ORIGINAL ARTICLE

Synergistic Associations of Depressive Symptoms and Executive Functions With Longitudinal Trajectories of Diabetes Biomarkers Among Urban-Dwelling Adults Without Diabetes

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ABSTRACT

Objective: Depressive symptoms and executive functions (EFs) have recently emerged as novel risk factors for type 2 diabetes, but it is unknown if these factors interact to influence diabetes pathophysiology across the life span. We examined the synergistic associations of depressive symptoms and EFs with longitudinal trajectories of diabetes diagnostic criteria among middle-aged and older adults without diabetes.

Methods: Participants were 1257 African American and White, urban-dwelling adults from the Healthy Aging in Neighborhoods of Diversity across the Life Span study who were assessed up to three times over a 13-year period (2004–2017). At baseline, participants completed the Center for Epidemiological Studies—Depression scale and measures of EFs—Trail Making Test Part B, verbal fluency, and Digit Span Backward—for a composite EFs score, and provided blood samples at each follow-up for glycated hemoglobin and fasting serum glucose.

Results: A total of 155 and 220 individuals developed diabetes or prediabetes at wave 3 and wave 4, respectively. Linear mixed-effects regression models adjusting for sociodemographic factors, diabetes risk factors, and antidepressant medications revealed significant three-way interactions of Center for Epidemiological Studies—Depression, EFs, and age on change in glycated hemoglobin ($b = -0.0001$, $p = .005$) and in fasting serum glucose ($b = -0.0004$, $p < .001$), such that among individuals with lower but not higher EFs, elevated depressive symptoms were associated with steeper age-related increases in diabetes biomarkers over time.

Conclusions: Depressive symptoms and lower EFs may interactively accelerate trajectories of key diagnostic criteria, thereby increasing the risk for earlier diabetes incidence. Identifying individuals in this high-risk group may be an important clinical priority for earlier intervention, which has the promise of preventing or delaying this debilitating disease.

Key words: diabetes risk, depressive symptoms, executive functions, longitudinal cohort study, life course perspective, prevention.

INTRODUCTION

Type 2 diabetes is a chronic degenerative endocrine disease that is highly prevalent worldwide, is among the leading causes of death, and results in high financial costs, lost productivity, and severe complications and disability (1). Recent studies indicate that the average age of diabetes diagnosis and onset of complications is decreasing (2), and that diabetes-related complications and functional status declines are occurring at earlier stages of disease pathophysiology (2–5). This research highlights the critical need to examine diabetes development and progression across the life span and determine novel factors contributing to earlier diabetes risk.

Although obesity, hypertension, poor diet, and physical inactivity are well-established risk factors for diabetes, they do not account for all the variance in the disease (6). Increases in depressive symptoms and decline in executive functions (EFs)—one domain of overall cognitive ability—are already established as two particularly debilitating sequelae of diabetes (7,8), but have more recently emerged as factors that precede and confer risk for diabetes development (7,9–15). Depressive symptoms are increasingly being considered vital to diabetes risk as an independent risk factor for the disease. Case in point, a recent meta-analysis of longitudinal studies revealed that depressed adults have up to a 60% greater risk of developing diabetes than nondepressed adults (9). Research has also shown that patients with depression have a 5 to 6 years' earlier diabetes onset than those without a history of depression (10). Moreover, depression shares a bidirectional relationship with

CES-D = Center for Epidemiological Studies—Depression, **EF** = executive function, **FG** = fasting serum glucose, **HANDLS** = Healthy Aging in Neighborhoods of Diversity across the Life Span, **HbA_{1c}** = glycated hemoglobin, **MRV** = medical research vehicle, **WRAT-3** = Wide Range Achievement Test, Third Edition

SDC Supplemental Digital Content

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socioeconomic factors such as poverty (16), which further exacerbate the effects of depression on diabetes risk. All in all, studies have concluded that depressive symptoms tend to begin early in life and, through a combination of biological, behavioral, and socioeconomic pathways, increase the risk of diabetes development throughout the life course (7).

EFs—the effortful mental processes required for reasoning, planning, organization, and complex attention, and cognitive flexibility (17)—are emerging as another important risk factor for diabetes onset. Because EFs are directly implicated in an individual's ability to maintain energy balance through self-monitoring and impulse control (17), individuals with lower levels of EFs are more likely to become overweight and to develop obesity, the principal risk factor for diabetes. Indeed, EFs have been shown to precede and predict obesity (11). Moreover, studies demonstrate that systems-level socioeconomic factors such as poverty and racial and other discrimination directly and indirectly impair cognitive capacity (18,19). In the context of these socioeconomic factors and/or lack of resources, obesity prevention may also not be possible, leading to increased severity or faster progression. Decrements in EFs are also independently associated with insulin resistance (20), hypertension (21), and higher systemic inflammation (22), which reflect the metabolic, vascular, and inflammatory systems involved in diabetes etiology. Furthermore, prior studies have observed deficits in EFs among individuals in prediabetic stages, among those with recent screen-detected diabetes, and even before diagnosis (12–15). These studies give credence to the notion that decrements in cognitive function may not only manifest very early in diabetes pathophysiology but may also precede and contribute to diabetes onset.

What is currently unclear is how depressive symptoms and EFs might interact to influence diabetes incidence and progression across the life span. Of particular concern is whether synergistic influences of depressive symptoms and lower EFs might accelerate diabetes trajectories, thus contributing to earlier diabetes risk and greater morbidity earlier in the life span. There is reason to expect such influence. Depressive symptoms and decrements in EFs are often comorbid and exacerbate one another (23). In addition, they share similar behavioral, neurobiological, and inflammatory pathways that may have a higher combined influence on diabetes risk (6). Understanding the combined influence of these factors will shed light on the yet murky temporal relations among these factors and has critical implications for informing risk prediction models and the earlier detection of at-risk individuals who may benefit from preventative interventions.

Consequently, the objective of this study was to examine the synergistic associations of depressive symptoms and EFs with longitudinal trajectories of two diagnostic criteria for diabetes, namely, glycated hemoglobin (HbA_{1c}) and fasting serum glucose (FG), among middle-aged and older adults without diabetes at baseline, using data from the Baltimore-based epidemiological cohort study Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS). Significant interactions of depressive symptoms and EFs were hypothesized such that adults with higher depressive symptoms and lower EFs would show a greater age-related increase in diabetes-related outcomes. Overall, this study aims to gain a deeper understanding of the psychological and neurocognitive mechanisms preceding and underlying the emergence of diabetes and its progression, and determine novel factors contributing to earlier diabetes onset.

METHODS

Participants and Parent Study Procedures

HANDLS is an ongoing longitudinal investigation of age-related health disparities attributable to race and socioeconomic status (24). The HANDLS sample is a fixed cohort of urban-dwelling adults drawn from 13 neighborhoods (contiguous census tracts) in the city of Baltimore, MD. Neighborhoods were selected for their likelihood of yielding participants who were African American or White men and women who had annual household incomes above or below 125% of the 2004 federal poverty level. All HANDLS participants self-identified their race as African American or White and were between the ages of 30 and 64 years at baseline. The institutional review board at the National Institutes of Health approved the HANDLS protocol.

