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# Investigating whether a combination of higher CRP and depression is differentially associated with worse executive functioning in a cohort of 43,896 adults

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## ABSTRACT

Many depressed individuals experience difficulties in executive functioning that contribute substantially to functional impairment. It is unknown whether a subtype of depression characterized by chronic inflammation is differentially associated with worse executive functioning. This study examined whether the combination of depression and higher C reactive protein (CRP) is differentially associated with worse executive functioning and whether this association is stronger in older adults. This cross-sectional study analyzed data collected from a population-representative sample of 43,896 adults aged 44.13 years ( $SD = 13.52$ ) who participated in the baseline assessment of the Lifelines cohort study. Multivariate regression models tested whether depressed individuals (established via structured interview) exhibiting higher levels of inflammation (indexed via high-sensitivity CRP assay following an overnight fast) performed worse on a behavioral test of executive functioning. Depression ( $B = -3.66$ , 95% CI:  $-4.82, -2.49$ ,  $p < .001$ ) and higher log-transformed CRP ( $B = -0.67$ , 95% CI:  $-0.87, -0.47$ ,  $p < .001$ ) were associated with worse executive functioning, after adjustment for age, sex, educational attainment, body mass index, smoking status, exposure to stressful life events and chronic stressors, sedentary behavior, and number of chronic medical conditions. Depressed individuals with higher log-transformed CRP exhibited differentially poorer executive functioning ( $B = -1.09$ , 95% CI:  $-2.07, -0.11$ ,  $p < .001$ ). This association did not differ based on age ( $B = 0.01$ , 95% CI:  $-0.08, 0.10$ ,  $p = .82$ ). Executive functioning is poorer in depressed individuals with higher CRP, even in early adulthood. Interventions that reduce inflammation may improve cognitive functioning in depression.

## 1. Introduction

Depression is characterized by an early onset, recurrent course, and high prevalence – all factors contributing to its severe disease burden (Erskine et al., 2015; Burcusa and Iacono, 2007; Kessler et al., 2003). Although the cardinal symptoms of depression are low mood and anhedonia (American Psychiatric Association, 2013), it is typically accompanied by a wide range of symptoms, including cognitive dysfunction. In fact, 227 unique symptom profiles exist by which an individual meets criteria for a depression diagnosis (Zimmerman et al., 2015) and this heterogeneous presentation suggests that multiple subtypes of depression may exist that are characterized by distinct etiologies, risk factors, and disrupted neurobiological systems (Kunugi et al.,

2015). There is considerable evidence that one depressive subtype may be characterized by a dysregulated immune system (Maes et al., 1992; Smith, 1991).

The immune system's rapid and non-specific response to antigens (innate immune system) and the slower, antibody-generating, specific response (adaptive immune system) are dysregulated in depression (Irwin and Miller, 2007). Research has predominantly focused on the role of the innate immune system in depression because it is known to induce "sickness behaviors" (e.g., anhedonia, fatigue) reminiscent of depression (Dantzer et al., 2008), although there is growing appreciation that multiple inflammatory subtypes may exist (Lynall et al., 2020). Activation of the innate immune response, whether through administration of a potent inflammatory cytokine (interferon- $\alpha$ ), a purified

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endotoxin, or vaccination, reliably induce depression (Dantzer et al., 2008; Schedlowski et al., 2014). Further, depressed individuals exhibit higher inflammatory biomarkers that index activation of the innate immune system, such as interleukin-6 (IL-6) and C-reactive protein (CRP) (Dowlati et al., 2010) and both IL-6 and CRP prospectively predict future depressive symptoms in observational studies (although the reverse also is observed) (Mac Giollabhui et al., 2020). A subgroup of depressed individuals (25–30%) display higher inflammatory biomarkers and, additionally, respond to medication designed to dampen inflammatory activity (Raison and Miller, 2011; Osimo et al., 2019). These studies provide compelling evidence that an inflammatory subtype of depression exists.

