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Long-term fasting insulin variability and cognitive function: Insights from the CARDIA study

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ABSTRACT

Background and aim: Fasting insulin variability has emerged as a potential marker of metabolic dysregulation, but its long-term implications for cognitive function remain unclear. This study aimed to clarify the role of long-term fasting insulin variability in predicting individual cognitive function risk.

Methods: We analyzed data from CARDIA study participants who underwent cognitive testing and had at least three insulin measurements. Fasting insulin was measured at 7 timepoints over 30 years. Intra-individual insulin variability was assessed using standard deviation (SD), coefficient of variation (CV), and average real variability (ARV). Cognitive function was evaluated using the Digit Symbol Substitution Test (DSST), Stroop Test, and Rey Auditory Verbal Learning Test (RAVLT), with results standardized to z-scores and combined into a global cognitive z-score. Multivariable linear models were used to assess associations with cognitive performance.

Results: In the 25-year analysis ($n = 2712$), higher long-term insulin variability was significantly associated with poorer global cognitive performance at year 25 after adjustment for demographic, lifestyle, and cardiometabolic covariates (CV-insulin: β=–0.719; 95% CI: –1.161 to –0.276; $P < 0.01$; SD-insulin: β=–0.019; 95% CI: –0.036 to –0.002; $P < 0.05$). These associations remained significant after additional adjustment for either concurrent insulin at year 25 or mean insulin levels over 25 years. Domain-specific analyses showed that higher insulin variability was associated with lower DSST z-scores (worse attention) and higher Stroop interference z-scores (worse executive function). Extended analyses over 30 years ($n = 2069$) yielded consistent results: higher CV-insulin was inversely associated with global cognitive z-scores (β=–0.837; 95% CI: –1.347 to –0.327), as well as with DSST (β=–0.347; 95% CI: –0.581 to –0.112) and RAVLT z-scores (β=–0.276; 95% CI: –0.522 to –0.031). These associations persisted after full adjustment for year 30 covariates and time-varying confounders across the follow-up, supporting the temporal robustness and clinical relevance of insulin variability as an independent predictor of cognitive function.

Conclusions: Greater long-term insulin variability is independently associated with poorer midlife cognitive performance. These findings highlight insulin variability as a potential marker of cognitive health risk.

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1. Introduction

Cognitive decline is an increasing public health concern amid global population aging. Growing evidence suggests that the pathophysiological processes leading to cognitive impairment and dementia may begin decades before clinical symptoms emerge, underscoring the importance of identifying early-life metabolic predictors of later-life cognitive dysfunction [1]. While type 2 diabetes is a well-established risk factor for cognitive decline and Alzheimer's disease [2], recent studies indicate that even subclinical metabolic disturbances—such as variability in fasting glucose or blood pressure—are associated with poorer cognitive performance in midlife [3,4].

Insulin, a key hormone in glucose homeostasis, also exerts direct effects on brain function, including regulation of neuronal glucose uptake, synaptic plasticity, and neuroinflammation. Greater intra-individual variability in insulin levels may indicate underlying dysregulation of metabolic or hypothalamic-pituitary-adrenal axis function. which could contribute to the progression of neurodegenerative processes over time [5–7]. However, the long-term impact of intra-individual variability in fasting insulin levels—distinct from average insulin levels—on cognitive decline remains poorly understood.

The Coronary Artery Risk Development in Young Adults (CARDIA) study provides a unique opportunity to evaluate these long-term associations, given its extensive metabolic profiling and standardized cognitive assessments over 30 years. Prior analyses from the CARDIA cohort have linked greater variability in fasting glucose and blood pressure during young adulthood with lower cognitive performance in midlife [3,8,9]. However, the role of fasting insulin variability in this context has not yet been examined. Thus, we aimed to investigate the association between fasting insulin variability during young adult and cognitive function at midlife by using the data from the CARDIA study.

2. Materials and methods

2.1. Study population

Detailed descriptions of the design and examinations of the CARDIA study have been published previously [9]. Briefly, CARDIA is a multicenter, longitudinal cohort study that enrolled 5115 healthy Black and White adults aged 18 to 30 years from four U.S. sites (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA) between 1985 and 1986. Participants underwent in-person examinations at baseline (year 0) and at follow-up visits in years 2, 5, 7, 10, 15, 20, 25, and 30. The study was approved by the institutional review boards at all participating sites and coordinating centers, and written informed consent was obtained at each visit.

