57$; 95%CI: 0.77,2.37; FDR p-value <0.008 & verbal memory $\beta = 1.85$; 95%CI: 1.03, 2.67; FDR corrected p-value 0.001), and alpha glycerophosphocholine (verbal learning $\beta = 1.44$; 95%CI: 0.65,2.23; FDR p-value 0.016 & verbal memory $\beta = 1.65$; 95%CI: 0.77, 2.52; FDR p-value 0.011) (Supplemental Table 2). In contrast, ADMA, pseudouridine, glucose, and sphingomyelins (C18:2 and C16:0) were associated with lower verbal learning and lower memory scores overtime (Fig. 3 & Supplemental Table 2). In Poisson models, we identified that some of these metabolites were also associated with cognitive impairment (i.e., <1SD mean test score) in verbal learning and memory, but none of them met the FDR threshold of statistical significance (Supplemental Fig. 2 & Supplemental Table 3).

Stratified analysis by serostatus revealed that metabolomics signatures (i.e., serotonin, taurine and niacinamide) identified in the overall sample were also associated with better verbal learning and memory scores among WWH (FDR p-values <0.05) and to a lesser extent among WWoH (Fig. 4). Similarly, glucose, ADMA, and pseudouridine were associated with worsening trajectories of verbal memory and learning among WWH (FDR p-values <0.05), and to a lesser degree among WWoH. Metabolite-set enrichment analyses showed involvements in tryptophan metabolism in both verbal learning and memory, bile acid biosynthesis in verbal learning, and histidine metabolism in verbal memory. However, none of these findings were statistically significant and could be related to incomplete pathway coverage (Supplemental Fig. 3 & Supplemental Table 4).

3.1. Mediation analysis results

We found that 4 (i.e., Thyroxine, X-2-O Methylguanosine, Pseudouridine, ADMA) out of 15 FDR-corrected metabolites associated with verbal learning and were also associated with employment. We