A subset of depressed individuals also exhibit cognitive dysfunction (particularly in episodic memory, attention, and executive functions) (Rock et al., 2014) which is observable at first onset of depression (Lee et al., 2012; Ahern and Semkowska, 2017), when depression is in remission (Rock et al., 2014; Semkowska et al., 2019), and is more severe following repeated depressive episodes (Hammar and Ardal, 2009). In addition, cognitive dysfunction in late-onset depression is associated with more pronounced deficits in verbal memory, processing speed, and executive functioning when compared to early onset depression (Haselbalch et al., 2011). The underlying mechanism(s) by which cognitive functioning is disrupted in depression is unknown; however, inflammation has been hypothesized to play a causal role (Carvalho et al., 2014). Chronic inflammation disrupts neuronal processes (e.g., synaptic plasticity/neurogenesis) and affects brain regions and their respective cognitive associates (e.g., hippocampus: episodic memory; dorsolateral prefrontal cortex/anterior cingulate cortex: executive function) – thereby linking inflammation with abnormal brain structure and function associated with both depression and cognitive dysfunction (Carvalho et al., 2014; McAfoose and Baune, 2009). Inflammation is associated with impaired cognition in medical disorders (Crisan et al., 2014; Huang et al., 2016; Li et al., 2014) and in population-based samples (Noble et al., 2010; Baune et al., 2008; Reichenberg et al., 2001; Singh-Manoux et al., 2014). It also is associated with worse cognitive functioning (primarily psychomotor speed/executive functioning) in depressed groups and non-depressed controls (Krogh et al., 2014; Chang et al., 2012; Goldsmith et al., 2016; Grassi-Oliveira et al., 2011) as well as in community samples of both depressed and non-depressed youth/youth with more or less severe depressive symptoms (Cullen et al., 2017; Mac Giollabhui et al., 2020). However, despite this evidence, results typically involve small, clinical samples of depressed adults and rarely included a wide age range.

Older depressed individuals with heightened inflammation may experience worse deficits in cognitive functioning. Although the prevalence of depression is lower in older adults, its occurrence is still common (Hasin et al., 2018) and older individuals are at greater risk of experiencing repeated depressive episodes across the lifespan, which is associated with lower hippocampal and prefrontal cortex volumes (Videbech and Ravnkilde, 2004; Sexton et al., 2013; Treadway et al., 2015) as well as worse episodic memory, processing speed, and executive functioning (Talarowska et al., 2015). Moreover, many older individuals experience “inflammaging”, a process characterized by higher, basal levels of circulating inflammatory cytokines (Franceschi et al., 2000), which in turn is associated with cognitive impairment and dementia in older individuals (Gorelick, 2010). Indeed, the association of CRP with future depressive symptoms is stronger in older samples (Mac Giollabhui et al., 2020). Together these findings suggest that the relationship between depression, inflammation and cognitive functioning may become stronger with age, but no study has investigated this across the lifespan.

As there is strong evidence that i) a subset of depressed individuals exhibit higher inflammatory biomarkers, ii) a subset of depressed individuals exhibit cognitive dysfunction, and iii) higher inflammatory biomarkers are associated with worse cognitive functioning, the current study examines whether it is the depressed individuals who exhibit

higher values on an inflammatory biomarker (CRP) that perform worse on a test of executive functioning, above and beyond individuals with either depression or higher CRP alone. Moreover, the study will examine whether these associations become stronger in older adults, given the increase in depression, cognitive dysfunction, and ‘inflammaging’ later in life. Data were drawn from the first wave of a prospective, population-based, Dutch, cohort study of 152,728 adults. We tested whether individuals with higher CRP and a current depression diagnosis (major depression or dysthymia assessed via a structured diagnostic interview) performed worse on a behavioral measure of executive functioning when controlling for important confounds, such as sex, adiposity, stress, and substance use. Specifically, we hypothesized that:

### 1.1. Hypothesis one

Depressed individuals who exhibit higher CRP values will perform worse on a test of executive functioning than individuals with either current depression or higher CRP alone, after adjustment for relevant covariates.

### 1.2. Hypothesis two

Older individuals who meet criteria for depression and exhibit higher CRP values will perform worse on a test of executive functioning than individuals who are younger, meet criteria for depression, or exhibit higher CRP alone, after adjustment for relevant covariates.

## 2. Materials and methods

### 2.1. Participants

Lifelines is a multidisciplinary, prospective, population-based cohort study examining in a unique three-generation design the health and health-related behaviors of 167,729 persons living in the 3 northern provinces of The Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical and psychological factors that contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics; data for the current study were drawn from 152,728 adults aged 18–93 years. Between 2006 and 2013, 167,729 participants living in the three northern provinces of The Netherlands (Friesland, Groningen and Drenthe) were recruited for a baseline assessment through the practices of the general practitioner (GP), of whom 152,728 were aged 18 years or older. All inhabitants in The Netherlands are registered with a general practitioner and 73% of invited GPs ( $n = 562/812$ ) agreed to take part. Initially, GP practices invited patients aged between 25 and 50 years to participate, unless the participating GP considered the patient ineligible based on severe psychiatric or physical illness, limited life expectancy (<5 years), or insufficient knowledge of the Dutch language to complete a Dutch questionnaire. From 333,307 potential participants who were contacted via mail, 81,652 completed a consent form. Following consent, participants received a baseline questionnaire as well as an invitation to complete a comprehensive health assessment at a Lifelines research site. Subsequently, participants were asked to indicate whether their family members (e.g., partners, parents, parents-in-law, children etc.) would be willing to participate in the study. An additional 64,489 participants (38%) were recruited via participating family members and a final 21,588 participants (13%) self-registered on the Lifelines website. Further information on study design, recruitment, and participants has been published (Scholtens et al., 2014).