For the present analysis, we included 3385 participants who completed the year 25 follow-up assessment. We excluded individuals with missing year 25 cognitive assessments ($n = 58$), fewer than three valid insulin measurements from years 0 to 25 ($n = 146$), missing insulin data at year 25 ($n = 14$), prevalent diabetes prior to or at year 25 ($n = 307$), or incomplete covariate data ($n = 148$). This resulted in a final analytic sample of 2712 participants for evaluating insulin variability over 25 years and cognitive performance at year 25 (Fig. 1).

For longitudinal analyses involving cognitive outcomes at year 30, we further excluded individuals with missing year 30 cognitive assessments ($n = 427$), missing insulin data at year 30 ($n = 24$), incident diabetes between years 25 and 30 ($n = 117$), or incomplete covariate data ($n = 75$). The final sample for these analyses included 2069 participants, which was used to evaluate the association between insulin variability (years 0 to 30) and cognitive performance at year 30 (Fig. 1).

To minimize potential confounding from glucose-lowering therapies, all participants included in the analyses were free from the use of any

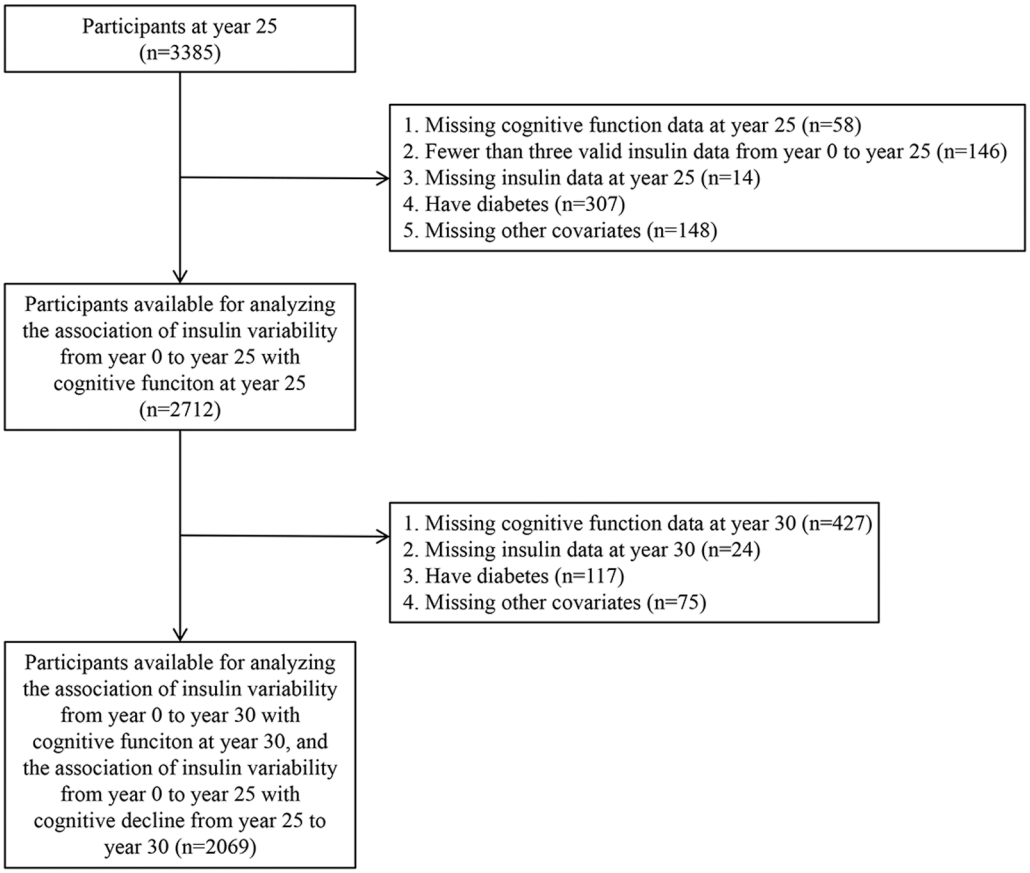

Fig. 1. Flowchart of participant selection for the analysis.

such medications, including exogenous insulin.

2.2. Measurements of insulin

Fasting insulin concentrations were measured in nonpregnant participants who reported fasting for at least 8 hours. At years 0, 7, 10, 15, and 20, insulin was assessed using a radioimmunoassay (Linco Research, St. Charles, Missouri), while at years 25 and 30, measurements were obtained using an Elecsys sandwich immunoassay (Roche Diagnostics, Rotkreuz, Switzerland) [5,10]. All assays followed standardized CARDIA protocols, and all blood samples were collected during the morning examination session after an overnight fast to minimize diurnal variation.