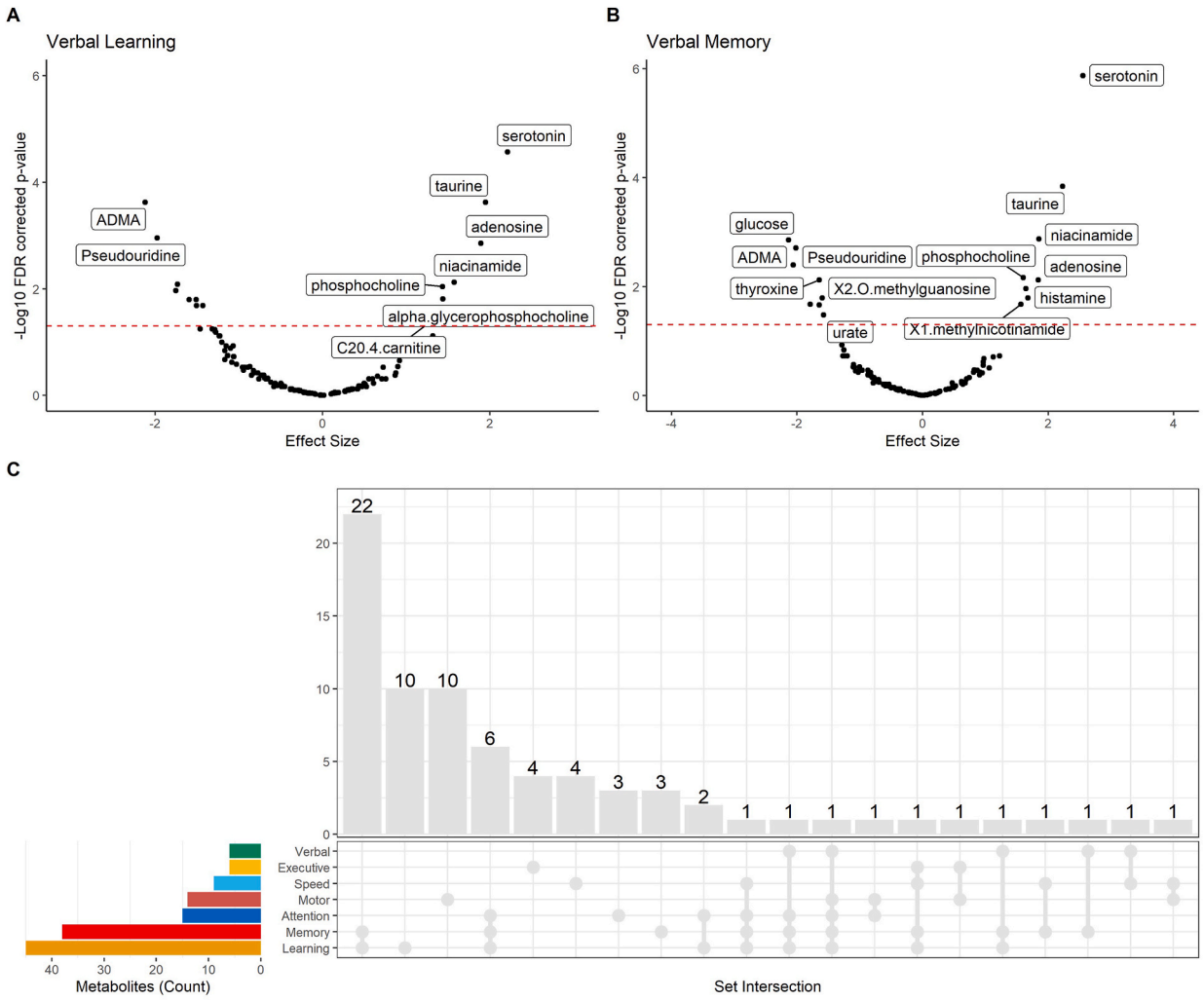

Fig. 2. A & B Volcano plots of metabolites and verbal learning and memory cognitive domains (declarative memory) in a subsample of the Women's Interagency HIV Study (ñ324). Significant metabolites are found above the dotted red line. **C.** Upset plot of common metabolites among seven cognitive domains. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

estimated that 30% (95%CI: 4.4%, 101.3%) of the effect of employment on verbal learning was mediated through these metabolite levels (Table 2). Similarly, 5 (i.e., X-1 Methylnicotinamide, Thyroxine, X-2-O Methylguanosine, Pseudouridine, ADMA) out of 16 FDR-corrected metabolites associated with verbal memory and were also associated with employment. We found that 35.6% (95%CI: 2.7%, 139.4%) of the effect of employment on verbal memory was mediated through these metabolite levels. Only urate was associated with income and both verbal learning and memory. Single mediation analysis results showed that 18.2% (95%CI: 2.1%, 72.3%) of the effect of income on verbal learning and 25.4% (95%CI: 170.8, 188.4%) of the effect of income on verbal memory were mediated through urate levels (Table 2).

4. Discussion

Circulating metabolites levels are informative of environmental and life style exposures and may be important predictors of cognitive deterioration and dementia risk (Fuller et al., 2023; Patti et al., 2012; Kuan et al., 2022; Toledo et al., 2017b; Bressler et al., 2017). In a subsample of the WIHS study, we identified multiple metabolomic signatures associated with declarative memory trajectories. Serotonin, taurine, adenosine, niacinamide, and alpha glycerophosphocholine were associated with higher verbal learning and higher memory scores over time; and in pathway analysis, serotonin was mapped to tryptophan metabolism, while taurine to bile acid biosynthesis. In contrast, ADMA, pseudouridine, glucose and sphingomyelins (C18:2 and C16:0) were strongly associated with worsening cognitive trajectories in both verbal learning and memory. Together, these findings underscore the importance of analyzing metabolomic signatures associated with domain-specific cognitive trajectories in adult women; altered metabolite levels could serve as surrogates and predictors of preclinical stages of Alzheimer's disease and related dementias (ADRD), in particular those strongly associated with changes in memory. Lastly, our mediation analysis results indicate that a sizable fraction of the effect of employment on verbal learning and memory was mediated through multiple metabolite levels, but only one metabolite was implicated in the relationship between income and cognitive tests trajectories. This suggests that unemployment and low income have a measurable impact on diverse cellular mechanisms implicated in cognitive changes, and intervening upon these mechanisms could potentially reduce socioeconomic inequities in cognitive performance.