From the 152,728 adults assessed at baseline, the current study utilized data from a sub-set of individuals who had completed a behavioral assessment of executive functioning ( $n = 87,567$ ; 57.34%), a diagnostic interview assessing mental health ( $n = 146,614$ ; 96.00%), and who had completed a blood draw ( $n = 56,849$ ; 37.22%). From the 47,017

individuals who had data on all three measures, we excluded a further 3,121 (6.63%) individuals who reported a medical diagnosis (it should be noted that certain individuals possessed comorbid conditions) characterized by (i) chronic alterations in immune functioning (Diabetes: 1,924; Rheumatoid Arthritis 2; Crohn's Disease: 134; Blood Clotting Disorder: 254; Multiple Sclerosis: 100), (ii) cognitive dysfunction (Epilepsy: 535; Stroke: 254; Dementia: 3; Schizophrenia: 40), or disrupted hepatic functioning (Hepatitis: 469; Liver Cirrhosis: 33) so that we could exclude the possibility that observed associations were attributable to individuals with these chronic conditions or that changes in CRP values or cognitive functioning were attributable primarily to underlying medical/psychiatric/neurological conditions. Exclusion criteria were broadly based on published recommendations (Ligthart et al., 1984; O'Connor et al., 2009). From the remaining 43,896 participants, a small number of individuals had missing data on specific variables (e.g., educational attainment was missing in 505 individuals) and the minimum  $N$  for primary analyses was 42,222. Missing data analyses are presented in detail as [Supplementary Information](#) and meaningful differences were not observed, although statistically significant differences were observed when comparing the analytic sample with the excluded sample. Within the analytic sample, 17,482 individuals were not related to other participants, 4,704 had one other relative included in the study, 1,772 had two or more relatives included, 809 had four or more relatives included, 408 had five or more relatives included, 229 had six or more relatives included, 148 had seven or more relatives included, and the remaining 3% had eight or more relatives included in the study.

## 2.2. Measures

### 2.2.1. Depressive disorder

The Mini International Neuropsychiatric Interview (MINI) is a brief structured interview designed to screen for anxiety and depressive disorders (Sheehan et al., 1998). Lifelines used an adapted version of a Dutch translation of the MINI that was administered by trained interviewers – details on the version used in Lifelines has been previously published (Wanders et al., 2016). Participants were considered to meet criteria for a depressive disorder if they met DSM-IV criteria for major depression or dysthymia at the time of the interview: namely endorsing at least five of nine depressive symptoms, with at least one symptoms consisting of sadness or anhedonia, over the last two weeks. Impairment was assessed in the MINI for dysthymia but not depression and consequently, impairment was not used as a criterion for major depression. The MINI has demonstrable reliability and validity (Lecrubier et al., 1997).

### 2.2.2. Executive functioning

The Ruff Figural Fluency Test (RFFT) is a reliable and valid (Ross, 2014) executive functioning measure that primarily assesses figural fluency, although performance also is likely reliant on other executive functions (Ruff et al., 1987). Respondents are asked to draw as many unique designs as possible within 60 seconds by connecting dots in different patterns. Dots are presented in an array of five-dot patterns arranged in five columns and seven rows; the arrangement of five-dot patterns dots is the same on each array. Participants complete five trials, with each trial either using different distractors or different patterns. The total number of unique designs was used as the dependent variable in the analyses, in line with previous Lifeline studies (Gulpers et al., 2018). In Lifelines, the RFFT was administered to all participants until April 2012, and subsequently in a random half of the sample. Data from participants who failed to generate a single unique design per trial ( $n = 181$ ) were removed.

### 2.2.3. C-reactive protein

Blood samples were obtained from participants before 10AM via venipuncture following an overnight fast. Complete details on blood specimen data collection are outlined in a methodological paper

describing the Lifelines Cohort (Scholtens et al., 2014). C-reactive protein was quantified using three separate methods over the course of baseline assessment [(84.58% of total CRP values; assessed in serum; CardioPhase hsCRP, Siemens Healthcare Diagnostics, Marburg, Germany), (12.90% of total CRP values; assessed in plasma; CardioPhase hsCRP, Siemens Healthcare Diagnostics, Marburg, Germany), and (2.52% of total CRP values; assessed in plasma; CRPL3, Roche Diagnostics, Mannheim, Germany)]. Assay method 2 and 3 were identical and only differed in terms of the manufacturer. A conversion formula ( $\text{new} = 0.92 \times \text{old} - 0.01$ ) was derived from an internal validation study using 39 samples, according to the AMC (alternative method comparison, Deming Regression) protocol in order that Method 1 could be compared with Method 2 and 3. For CardioPhase hsCRP, the intra-assay coefficient of variability was 3.45% and the inter-assay coefficient of variability was 3.15%. For CRPL3, the intra-assay coefficient of variability was 4.15% and the inter-assay coefficient of variability was 5.8%.