Baseline data collection for HANDLS (wave 1) occurred between 2004 and 2009. After initial selection, participants were excluded from further participation in the larger HANDLS study if they were unable to provide informed consent, were pregnant, were within 6 months of active cancer treatment, self-reported a diagnosis of AIDS, were unable to provide valid government-issued identification, or did not have a verifiable address. Medical history, physical examination, physical performance battery, cognitive testing, and other assessment were collected within participants' households and on medical research vehicles (MRVs) located within participants' neighborhoods. The next two waves of complete data collection occurred on MRVs between 2009–2013 (wave 3) and 2013–2017 (wave 4).

In total, 3720 participants were enrolled in HANDLS, of whom 2799 completed the MRV visit at wave 1, 2468 completed wave 3, and 2147 completed wave 4. For the present study's data analyses, participants were excluded from the study if they had a history of diabetes or prediabetes at baseline based on a self-reported diabetes diagnosis, self-reported use of diabetes medications, and/or FG ≥100 mg/dl). In addition, participants' data were excluded if they reported any of the following conditions at each wave: stroke, heart failure, dementia, HIV/AIDS, schizophrenia, epilepsy, multiple sclerosis, or Parkinson disease. In addition, participants who became pregnant between two waves had their data excluded at the latter wave (applies to waves 3 and 4 only). Of note, to avoid biasing the data set, if a participant met the inclusion criteria at an earlier wave but later developed one of these conditions before a later wave, the former data were included in the study, whereas the latter data were excluded. In the present study, there were 1257 participants (57.2% female, 57.0% African American, 37.9% living in poverty) with data for all predictors and at least one outcome at one or more waves. Of note, we did not exclude participants who had data at only one time point, as this is not necessary in linear mixed-effects regression (25), and doing so would have risked biasing the sample. Therefore, the present study's sample comprised 1144 participants with wave 1 data, 827 participants with wave 3 data, and 652 with wave 4 data. There were 501 participants with data at all three waves. Binary logistic regression was used to examine sociodemographic differences between participants with data at all three HANDLS waves and those with data at only one or two HANDLS waves. Participants with complete data were significantly younger ($b = -0.02$, $p = .008$) and had higher literacy ($b = 0.02$, $p = .031$), but demonstrated no difference in sex ($b = -0.09$, $p = .440$), race ($b = -0.03$, $p = .825$), or poverty status ($b = -0.08$ $p = .524$). Supplementary Table S1 (Supplemental Digital Content, http://links.lww.com/PSYMED/A822) presents characteristics of participants with complete data at all waves.

Measures

Primary Predictor Variables

Depressive Symptoms

Depressive symptoms were assessed with the widely established 20-item Center for Epidemiologic Studies—Depression (CES-D) scale (26), which has strong psychometric properties and has been used across wide age ranges (26,27). The CES-D scale was administered during the household

interview at baseline. Participants responded to items on a 4-point scale ranging from 0 (rarely) to 3 (mostly). Possible scores ranged from 0 to 60, with higher scores indicating greater depressive symptoms.

Executive Functions

To assess a broad construct of EFs, a composite score was computed from the summation of standardized scores from three neuropsychological tests of EF-related domains: a) cognitive flexibility, as measured by the Trail Making Test Part B; b) working memory, as measured by the Digit Span Backward test; and c) category verbal fluency, as measured by the Animal Naming test. All tests were administered using standard procedures on the MRV at baseline. We used an EF composite score given previous literature demonstrating that composite measures of broader domains are more reliable than individual cognitive tests (25,28). Of note, the commonly applied time cutoff for Trail Making Test Part B is 300 seconds (29). However, we extended the cutoff to 600 seconds to allow for greater variability in task performance. Given skewness in this variable, it was log-transformed to normalize the distribution.

Outcome Variables

HbA_{1c} and FG

Changes in HbA_{1c} (in percent) and FG (in milligrams per deciliter) were modeled as the primary outcome variables in the present study. Blood was drawn on the MRVs after participants fasted overnight. Blood samples were sent to Quest Diagnostics (Nichols Institute Chantilly, Centreville, Virginia; www.questdiagnostics.com) for analysis using standard laboratory procedures and equipment. HbA_{1c} was measured using the immunoturbidimetric method, and FG was measured using a spectrophotometer (AU5400 Immuno Chemistry Analyzer; Olympus, Center Valley, Pennsylvania).

Adjustment Variables

Sociodemographic Information

Participants reported their age, biological sex (0, women; 1, men), self-identified race (0, White; 1, African American), and annual household income at baseline. Annual household income at baseline (adjusted for household size) was used to determine a participant's poverty status using a cutoff of 125% of the 2004 Health and Human Services poverty guidelines (0, household income above poverty cutoff; 1, household income below poverty cutoff). Participants also completed the Wide Range Achievement Test, Third Edition (WRAT-3), a widely administered measure of literacy, on the MRV at baseline. The WRAT-3 Word Reading subtest was used as a proxy for quality of education in the present study.

Sensitivity Variables

Antidepressant medication, lifetime cigarette use, lifetime alcohol use, hypertension, waist circumference, and diabetes diagnoses were examined as additional covariates in sensitivity analyses. During the MRV visits, participants completed a comprehensive medical history assessment and physical examination with a physician or nurse practitioner. Participants self-reported current antidepressant medication use during the medical history assessment (coded as 0 [no] and 1 [yes]). Participants self-reported cigarette smoking and alcohol use history (at all waves) during the medical history assessment, which were dichotomized for the present analyses (coded as 0 [never used regularly] and 1 [ever used regularly]). Hypertension (assessed at all waves on the MRVs) was diagnosed based on self-reported diagnosis, self-reported use of antihypertensive medications (diuretics, blockers, angiotensin inhibitors, or vasodilators), and/or resting systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg. Hypertension was modeled as a dichotomous variable (coded as 0 [no] and 1 [yes]) in the present study. Waist circumference was measured in centimeters. Finally, new diabetes diagnoses at waves subsequent to baseline were determined using the same criteria that were used to exclude participants at baseline (see the previous section, Participants and Parent Study Procedures). Thus, for participants without diabetes at baseline, a diabetes diagnosis at waves 3 or 4 was included as an additional dichotomous covariate (coded as 0 [no] and 1 [yes]).

Statistical Analysis

Main Analyses

Statistical analyses were conducted using the "lme4" package within R version 3.5.2 (30,31). Linear mixed-effects regression models, with the intercept modeled as a random effect, were used to examine prospective interactive relations of a) CES-D by age, b) EF by age, and c) CES-D by EF by age with HbA_{1c} and FG in separate, parallel models. We used a growth model formulation in which change in the HbA_{1c} and FG is assessed by time, which is indexed by age in our analyses. Sex, self-identified race, poverty status, and literacy were modeled as adjustment variables in all analyses. Significant interactions (i.e., $p < .05$) were then probed and plotted to assist with interpretation.