Numerous studies have linked metabolite species in cerebrospinal fluid and plasma to Alzheimer's disease progression, structural brain changes, and cognitive functioning (Varma et al., 2018; Toledo et al., 2017a; Bressler et al., 2017; Wang et al., 2020; Fleszar et al., 2019). A recent study found that 11-metabolites (two of which were associated with declarative memory in our study, serotonin and glycerophosphocholine) in blood could discriminate Alzheimer's disease

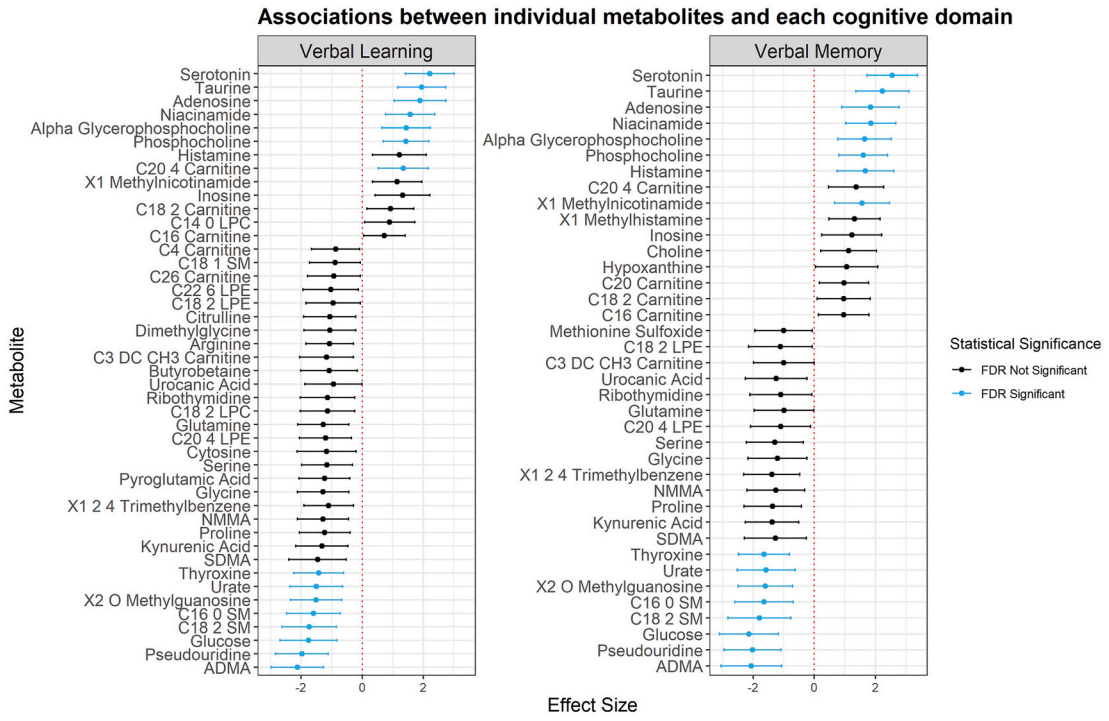

Fig. 3. Forest plot indicating the linear association between metabolites and verbal learning and memory domains in a subsample of the Women's Interagency HIV Study (ñ324). Effect size denotes a change in verbal learning or memory scores for 1SD above the mean metabolite levels.

