



Depression and worry symptoms predict future executive functioning impairment via inflammation

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Original Article

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Abstract

Background. Scar models posit that heightened anxiety and depression can increase the risk for subsequent reduced executive function (EF) through increased inflammation across months. However, the majority of past research on this subject used cross-sectional designs. We therefore examined if elevated generalized anxiety disorder (GAD), major depressive disorder (MDD), and panic disorder (PD) symptoms forecasted lower EF after 20 months through heightened inflammation.

Methods. Community-dwelling adults partook in this study ($n = 614$; $M_{AGE} = 51.80$ years, 50% females). Time 1 (T1) symptom severity (Composite International Diagnostic Interview – Short Form), T2 (2 months after T1) inflammation serum levels (C-reactive protein, fibrinogen, interleukin-6), and T3 (20 months after T1) EF (Brief Test of Adult Cognition by Telephone) were assessed. Structural equation mediation modeling was performed.

Results. Greater T1 MDD and GAD (but not PD) severity predicted increased T2 inflammation (Cohen's $d = 0.21$ – 1.92). Moreover, heightened T2 inflammation forecasted lower T3 EF ($d = -1.98$ to -1.87). T2 inflammation explained 25–32% of the negative relations between T1 MDD or GAD and T3 EF. T1 GAD severity predicting T3 EF via T2 inflammation path was stronger among younger (*v.* older) adults. Direct effects of T1 MDD, GAD, and PD forecasting decreased T3 EF were found ($d = -2.02$ to -1.92). Results remained when controlling for socio-demographic, physical health, and lifestyle factors.

Conclusions. Inflammation can function as a mechanism of the T1 MDD or GAD–T3 EF associations. Interventions that successfully treat depression, anxiety, and inflammation-linked disorders may avert EF decrements.

Executive function (EF) refers to a set of intricate, higher-order, and multi-domain cognitive control systems integral for directing myriad behavioral and cognitive processes (Goldstein & Naglieri, 2014). We depend on our EF domains such as working memory (WM; ability to retain and alter data in real-time) and inhibition (capacity to refrain from autopilot tendencies). EF capacities also help us to effectively plan, attain goals, regulate emotions, make decisions, and resolve conflicts. Relatedly, EF deficits have been associated with problems in school and work performance, social relationships, and mental health in daily life (Alvarez & Emory, 2006; Follmer, 2018; Snyder, Miyake, & Hankin, 2015; Zainal & Newman, 2018). Thus, understanding the factors related to future EF impairment is important.

Allostatic load presents as a key risk factor for subsequent EF decrements. Such allostatic load is defined as the long-term accumulation of chronic, stress-induced, wear-and-tear of the hypothalamic-pituitary-adrenal (HPA) axis and associated physiological systems (McEwen & Gianaros, 2011). It has also been defined as increased blood serum pro-inflammatory cytokines, such as C-reactive protein (CRP), fibrinogen, and interleukin-6 (IL-6) (Hostinar, Lachman, Mroczek, Seeman, & Miller, 2015). IL-6 is a proinflammatory cytokine produced by T-cells, non-immune cells, and unique white blood cells (Hartman & Frishman, 2014). It catalyzes the creation of CRP and fibrinogen (acute-phase inflammatory assays concentrated in the liver and associated organs). CRP denotes complex proteins generated by advanced cancer, bodily infection, injury, or trauma (McEwen, 2007). Fibrinogen is a glycoprotein that produces the fibrin enzyme in the liver and is involved in platelet aggregation, such that undue levels of fibrinogen indicate vascular endothelium abnormalities (Petersen, Ryu, & Akassoglou, 2018).

Scar theories propose that greater depression and anxiety symptoms may forecast subsequent worse EF across prolonged timescales via increased allostatic load (Lupien, McEwen, Gunnar, & Heim, 2009). Specifically, heightened inflammation is considered a ‘physiological scar’ of prior increased mental disorder symptoms due to prolonged HPA dysregulation (e.g. excessive cortisol) (Pariante, 2017). Moreover, scar theories postulate that elevated depression and anxiety can raise subsequent inflammation levels and impair future EF across years by adversely altering WM, learning, and emotion regulation-related brain areas (e.g. prefrontal

cortices, hippocampus, amygdala) (Allott, Fisher, Amminger, Goodall, & Hetrick, 2016; Lucassen et al., 2014). Collectively, scar models theorize that increased depression and anxiety can forecast future elevated inflammation and lower EF across months and years.

Congruent with scar models, diverse studies indicated that greater common psychiatric disorder severity and perseverative cognitions forecasted decline in EF and associated cognitive functioning across years. For example, rise in dispositional negative affect as well as inordinate worry, anxiety, and depression symptoms predicted subsequent decrements in WM, inhibition, processing speed, and episodic memory 3–17 years later in several population-based studies, with small-to-large effect sizes (Bennett & Thomas, 2014; Gimson, Schlosser, Huntley, & Marchant, 2018; Zainal & Newman, *in press*; Zainal & Newman, 2021). Overall, it is plausible that higher major depressive disorder (MDD), generalized anxiety disorder (GAD), and panic disorder (PD) symptoms would precede and relate to lower EF months and years later.

Further supporting scar theories, nine studies evidenced that elevated anxiety and depression were associated with heightened inflammation over several years. Middle-aged adults with greater baseline GAD, PD, and post-traumatic stress disorder severity displayed more growth in high-sensitivity CRP serum levels following 5–16 years (Copeland, Shanahan, Worthman, Angold, & Costello, 2012b; Glaus et al., 2018; Sumner et al., 2017). Likewise, higher depression symptoms coincided with greater upsurge in CRP, fibrinogen, or IL-6 across 2–12 years in ethnic- and age-diverse adult samples (Copeland, Shanahan, Worthman, Angold, & Costello, 2012a; Deverts et al., 2010; Matthews et al., 2007; Niles, Smirnova, Lin, & O'Donovan, 2018; Stewart, Rand, Muldoon, & Kamarck, 2009; Von Känel, Bellingrath, & Kudielka, 2009).

Moreover, at least 18 studies have shown that higher inflammation levels dovetailed with future reduced EF and related cognitive domains. Increased IL-6, CRP, or fibrinogen were independently associated with lower EF, global cognition, language, memory, or spatial reasoning across 3 months and up to 17 years in community-dwelling and patient populations (Gallacher et al., 2010; Krogh et al., 2014; Mooijaart et al., 2013; Weaver et al., 2002; Zheng & Xie, 2018). In a recent meta-analysis, elevated CRP, fibrinogen, and IL-6 were predictive of future major neurocognitive disorder syndromes (e.g. over periods as long as 25 years; Darweesh et al., 2018) across North America, Europe, and Asia.