Sensitivity Analyses

Subsequent sensitivity analyses for models that yielded significant interaction effects were conducted through hierarchical entry of additional adjustment variables. Changes in significance of the interaction effect were monitored across steps. Analyses proceeded in the following order: a) antidepressant medication use, lifetime cigarette use, and lifetime alcohol use (model 2); b) hypertension and waist circumference (model 3); and c) diabetes diagnosis at waves 3 and 4 (model 4) to understand whether new diagnoses after the baseline visit had any impact on our results. Of note, the antidepressant medication use variable was time-invariant given our inclusion of data collected only at baseline. Finally, all analyses were rerun after excluding participants who had wave 1 HbA_{1c} ≥5.7% at baseline, but who were not classified as having diabetes or prediabetes by history or FG values.

RESULTS

Descriptive Results

As shown in Table 1, the sample was predominantly middle aged, with the mean (standard deviation [SD]) age varying from 47 (9.3) years at baseline and 55 (9.0) years at wave 4. Slightly more than half of the sample consisted of women (57%) and of African Americans (57%). Consistent with the sample design of the HANDLS study, 38% of the sample had annual household incomes below 125% of the federal poverty level. The literacy level of the sample based on the WRAT-3 Word Reading score was in the 15 to 57 range. Regarding our primary predictor variables, the mean (SD) CES-D score for the sample at baseline of 14.7 (11.4) was below the well-established cutoff score of 16 signifying clinically significant depression symptoms. Accordingly, roughly 10% of the sample endorsed taking antidepressant medications. Regarding our primary outcome variables, the mean HbA_{1c} values varied from the normal range at baseline (M [SD] = 5.6% [0.5%]) to the prediabetic range at wave 4 (M [SD] = 5.8% [0.8%]), whereas the mean FG values remained in the normal range from baseline (M [SD] = 89.3 [6.7] mg/dl) to wave 4 (M [SD] = 95.6 [26.4] mg/dl). There were 157 participants diagnosed with diabetes or prediabetes at wave 3 (18.9% of wave 3 study sample) and an additional 64 participants at wave 4 (9.8% of wave 4 study sample). Supplementary Table S2 (Supplemental Digital Content, http://links.lww.com/PSYMED/A822) presents the bivariate correlations between depressive symptoms, EF, and our primary outcome variables at each wave (and change therein). Depressive symptoms were significantly correlated with FG at wave 1 ($r = -0.07$), whereas EFs was significantly correlated with HbA_{1c} at all waves (r values = −0.14, −0.09, −0.08,

TABLE 1. Participant Characteristics (N = 1257)

	Wave 1	Wave 3	Wave 4
Time-invariant variables[a]			
African Americans, *n* (%)	716 (57.0)	—	—
Women, *n* (%)	719 (57.2)	—	—
Below 125% poverty level, *n* (%)	476 (37.9)	—	—
Literacy: WRAT-3 word reading, M (SD)	42.8 (7.8)	—	—
Depressive symptoms, M (SD)	14.7 (11.4)	—	—
Executive functions composite, M (SD)	0.3 (2.3)	—	—
TMT-B (nontransformed), M (SD), s	127.8 (132.8)	—	—
Digit Span Backward, M (SD)	5.7 (2.3)	—	—
Animal Naming, M (SD)	19.1 (5.5)	—	—
Antidepressant medications, M (SD), %	123 (9.8)	—	—
Time-varying variables[b]			
Age, M (SD), y	46.8 (9.3)	51.8 (8.9)	55.1 (9.0)
Waist circumference, M (SD), cm	96.7 (31.3)	99.1 (15.8)	101.9 (16.7)
BMI, M (SD), kg/m^2	28.5 (7.1)	29.0 (7.1)	29.6 (7.3)
Hypertension, *n* (%)	396 (34.6)	375 (45.3)	341 (52.3)
Cigarette user, ever, *n* (%)	757 (66.2)	566 (68.3)	470 (72.1)
Alcohol user, ever, *n* (%)	971 (84.9)	729 (88.1)	581 (89.1)
HbA_{1c}, M (SD), %	5.6 (0.5)	5.3 (0.6)	5.8 (0.8)
Fasting glucose, M (SD), mg/dl	89.3 (6.7)	92.7 (17.8)	95.6 (26.5)
Diabetes or prediabetes diagnosis, *n* (%)	—	155 (18.7)	220 (33.7)

WRAT-3 = Wide Range Achievement Test, Third Edition; M (SD) = mean (standard deviation); TMT-B = Trail Making Test Part B; HbA_{1c} = hemoglobin A_{1c}.

[a]Race, sex, poverty status, literacy, depressive symptoms, executive functioning, and antidepressant medication use were collected at wave 1 only and were available for all participants.

[b]Age, waist circumference, hypertension, cigarette use, alcohol use, HbA_{1c}, and fasting glucose were time-varying and sample sizes varied across waves because of incomplete data: *n* (wave 1) = 1144; *n* (wave 3) = 827; *n* (wave 4) = 652.

respectively) and with FG at wave 3 (r = −0.08). Finally, regarding diabetes risk factors included as covariates, between 34% (wave 1) and 53% (wave 4) of the sample had hypertension and a majority had a history of regular cigarette (66%–72%) and/or alcohol (85%–89%) use. Participants in the sample had average waist circumferences between 96.7 cm at baseline and 101.0 cm at wave 4. Although not included as a covariate, body mass indexes were predominantly in the overweight range between baseline (M [SD] = 28.5 [7.1] kg/m^2) and wave 4 (M [SD] = 29.7 [7.3] kg/m^2).

CES-D Predicting Age-Related HbA_{1c} and FG Trajectories

In the base models, findings revealed significant two-way interactions of CES-D by age with HbA_{1c} (b = 0.0003, p = .041) and FG (b = 0.01, p = .011; Table 2). As shown in Figure 1, greater depressive symptoms were associated with steeper age-related increases in HbA_{1c} and FG. Sensitivity analyses revealed that the two-way interaction of CES-D by age with HbA_{1c} and with FG remained significant in model 2 (p values < .05) after adjustment for antidepressant medications, lifetime cigarette use, and lifetime alcohol use. When hypertension and waist circumference were added in model 3, this interaction was attenuated to nonsignificance in the model predicting HbA_{1c} (b = 0.0003, p = .051; Table 2) but remained significant in the model predicting FG (b = 0.01, p = .013). After additional adjustment for diabetes diagnosis at waves 3 and 4 in model 4, the CES-D by age interaction remained nonsignificant for HbA_{1c} (b = 0.0002, p = .097; Table 2) and significant for FG (b = 0.01, p = .033).

EF Predicting Age-Related HbA_{1c} and FG Trajectories

Next, analyses revealed nonsignificant two-way interactions of EF by age with HbA_{1c} (b = 0.0003, p = .689) and FG (b = −0.01, p = .489; Table 3) in the base models. As such, subsequent sensitivity analyses were not conducted.