participants from those cognitively normal. Among these metabolites, serotonin was downregulated in Alzheimer's disease participants, while glycerophosphocholine was upregulated (Jia et al., 2022). Our results are consistent with those findings in which higher serotonin levels was associated with better cognitive test scores on verbal learning and memory but differed with respect to glycerophosphocholine; we found that elevated glycerophosphocholine levels were correlated with better verbal learning and memory test scores. A plausible explanation for these conflicting results is that observed increases in glycerophosphocholine levels in Alzheimer's disease participants may have different pathological substrates (e.g., they could be induced by amyloid toxicity) than in our study which included younger women in which the observed cognitive changes may be multifactorial. Other studies note that higher concentrations of glycerophosphocholine may be indicative of cholinergic activity in participants without dementia, and is also consistent with studies finding glycerophosphocholine facilitates the release of choline and improve learning and memory (Parnetti et al., 2007) or memory and attention (Parnetti et al., 2001). Another study within the Religious Order Study and the Memory and Aging Project, identified that 44 metabolite signatures (in both serum and brain tissue) were associated with cognitive impairment. These set of metabolites were annotated to bile acid biosynthesis, free fatty acid biosynthesis, and biosynthesis of free fatty acids (Wang et al., 2020). Although our pathway analyses did not yield statistically significant results, taurine – a top metabolite associated with verbal learning and memory - and glycine were mapped to the bile acid biosynthesis pathway, suggesting that this may be a mechanism also implicated in cognitive performance. Taurine, an amino acid present in almost every tissue, exhibits a myriad of biological functions such as bile salt conjugation and immunomodulation, has important neuroprotective effects and plays a crucial role in improving memory tasks (Chen et al., 2019; Oh et al., 2020). Glycine, another amino acid, has shown cognitive enhancing properties and considerable improvements on retrieval of information. Moreover, a study assessing metabolomic signatures of Alzheimer's disease progression found sphingomyelin with acyl residue sums (C16:0 and C18:1) to be associated with increased hazard ratio of incident dementia (Varma et al., 2018). Similarly, we identified that sphingomyelins (C16:0, C18:2 and C18:1; the latter was not significant after FDR correction) were strongly associated with poor cognitive test performance in both verbal learning and memory. In general, our findings align with an increasing body of epidemiological studies demonstrating that metabolomic signatures may serve as surrogate biomarkers of Alzheimer's disease onset, monitoring of cognitive functioning, and potentially therapeutic targets for intervention. Lastly, our results indicated that hydroxyproline and cotinine were associated with lower motor function over time, which aligns with prior reports suggesting hydroxyproline is a surrogate of severity and progression of muscle spasticity in cerebral palsy, and that serum cotinine concentrations are associated with a higher prevalence of frailty in non-smoking older adults (Htwe et al., 2017; Craciun et al., 2022).

To our knowledge few studies have explored the link between socioeconomic conditions, altered metabolite levels, and cognitive changes, but none in adult women (Robinson et al., 2021; He et al., 2022). In this study, we examined two individual level socioeconomic factors – income and employment. Although these indicators may be correlated, we still found that distinct metabolic signatures mediate the effect of each exposure on verbal learning and memory, which may signal that specific metabolites are susceptible to different socioeconomic factors. Throughout this study, we found that verbal learning and memory were the most affected cognitive domain. A plausible mechanism for these findings is that declarative memory may be the most susceptible system to the deleterious effects of socioeconomic factors and metabolite-mediated pathways. This is supported by prior studies finding that children from lower socioeconomic backgrounds perform worse on declarative and working memory tasks than their higher socioeconomic status counterparts (Noble et al., 2015; Leonard et al., 2015; Olson et al., 2021). Socioeconomic disparities in early life have been associated with declarative memory and with changes in brain morphological correlates such as hippocampal volume and the medial temporal lobe (McEwen and Gianaros, 2010). Moreover, low socioeconomic status in childhood has long-term effects on declarative memory that persist into middle age and are associated with even faster cognitive