Therefore, we aimed to determine if increased MDD, GAD, and PD would predict lower subsequent global EF through elevated inflammation. This focus is valuable for a number of reasons. Our longitudinal study can improve understanding of possible causal relations as it extends prior mostly cross-sectional relations among psychopathology, EF, and inflammation (e.g. Renna, O'Toole, Spaeth, Lekander, & Mennin, 2018). Relatedly, we utilized structural equation modeling (SEM) (*v.* manifest regression) methods which reduce measurement unreliability-related error and enhance power (Maslowsky, Jager, & Hemken, 2015). Moreover, the role of CRP, fibrinogen, and IL-6 has been understudied in the connections among inflammation, psychopathology, and EF (Daniels, Olsen, & Tyrka, 2020). Many countries worldwide are currently experiencing public health and economic challenges related to widespread inflammation-linked neuropsychiatric disorders (Prince et al., 2016; Steel et al., 2014). Our efforts may thus inform the creation

and fine-tuning of evidence-based interventions. On the basis of scar theories and data, we predicted that greater MDD, GAD, and PD severity would distinctively forecast increased inflammation after 2 months. Further, we hypothesized that such heightened inflammation would subsequently predict lower latent global EF after 18 months. Also, based on *interactive scar models* (Majd, Saunders, & England, 2020), we investigated if and how age, gender, education, income, physical health, lifestyle, and medication usage factors moderated these mediation models or potentially functioned as notable covariates.

Method

Participants

This secondary analysis used the publicly available Midlife Development in the United States (MIDUS) Refresher datasets with three time-points: 2012 [Time 1 (T1)]; 2012 (T2; 2 months after T1); and 2014 (T3; 20 months after T1 and 18 months after T2) (Ryff & Lachman, 2018; Ryff et al., 2017; Weinstein, Ryff, & Seeman, 2019). At T1, participants ($n = 614$) averaged 51.80 years old (*s.d.* = 13.40, range = 25–76 years). Females comprised 50.33% of the sample, 49.67% had college education, and all of the participants identified as Whites.

Measures

Table 1 displays descriptive statistics and a correlation matrix of the primary variables. The present study selected participants who consented to partake in the face-to-face psychiatric interview, biomarker assay procedures, and behavioral EF tests (Love, Seeman, Weinstein, & Ryff, 2010). At T1, participants' past-year MDD, GAD, and PD symptoms were evaluated. At T2, participants' inflammation levels were assessed. At T3, a behavioral EF measure was administered. Neither inflammation nor EF was measured at T1.

T1 psychiatric disorder symptom severity

Past-12-month MDD, GAD, and PD severity were measured using the Composite International Diagnostic Interview – Short Form (CIDI-SF) (aligned with the Diagnostic and Statistical Manual – Fourth Edition; DSM-IV) (Abel, 1994; American Psychiatric Association, 1987; Kessler, Andrews, Mroczek, Ustun, & Wittchen, 1998; Wittchen, 1994). To assess MDD severity, respondents disclosed if they encountered depression symptoms in the past year (seven-item; appetite changes, concentration problems, fatigue, loss of interest, low self-worth, sleep issues, suicidality). To evaluate past-year GAD severity, participants reported the extent they faced symptoms intertwined with excessive worries most days (10-item; concentration problems, easily fatigued, difficulty staying asleep, irritability, low energy, keyed up, mind going blank, muscle tension, restlessness, trouble falling asleep). To measure PD severity, participants stated the degree they experienced panic symptoms in the past 12 months (six-item; accelerated heart rate, chest or stomach discomfort, chills or hot flashes, sense of unreality, sweating, trembling or shaking). The CIDI-SF has demonstrated good specificity (93.9–99.8%), sound sensitivity (89.6–96.6%), and high internal consistency ($\alpha = 0.948$ – 0.989 in this study) (Kessler et al., 1998).

Table 1. Descriptive statistics and correlation matrix of main study variables

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Age	-												
2. Female	-.11**	-											
3. T1 MDD SX	-.12**	.11**	-										
4. T1 GAD SX	-.07	.08	.29***	-									
5. T1 PD SX	-.09*	.15***	.32***	.23***	-								
6. T2 VF	-.20***	-.011	-.04	-.06	-.07	-							
7. T2 NS	-.13**	-.16***	-.12**	-.10*	-.12**	.35***	-						
8. T2 BC	-.27***	-.14***	-.08*	-.08*	-.11*	.34***	.44***	-					
9. T2 SGST	.05	-.03	-.08	-.09*	-.05	.13**	.24***	.22***	-				
10. T2 BDS	-.09*	-.10	-.11**	-.09*	-.12**	.22***	.41***	.36***	.23***	-			
11. T3 IL-6	.40***	-.02	.05	.09*	.01	-.24***	-.22***	-.23***	-.04	-.09*	-		
12. T3 CRP	.04	.15***	.14***	.09*	.01	-.14***	-.17***	-.13**	-.08	-.08*	.54***	-	
13. T3 FGN	.25***	.12**	.08*	.031	.05	-.08*	-.13**	-.17***	-.08	-.05	.45***	.51***	-
<i>M</i> or <i>n</i>	51.78	309	0.78	0.16	0.47	21.41	2.80	41.60	0.98	5.21	0.71	0.28	5.81
s.d. or %	13.44	50.33	1.88	0.97	1.24	6.21	1.47	10.84	0.03	1.52	0.53	0.79	0.13
Min	25.00	-	0.00	0.00	0.00	4.00	0.00	8.00	0.93	0.00	0.00	-0.71	5.65
Max	76.00	-	7.00	10.00	6.00	44.00	5.00	90.00	1.00	8.00	1.38	1.36	5.99
Skewness	-0.16	-0.01	2.18	6.84	2.81	0.20	-0.15	0.28	-0.76	0.12	-0.05	0.10	0.08
Kurtosis	-1.02	-2.01	3.13	50.86	7.21	0.02	-1.00	0.35	-1.04	-0.39	-1.51	-1.50	-1.43

M, mean; *n*, number of participants; s.d., standard deviation; Min, minimum; Max, maximum; BC, backward counting; CRP, C-reactive protein; BDS, digit backward span; FGN, fibrinogen; GAD, generalized anxiety disorder; IL-6, interleukin-6; MDD, major depressive disorder; NS, number series; PD, panic disorder; SGST, stop-and-go-switch task mixed task; SX, symptom severity; T1, time 1; T2, time 2; T3, time 3; VF, verbal fluency.