CES-D by EF Interactions Predicting Age-Related HbA_{1c} and FG Trajectories

Finally, analyses revealed a significant three-way interaction of CES-D by EFs by age with HbA_{1c} (b = −0.0002, p = .012) and FG (b = −0.01, p = .006; Table 4) in base models. As shown in Figure 2, among those with lower EFs, greater depressive symptoms were associated with steeper age-related increases in HbA_{1c} and FG. Similar but less pronounced trends were observed among those with average EF. In contrast, no differences in age-related HbA_{1c} or FG trajectories as a function of depressive symptoms were observed among those with higher EF. Sensitivity analyses (Table 4) revealed that the significant three-way interaction of CES-D by EF by age with HbA_{1c} and FG remained significant after further adjustment for a) antidepressant medications, lifetime cigarette use, and lifetime alcohol use in model 2 (HbA_{1c}: b = −0.0002, p = .012; FG: b = −0.01, p = .006); b) hypertension and waist circumference in model 3 (HbA_{1c}: b = −0.0001, p = .011; FG: b = −0.004,

TABLE 2. Relations of Depressive Symptoms With Age-Related Trajectories of Glycated Hemoglobin and Fasting Glucose in the HANDLS Study (N = 1257)

(a) Glycated Hemoglobin	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
Depressive symptoms by age	0.0003*	0.0003*	0.0003	0.0002
Depressive symptoms	0.003*	0.003*	0.003	0.002
Age	0.01***	0.01***	0.01***	0.003
Race (0, White; 1, AA)	0.17***	0.17***	0.16***	0.16***
Sex (0, women; 1, men)	−0.02	−0.02	−0.01	−0.02
Poverty status (0, above; 1, below)	0.02	0.02	0.02	0.01
WRAT-3 Word Reading	−0.004	−0.004	−0.003	−0.004
Antidepressant medication use (0, no; 1, yes)		0.01	−0.01	0.00004
Cigarette use (0, never; 1, ever)		0.004	0.01	0.01
Alcohol use (0, never; 1, ever)		−0.05	−0.04	−0.05
Hypertension (0, no; 1, yes)			0.09***	0.08**
Waist circumference			0.002***	0.002***
Diabetes diagnosis at follow-up wave (0, no; 1, yes)				0.40***

(b) Fasting Glucose	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[c]
Depressive symptoms by age	0.01**	0.01*	0.01*	0.01*
Depressive symptoms	0.09*	0.09*	0.08*	0.05
Age	0.15*	0.15*	0.11	−0.08
Race (0, White; 1, AA)	−1.37	−1.42	−1.50	−1.87*
Sex (0, women; 1, men)	3.15***	3.12**	3.25***	2.82***
Poverty status (0, above; 1, below)	−0.25	−0.28	−0.31	−0.91
WRAT-3 Word Reading	−0.08	−0.08	−0.07	−0.07
Antidepressant medication use (0, no; 1, yes)		−0.59	−1.08	−0.65
Cigarette use (0, never; 1, ever)		0.09	0.24	0.10
Alcohol use (0, never; 1, ever)		−0.22	−0.11	−0.71
Hypertension (0, no; 1, yes)			1.72*	1.01
Waist circumference			0.05***	0.03*
Diabetes diagnosis at follow-up wave (0, no; 1, yes)				18.22***

HANDLS = Healthy Aging in Neighborhoods of Diversity across the Life Span; AA = African American; WRAT-3 = Wide Range Achievement Test, Third Edition.

*$p < .05$.

**$p < .01$.

***$p < .001$.

[a]Model 1 adjusts for age, self-identified race, sex, poverty status, and literacy.

[b]Model 2 adjusts for all covariates in model 1 and additionally adjusts for antidepressant medication use, lifetime cigarette use, and lifetime alcohol use.

[c]Model 3 adjusts for all covariates in models 1 and 2, and additionally adjusts for hypertension and waist circumference.

[d]Model 4 adjusts for all covariates in models 1, 2, and 3, and additionally adjusts for diabetes diagnosis at waves 3 and 4.

p = .006); and c) diabetes diagnosis at follow-up waves in model 4 (HbA_{1c}: $b = -0.0001$, p = .037; FG: $b = -0.003$, p = .037). Among the covariates included in this fully adjusted model 4, race, waist circumference, and diabetes diagnosis at follow-up remained predictive of both age-related HbA_{1c} and FG trajectories.

Sensitivity Analyses With HbA_{1c} Exclusion at Baseline

There were 487 participants with wave 1 $HbA_{1c} \geq 5.7\%$ who were not diagnosed with diabetes or prediabetes by history or FG values. These participants were excluded, and analyses were rerun with the remaining sample of 770 participants (56.5% women, 46.4% African American, 35.8% living in poverty; see Supplementary Table S3 [Supplemental Digital Content, http://links.lww.com/PSYMED/A822] for subsample participant characteristics). In this subsample, two-way interaction of CES-D by age with HbA_{1c} and FG became nonsignificant ($p \geq .05$) in base models and after adjustment for covariates (Supplementary Table S4, http://links.lww.com/PSYMED/A822). The EF by age interaction with HbA_{1c} and FG remained nonsignificant in base models ($p \geq .05$), consistent with the findings in the overall sample (Supplementary Table S5, http://links.lww.com/PSYMED/A822). Nonetheless, in this reduced sample, the three-way interaction of CES-D by EF by age remained significant in base models with HbA_{1c} ($b = -0.0001$, p = .012) and FG ($b = -0.01$, p = .006; Supplementary Table S6, http://links.lww.com/PSYMED/A822). Greater depressive symptoms were associated with steeper age-related increases in HbA_{1c} and

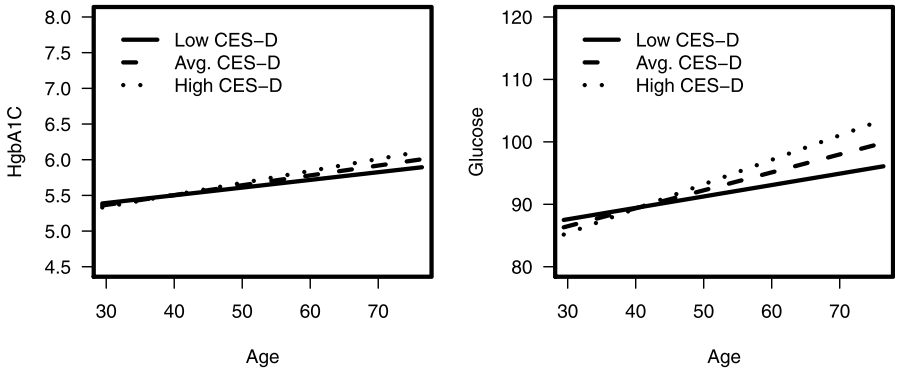

FIGURE 1. Plots illustrating the association of elevated depressive symptoms with steeper age-related increases in (A) HbA_{1c} and (B) FG.