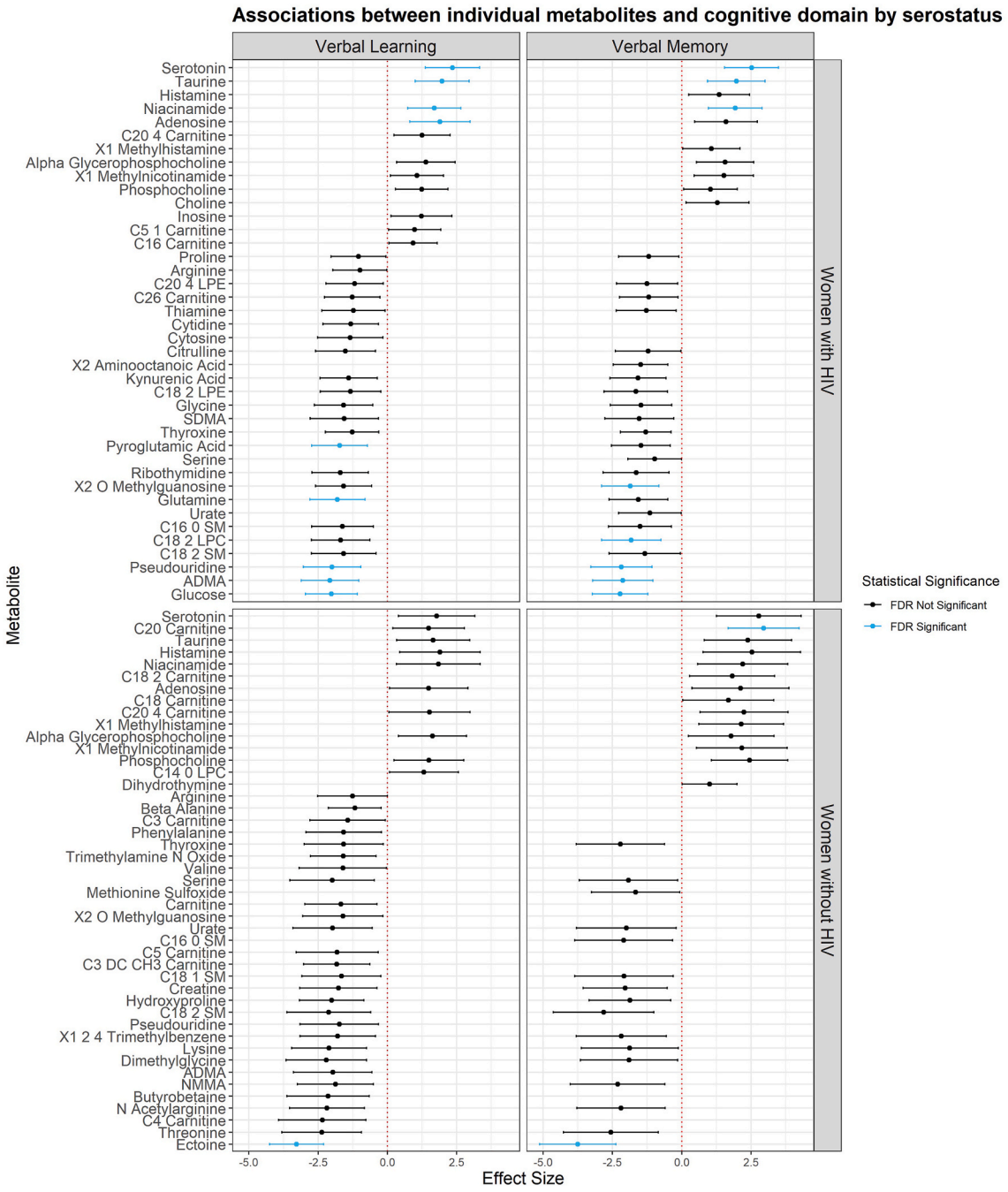

Fig. 4. Forest plot indicating the association between metabolites and verbal learning and memory domains stratified by serostatus in a subsample of the Women's HIV Interagency Study (n=324). Effect size denotes a change in verbal learning or memory scores for 1SD above the mean metabolite level.