Inflammation serum levels have been log transformed to achieve univariate normal distributions of the data. IL-6 was originally measured in pg/ml, fibrinogen in mg/dl, and CRP in $\mu\text{g/ml}$.

*** $p \leq 0.001$; ** $p \leq 0.01$; * $p \leq 0.05$.

Table 2. Descriptive statistics of potential moderators or covariates

	<i>M</i> or <i>n</i>	s.d. or %	Min	Max	Skewness	Kurtosis
Household income (\$)	88 028.09	67 051.84	0.00	300 000.00	1.14	1.41
Body mass index	28.83	6.96	16.82	66.26	1.43	3.35
Number of chronic illnesses	1.77	1.75	0.00	6.00	0.73	-0.57
Number of prescription medications	2.76	3.55	0.00	21.00	1.68	3.54
Tertiary education (%)	405	65.96	-	-	-0.36	-0.67
Smoker (%)	260	42.35	-	-	0.31	-1.91
Physical exercise (at least 3×/week) (%)	466	75.90	-	-	-1.21	-0.53

M, mean; *n*, number of participants; s.d., standard deviation; Min, minimum; Max, maximum.

T2 pro-inflammatory cytokine assays

Participants fasted overnight before visiting the laboratory for their biomarker assays to be collected following established operating procedures (Love et al., 2010). The biomarker assays were frozen at -60 to -80°C using dry ice while being shipped to the laboratory where they were deposited for batch assessments every month to ensure standardization across multiple data collection locations (Weinstein et al., 2019). Plasma CRP was assessed with a BNII nephelometer harnessing a particle-enhanced immunonephelometric assay (Dade Behring Inc., Deerfield, IL, USA). Blood serum IL-6 was measured using an enzyme-linked immunosorbent assay (Quantikine® High-sensitivity ELISA kit #HS600B; R&D Systems, Minneapolis, MN, USA) (Friedman & Herd, 2010). Plasma fibrinogen antigen was quantified with the BNII nephelometer (N Antiserum to Human Fibrinogen; Siemens, Malvern, PA, USA) by an immunochemical reaction alongside using a tailored and partially automated Clauss method (Clauss, 1957). All inflammation concentration values were computed in duplicate. To ensure all assays fell within normality, any inflammation markers >10 pg/ml were rerun in diluted sera (Morozink, Friedman, Coe, & Ryff, 2010). For all inflammation markers, coefficients of variance within- and across-laboratories were within appropriate bounds (1.08–15.66%) (Weinstein et al., 2019).

T3 global executive functioning

The Brief Test of Adult Cognition by Telephone was administered to assess global EF (Lachman, Agrigoroaei, Tun, & Weaver, 2014). It comprised the following five subtests: (1) Backward Counting (correctly counting as many numbers backwards from 100 within 30 s); (2) Backward Digit Span (reiterating backwards number strings of growing size in the accurate order); (3) Category Verbal Fluency (stating as many distinct food or animals within 60 s); (4) Number Series (detecting a pattern and finishing a digit string with the last number accurately); and (5) Stop-and-Go Switch Task (set-shifting and inhibition assessments that consist of rotating blocks of normal and reverse sets). It has demonstrated strong 4-week retest reliability ($r = 0.82$ – 0.83) (Lachman et al., 2014), alongside excellent discriminant validity (e.g. $rs = 0.16$ – 0.17 with recall tests) and good construct validity (e.g. $rs = 0.41$ – 0.52 with unique EF assessments) (Lachman et al., 2014).

Potential moderators or covariates

The following variables were tested as potential moderators or covariates of our mediation models based on previous research

(Beydoun et al., 2019; Eyre & Baune, 2012; Friedman & Herd, 2010; Spyridaki, Avgoustinaki, & Margioris, 2016): age, gender (female *v.* male), income (i.e. self-reported household total income from pension, social security, wage, and other sources), education status (presence of tertiary education), body mass index (BMI) (kg/m^2), number of past-year chronic health conditions (related to AIDS/HIV, alcohol/drug problem, anxiety/depression, diabetes, dry/sore skin, face rash, gum/mouth, hair loss, hand rash, hemorrhoids, hernia, hypertension, itch, lupus/autoimmune, migraine, neurological disorder, pimples, scaly skin, sleep, stroke, swallowing, sweating, teeth trouble, ulcer, warts), exercise habit (presence of exercise at least 20 min 3 times/week), and medication consumption (i.e. use of antidepressants, anti-hypertensives, anti-platelets, coagulant modifiers, cholesterol medications, coagulant modifiers, gastrointestinal agents, and hormone modifiers) (cf. Table 2 for the descriptive statistics).

Data analyses

Following best practices, the inflammatory markers blood concentration levels were log-transformed (Hostinar et al., 2015). Further, outliers were Winsorized (i.e. anomalous values were replaced with the 99th percentile value of that specific variable) (Liao, Li, & Brooks, 2016). To this end, the descriptive statistics of all EF and inflammation item indicators were within normal limits (skewness = -0.15 to -0.28 ; kurtosis = -1.51 to -0.35).

We conducted confirmatory factor analysis (CFA) and mediation SEM analyses using the *lavaan* R package (Rosseeel, 2012) with *RStudio* (Version 1.3.959). To reduce measurement error and increase power (Tomarken & Waller, 2005), we formed a latent T2 inflammation composite by treating each CRP, fibrinogen, and IL-6 marker as manifest indicators in a CFA, similar to Hostinar et al. (2015). Further, based on a psychometric validation study (Lachman et al., 2014), a latent EF construct was formed. To assess model fit, we used the χ^2 goodness-of-fit statistic alongside the confirmatory fit index (CFI; Bentler, 1990) and root mean square error of approximation (RMSEA; Steiger, 1990). Maximum likelihood with robust standard error estimators was used to accommodate any non-normality in the data (Li, 2016). In addition, we used a product-of-coefficients ($a \times b$) of the indirect effect method. Specifically, we performed mediation analyses for the regression coefficients of T1 MDD, GAD, or PD symptom severity predicting T2 inflammation (a path), and T2 inflammation forecasting T3 EF (b path), over and above the direct effect (c' path; T1 disorder severity–T3 EF relation).