### 2.2.4. Covariates

Age, sex, and educational attainment were reported by participants. Educational attainment was determined using a single-item question and categorized as: 'low' [no education, primary education, lower/preparatory vocational education, lower general secondary education (leaving secondary school aged < 16 years)], 'moderate' (intermediate vocational education/apprenticeship, higher secondary education), and 'high' (higher vocational education, university).

Height was measured to the closest 0.1 cm and body weight was measured without shoes to 0.1 kg precision to estimate body mass index (BMI). Smokers were identified as individuals who have smoked over the last month. The List of Threatening Experiences (LTE) assesses (Yes/No) whether participants have experienced 12 major categories of stressful life events (Brugha and Cragg, 1990). The Long-term Difficulties Inventory (LDI) is a self-report questionnaire assessing chronic stress and evaluates whether individuals experience aspects of life (e.g., finances/social relationships) with difficulty/stress using a three-point scale (not stressful/slightly stressful/very stressful) (Hendriks et al., 1990). Sedentary behavior was estimated as the average number of minutes spent watching television, with impossible values (i.e., >1,440 min,  $n = 36$ ) removed. A composite measure was created counting the number of chronic medical conditions participants reported. Participants reported by questionnaire whether they were diagnosed with any of the following conditions: cardiovascular disease ( $n = 3495$ ; e.g., aortic aneurysm, arrhythmia, heart attack), chronic obstructive pulmonary disease ( $n = 2255$ ), asthma ( $n = 3635$ ), fibromyalgia ( $n = 1$ ), or irritable bowel syndrome ( $n = 4134$ ). Of 43,896 participants, 8823 individuals reported having one condition, 1858 endorsed two conditions, and 315 endorsed three or more conditions with 30 individuals reporting four conditions and three individuals reported five conditions; due to the small number of individuals with more than three conditions, this variable was scored as: no conditions, one condition, two conditions, or three or more conditions.

## 2.3. Analyses

Analyses were conducted in R 3.5.2 (Team RC, 2018). Multivariable regression models were estimated using 'lmer4' (Bates et al., 1406) and graphed using 'ggplot2' (Wickham, 2016). CRP was log-transformed to impose a normal distribution and continuous predictor variables were mean-centered. Four iterative models were tested: Model 1 included depression diagnosis, CRP and demographic variables; Model 2 included Model 1 variables and added health-related variables; Model 3 added an interaction term (depression diagnosis  $\times$  log-transformed CRP) to the variables included in Model 2. This model tested hypothesis 1 that, after adjustment for known relevant covariates (incorporated in models 1 and 2), the combination of being depressed and high CRP values would be associated with poorer executive functioning than their separate associations. In model 4, we also included a three-way interaction term (in

addition to lower-order interaction terms) to test whether a potential interaction of depression diagnosis and log-transformed CRP differed by age. This model tested that the hypothesized association of hypothesis 1 would be stronger in older than younger respondent. CRP values >10 mg/L were retained in analyses because there is accumulating evidence that 10 mg/L is not a sensitive cut-off of acute illness or injury (Mac Giollabhui et al., 2020); however, sensitivity analyses evaluated whether removing these values substantially influenced results. Results were replicated (i) when missing data for covariates were imputed using the ‘mice’ package (Sv et al., 2010:) and (ii) including individuals with medical/psychiatric conditions that were removed from the analytic sample. Full details on the multiple imputation methodology are outlined in the ‘mice’ package documentation (Sv et al., 2010). Random intercept hierarchical linear modelling was additionally performed using the ‘lmer’ package to estimate whether parameters changed when clusters of observation were nested within families (e.g., children, parents, grandparents, sons, siblings, grandparents, aunts, uncles, cousins, etc.). The threshold for statistical significance was set so alpha is equal to 0.05 and hypothesis tests were two-sided. Unstandardized beta coefficients were reported given that the metric of the dependent variable is inherently meaningful and intuitive.

### 3. Results

The characteristics of the sample are described in Table 1. Due to the large sample size, almost all correlations between the study variables meet the criteria for statistical significance (Table 2). Notably, poorer executive functioning was associated with depression and higher CRP values. Lower levels of education were more substantially associated with poorer executive functioning, as were older age, more chronic stress, and higher levels of sedentary behaviors. Depression was most substantially associated with experience of stressful life events and chronic stress. Higher CRP values were most substantially associated with lower educational attainment, being female, higher levels of sedentary behavior, and depression.