decline in late life (Leonard et al., 2015). These findings raise the possibility that socioeconomic factors do not affect all cognitive systems in a similar fashion, and that some domains may be more uniquely impaired than others. Our mediation analysis demonstrated that declarative memory was particularly susceptible to the mediated effects of metabolite levels in the relationship between low income and unemployment and cognitive outcomes in middle-aged women. Our findings add to an emergent area of research that employs high-throughput omics data to explore several biological pathways by which socioeconomic factors are embodied (Robinson et al., 2021; Krieger, 2005). Given that we identify multiple metabolites to be associated with one of our exposures of interest (employment) and outcomes (verbal learning and memory), we employed regression-based multiple mediation analysis to estimate the proportion of the effect of employment on cognitive trajectories that was mediated through various metabolites. Notably, some of these metabolites may be correlated and future research should investigate whether other advanced mediation frameworks such as high-dimensional mediation analysis are better suited to identify mediation effects when using correlated metabolomic data. Additionally, although we explore two socioeconomic factors, future studies should explore multi-level dimensions including individual, neighborhood, or other geographic dimensions of socioeconomic adversity. Our study focused on mid-life, and follow-up work should test if early exposure to low income and unemployment drives metabolomic changes in mid and late-life to later affect learning and memory trajectories.

Our study has some limitations. Although our analysis was longitudinal with repeated measures of our outcome (cognitive testing) overtime, there was a lag between the metabolomic assessment and the first

Table 2
Multiple mediation analysis results using metabolite levels as mediators between employment and income (exposures) with verbal learning and verbal memory (i.e., declarative memory outcomes) in a subsample of the WIHS.

Parameter	HVLT-R Total Learning (Verbal Learning)									
	Employment[a]					Income[c]				
	Estimate	SE	95% LB	95% UB	p-value	Estimate	SE	95% LB	95% UB	p-value
Controlled Direct Effect	1.56	0.849	−0.051	3.242	0.062	1.75	0.901	0.09	3.545	**0.046**
Pure Natural Direct Effect	1.56	0.849	−0.051	3.242	0.062	1.75	0.901	0.09	3.545	**0.046**
Total Natural Direct Effect	1.56	0.849	−0.051	3.242	0.062	1.75	0.901	0.09	3.545	**0.046**
Pure Natural Indirect Effect	0.667	0.292	0.12	1.287	**0.014**	0.39	0.233	−0.015	0.869	0.06
Total Natural Indirect Effect	0.667	0.292	0.12	1.287	**0.014**	0.39	0.233	−0.015	0.869	0.06
Total Effect	2.227	0.881	0.483	3.97	**0.01**	2.14	0.919	0.357	4.051	**0.016**
Percent Mediated	0.3	0.563	0.044	1.013	**0.024**	0.182	2.543	−0.021	0.723	0.072
	HVLT-R delay free recall (Verbal Memory)									
Parameter	**Employment[b] Estimate**	**SE**	**95% LB**	**95% UB**	**p-value**	**Income[c] Estimate**	**SE**	**95% LB**	**95% UB**	**p-value**
Controlled Direct Effect	1.389	0.958	−0.51	3.329	0.146	1.267	1.071	−0.862	3.35	0.248
Pure Natural Direct Effect	1.389	0.958	−0.51	3.329	0.146	1.267	1.071	−0.862	3.35	0.248
Total Natural Direct Effect	1.389	0.958	−0.51	3.329	0.146	1.267	1.071	−0.862	3.35	0.248
Pure Natural Indirect Effect	0.768	0.342	0.16	1.477	**0.014**	0.431	0.255	0.035	0.983	**0.032**
Total Natural Indirect Effect	0.768	0.342	0.16	1.477	**0.014**	0.431	0.255	0.035	0.983	**0.032**
Total Effect	2.157	0.985	0.225	4.06	**0.03**	1.699	1.092	−0.441	3.786	0.138
Percent Mediated	0.356	2.491	0.027	1.394	**0.044**	0.254	3.355	−1.708	1.884	0.15