Further, we used bootstrapping with 10 000 resampling draws (Deng, Yang, & Marcoulides, 2018) and reported the unstandardized regression coefficients (β) and 95% confidence intervals (CI). The ratio of the indirect affect ($a \times b$) to the total effect, $c = a \times b + c'$, constitutes the mediation effect size (percentage of variance that the T2 inflammation mediator explained the T1 disorder severity–T3 EF association) (Wen & Fan, 2015).

Following recommendations (Jacobson & Newman, 2014; Maslowsky et al., 2015), we tested whether and how the a , b , and c' paths were moderated by distinct levels across categorical factors (male *v.* female, absence *v.* presence of exercise, smoking status, or specific medication consumption) and by above *v.* below median values of continuous factors (age, BMI, education, income, number of chronic physical conditions). Therefore, we dichotomized continuous factors to allow for tests of group differences in model comparability. Group differences were determined by constraining the a , b , and c' path regression weights to be equal across groups, and by testing any change in the χ^2 goodness-of-fit index. Significant moderation would be denoted by statistically significant change juxtaposing Model 1 (restricted factor loadings and regression weights to equality across groups) to Model 2 (restricted all factor loadings and freed all regression weights across groups). Moreover, we investigated if the pattern of results remained similar after adjusting for these factors as covariates in the model.

Overall, there were 0.45% missing data points, which were managed using full information maximum likelihood (FIML). FIML (*v.* listwise deletion) was a suitable method as our data were missing at random (Graham, 2009) [Little's MCAR test: $\chi^2(60) = 69.16$, $p = 0.19$]. To determine the magnitude of effects, we computed Cohen's d with the formula $d = 2t/\sqrt{df}$ (Dunlap, Cortina, Vaslow, & Burke, 1996; Dunst, Hamby, & Trivette, 2004; Lakens, 2013). Specifically, d values of 0.2, 0.5, and 0.8 denote small, moderate, and large effect sizes, respectively (Cohen, 1988).

Power analyses

We conducted an *a priori* Monte Carlo power analysis (Zhang, 2014) using Mplus Version 7.0 by specifying a conservative estimate of Cohen's $d = 0.15$ for the regression weights of the a , b , and c' paths. We observed 94.6–96.1% power to detect the a , b , and c' paths. Further, there was 82.9% power to identify the indirect mediation path. Thus, our sample size was adequately powered to conduct the mediation analyses.

Results

Measurement model

CFA showed that the separate measurement models had excellent fit for either T1 MDD, GAD, or PD as predictors of T2 inflammation and T3 EF latent composites [$\chi^2(25) = 42.61$ – 48.92 , $p = .003$ – $.015$, CFI = .97–.98, RMSEA = .036–.041]. Statistically significant standardized factor loadings (all $ps < 0.001$) were observed for the indicators of latent T2 inflammation (three-item; $\beta_s = 0.63$ – 0.77) and T3 EF (five-item; $\beta_s = 0.33$ – 0.73).

Mediation models

Tables 3–5 alongside Figs 1–3 present the mediation models for T1 MDD, GAD, and PD severity functioning as predictors, respectively.

Table 3. Mediation model of T1 MDD severity predicting T3 executive function via T2 inflammation

	β (s.e.)
Regression slopes: all samples	
T1 MDD severity \rightarrow T3 executive function	–0.17* (0.09)
T1 MDD severity \rightarrow T2 inflammation	0.03** (0.01)
T2 inflammation \rightarrow T3 executive function	–2.55*** (0.53)
T1 MDD severity \rightarrow T2 inflammation \rightarrow T3 executive function	–0.08** (0.03)

CFI, confirmatory fit index; β , unstandardized regression weight estimate; MDD, major depressive disorder; RMSEA, root mean square error of approximation; s.e., standard error. Model fit indices: $\chi^2(25) = 47.95$, $p = .004$, CFI = .97, RMSEA = .04. *** $p < .001$; ** $p < .01$; * $p < .05$.

T1 MDD predicting T3 EF via T2 inflammation

The mediation model showed good fit [$\chi^2(25) = 47.95$, $p = .004$, CFI = .97, RMSEA = .041]. Regarding the direct effect, higher T1 MDD severity was significantly related to lower T3 EF after 20 months [$\beta = -0.17$, 95% CI (–0.34 to –0.002), $d = -0.79$], with a large effect size. In addition, higher T1 MDD severity substantially predicted greater T2 inflammation 2 months later [$\beta = 0.03$, 95% CI (0.01–0.05), $d = 1.23$], and more T2 inflammation was considerably related to lower T3 EF following 18 months [$\beta = -2.55$, 95% CI (–3.58 to –1.51), $d = -1.92$], with large effect sizes. The T1 MDD severity forecasting T3 EF via T2 inflammation indirect mediation path was also significantly large [$\beta = -0.08$, 95% CI (–0.13 to –0.002), $d = -1.04$]. T2 inflammation explained 30.36% of the T1 MDD severity–T3 EF association variance.

These variables were not significant moderators: age [$\Delta\chi^2(3) = 2.89$, $p = .41$], gender [$\Delta\chi^2(3) = 4.67$, $p = .20$], BMI [$\Delta\chi^2(3) = 4.59$, $p = .20$], number of physical health problems [$\Delta\chi^2(3) = 7.35$, $p = .07$], income [$\Delta\chi^2(3) = 1.90$, $p = .59$], education [$\Delta\chi^2(3) = 1.29$, $p = .73$], smoking status [$\Delta\chi^2(3) = 4.37$, $p = .22$], number of medications used [$\Delta\chi^2(3) = 2.62$, $p = .45$], and physical exercise status [$\Delta\chi^2(3) = 5.06$, $p = .17$]. Further, the mediation effect of T1 MDD severity forecasting reduced T3 EF through T2 inflammation remained statistically significant after adjusting age, gender, BMI, income, education, number of medications consumed, and physical exercise status ($d = -0.92$ to -0.77).¹

T1 GAD predicting T3 EF via T2 inflammation

The mediation model of T1 GAD severity predicting T3 EF via T2 inflammation had good fit [$\chi^2(25) = 46.09$, $p = .006$, CFI = .98, RMSEA = .037]. Greater T1 GAD severity substantially forecasted lower T3 EF [$\beta = -0.33$, 95% CI (–0.54 to –0.11), $d = -1.19$]. Increased T1 GAD severity significantly predicted higher T2 inflammation [$\beta = 0.06$, 95% CI (0.04–0.09), $d = 1.92$], and T2 inflammation substantially forecasted lower T3 EF [$\beta = -2.56$, 95% CI (–3.61 to –1.52), $d = -1.92$]. For the entire sample, T2 inflammation significantly mediated the T1 GAD–T3 EF path [$\beta = -0.16$, 95% CI (–0.25 to –0.07), $d = -1.34$], and accounted for 32.22% of the variance of the T1 GAD–T3 EF relation.