#### 3.1. Regression analyses

Multivariable regression analysis (Table 3) indicated that depression and higher CRP values were both associated with worse executive functioning when controlling for demographic characteristics (Model 1) and health-related variables (Model 2). The magnitude of the

**Table 1**  
Sample characteristics.

Measures	Analytic Sample (n = 43,896)
Age [Mean (SD)]	44.13 (13.52)
Sex (% Female)	58%
Education [N (%)]	
Lower	13,406 (31%)
Moderate	17,296 (40%)
Higher	12,666 (29%)
RFFT (Unique designs) [N (SD)]	81.81 (26.04)
Depression diagnosis, Major Depression/Dysthymia, Current	3%
C-reactive protein (mg/L), [Median (Interquartile range); Mean (SD)]	1.2 (0.60, 2.80); 2.58 (4.70)
Body mass index [Mean (SD)]	26.11 (4.55)
Stressful life events (LTE) [Mean (SD)]	1.03 (1.27)
Chronic stress (LDI) [Mean (SD)]	2.45 (2.50)
Sedentary behavior [minutes spent watching television; Mean (SD)]	145.1 (87.58)
Chronic medical conditions [Mean (SD)]	0.30 (0.48)

Lower = no education, primary education, lower/preparatory vocational education, lower general secondary education; Moderate = intermediate vocational education/apprenticeship, higher secondary education; Higher = higher vocational education, university.

association was modest for both variables. In Model 3, depression interacted with CRP such that individuals with a depression diagnosis and higher CRP exhibited worse executive functioning, although again the magnitude of the association was modest – see Fig. 1 for a visual depiction and see Supplementary Table 1 for standardized coefficients. Testing of simple slopes was conducted in order to probe and report the magnitude of the difference between the depressed and non-depressed participants at different levels of CRP (-1 SD CRP = -2.11,  $t(42196) = -2.3, p = .02$ ; Mean CRP = -3.45,  $t(42196) = -5.7, p < .001$ ; +1 SD CRP = -4.79,  $t(42196) = -6.1, p < .001$ ; +2 SD CRP = -6.14,  $t(42196) = -4.8, p < .001$ ) – note that due to a floor (not detectable CRP values, values were not observed at 2 standard deviations below the mean). In an additional model that included a three-way interaction term (depression diagnosis × CRP × age, in addition to all relevant lower-order interactions), no interaction terms other than depression by CRP was significant. In sensitivity analyses where CRP values ≥ 10 mg/L were excluded, results were comparable and the only notable difference was a small increase in the size of the interaction term ( $B = -1.80, SE = 0.58$ ). No notable differences were observed when missing covariate data were handled using multivariate imputation for chained equations nor when individuals with medical/psychiatric conditions who were excluded from primary analyses were included in the analytic sample. In a random intercept hierarchical linear model when family membership is modelled as a random effect, no substantial differences in any of the parameter estimates were observed – see Supplementary Table 2 for complete information on parameter estimates.

### 4. Discussion

This is the first study to investigate whether the combination of depression and higher C reactive protein is differentially associated with worse executive functioning across the lifespan. Based on a Dutch, population-representative sample of 43,896 people, not only was depression and higher CRP values associated with worse executive functioning, but those with depression and higher CRP values performed differentially worse, although the size of the cumulative association was small. Importantly, in this sample of adults aged 18–93 years, and therefore representing a broad spectrum of the human lifespan, there was no evidence that the cumulative association of depression and CRP on executive functioning was stronger later in life. These associations were independent of a broad range of demographic and health-related factors associated with depression, CRP, and executive functioning, and importantly, could be observed in the general population, as opposed to clinical studies which constitute the majority of previous studies.

This is the first study to demonstrate that depressed individuals with higher CRP performed worse on a behavioral assessment of executive functioning compared to those who were either depressed or exhibited higher CRP alone. These findings agree with prior clinical (Krogh et al., 2014; Chang et al., 2012; Goldsmith et al., 2016; Grassi-Oliveira et al., 2011) and population-based studies (Zheng and Xie, 2018) reporting that higher inflammatory biomarkers are associated with worse cognitive functioning in depressed individuals and in non-depressed controls or population-based samples. However, it goes further to suggest that the combination of depression and higher CRP amplify this deleterious association. These results cannot speak to whether cognitive deficits are generalized in nature or driven by deficits in specific cognitive functions, such as psychomotor speed (Mac Giollabhui et al., 2020; Miller and Raison, 2016). However, it should be noted that the magnitude of the cumulative association was very small and should be considered alongside more substantial associations of demographic and somatic health-related variables. When considered as a whole, these results suggest that inflammatory processes are implicated in cognitive dysfunction in depression, but the relationship is unlikely to be unique to depression and further that other pathways exist that lead from depression to cognitive dysfunction.