For each participant with at least three valid insulin measurements across examination years, long-term intra-individual fasting insulin variability was quantified using three established metrics: the standard deviation (SD), the coefficient of variation (CV), and the average real variability (ARV). CV-insulin was computed as the SD divided by the mean insulin level [11]. ARV-insulin was calculated by summing the absolute differences between successive insulin values and dividing the total by the number of intervals between measurements [12].

Although only 3–7 measurements were available over 25–30 years, these metrics are widely used in major longitudinal cohorts to quantify long-term biological variability across exam cycles [13]. ARV, originally developed for short-term repeated measures, has also been applied in multi-year epidemiologic analyses to capture long-term metabolic instability. Thus, SD, CV, and ARV in this study reflect long-term physiological shifts rather than short-term fluctuations.

2.3. Measurement of cognitive function

Trained and certified CARDIA technicians administered three standardized cognitive tests at the year 25 and year 30 examinations: the digit symbol substitution test (DSST), the Stroop Test, and the rey auditory verbal learning test (RAVLT). The DSST, a subtest of the Wechsler adult intelligence scale, assesses attention and psychomotor speed by requiring participants to match numbers (1–9) with corresponding symbols within 120 s (score range: 0–133), with higher scores indicating better performance [8]. The RAVLT evaluates verbal learning and memory based on the immediate recall of a 15-word list following a 10-minute delay (score range: 0–15), where higher scores reflect better memory retention [14]. The Stroop test measures executive function through three subtests involving color-word interference tasks. We calculated an interference score by subtracting performance on subtest II from subtest III, with higher values representing worse executive function [15].

All cognitive test scores were treated as continuous variables. To account for differences in scale across tests, raw scores were converted into z-scores using the sample mean and SD at each examination [16]. A composite global cognitive z-score was then derived as follows: global cognitive z-score=(DSST z-score)+(RAVLT z-score)–(Stroop interference z-score), with each component weighted equally [17].

2.4. Measurements of other covariates

Demographic characteristics, smoking and drinking status, educational attainment, physical activity, and medication use were collected using standardized questionnaires and protocols. Smoking status was categorized as current, former, or never. Blood pressure was measured after participants had been seated for at least 5 min; the average of the second and third readings was recorded. Hypertension was defined as the use of antihypertensive medications, a prior diagnosis of hypertension, or having three consecutive systolic blood pressure (SBP) readings $\geq$140 mmHg or diastolic blood pressure (DBP) readings $\geq$90 mmHg. Diabetes was defined as a fasting glucose (FG) $\geq$126 mg/dL or the use of glucose-lowering medications. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Laboratory assessments, including total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, and FG, were performed as previously described [18]. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI 2021 creatinine equation: $eGFR = 142 \times \min(\text{serum creatinine}/\kappa, 1)^{\alpha} \times \max(\text{serum creatinine}/\kappa, 1)^{-1.200} \times 0.9938^{\text{Age}} \times (1.012 \text{ if female})$, where κ is 0.7 for women and 0.9 for men, and α is -0.241 for women and -0.302 for men [19].

2.5. Statistical analysis

Continuous variables with normal distribution were presented as mean±SD, whereas skewed data were expressed as median with interquartile range. Categorical variables were summarized as counts and percentages. Group comparisons were performed using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test for continuous variables, and the Chi-square (χ^2) test for categorical variables. Multivariable linear regression models were employed to assess the associations of the SD-insulin, CV-insulin and ARV-insulin with individual cognitive test z-scores and the global cognitive z-score. Models were adjusted for age, sex, race, BMI, education level, smoking status, drinking status, SBP, hypertension status, eGFR, FG, LDL-C, triglycerides, and physical activity. To examine whether the associations between insulin variability and cognitive function were independent of insulin level, additional adjustments were made for: (1) insulin level at the time of cognitive assessment and (2) the mean insulin level during the insulin variability measurement period.

All analyses were conducted using SPSS version 23.0 (IBM Corp.) and R version 3.6.1. A two-sided P value <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics of the study population

As shown in Table 1, the analytic cohort for the 25-year analysis included 2712 participants. The mean age was 50.1 $\pm$ 3.6 years; 43.9 % were male ($n = 1190$), 56.9 % were White ($n = 1543$), and 28.2 % had hypertension ($n = 764$). Compared with participants in the lower tertiles of CV-insulin, those in the highest tertile were more likely to be Black, current smokers, and have a high school education level. They also exhibited higher SBP, FG, and eGFR, but lower total cholesterol and LDL-C levels. In addition, they had a higher prevalence of hypertension, greater use of antihypertensive therapy, persistently elevated insulin levels across all visits, and poorer performance on the DSST, RAVLT, Stroop Test, and the global cognitive z-score. These trends were also observed in the cohort of 2069 participants for the 30-year analysis (Supplementary Table 1).