FG among those with lower EF; conversely, there were no differences in age-related changes in these markers among those with average or higher EF. Consistent with analyses in the overall sample, findings revealed that the significant three-way interaction of CES-D by EF by age with HbA_{1c} and FG remained significant after further adjustment for a) antidepressant medications, lifetime cigarette use, and lifetime alcohol use in model 2 (HbA_{1c}: $b = -0.0001$, $p = .001$; FG: $b = -0.0001$, $p < .001$); b) hypertension and waist circumference in model 3 (HbA_{1c}: $b = -0.0001$, $p = .001$; FG: $b = -0.01$, $p < .001$); and c) diabetes diagnosis at follow-up waves in model 4 (HbA_{1c}: $b = -0.0001$, $p = .005$; FG: $b = -0.003$, $p < .001$).

DISCUSSION

To our knowledge, this is the first study to examine the interactive longitudinal relations of depressive symptoms and EFs to age-related changes in key diabetes biomarkers among a diverse sample of adults initially free of diabetes. Our primary analyses revealed interactions between depressive symptoms and EFs predicting longitudinal trajectories of diabetes biomarkers—HbA_{1c} and FG—for 13 years of follow-up. This interaction was significant in models adjusted for sociodemographic factors and literacy and remained significant after further adjustments for substance use, antidepressant medications, and diabetes risk factors hypertension and waist circumference. In addition, new diabetes diagnoses during follow-up—155 individuals at wave 3 and 220 individuals at wave 4—did not seem to be driving the overall effect, and either diabetes biomarker outcome demonstrated consistent patterns or results. These results indicate that among individuals with low EF, elevated depressive symptoms are associated with steeper age-related increases in FG and HbA1c over time. In contrast, among those with higher EF, no differences in age-related trajectories of diabetes biomarkers were observed as a function of depressive symptoms. These findings suggest that depressive symptoms and lower EF may interactively accelerate diabetes pathophysiology and increase the risk of earlier diabetes onset.

Our observed findings showing significant two-way interactions of depressive symptoms by age are in line with the well-established literature and meta-analyses that demonstrate the deleterious effects of both elevated depressive symptoms and clinical depression on diabetes incidence (9,32) and its chief precursor insulin resistance (33). It is relatively more novel to view variability in cognitive function and particularly in EFs as a potential risk factor for diabetes onset, although several hypothesized mechanisms give credence to this possibility (11,20–22) and several prior studies, but not all (34), have either directly or indirectly provided evidence for this prospective association. Among the few studies that have *directly* linked neurocognitive domains to diabetes risk, Mõttus et al. (35) demonstrated that lower general cognitive ability in adolescence predicted the risk of developing diabetes in middle adulthood. In another study, Murdock et al. (22) demonstrated that measures of inhibitory control and fluid reasoning, but not measures of working memory, or processing speed predicted the increased risk of diabetes. Relatively more studies have demonstrated *indirect* EF-to-diabetes links, principally through obesity. Obesity has been connected to cognitive decline across the life span, and various studies have shown that EFs precede and predict obesity (11), suggesting that lower EFs in conjunction with obesity pathophysiology

TABLE 3. Relations of Executive Functions With Age-Related Trajectories of Glycated Hemoglobin and Fasting Glucose in the HANDLS Study ($N = 1257$)

(a) Glycated Hemoglobin	*b*	SE	*p*
Executive functions by age	0.0003	0.001	.688
Executive functions	0.01	0.01	.450
Age	0.01	0.001	<.001
Race (0, White; 1, AA)	0.17	0.03	<.001
Sex (0, women; 1, men)	−0.03	0.03	.372
Poverty status (0, above; 1, below)	0.04	0.03	.266
WRAT-3 Word Reading	−0.01	0.003	.025

(b) Fasting Glucose	*b*	SE	*p*
Executive functions by age	−0.01	0.02	.489
Executive functions	0.11	0.26	.663
Age	0.28	0.04	<.001
Race (0, White; 1, AA)	−1.56	0.96	.106
Sex (0, women; 1, men)	2.99	0.90	.001
Poverty status (0, above; 1, below)	0.18	0.94	.845
WRAT-3 Word Reading	−0.12	0.07	.099

HANDLS = Healthy Aging in Neighborhoods of Diversity across the Life Span; AA = African American; WRAT-3 = Wide Range Achievement Test, Third Edition.
Models adjust for age, self-identified race, sex, poverty status, and literacy.

TABLE 4. Independent and Interactive Relations of Depressive Symptoms and EFs With Age-Related Trajectories of Glycated Hemoglobin and Fasting Glucose in the HANDLS Study (N = 1257)

(a) Glycated Hemoglobin	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
Depressive symptoms by EF by age	−0.0002*	−0.0002*	−0.0001*	−0.0001*
Depressive symptoms by EF	−0.001	−0.001	−0.001	−0.001
Depressive symptoms by age	0.0003*	0.0003*	0.0003*	0.0003*
EF by age	0.003*	0.003*	0.003*	0.002*
Depressive symptoms	0.003	0.003	0.003	0.002
EF	0.02	0.02	0.02	0.01
Age	0.01***	0.01***	0.01**	0.002
Race (0, White; 1, AA)	0.18***	0.18***	0.17***	0.16***
Sex (0, women; 1, men)	−0.02	−0.02	−0.01	−0.02
Poverty status (0, above; 1, below)	0.03	0.02	0.02	0.01
WRAT-3 Word Reading	−0.01*	−0.01*	−0.01	−0.004
Antidepressant medication use (0, no; 1, yes)		0.01	−0.01	0.01
Cigarette use (0, never; 1, ever)		0.004	0.01	0.01
Alcohol use (0, never; 1, ever)		−0.05	−0.04	−0.01
Hypertension (0, no; 1, yes)			0.09***	0.08**
Waist circumference			0.02***	0.02***
Diabetes diagnosis at follow-up wave (0, no; 1, yes)				0.39***

(b) Fasting Glucose	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
Depressive symptoms by EF by age	−0.01**	−0.01**	−0.004**	0.003*
Depressive symptoms by EF	−0.03	−0.03	−0.03	−0.02
Depressive symptoms by age	0.01**	0.01*	0.01*	0.01*
EF by age	0.06*	0.06*	0.06*	0.05
Depressive symptoms	0.08	0.08	0.08	0.04
EF	0.59	0.60	0.59	0.21
Age	0.14*	0.14*	0.10	−0.11
Race (0, White; 1, AA)	−1.18	−1.23	−1.30	−1.84*
Sex (0, women; 1, men)	3.19***	3.16***	3.28***	2.86***
Poverty status (0, above; 1, below)	−1.72	−0.20	−0.23	−0.91
WRAT-3 Word Reading	−0.11	−0.11	−0.10	−0.08
Antidepressant medication use (0, no; 1, yes)		−0.64	−1.11	−0.62
Cigarette use (0, never; 1, ever)		0.11	0.25	0.10
Alcohol use (0, never; 1, ever)		0.23	0.13	−0.70
Hypertension (0, no; 1, yes)			1.67*	0.99
Waist circumference			0.05***	0.03*
Diabetes diagnosis at follow-up wave (0, no; 1, yes)				18.15***

HANDLS = Healthy Aging in Neighborhoods of Diversity across the Life Span; EF = executive function; AA = African American; WRAT-3 = Wide Range Achievement Test, Third Edition.