**Table 2**  
Bivariate correlations of study variables for 42,396 participants.

Measure	2	3	4	5	6	7	8	9	10	11	12
1. Executive functioning (RFFT)	-.04 <sup>a</sup>	-.07 <sup>a</sup>	.36 <sup>a</sup>	-.32 <sup>a</sup>	.03 <sup>a</sup>	-.05 <sup>a</sup>	.12 <sup>a</sup>	-.16 <sup>a</sup>	-.06 <sup>a</sup>	-.10 <sup>a</sup>	-.02 <sup>a</sup>
2. Depression diagnosis	-	.04 <sup>a</sup>	-.07 <sup>a</sup>	-.02 <sup>a</sup>	.04 <sup>a</sup>	.16 <sup>a</sup>	.24 <sup>a</sup>	.06 <sup>a</sup>	.08 <sup>a</sup>	.04 <sup>a</sup>	.07 <sup>a</sup>
3. C-reactive protein (log-transformed)	-	-	-.10 <sup>a</sup>	.01 <sup>b</sup>	.14 <sup>a</sup>	.05 <sup>a</sup>	.02 <sup>a</sup>	.12 <sup>a</sup>	.06 <sup>a</sup>	.36 <sup>a</sup>	.07 <sup>a</sup>
4. Educational attainment	-	-	-	-.23 <sup>a</sup>	-.02 <sup>a</sup>	-.08 <sup>a</sup>	.10 <sup>a</sup>	-.25 <sup>a</sup>	-.05 <sup>a</sup>	-.15 <sup>a</sup>	-.11 <sup>a</sup>
5. Age	-	-	-	-	-.03 <sup>a</sup>	0.01	-.25 <sup>a</sup>	.13 <sup>a</sup>	.07 <sup>a</sup>	.16 <sup>a</sup>	-.12 <sup>a</sup>
6. Sex	-	-	-	-	-	.02 <sup>a</sup>	.10 <sup>a</sup>	.03 <sup>a</sup>	.07 <sup>a</sup>	-.07 <sup>a</sup>	-.04 <sup>a</sup>
7. Stressful life events (LTE)	-	-	-	-	-	-	.33 <sup>a</sup>	.08 <sup>a</sup>	.10 <sup>a</sup>	.06 <sup>a</sup>	.10 <sup>a</sup>
8. Chronic stress (LDI)	-	-	-	-	-	-	-	-.04 <sup>a</sup>	.12 <sup>a</sup>	0.00	.09 <sup>a</sup>
9. Sedentary behavior	-	-	-	-	-	-	-	-	.06 <sup>a</sup>	.16 <sup>a</sup>	.08 <sup>a</sup>
10. Chronic medical conditions	-	-	-	-	-	-	-	-	-	.06 <sup>a</sup>	.01 <sup>c</sup>
11. Body mass index	-	-	-	-	-	-	-	-	-	-	-.03 <sup>a</sup>
12. Smoking Status	-	-	-	-	-	-	-	-	-	-	-

Probability <sup>a</sup> =  $P < .001$ ; <sup>b</sup> =  $P = .005$ ; <sup>c</sup> =  $P = .01$ ; RFFT = Ruff Figural Fluency Test; LTE = List of Threatening Experiences; LDI = Long-term Difficulties Inventory.

**Table 3**  
Regression models reporting unstandardized coefficients standard errors, and confidence intervals predicting executive functioning estimated using the Ruff Figural Fluency Test (RFFT).