Age moderated this mediation model, which showed acceptable fit [$\chi^2(56) = 97.38$, $p < .001$, CFI = .96, RMSEA = .049]. T1 GAD predicted reduced T3 EF via T2 inflammation significantly more strongly in younger compared to older adults [$\Delta\chi^2(3) = 11.19$, $p = .011$]. Simple slopes analyses showed that for younger adults, higher T1 GAD predicted lower T3 EF [$\beta = -0.59$, 95%

Table 4. Mediation model of T1 GAD severity predicting T3 executive function via T2 inflammation

	β (s.e.)
Regression slopes: younger adults	
T1 GAD severity → T3 executive function	-0.54*** (0.17)
T1 GAD severity → T2 inflammation	0.09*** (0.02)
T2 inflammation → T3 executive function	-2.19*** (0.65)
T1 GAD severity → T2 inflammation → T3 executive function	-0.19** (0.07)
Regression slopes: older adults	
T1 GAD severity → T3 executive function	-0.09 (0.14)
T1 GAD severity → T2 inflammation	0.02 (0.02)
T2 inflammation → T3 executive function	-1.96* (0.77)
T1 GAD severity → T2 inflammation → T3 executive function	-0.04 (0.04)

CFI, confirmatory fit index; β , unstandardized regression weight estimate; GAD, generalized anxiety disorder; RMSEA, root mean square error of approximation; s.e., standard error. Model fit indices: $\chi^2(56) = 97.38$, $p = 0.001$, CFI = 0.96, RMSEA = 0.049. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

Table 5. Mediation model of T1 PD severity predicting T3 executive function via T2 inflammation

	β (s.e.)
Regression slopes: all samples	
T1 PD severity → T3 executive function	-0.39** (0.15)
T1 PD severity → T2 inflammation	0.01 (0.02)
T2 inflammation → T3 executive function	-2.65*** (0.53)
T1 PD severity → T2 inflammation → T3 executive function	-0.02 (0.04)

CFI, confirmatory fit index; β , unstandardized regression weight estimate; PD, panic disorder; RMSEA, root mean square error of approximation; s.e., standard error. Model fit indices: $\chi^2(25) = 42.44$, $p = .016$, CFI = .98, RMSEA = .036. *** $p < 0.001$; ** $p < 0.01$.

CI (-0.92 to -0.25), $d = -0.92$]. Further, among younger adults, greater T1 GAD severity substantially predicted higher T2 inflammation level [$\beta = 0.09$, 95% CI (0.05–0.12), $d = 1.25$], and heightened T2 inflammation considerably forecasted decreased T3 EF [$\beta = -2.19$, 95% CI (-3.47 to -0.90), $d = -0.73$]. Further, the mediation path was significant for younger adults [$\beta = -0.19$, 95% CI (-0.33 to -0.05), $d = -0.73$], such that T2 inflammation accounted for 24.48% of the T1 GAD–T3 EF relation. On the other hand, in older adults, no direct effect was observed [$\beta = -0.09$, 95% CI (-0.33 to 0.16), $d = -0.18$]. Further, among older adults, T1 GAD severity did not predict T2 inflammation [$\beta = 0.02$, 95% CI (-0.02 to 0.06), $d = 0.30$], but greater T2 inflammation level significantly forecasted lower T3 EF [$\beta = -1.88$, 95% CI (-3.41 to -0.35), $d = -0.64$]. For older adults, the path of T1 GAD predicting T3 EF through T2 inflammation was not significant [$\beta = -0.04$, 95% CI (-0.11 to 0.04), $d = -0.27$].

No other moderator effects were observed as follows: gender [$\Delta\chi^2(3) = 4.30$, $p = .23$], BMI [$\Delta\chi^2(3) = 0.28$, $p = .96$], number of physical health problems [$\Delta\chi^2(3) = 1.09$, $p = .78$], income [$\Delta\chi^2(3) = 0.19$, $p = .98$], education [$\Delta\chi^2(3) = 3.27$, $p = .35$], smoking status [$\Delta\chi^2(3) = 1.45$, $p = .70$], number of medications used

[$\Delta\chi^2(3) = 3.84$, $p = .28$], and physical exercise status [$\Delta\chi^2(3) = 7.80$, $p = .06$]. In addition, the mediation path of T1 GAD severity predicting lower T3 EF through T2 inflammation stayed statistically significant after controlling for age, gender, BMI, number of physical health problems, income, education level, smoking status, number of medications consumed, and physical exercise status ($d = -1.19$ to -0.91).

T1 PD predicting T3 EF via T2 inflammation

The mediation model displayed good fit [$\chi^2(25) = 42.44$, $p = .016$, CFI = 0.98, RMSEA = .036]. Higher T1 PD severity significantly predicted lower T3 EF [direct effect: $\beta = -0.39$, 95% CI (-0.64 to -0.09), $d = -1.07$]. T1 PD severity was not significantly related to T2 inflammation [$\beta = 0.01$, 95% CI (-0.02 to 0.04), $d = 0.21$], but T2 inflammation level significantly forecasted reduced T3 EF [$\beta = -2.65$, 95% CI (-3.68 to -1.62), $d = -2.02$]. T2 inflammation did not substantially mediate the path of T1 PD predicting T3 EF [$\beta = -0.02$, 95% CI (-0.10 to 0.06), $d = -0.21$].

None of the following moderators emerged as significant: age [$\Delta\chi^2(3) = 1.69$, $p = .64$], gender [$\Delta\chi^2(3) = 3.07$, $p = .38$], BMI [$\Delta\chi^2(3) = 0.81$, $p = .85$], number of physical health problems [$\Delta\chi^2(3) = 4.80$, $p = .19$], income [$\Delta\chi^2(3) = 1.25$, $p = .74$], education [$\Delta\chi^2(3) = 0.29$, $p = .96$], smoking status [$\Delta\chi^2(3) = 2.25$, $p = .52$], number of medications used [$\Delta\chi^2(3) = 2.02$, $p = .57$], and physical exercise status [$\Delta\chi^2(3) = 2.89$, $p = .41$]. Moreover, the mediation path of T1 PD symptoms forecasting T3 EF via T2 inflammation remained statistically non-significant after adjusting for age, gender, BMI, number of physical health problems, income, education, smoking status, number of medications consumed, and physical exercise status ($d = -0.22$ to -0.19).