*$p < .05$.

**$p < .01$.

***$p < .001$.

[a]Model 1 adjusts for age, self-identified race, sex, poverty status, and literacy.

[b]Model 2 adjusts for all covariates in model 1 and additionally adjusts for antidepressant medication use, lifetime cigarette use, and lifetime alcohol use.

[c]Model 3 adjusts for all covariates in models 1 and 2, and additionally adjusts for hypertension, and waist circumference.

[d]Model 4 adjusts for all covariates in models 1, 2, and 3, and additionally adjusts for diabetes diagnosis at waves 3 and 4.

can precipitate diabetes incidence. These studies do not align with the lack of significant EF by age interaction on diabetes risk trajectories observed in the present study. It is possible that the discrepancy between these prior studies and our findings is related to differences in the characteristics of the study samples or to differences in the measurement of key variables.

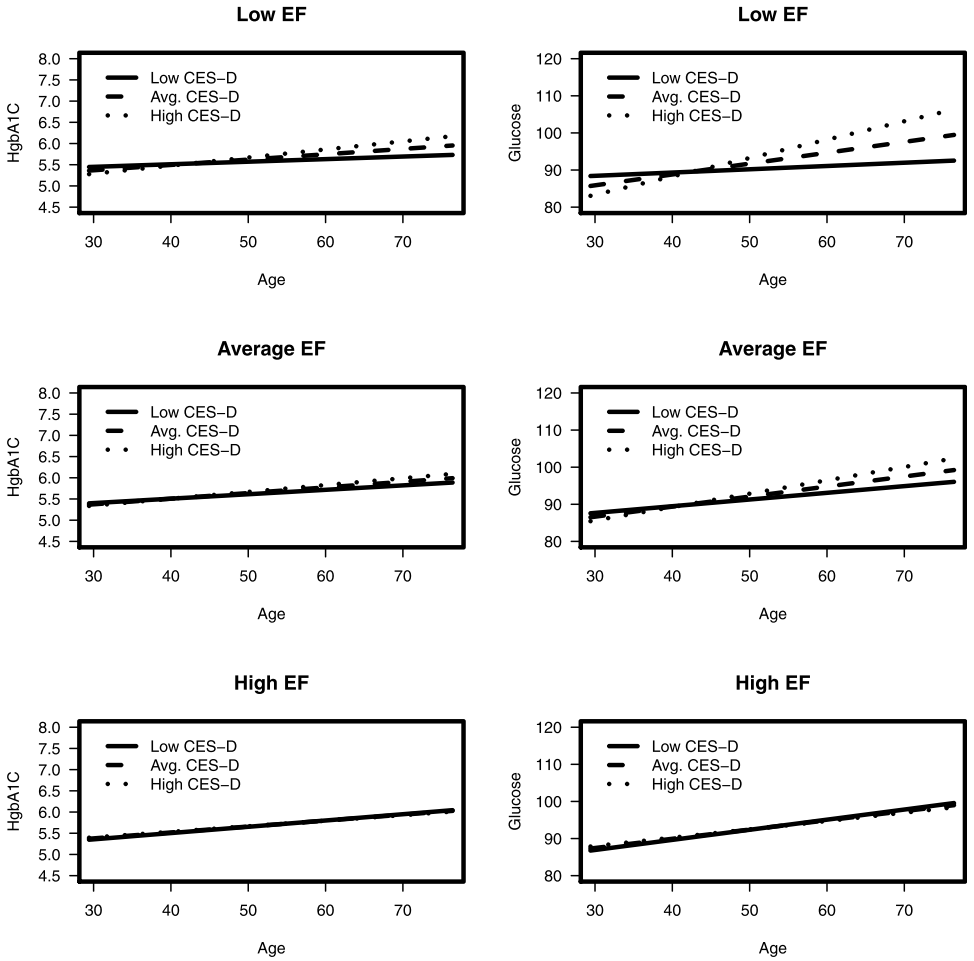

FIGURE 2. Plots disentangling the significant three-way interaction of CES-D by EF by age with diabetes biomarkers in base models. Top row: greater depressive symptoms associated with steeper age-related increases in HbA_{1c} and FG among those with lower EF. Middle row: less pronounced, trends observed among those with average EF. Bottom row: no differences in age-related HbA_{1c} or FG trajectories as a function of depressive symptoms observed among those with higher EF.

To our knowledge, no prior study has examined the synergistic effects of depressive symptoms and EF on diabetes incidence. Among individuals *with* diabetes, a larger literature has demonstrated complex interrelations among depressive symptoms, EFs, and diabetes (36). Adults with diabetes exhibit clinical depression at twice the rate of adults without diabetes, underscoring the bidirectional depression-diabetes association. Adults with diabetes also show neurophysiological alterations in the prefrontal cortex and consequent deficits in EFs, as do individuals with depression (37). A few recent studies report that adults with comorbid diabetes and depression have a greater rate of decline in EFs and overall cognitive function than adults with either condition alone (38,39). In turn, worsening executive functioning in diabetes is likely to impair glycemic control and diabetes self-management (38,40). Given that a majority of these studies have not examined these three conditions together, the temporal relations among these three conditions and their underlying mechanisms are not yet clearly understood (41).

Although the mechanisms underlying the synergistic associations of depressive symptoms and low EFs on diabetes pathology are likely to include the contributions of socioeconomic, biological, and behavioral factors, and parsing apart the complex causal pathways remains a major challenge, there seem several possibilities as to how depressive symptoms and EFs might interact to promote diabetes pathology. A first possibility is the direct influence of depression on EF. There is now considerable evidence linking depression with cognitive impairment, including data indicating that depressive symptoms precede declines in cognition across the life span (41). In fact, the National Institute of Mental Health's Research Domain Criteria (42) has established cognitive impairment to be a core domain of a diagnosis for major depressive disorder. The overall evidence indicates that depression has a particularly deleterious effect on higher-order EFs such as planning, monitoring, reasoning, and self-regulation (43). In addition, rumination in depression can deplete working memory resources (44). From a behavioral standpoint, common maladaptive health behaviors associated with elevated depressive symptoms, such as a lack of a healthy diet, being sedentary, and smoking and alcohol use, can also negatively impact executive functioning (12,41). Although these negative health behaviors associated with depression impair glucose metabolism and insulin sensitivity, these preclinical conditions themselves can impair executive functioning (41). In turn, depressive symptoms and EFs

share similar behavioral, neurobiological, and inflammatory pathways that may have a higher combined influence on diabetes risk (6). Just as likely, these affective and cognitive symptoms could further impair an individual's ability to undertake health behaviors that could worsen the management of the metabolic risk factors linked to diabetes incidence.