3.2. Association between 25-year insulin variability and cognitive function

In multivariable-adjusted linear regression models, higher 25-year insulin variability was significantly associated with lower global cognitive performance. Both SD-insulin (β=–0.019, 95 % CI: –0.036 to –0.002) and CV-insulin (β=–0.719, 95 % CI: –1.161 to –0.276) were inversely related to the global cognitive z-score in fully adjusted models. These associations remained significant after additional adjustment for concurrent insulin levels at year 25 or the average insulin levels across 25 years (Table 2). Similarly, greater insulin variability was linked to lower DSST z-scores and higher Stroop z-scores, reflecting poorer attention and executive function. Full model fit statistics are provided in Supplementary Tables 2–4.

Table 1
Characteristics of participants by tertile of CV-insulin from year 0 to year 25.

Variables*	Total (n = 2712)	Tertile 1 (n = 904)	Tertile 2 (n = 904)	Tertile 3 (n = 904)	P value
Age, years	50.1 ± 3.6	50.4 ± 3.5	50.3 ± 3.5	50.0 ± 3.5	0.075
Male, n (%)	1190 (43.9 %)	413 (45.7 %)	382 (42.3 %)	395 (43.7 %)	0.337
White, n (%)	1543 (56.9 %)	544 (60.2 %)	543 (60.1 %)	456 (50.4 %)	<0.001
BMI, kg/m^2	29.4 ± 6.4	29.1 ± 5.7	28.7 ± 6.4	29.6 ± 6.7	0.078
SBP, mm Hg	119.0 ± 15.7	117.6 ± 14.2	117.9 ± 15.5	119.4 ± 15.9	0.041
DBP, mm Hg	74.3 ± 11.1	73.3 ± 10.2	73.4 ± 10.9	74.6 ± 11.5	0.076
Smoking status, n (%)					0.001
Never	1705 (62.9 %)	580 (64.2 %)	587 (64.9 %)	538 (59.5 %)	
Former	576 (21.2 %)	187 (20.7 %)	203 (22.5 %)	186 (20.6 %)	
Current	431 (15.9 %)	137 (15.2 %)	114 (12.6 %)	180 (19.9 %)	
Drinkers, n (%)	2172 (80.1 %)	734 (81.2 %)	745 (82.4 %)	693 (76.7 %)	0.005
Education level, n (%)					<0.001
High school	550 (20.3 %)	155 (17.1 %)	161 (17.8 %)	234 (25.9 %)	
College	1436 (52.9 %)	479 (53.0 %)	486 (53.8 %)	471 (52.1 %)	
Graduate school	726 (26.8 %)	270 (29.9 %)	257 (28.4 %)	199 (22.0 %)	
Hypertension, n (%)	764 (28.2 %)	217 (24.0 %)	236 (26.1 %)	311 (34.4 %)	<0.001
Antihypertensive medication, n (%)	600 (22.1 %)	173 (19.1 %)	177 (19.6 %)	250 (27.7 %)	<0.001
Physical activity	290.0 (142.0, 503.8)	294.0 (141.0, 492.5)	312.0 (153.0, 524.5)	280.0 (134.5, 506.8)	0.114
eGFR, mL/min/ 1.73 m^2	95.5 ± 19.8	94.4 ± 18.0	93.7 ± 18.0	95.7 ± 21.7	0.111
FG, mg/dL	94.3 ± 14.2	94.4 ± 9.0	93.5 ± 13.8	94.7 ± 18.2	<0.001
TC, mg/dL	193.4 ± 35.4	196.2 ± 34.8	195.3 ± 34.9	189.8 ± 35.6	0.001
HDL-C, mg/dL	58.8 ± 17.9	58.4 ± 16.4	60.4 ± 18.7	57.9 ± 17.7	0.342
LDL-C, mg/dL	113.4 ± 31.7	116.8 ± 31.6	114.5 ± 31.1	110.3 ± 31.7	<0.001
Triglycerides, mg/ dL	90.0 (67.0, 127.0)	92.0 (69.0, 126.0)	86.0 (64.0, 122.5)	90.0 (67.0, 133.8)	0.394
Insulin, μU/mL					
Year 0	10.7 ± 4.5	10.6 ± 3.5	10.3 ± 3.9	11.0 ± 5.2	0.025
Year 7	12.6 ± 7.6	11.4 ± 3.9	11.5 ± 4.7	14.5 ± 11.3	<0.001
Year 10	12.5 ± 7.6	11.4 ± 4.2	11.5 ± 35.1	13.7 ± 9.5	0.015
Year 15	13.3 ± 9.5	11.4 ± 4.5	12.2 ± 6.4	15.6 ± 14.9	0.002
Year 20	15.0 ± 8.8	12.6 ± 4.9	14.1 ± 6.4	18.3 ± 12.6	<0.001
Year 25	10.4 ± 7.7	9.9 ± 4.5	9.0 ± 6.3	11.6 ± 10.7	<0.001
Year 25 DSST z-score	0 (−0.7, 0.7)	0.1 (−0.5, 0.8)	0.2 (−0.6, 0.8)	−0.1 (−0.8, 0.6)	0.014
Year 25 RAVLT z-score	0.2 (−0.8, 0.8)	0.2 (−0.5, 0.8)	0.2 (−0.5, 0.8)	−0.1 (−0.8, 0.8)	<0.001
Year 25 Stroop z-score	−0.2 (−0.7, 0.5)	−0.2 (−0.7, 0.3)	−0.3 (−0.8, 0.3)	−0.1 (−0.6, 0.5)	<0.001
Year 25 Global z-score	0.2 (−1.4, 1.6)	0.3 (−1.1, 1.7)	0.4 (−1.1, 1.8)	−0.2 (−1.8, 1.3)	<0.001