[a] Model used Thyroxine, X.2.O.Methylguanosine, Pseudouridine, ADMA as mediators between exposure and outcomes. Confounding variables included: race, income, drinking, smoking, body mass index, drug use, hypertension, diabetes, hepatitis C status, number of cognitive visits.
[b] Model used X.1. Methylnicotinamide, Thyroxine, X.2.O.Methylguanosine, Pseudouridine, ADMA between exposure and outcomes. Confounding variables included: race, income, drinking, smoking, body mass index, drug use, hypertension, diabetes, hepatitis C status, number of cognitive visits.
[c] Model used urate as mediator between exposure and outcomes. Confounding variables included: race, employment status, drinking, smoking, body mass index, drug use, hypertension, diabetes, hepatitis C status, number of cognitive visits.

cognitive test. Further, we only had one measure of metabolites (our exposure), and some of these metabolites are dynamic and their concentrations change over time. Therefore, future work should analyze cognitive test performance as a function of changes in metabolite concentrations. In addition, we did not have any information on diet quality and time of last meal, these factors substantially differ between socioeconomic groups and affect metabolite concentrations. We are unable to quantify to what degree these residual confounding effects might have affected our results. Lastly, in stratified analysis by serostatus, we observed that metabolomic predictors associated with declarative memory had a similar effect size and direction in WWH and WWoH. However, the small sample size of the seronegative group may have hindered our ability to detect statistically significant effects in this group of women.

Despite the small sample size and the single baseline metabolomic assessment, there are notable strengths to highlight in this study. For instance, our analysis was longitudinal with repeated measures of cognitive function, indicating that identified metabolites could inform future work on metabolomics signatures of progressive cognitive deterioration and Alzheimer's disease risk among adult women. We used sensitivity models to test the robustness of our results, and although metabolites levels were not significantly associated with cognitive impairment categories, the directionality of the effects was consistent with our main models. Our analysis included a comprehensive set of covariates such as socioeconomic factors, lifestyle indicators, and comorbid conditions to de-confound the relationship between metabolite levels and learning and memory. Finally, our study included adult women from diverse racial and socioeconomic backgrounds, these unique social experiences could inform future studies exploring the link between socioeconomic factors associated with metabolomic disfunction, and cognitive performance in middle-aged women.

In conclusion, we identified a panel of metabolomic signatures associated with cognitive trajectories, most notably with verbal learning and memory. Findings suggest differences in distinct metabolites may portend risk for cognitive impairment in specific domains. However, these results require validation in larger sample with repeated metabolite measures. Our sample of participants were mostly low-income women of color, and our mediation results adds to our understanding on underlying biological contributors pathways linking socioeconomic factors to cognitive performance in this vulnerable group of women. Future research should focus on unveiling these potential links and identifying biological targets and health policy interventions to reduce health inequities in cognitive aging.

CRediT authorship contribution statement

César Higgins Tejera: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Raha Dastgheyb:** Writing – review & editing, Writing – original draft, Supervision. **Eran F. Shorer:** Writing – review & editing, Writing – original draft. **Susie Lee:** Writing – review & editing, Writing – original draft. **Deborah Gustafson:** Writing – review & editing, Writing – original draft. **Anjali Sharma:** Writing – review & editing, Writing – original draft. **Gypsyamber D'Souza:** Writing – review & editing, Writing – original draft. **Kathleen M. Weber:** Writing – review & editing, Writing – original draft. **Qibin Qi:** Writing – review & editing, Writing – original draft. **Leah H. Rubin:** Writing – review & editing, Writing – original draft, Conceptualization. **Kathryn C. Fitzgerald:** Writing – review & editing, Writing – original draft.

Consent statement

Consent was not necessary for this secondary data analysis with de-identified data.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2026.101223.

Data availability

The authors do not have permission to share data.

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