A second possibility is that these synergistic effects occur through obesity, which is correlated with both elevated depressive symptoms and reduced cognitive performance including attention and psychomotor skills (34,45). Studies report that when elevated depressive symptoms are present in conjunction with lower EF, particularly inhibitory control, the resulting effect is weight gain (46,47). Thus, the concurrent presence of both negative affective and cognitive symptoms could increase the rate of weight gain over time, which could accelerate the progression to incident diabetes. It should be noted that our observed findings remained after adjustment for waist circumference—a measure of central adiposity—indicating that obesity may be just one of the underlying mechanisms for these synergistic effects.

A final possibility pertains to unmeasured common factors underlying both depressive symptoms and EFs that might promote diabetes pathology and onset of disease. The role of systems-level socioeconomic factors such as racial discrimination and adverse childhood experiences is especially relevant here. Because these factors contribute to and interact with both depressive symptoms and EFs, it is also possible that they may combine to produce accelerated diabetes risk trajectories. For example, exposure to racial discrimination is known to impair cognitive abilities across several domains and deteriorate psychological well-being (19,48). Future research should concentrate on understanding this complex interactive milieu of cognitive, affective, and socioeconomic factors underlying diabetes pathology to better understand points of intervention at the individual and systems levels.

Limitations of the current study warrant discussion. First, we were unable to distinguish between type 1 and type 2 diabetes in our sample. However, given our diagnostic criteria, it is reasonable to assume that any individuals with type 1 or type 2 diabetes mellitus were excluded at baseline. Moreover, type 2 diabetes represents the vast majority, accounting for 90% to 95% of all diabetes cases, and new-onset type 1 diabetes is rare in middle-aged adults (2). Second, because we only examined the EF domain, one aspect of overall cognitive functioning, our results cannot speak to whether interactive relations may exist between depressive symptoms and other cognitive domains such as learning and memory. Third, we observed high attrition in our sample from wave 1 (n = 1144) to wave 4 (n = and 652), and participants with complete data at all three waves had slightly younger age and higher literacy than participants with data at only one or two waves. However, sex, race, and poverty status did not differ between these two groups. It should also be noted that the roughly 50% attrition from wave 1 to wave 4 likely led to an underestimate of our key associations. Distinct strengths of the current study also warrant acknowledgment, including the large socioeconomically diverse, biracial, population-based sample that included a large number of individuals living in poverty (approximately 40% of the sample), and a longitudinal study design that allowed for the examination of progression of diabetes biomarkers over time. Moreover, our models withstood extensive statistical adjustments for sociodemographic factors, diabetes risk factors, and diabetes diagnosis during follow-up, indicating that the influences of depressive symptoms and EF on diabetes risk extend beyond these factors.

The findings of the current study suggest for the first time that depressive symptoms and lower EF may work interactively to accelerate diabetes pathophysiology and increase the risk of earlier diabetes onset. Future investigations can strengthen the argument that depressive symptoms and EFs represent causal interactive factors underlying diabetes pathophysiology in midlife, if not earlier. In addition to replicating these results using other longitudinal data, particularly data that include diverse race/ethnicity groups (e.g., Hispanic/Latinos, South Asians) and age cohorts, future research in this area should try to a) investigate multiple domains of cognitive function (e.g., EFs, memory, language) and affect (e.g., depressive symptoms, anxiety) simultaneously to deconstruct the complex interactive influences of cognitive and affective symptoms on diabetes pathology; b) distinguish population-based samples such as ours with preclinical depressive symptoms from clinical samples with major depressive disorder, as it is possible that the synergistic effects of major depressive disorder and low EF on diabetes pathophysiology may be distinct in terms of strength or other characteristics; c) understand the interplay between individual-level (e.g., depressive symptoms, hypertension, substance use) and systems-level contributors (e.g., racial discrimination, health care access and quality) to diabetes pathology; and d) empirically test biobehavioral mechanisms using advanced techniques such as structural equation modeling.

The rate of diabetes incidence is already alarmingly high. This rate is expected to double by 2030 (1) because of the effects of urbanization, changes in life-style, and aging. Depression and deficits in EFs that constitute strong risk factors for diabetes and its sequelae (e.g., future cognitive decline and dementia) also represent leading causes of morbidity and mortality in the United States and worldwide. Thus, there is a dire need for preventive health efforts at individual and systems levels to reduce the burden of concurrent depressive symptoms and cognitive dysfunction and, in doing so, decrease the rate of diabetes. These preventative efforts include developing new risk prediction models or adapting current models such as the ADA Diabetes Risk Test (49) to include depressive symptoms and their interactions with cognitive function in conjunction with traditional diabetes risk factors. Thus, identifying high-risk individuals with comorbid depressive symptoms and low EFs could become an early clinical priority, and programs such as the Diabetes Prevention Program (50) could be adapted for this high-risk group. In turn, these interventions, administered earlier in the life span, have the promise of preventing or delaying this debilitating disease and its sequelae.

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REFERENCES

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2020:12–5.
2. Koopman RJ, Mainous AG 3rd, Diaz VA, Geesey ME. Changes in age at diagnosis of type 2 diabetes mellitus in the United States, 1988 to 2000. Ann Fam Med 2005;3:60–3.