Note: *Variables were assessed at year 25 unless otherwise indicated. Continuous variables were expressed as mean±standard deviation or median (interquartile range), and categorical variables were expressed as n (%). *BMI*: body mass index, *CV*: coefficient of variation, *DBP*: diastolic blood pressure, *DSST*: digit symbol substitution, *eGFR*: estimate glomerular filtration ratio, *FG*: fasting glucose; *HDL-C*: high-density lipoprotein cholesterol; *LDL-C*: low-density lipoprotein cholesterol; *RAVLT*: rey-auditory verbal learning test, *SBP*, systolic blood pressure, *TC*: total cholesterol.

3.3. Time-varying analyses in the 30-year analysis

To validate the robustness of the 25-year findings, we conducted time-varying analyses using a 30-year analytic cohort and repeated the full modeling strategy applied in the primary analysis. Specifically, insulin variability was recalculated using all available measurements from years 0 to 30, and cognitive performance at year 30 was evaluated using the same standardized procedures as in year 25.

Extended analyses using 30-year insulin variability measures yielded consistent and robust results CV-insulin remained significantly inversely associated with the global cognitive z-score at year 30 (β=–0.837, 95 % CI: –1.347 to –0.327), as well as with DSST (β=–0.347, 95 % CI: –0.581 to –0.112) and RAVLT z-scores (β=–0.276, 95 % CI: –0.522 to –0.031) (Table 3). Full model fit statistics are provided in Supplementary Tables 5–7. These time-varying analyses further strengthen the evidence supporting insulin variability as a long-term predictor of cognitive performance.

4. Discussion

In this 30-year prospective cohort study of a community-based U.S. population, we found that: (1) greater intra-individual variability in fasting insulin from early adulthood to midlife was independently associated with poorer global cognitive performance at midlife; (2) higher insulin variability was also significantly associated with worse performance across specific cognitive domains, including attention (DSST), executive function (Stroop Test), and verbal memory (RAVLT); (3) these associations remained robust after adjustment for demographic, lifestyle, and cardiometabolic covariates, as well as for either mean insulin levels during the same period or concurrent insulin levels at the time of cognitive assessment; (4) similar associations were observed when insulin variability was assessed over the 30-year period.

Our findings extend prior analyses showing that long-term variability in fasting glucose and blood pressure is linked to adverse cognitive outcomes, by demonstrating that fasting insulin variability—an under-recognized metabolic trait—is also a strong predictor of midlife cognitive health [3,20]. Compared with glycemic or blood pressure variability, insulin variability may reflect earlier or subtler dysregulation of metabolic homeostasis, integrating effects of peripheral insulin resistance, β-cell dysfunction, and central insulin signaling abnormalities [21–24]. Compelling experimental and clinical evidence underscores the critical role of insulin signaling in regulating cerebral glucose utilization, neuronal metabolism, and synaptic function [25–29]. Despite this biological relevance, fasting insulin are not routinely incorporated into longitudinal assessments of cognitive risk. Our findings address this gap by identifying variability in insulin levels as a novel risk factor for cognitive decline. Importantly, the persistence

Table 2
Association of insulin variability during year 0 to year 25 with cognitive function in year 25.