Discussion

Offering partial support for scar theories, these novel results indicated that heightened inflammation may be a mechanism by which greater MDD and GAD (but not PD) symptom severity results in decreased EF after 20 months. Therefore, increased MDD and GAD severity may render mid-life adults susceptible to higher CRP, fibrinogen, and IL-6 levels 2 months later, and elevated systemic inflammation thereby forecasted reduced EF following 18 months (explaining 25–32% of the T1 MDD–T3 EF and T1 GAD–T3 EF 20-month dimensional relations). Further, the effect of T1 GAD severity negatively predicting T3 EF via T2 inflammation was stronger among younger adults relative to their older counterparts. Despite the fact that it has been often postulated that higher MDD and GAD symptoms would predict subsequent lower EF through inflammation over months and years (e.g. 3–18 years) (e.g., Zainal & Newman, 2021), to our awareness, this is the first study to empirically evaluate that notion. We provide a number of possible theoretical explanations for these findings.

The observation that pathological worry was related to lower T3 EF via increased inflammation more strongly among younger than older adults is counter-intuitive. This is in light of the reality that older adults are more at risk of persistent health issues and accumulate greater inflammation serum levels (Brüünsgaard & Pedersen, 2003). However, this counter-instinctual result may be partly explained by the fact that people tend to select mood-uplifting social situations as well as savor and recall positive memories as they age (Carstensen et al., 2011).

Further, greater initial MDD and GAD (but not PD) severity forecasted higher future CRP, fibrinogen, and IL-6 levels for the

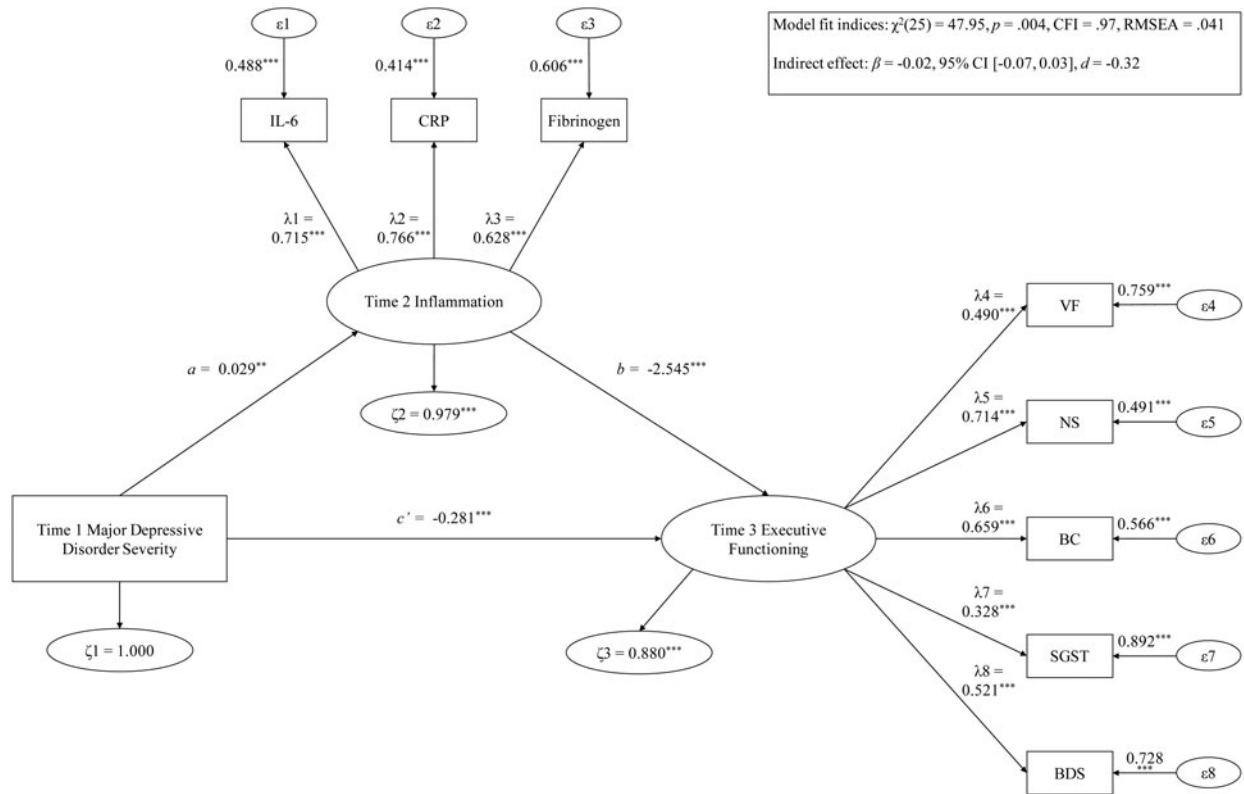


Fig. 1. Hypothesis 1 examining T1 MDD severity predicting T3 EF via T2 inflammation.

Note: *** $p < .001$; ** $p < .01$; * $p < .05$. λ , factor loading; ϵ , item error variance; ζ , residual error variance; BC, backward counting; BDS, digit backward span; CFI, confirmatory fit index; CRP, C-reactive protein; d = Cohen's d effect size; IL-6, interleukin-6; RMSEA, root mean square error of approximation; SGST, stop-and-go-switch task mixed task; SX, symptom severity; T1, time 1; T2, time 2; T3, time 3; VF, verbal fluency.