3. Diabetes Prevention Program Research Group. The prevalence of retinopathy in impaired glucose tolerance and recent-onset diabetes in the Diabetes Prevention Program. Diabet Med 2007;24:137–44.
4. Meigs JB, D'Agostino RB Sr., Nathan DM, Rifai N, Wilson PW, Framingham Offspring Study. Longitudinal association of glycemia and microalbuminuria: the Framingham Offspring Study. Diabetes Care 2002;25:977.
5. Nichols GA, Brown JB. Functional status before and after diagnosis of type 2 diabetes. Diabet Med 2004;21:793–7.
6. Bi Y, Wang T, Xu M, Xu Y, Li M, Lu J, Zhu X, Ning G. Advanced research on risk factors of type 2 diabetes. Diabetes Metab Res Rev 2012;28:32–9.
7. Golden SH, Lazo M, Carnethon M, Bertoni AG, Schreiner PJ, Diez Roux AV, Lee HB, Lyketsos C. Examining a bidirectional association between depressive symptoms and diabetes. JAMA 2008;299:2751–9.
8. Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes—systematic overview of prospective observational studies. Diabetologia 2005;48:2460–9.
9. Rotella F, Mannucci E. Depression as a risk factor for diabetes: a meta-analysis of longitudinal studies. J Clin Psychiatry 2013;74:31–7.
10. Katon W, Lyles CR, Parker MM, Karter AJ, Huang ES, Whitmer RA. Association of depression with increased risk of dementia in patients with type 2 diabetes: the Diabetes and Aging Study. Arch Gen Psychiatry 2012;69:410–7.
11. Gunstad J, Paul RH, Cohen RA, Tate DF, Spitznagel MB, Gordon E. Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. Compr Psychiatry 2007;48:57–61.
12. Ruis C, Biessels GJ, Gorter KJ, van den Donk M, Kappelle LJ, Rutten GEHM. Cognition in the early stage of type 2 diabetes. Diabetes Care 2009;32:1261–5.
13. Roriz-Filho JS, Sa-Roriz TM, Rosset I, Camozzato AL, Santos AC, Chaves ML, Moriguti JC, Roriz-Cruz M. (Pre)diabetes, brain aging, and cognition. Biochim Biophys Acta 2009;1792:432–43.
14. Huang RR, Jia BH, Xie L, Ma SH, Yin JJ, Sun ZB, Le HB, Xu WC, Huang JZ, Luo DX. Spatial working memory impairment in primary onset middle-age type 2 diabetes mellitus: an ethology and BOLD-fMRI study. J Magn Reson Imaging 2016;43:75–87.
15. He XS, Wang ZX, Zhu YZ, Wang N, Hu X, Zhang DR, Zhu D-F, Zhou JN. Hyperactivation of working memory-related brain circuits in newly diagnosed middle-aged type 2 diabetics. Acta Diabetol 2015;52:133–42.
16. Ridley M, Rao G, Schilbach F, Patel V. Poverty, depression, and anxiety: causal evidence and mechanisms. Science 2020;370.
17. Lezak MD, Howieson DB, Loring DW, Fischer JS. Neuropsychological Assessment. New York, NY: Oxford University Press; 2004.
18. Mani A, Mullainathan S, Shafir E, Zhao J. Poverty impedes cognitive function. Science 2013;341:976–80.
19. Ozier EM, Taylor VJ, Murphy MC. The cognitive effects of experiencing and observing subtle racial discrimination. J Soc Issues 2019;75:1087–115.
20. Abbatecola AM, Paolisso G, Lamponi M, Bandinelli S, Lauretani F, Launer L, Ferrucci L. Insulin resistance and executive dysfunction in older persons. J Am Geriatr Soc 2004;52:1713–8.
21. Vicario A, Martinez CD, Baretto D, Casale AD, Nicolosi L. Hypertension and cognitive decline: impact on executive function. J Clin Hypertens (Greenwich) 2005;7:598–604.
22. Murdock KW, LeRoy AS, Lacourt TE, Duke DC, Heijnen CJ, Fagundes CP. Executive functioning and diabetes: the role of anxious arousal and inflammation. Psychoneuroendocrinology 2016;71:102–9.
23. Wilson RS, Capuano AW, Boyle PA, Hoganson GM, Hizel LP, Shah RC, Nag S, Schneider JA, Arnold SE, Bennett DA. Clinical-pathologic study of depressive symptoms and cognitive decline in old age. Neurology 2014;83:702–9.
24. Evans MK, Lepkowski JM, Powe NR, LaVeist T, Kuczmarski MF, Zonderman AB. Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS): overcoming barriers to implementing a longitudinal, epidemiologic, urban study of health, race, and socioeconomic status. Ethn Dis 2010;20:267–75.
25. Gueorguieva R, Krystal JH. Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry. Arch Gen Psychiatry 2004;61:310–7.
26. Radloff L. The center for epidemiologic studies depression index. Appl Psychol Measur 1977;1:385–401.
27. Lewinsohn PM, Seeley JR, Roberts RE, Allen NB. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. Psychol Aging 1997;12:277–87.
28. Bender AC, Austin AM, Grodstein F, Bynum JPW. Executive function, episodic memory, and Medicare expenditures. Alzheimers Dement 2017;13:792–800.
29. Strauss E, Sherman EM, Spreen O. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. 3rd ed. New York, NY: Oxford University Press; 2006.
30. Bates D, Maechler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Softw 2015;67:1–48.
31. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2013.
32. Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia 2006;49:837–45.
33. Khambaty T, Stewart JC, Muldoon MF, Kamarck TW. Depressive symptom clusters as predictors of 6-year increases in insulin resistance: data from the Pittsburgh Healthy Heart Project. Psychosom Med 2014;76:363–9.
34. Favieri F, Forte G, Casagrande M. The executive functions in overweight and obesity: a systematic review of neuropsychological cross-sectional and longitudinal studies. Front Psychol 2019;10:2126.
35. Mõttus R, Luciano M, Starr JM, Deary IJ. Diabetes and life-long cognitive ability. J Psychosom Res 2013;75:275–8.
36. Danna SM, Graham E, Burns RJ, Deschênes SS, Schmitz N. Association between depressive symptoms and cognitive function in persons with diabetes mellitus: a systematic review. PLoS One 2016;11:e0160809.
37. Geijselaers SLC, Sep SJS, Stehouwer CDA, Biessels GJ. Glucose regulation, cognition, and brain MRI in type 2 diabetes: a systematic review. Lancet Diabetes Endocrinol 2015;3:75–89.
38. Black S, Kraemer K, Shah A, Simpson G, Scogin F, Smith A. Diabetes, depression, and cognition: a recursive cycle of cognitive dysfunction and glycemic dysregulation. Curr Diab Rep 2018;18:118.
39. Demakakos P, Muniz-Terrera G, Nouwen A. Type 2 diabetes, depressive symptoms and trajectories of cognitive decline in a national sample of community-dwellers: a prospective cohort study. PLoS One 2017;12:e0175827.
40. Feil DG, Zhu CW, Sultzer DL. The relationship between cognitive impairment and diabetes self-management in a population-based community sample of older adults with type 2 diabetes. J Behav Med 2012;35:190–9.
41. Schmitz N, Deschênes SS, Burns RJ, Danna SM, Franco OH, Ikram MA, Kivimäki M, Singh-Manoux A, Tiemeier H. Cardiometabolic dysregulation and cognitive decline: potential role of depressive symptoms. Br J Psychiatry 2018;212:96–102.
42. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry 2010;167:748–51.
43. Marazziti D, Consoli G, Picchetti M, Carlini M, Faravelli L. Cognitive impairment in major depression. Eur J Pharmacol 2010;626:83–6.
44. Yang Y, Cao S, Shields GS, Teng Z, Liu Y. The relationships between rumination and core executive functions: a meta-analysis. Depress Anxiety 2017;34:37–50.
45. Pereira-Miranda E, Costa PRF, Queiroz VAO, Pereira-Santos M, Santana MLP. Overweight and obesity associated with higher depression prevalence in adults: a systematic review and meta-analysis. J Am Coll Nutr 2017;36:223–33.
46. Stinson EJ, Krakoff J, Gluck ME. Depressive symptoms and poorer performance on the Stroop Task are associated with weight gain. Physiol Behav 2018;186:25–30.
47. Yamagata AS, Mansur RB, Rizzo LB, Rosenstock T, McIntyre RS, Brietzke E. Selfish brain and selfish immune system interplay: a theoretical framework for metabolic comorbidities of mood disorders. Neurosci Biobehav Rev 2017;72:43–9.
48. Schmitt MT, Branscombe NR, Postmes T, Garcia A. The consequences of perceived discrimination for psychological well-being: a meta-analytic review. Psychol Bull 2014;140:921–48.
49. 2. Classification and Diagnosis of Diabetes. Standards of medical care in diabetes—2021. Diabetes Care 2021;44:S15–33.
50. Diabetes Prevention Program (DPP) Research Group. The Diabetes Prevention Program (DPP): description of lifestyle intervention. Diabetes Care 2002;25:2165–71.