Insulin variability	Model 1		Model 2		Model 3		Model 4	
	β (95 % CI)	*P* value	β (95 % CI)	*P* value	β (95 % CI)	*P* value	β (95 % CI)	*P* value
SD-insulin								
DSST z-score	−0.031 (−0.039, −0.022)	<0.001	−0.009 (−0.017, −0.001)	0.029	−0.010 (−0.018, −0.002)	0.020	−0.020 (−0.032, −0.008)	0.001
RAVLT z-score	−0.016 (−0.025, −0.008)	<0.001	0.002 (−0.006, 0.010)	0.651	0.002 (−0.006, 0.011)	0.591	0.005 (−0.008, 0.017)	0.448
Stroop z-score	0.031 (0.022, 0.040)	<0.001	0.012 (0.003, 0.021)	0.006	0.012 (0.003, 0.021)	0.009	0.011 (−0.002, 0.024)	0.101
Global z-score	−0.078 (−0.098, −0.058)	<0.001	−0.019 (−0.036, −0.002)	0.029	−0.020 (−0.038, −0.002)	0.033	−0.026 (−0.052, −0.001)	0.045
CV-insulin								
DSST z-score	−0.778 (−1.015, −0.541)	<0.001	−0.363 (−0.568, −0.158)	0.001	−0.365 (−0.570, −0.159)	0.001	−0.413 (−0.632, −0.195)	<0.001
RAVLT z-score	−0.402 (−0.640, −0.163)	0.001	−0.032 (−0.245, 0.182)	0.773	−0.031 (−0.245, 0.184)	0.780	−0.033 (−0.261, 0.195)	0.779
Stroop z-score	0.673 (0.435, 0.911)	<0.001	0.324 (0.101, 0.548)	0.004	0.320 (0.096, 0.543)	0.005	0.269 (0.032, 0.507)	0.026
Global z-score	−1.852 (−2.392, −1.313)	<0.001	−0.719 (−1.161, −0.276)	0.001	−0.715 (−1.158, −0.272)	0.002	−0.715 (−1.187, −0.244)	0.003
ARV-insulin								
DSST z-score	−0.026 (−0.034, −0.019)	<0.001	−0.007 (−0.014, 0)	0.063	−0.007 (−0.014, 0)	0.055	−0.013 (−0.023, −0.003)	0.008
RAVLT z-score	−0.016 (−0.024, −0.008)	<0.001	0 (−0.007, 0.008)	0.921	0.001 (−0.007, 0.008)	0.889	0.001 (−0.009, 0.011)	0.834
Stroop z-score	0.026 (0.018, 0.034)	<0.001	0.008 (0, 0.016)	0.037	0.008 (0.000, 0.016)	0.052	0.004 (−0.007, 0.015)	0.452
Global z-score	−0.068 (−0.086, −0.051)	<0.001	−0.015 (−0.030, 0.001)	0.062	−0.014 (−0.030, 0.001)	0.071	−0.016 (−0.038, 0.005)	0.133

Note: Model 1: unadjusted. Model 2: adjusted for year 25 age, body mass index, drinking status, education level, estimate glomerular filtration ratio, fasting plasma glucose, hypertension, low-density lipoprotein cholesterol, physical activity, race, sex, smoking status, systolic blood pressure, and triglycerides. Model 3: adjusted for model 2 covariates plus year 25 insulin. Model 4: adjusted for model 2 covariates plus average insulin from year 0 to year 25. *ARV*: average real variability, *CV*: coefficient of variation, *DSST*: digit symbol substitution, *RAVLT*: rey-auditory verbal learning test, *SD*: standard deviation.

Table 3
Association of insulin variability during year 0 to year 30 with cognitive function in year 30.