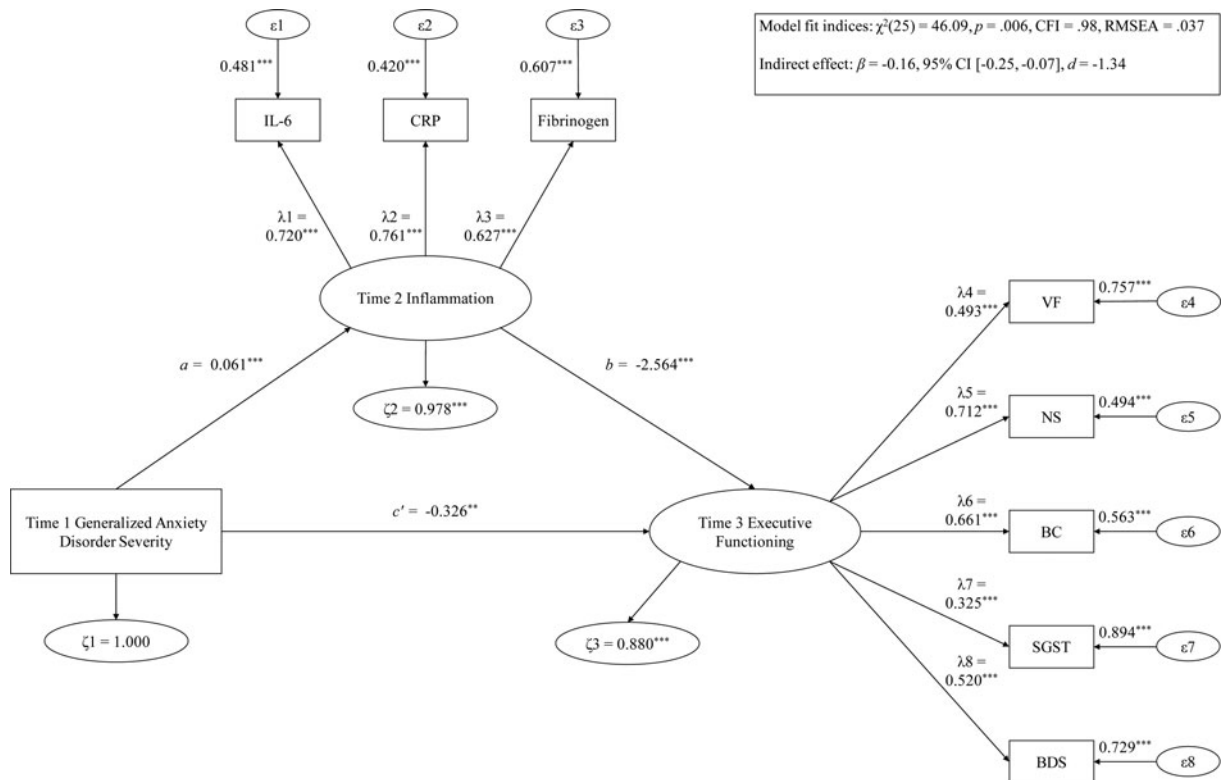


Fig. 2. Hypothesis 1 examining T1 GAD severity predicting T3 EF via T2 inflammation.

Note: *** $p < .001$; ** $p < .01$; * $p < .05$. λ , factor loading; ϵ , item error variance; ζ , residual error variance; BC, backward counting; BDS, digit backward span; CFI, confirmatory fit index; CRP, C-reactive protein; FGN, fibrinogen; IL-6, interleukin-6; NS, number series; RMSEA, root mean square error of approximation; SGST, stop-and-go-switch task mixed task; T1, time 1; T2, time 2; T3, time 3; VF, verbal fluency.

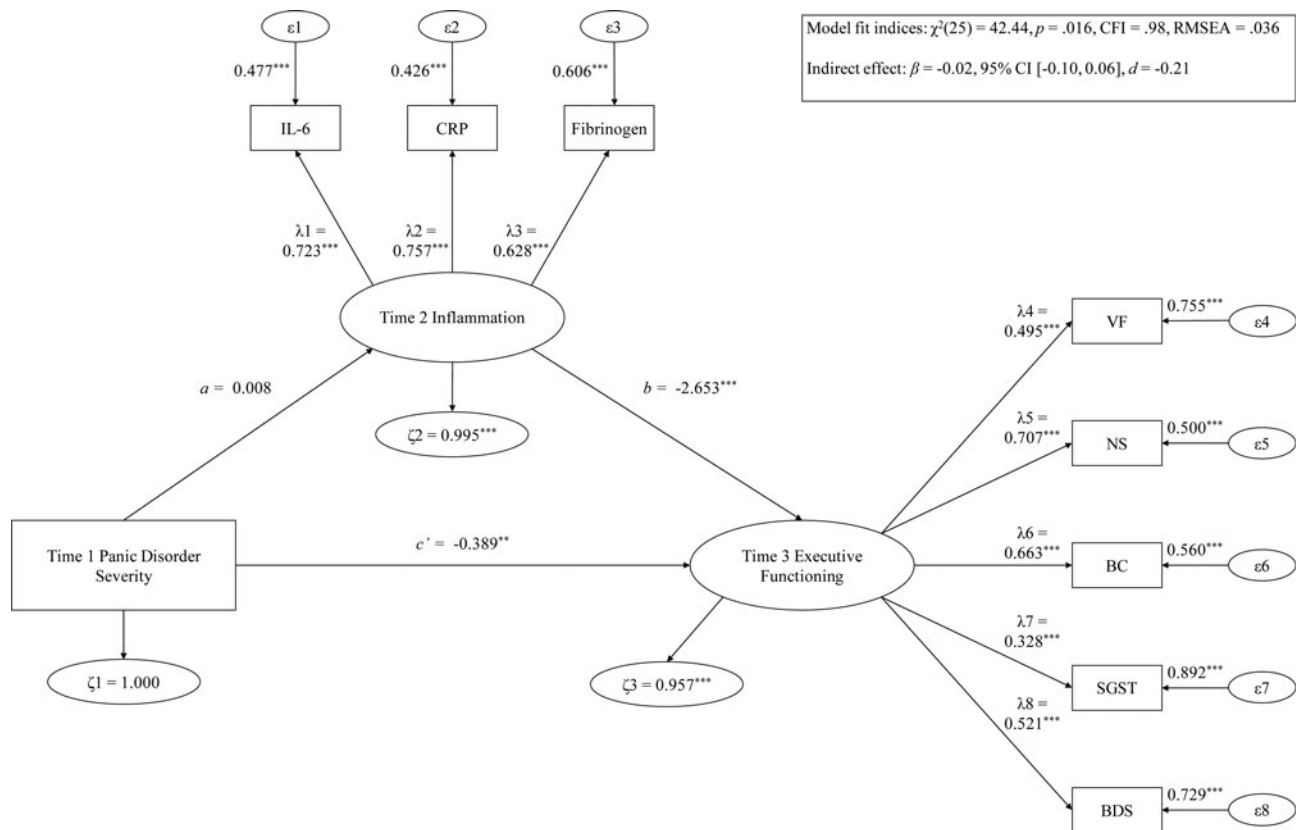


Fig. 3. Hypothesis 1 examining T1 PD severity predicting T3 EF via T2 inflammation.