Predictor Variables	Dependent variable: Ruff Figural Fluency Test (RFFT)					
	Model 1		Model 2		Model 3	
	Unstandardized beta coefficient (standard error)	95% Confidence Interval	Unstandardized beta coefficient (standard error)	95% Confidence Interval	Unstandardized beta coefficient (standard error)	95% Confidence Interval
Depression Diagnosis	-3.50(0.56) <sup>a</sup>	-4.59, -2.38	-3.70(0.59) <sup>a</sup>	-4.83, -2.50	-3.40(0.60) <sup>a</sup>	-4.63, -2.27
C-reactive protein (log-transformed)	-0.78(0.09) <sup>a</sup>	-0.97, -0.60	-0.67(0.10) <sup>a</sup>	-0.83, -0.43	-0.63(0.10) <sup>a</sup>	-0.83, -0.43
Age	-0.47(0.01) <sup>a</sup>	-0.48, -0.45	-0.44(0.01) <sup>a</sup>	-0.46, -0.42	-0.44(0.01) <sup>a</sup>	-0.46, -0.42
Sex (Female)	1.70(0.20) <sup>a</sup>	1.29, 2.09	1.62(0.21) <sup>a</sup>	1.22, 2.04	1.60(0.21) <sup>a</sup>	1.22, 2.04
Education attainment (Reference = Low)						
Moderate	8.50(0.25) <sup>a</sup>	8.01, 8.98	7.90(0.25) <sup>a</sup>	7.39, 8.37	7.90(0.25) <sup>a</sup>	7.39, 8.37
High	18.00(0.26) <sup>a</sup>	17.05, 18.09	16.00(0.28) <sup>a</sup>	15.92, 17.01	16.00(0.28) <sup>a</sup>	15.92, 17.01
Body mass index			0.02(0.03)	-0.03, 0.08	0.03(0.03)	-0.03, 0.08
Stressful life events			-0.43(0.09) <sup>a</sup>	-0.60, -0.26	-0.43(0.09) <sup>a</sup>	-0.60, -0.26
Chronic stress			0.46(0.05) <sup>a</sup>	0.37, 0.56	0.46(0.05) <sup>a</sup>	0.37, 0.56
Sedentary behavior			-0.015(0.001) <sup>a</sup>	-0.017, -0.012	-0.015(0.001) <sup>a</sup>	-0.017, -0.012
Smoking status			-0.34(0.25)	-0.83, 0.14	-0.34(0.25)	-0.83, 0.14
Health-related medical conditions			-0.95(0.18) <sup>a</sup>	-1.30, -0.61	-0.95(0.18) <sup>a</sup>	-1.30, -0.61
Interaction (Depression diagnosis × C-reactive protein)					-1.10(0.50) <sup>b</sup>	-2.08, -0.12
Intercept	73.00(0.22) <sup>a</sup>	72.50, 73.38	74.00(0.24) <sup>a</sup>	73.19, 74.15	74.00(0.24) <sup>a</sup>	73.19, 74.15

Probability: <sup>a</sup> =  $P < .001$ ; <sup>b</sup> =  $P = 0.03$ .

There is compelling evidence that cognitive deficits are more pronounced in late-onset depression (Hasselbalch et al., 2011) and inflammatory biomarkers also are associated with cognitive dysfunction in middle-aged and elderly samples, although there is substantial variability in the magnitude of observed associations and in the domains of cognitive impairment (Noble et al., 2010; Jenny et al., 2012; Teunissen et al., 2003). The predominance of studies investigating inflammation in older samples reflects interest in the role of ‘inflammageing’ in senescence (Franceschi et al., 2000). Surprisingly, this study did not find evidence that the combination of depression and higher CRP were differentially associated with worse executive dysfunction later in life. Instead, these results contribute to a growing body of research suggesting that both depression (Ahern and Semkowska, 2017; Mac Giollabhui et al., 2019) and inflammatory biomarkers (Mac Giollabhui et al., 2020) are linked with worse cognitive functioning across the lifespan. Indeed, in a study of adolescents, BMI was prospectively associated with increases in depressive symptoms and decreases in executive functioning, with the association of BMI and executive functioning mediated by an inflammatory cytokine (interleukin-6) (Mac Giollabhui et al., 2020). Further work is needed to characterize the pathways leading from activated inflammatory physiology to cognitive dysfunction in depression. Whereas a common genetic liability for adiposity and higher inflammatory biomarkers may lead to cognitive dysfunction and

depression for some, for others it may be health-related factors associated with low socioeconomic status (e.g., poor diet) that leads to adiposity and higher inflammatory biomarkers (Muscatell et al., 2018). In other cases, it is likely that behaviors (e.g., sedentary behaviors, poor diet) that follow depression lead to a pro-inflammatory state, and resultant cognitive dysfunction (Berk et al., 2013). Indeed, each of these explanations are probably partially true, which may account for the bidirectional association of depression and inflammatory biomarkers reporting by Mac Giollabhui et al. (2020) in their comprehensive meta-analysis. Thus, it is likely that different mechanisms are at play in different individuals linking depression, inflammation and cognitive dysfunction, and importantly, only a subgroup of depressed individuals (approximately 25–30%) exhibit increased levels of inflammation, which likely contributes to discrepant findings (Osimo et al., 2019).