	Model 1		Model 2		Model 3		Model 4	
Insulin variability	β (95 % CI)	*P* value	β (95 % CI)	*P* value	β (95 % CI)	*P* value	β (95 % CI)	*P* value
SD-insulin								
DSST z-score	−0.035 (−0.045, −0.025)	<0.001	−0.006 (−0.016, 0.003)	0.177	−0.009 (−0.019, 0.001)	0.072	−0.019 (−0.032, −0.005)	0.007
RAVLT z-score	−0.029 (−0.039, −0.018)	<0.001	−0.006 (−0.016, 0.004)	0.237	−0.007 (−0.018, 0.004)	0.192	−0.012 (−0.026, 0.002)	0.099
Stroop z-score	0.025 (0.015, 0.036)	<0.001	0.004 (−0.006, 0.014)	0.428	0.003 (−0.008, 0.014)	0.579	0.002 (−0.014, 0.017)	0.842
Global z-score	−0.089 (−0.113, −0.066)	<0.001	−0.016 (−0.037, 0.004)	0.111	−0.019 (−0.041, 0.002)	0.082	−0.032 (−0.062, −0.003)	0.032
CV-insulin								
DSST z-score	−0.728 (−1.003, −0.454)	<0.001	−0.347 (−0.581, −0.112)	0.004	−0.363 (−0.600, −0.127)	0.003	−0.407 (−0.653, −0.161)	0.001
RAVLT z-score	−0.656 (−0.931, −0.382)	<0.001	−0.276 (−0.522, −0.031)	0.027	−0.281 (−0.528, −0.034)	0.026	−0.300 (−0.557, −0.043)	0.022
Stroop z-score	0.488 (0.212, 0.763)	0.001	0.214 (−0.047, 0.476)	0.108	0.206 (−0.058, 0.469)	0.126	0.196 (−0.078, 0.470)	0.160
Global z-score	−1.872 (−2.496, −1.249)	<0.001	−0.837 (−1.347, −0.327)	0.001	−0.850 (−1.364, −0.336)	0.001	−0.903 (−1.437, −0.368)	0.001
ARV-insulin								
DSST z-score	−0.036 (−0.047, −0.026)	<0.001	−0.006 (−0.015, 0.004)	0.246	−0.008 (−0.017, 0.002)	0.135	−0.016 (−0.029, −0.002)	0.020
RAVLT z-score	−0.028 (−0.039, −0.018)	<0.001	−0.004 (−0.013, 0.006)	0.461	−0.004 (−0.015, 0.006)	0.427	−0.007 (−0.021, 0.007)	0.336
Stroop z-score	0.029 (0.018, 0.039)	<0.001	0.007 (−0.004, 0.017)	0.208	0.006 (−0.005, 0.017)	0.279	0.007 (−0.008, 0.021)	0.379
Global z-score	−0.094 (−0.117, −0.070)	<0.001	−0.016 (−0.036, 0.004)	0.126	−0.018 (−0.039, 0.004)	0.104	−0.029 (−0.058, 0.000)	0.048

Note: Model 1: unadjusted. Model 2: adjusted for year 30 age, body mass index, drinking status, education level, estimate glomerular filtration ratio, fasting plasma glucose, hypertension, low-density lipoprotein cholesterol, physical activity, race, sex, smoking status, systolic blood pressure, and triglycerides. Model 3: adjusted for model 2 covariates plus year 30 insulin. Model 4: adjusted for model 2 covariates plus average insulin from year 0 to year 30. *ARV*: average real variability, *CV*: coefficient of variation, *DSST*: digit symbol substitution, *RAVLT*: rey-auditory verbal learning test, *SD*: standard deviation.

of associations after adjustment for mean or concurrent insulin levels indicates that long-term fluctuations hold prognostic significance, a pattern also observed with other physiological parameters where variability predicts outcomes independently of mean exposure.

An additional observation in our analysis was that variability metrics and cognitive domains showed slightly different patterns between the year 25 and year 30 cohorts. Higher SD-insulin and CV-insulin, but not ARV-insulin, were associated with DSST and Stroop outcomes at year 25, whereas only CV-insulin remained significant and was associated with DSST and RAVLT at year 30. These differences likely reflect (1) the

distinct statistical properties of variability measures—CV is less affected by absolute insulin magnitude and therefore more stable across long follow-up intervals; (2) differences in cognitive domain sensitivity, as DSST and Stroop detect midlife executive-attention deficits earlier, while RAVLT may capture later-emerging memory decline; and (3) cohort differences in sample size and variance structure at year 30. Despite these differences, the consistent association of CV-insulin observed across analyses reinforces its robustness as an indicator of long-term insulin instability for monitoring changes in cognitive function.