Note: *** $p < .001$; ** $p < .01$; * $p < .05$. λ , factor loading; ϵ , item error variance; ζ , residual error variance; BC, backward counting; BDS, digit backward span; CFI, confirmatory fit index; CRP, C-reactive protein; FGN, fibrinogen; IL-6, interleukin-6; NS, number series; RMSEA, root mean square error of approximation; SGST, stop-and-go-switch task mixed task; T1, time 1; T2, time 2; T3, time 3; VF, verbal fluency.

entire sample. Findings concur with the fact that elevated depression, GAD, and post-traumatic stress disorder were related to subsequent increased inflammation 3–31 years later among young, mid-life, and older community adults in the United States (Copeland et al., 2012a, 2012b; Niles et al., 2018), Finland (Liukkonen et al., 2006, 2011), and Switzerland (Glaus et al., 2018; Wagner et al., 2015). Persons with GAD and MDD could be vulnerable to increased inflammation buildup across years due to habitual repetitive negative thinking that could prolong stress reactivity alongside ‘wear-and-tear’ of the HPA and sympathetic nervous systems (cf. *perseverative cognition theory*; Ottaviani et al., 2016). This notion has been supported by prior studies (e.g. Moriarity et al., 2020). Relatedly, poor lifestyle choices related to MDD and GAD (e.g. unhealthy sleep, dietary, and nutrition patterns) may dysregulate the HPA by prompting an intrinsic inflammatory reaction, reflected by a rise in CRP, fibrinogen, IL-6, and other assays (e.g. IL-1 β , tumor necrosis factor) across months (Furtado & Katzman, 2015). Future cross-panel longitudinal studies can test these conjectures.

Notably, heightened inflammation consistently predicted future reduced EF. This result extends numerous single-session experiments which showed that inducing inflammation could adversely affect future performance-based EF (Bollen, Trick, Llewellyn, & Dickens, 2017). Conceivably, greater CRP, fibrinogen, and IL-6 levels may lead to harmful neurological changes in EF and learning-related brain regions across long durations (cf. *neurological scar theories*). For instance, increased CRP and IL-6 have been linked to decreased cerebral blood flow in the

prefrontal cortex, anterior cingulate cortex, and medial temporal lobe 5 years later (Warren et al., 2018). Moreover, accrual of systemic inflammation could negatively change activity in the locus coeruleus norepinephrine system entwined with EF by increasing cellular oxidative stress (Balter et al., 2019). Relatedly, elevated inflammation may have over time altered the kynurenine brain pathway that creates quinolinic acid (a noxious metabolite), alongside adversely affecting dopamine, glutamate, and serotonin pathways implicated in anxiety, motivation, attentional control, and EF (Mac Giollabhui et al., 2020; Miller & Raison, 2016). Thus, incorporating MRI, inflammation, and behavioral EF measures to evaluate these hypotheses appears to be a worthwhile avenue for future prospective research.

Additionally, direct effects were found, wherein elevated MDD, GAD, and PD predicted reduced EF following 20 months. Also, increased T1 GAD forecasted lower T3 EF more strongly among younger than older adults. Findings contribute to an important knowledge gap on psychopathology–EF associations considering the dearth of prospective studies on this subject (Snyder et al., 2015, p. 328). Further, the results suggest that pathological worry and depressed mood may trigger processes that lead to long-term brain dysfunction (Bosaipo, Foss, Young, & Juruena, 2017; Zainal & Newman, *in press*). It would be fruitful for subsequent investigations to continue to evaluate cognitive scar hypotheses.

Some shortcomings of this study deserve mention. First, we cannot draw causal inferences from this naturalistic study. Second, we were unable to test the *vulnerability theory* (i.e.

increased inflammation and EF deficits may prognosticate future greater MDD, GAD, and PD symptoms) as inflammation and EF were not measured at baseline. The relations among common psychiatric symptoms, inflammation, and EF have been found to be bi-directional and intricate (Majd et al., 2020; Zainal & Newman, 2018), and thus merit further attention. Relatedly, we cannot draw any definitive conclusions on whether inflammation increased from baseline and led to any of our findings because inflammation was not assessed initially or before symptom data were collected. Further, our findings may be explained by unmeasured third variables (e.g. genetics; Averill et al., 2019) that warrant consideration. Also, as the psychiatric symptom assessments in this study were aligned with the DSM-III-R, future studies should evaluate our propositions with DSM-5-derived measures. Additionally, considering the all-White sample herein and evidence that inflammation levels can differ among ethnicities (Zahodne, Kraal, Zaheed, Farris, & Sol, 2019), it would be valuable for succeeding investigations to test these hypotheses in culturally-diverse samples.

If future studies were to replicate the pattern of results herein, some clinical implications justify attention. It is tenable that effectively treating MDD, GAD, and PD in younger, mid-life, and older adults may decrease the odds of subsequent elevated inflammation and EF decrements. Empirical data that cognitive-behavioral skills and lifestyle-enhancing interventions can remarkably reduce widespread psychiatric disorder symptoms and inflammation as well as improve EF and related cognitive capacities (Zainal & Newman, 2020). Further, attempts to better understand the effectiveness of pharmacological therapies, their interaction with inflammation (Strawbridge et al., 2015), alongside the anxiolytic and anti-depressant effects of vitamin supplementation (Su et al., 2018) have been ensuing. These efforts, especially with the use of gold-standard randomized controlled trials, merit sustained consideration due to their prospect to *personalize* therapies for anxiety and depressive disorders.

Data

This secondary analysis used the publicly available MIDUS Refresher datasets with three time-points: 2012 [Time 1 (T1)]; 2012 [Time 2 (T2) – 2 months after T1]; and 2014 [Time 3 (T3) – 20 months after T1 and 18 months after T2] (Ryff & Lachman, 2018; Ryff et al., 2017; Weinstein et al., 2019). This study was exempted from IRB approval as it used a publicly available dataset that can be obtained from the following online data repository: <https://www.icpsr.umich.edu/web/NACDA/studies/36901>. The authors are willing to provide R syntax and output files of the analyses conducted in this study upon request.

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Conflict of interest. None.

Ethical standards. This study was conducted in compliance with the American Psychological Association (APA) ethical standards in the treatment of human participants and approved by the institutional review board (IRB).

Informed consent was obtained from participants as per IRB requirements at Harvard University, Georgetown University, University of California at Los Angeles, and University of Wisconsin. Since this study used a publicly available dataset, it was exempt from IRB approval.

Note

1 When testing covariates for models examining MDD, GAD, and PD as unique predictors, we used separate models for each covariate because adding all potential covariates or only those significantly related with T3 EF outcome to one model severely degraded model fit.

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