This pattern mirrors findings in other physiological systems. For example, analyses from large cohorts have shown that greater long-term variability in blood pressure, fasting glucose, and lipid levels is independently associated with higher risks of stroke, cardiovascular events, and cognitive decline, even after accounting for average levels. Similarly, in the Whitehall II study, greater midlife glycemic variability predicted poorer cognitive outcomes in later life [3,29,30]. To our knowledge, no prior longitudinal cohort has specifically examined fasting insulin variability as an independent metabolic trait in relation to cognitive function. By demonstrating consistent associations across two analytic timeframes (25 and 30 years), our results extend existing evidence and suggest that insulin variability may serve as an earlier and more sensitive indicator of metabolic dysregulation than glucose variability, potentially reflecting long-term changes in β-cell function, insulin sensitivity, and central insulin signaling. The consistency of associations across multiple cognitive domains further supports the hypothesis that cumulative metabolic instability contributes to neurocognitive decline.

To reduce potential bias, all insulin measurements were collected after an overnight fast during morning examinations. Importantly, the potential influence of diabetic status and glucose-lowering therapies warrants consideration. Individuals with prevalent or incident diabetes were excluded to avoid confounding from overt metabolic dysregulation or treatment effects; however, early disturbances in insulin dynamics may precede diabetes onset by years and may partly explain the observed associations. Moreover, glucose-lowering medications—including metformin, insulin, and incretin-based agents—can alter insulin secretion patterns, and insulin sensitivity that may affect cognitive outcomes. These methodological safeguards minimize confounding from diurnal variation, hyperglycemia, and pharmacologic effects.

A central conceptual issue is whether insulin values obtained years apart can meaningfully represent "variability." Long-term intra-individual variability differs fundamentally from short-term within-day or within-week fluctuations and instead captures multi-year physiological shifts in β-cell function, insulin sensitivity, and hormonal regulation. This approach is consistent with established methodology in major longitudinal studies including the CARDIA cohort [5,8,11,12], where 3–7 repeated measurements across examination cycles are widely accepted for quantifying long-term variability in insulin, glucose, blood pressure, and lipid traits. Furthermore, although ARV was initially developed for short-interval measurements, the convergent results obtained using various variability indexes including SD, CV, and ARV in our study further support the conceptual validity of long-term insulin variability as an exposure construct.

Mechanistically, insulin plays a pivotal role in regulating cerebral glucose uptake, neuronal survival, and synaptic plasticity. Experimental studies indicate that impaired insulin signaling in the brain contributes to neurodegeneration and cognitive dysfunction [31–33]. Repeated fluctuations in peripheral insulin levels may exacerbate neuroinflammation, oxidative stress, and endothelial dysfunction, thereby compromising neurovascular integrity and promoting neuronal aging [34,35]. Although direct evidence linking insulin variability per se to these mechanisms remains limited, the established vascular and central actions of insulin provide biologically plausible pathways that warrant further investigation.

This study has several notable strengths, including the use of a well-characterized, biracial, community-based cohort with repeated insulin and cognitive assessments over three decades, standardized data collection protocols, and comprehensive covariate adjustment. However, limitations should be acknowledged. First, insulin assays differed across examination years, which may introduce measurement variability despite calibration efforts. Second, residual confounding cannot be excluded. Third, exclusion of individuals with diabetes limits generalizability to treated populations. Finally, long-term intra-individual insulin variability is not yet an established clinical metric, and our results do not imply immediate clinical applicability. Further investigation is required to clarify the role of long-term insulin instability in cognitive decline before it can be integrated into clinical practice.

5. Conclusion

In conclusion, our findings identify long-term intra-individual variability in fasting insulin as a novel and independent metabolic correlate of cognitive performance in midlife, distinct from mean insulin levels or diabetes status. These results suggest that maintaining stable insulin regulation from early adulthood may confer neuroprotective benefits and could serve as a promising target for early preventive strategies to promote lifelong cognitive health.

Data sharing

All data are available upon reasonable request to the corresponding author.

Declaration of generative AI and AI-assisted technologies

The authors declare that no generative AI or AI-assisted technologies were used in the writing of this manuscript or in the creation of figures, images, or artwork.

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CRediT authorship contribution statement

Bo-Shui Huang: Visualization, Investigation, Formal analysis, Data curation. **Zuo-Yu Huang:** Writing – original draft, Investigation, Formal analysis. **Yu-Hong Zeng:** Visualization, Validation, Software, Data curation. **Kun-Hao Bai:** Methodology, Investigation. **Jing-Bin Guo:** Methodology, Investigation. **Jun Weng:** Writing – review & editing, Supervision. **Ze-Hua Li:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **Qing-Yun Hao:** Writing – original draft, Validation, Software.

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.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100487.

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