Depression and inflammation were both associated with worse executive functioning; however, the magnitude of the associations were small, and although this is generally characteristic of effect sizes in psychological science (Button et al., 2013), results should be considered within a broader context. To provide a helpful point of reference for readers, normative data from a Dutch adult sample suggest that performance on the RFFT declines steadily from early adulthood onwards and that five years of aging is associated with a performance decline of 4–4.5 designs generated on the RFFT (Izaks et al., 2011). The

## Executive Functioning by CRP and Depression Status

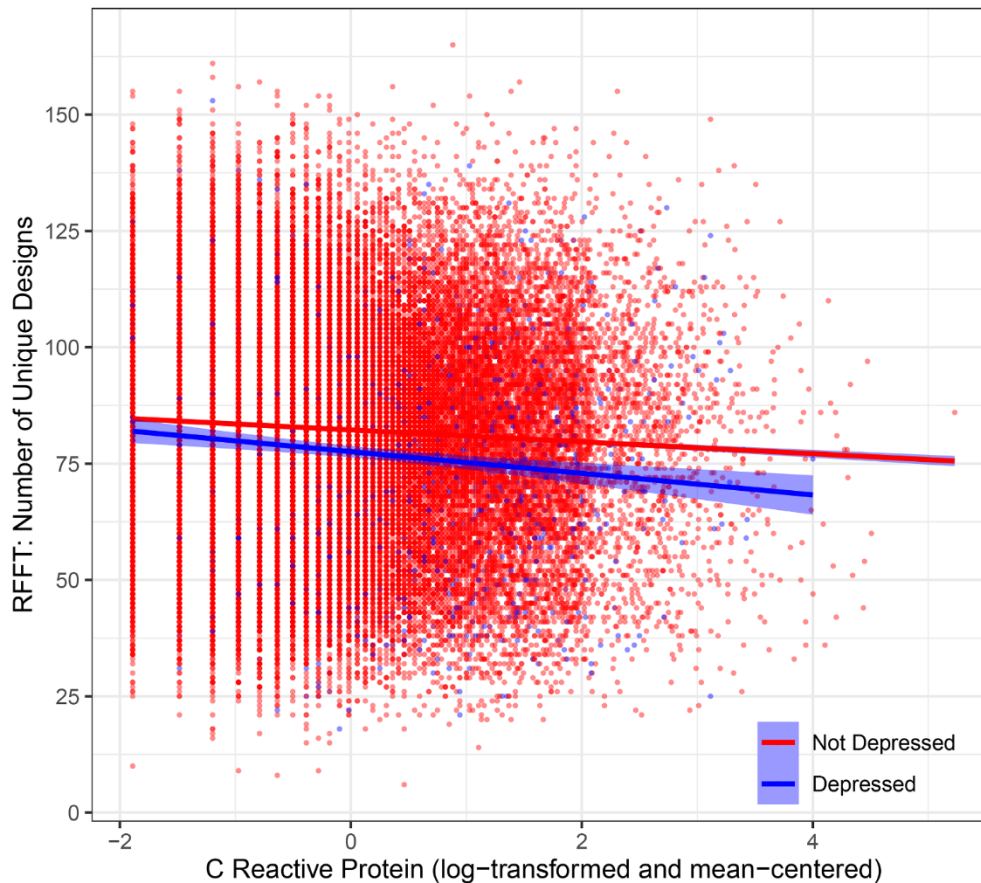


Fig. 1. Interaction of depression status and log-transformed C-reactive protein predicting executive functioning.

associations of depression (3.7), inflammation (0.7 per *SD* increase in CRP), and their combination (depressed individuals with CRP values at the mean/+1 *SD*/+2 *SD*) generated, respectively, 3.5, 4.8, and 6.1 fewer designs. Therefore, the strength of the association of these factors with executive functioning was modest in size, particularly when compared to the associations of educational level, aging and sedentary behavior with executive functioning.

Nonetheless, readers should consider the degree to which depression can lead to worse cognitive functioning via stress generation, sedentary behavior, and even worse educational attainment (Hammen, 1991; Dalsgaard et al., 2020). Similarly caution should be exercised in the case of CRP because, for instance, there is considerable overlap between CRP and BMI – in fact, it is estimated that adipose tissue is responsible for 30% of circulating interleukin-6 (a pro-inflammatory cytokine that directly stimulates CRP production and plays a critical role in activation of the innate immune system) (Mohamed-Ali et al., 1997). Indeed, there is evidence of a common genetic liability for adiposity, increased inflammatory biomarkers, and depression (Khandaker et al., 2019; Milaneschi et al., 2017). Consequently, caution should be exercised when interpreting the association of depression independent of chronic stress, or of CRP independent of BMI. Moreover, there is a growing need to characterize the temporal sequence and causal relationships between overlapping constructs, such as: diet, stress, sedentary behaviors, adiposity, inflammatory biomarkers, and depression (Michigan et al., 2011; Minihane et al., 2015; Mac Giollabhui, 2021).

This study possesses notable strengths as well as limitations. Although CRP is a crude measure of inflammatory physiology (Del Giudice and Gangestad, 2018), it is a widely used and reliable. Moreover, the precision of our estimate was improved through assessment in

fasting participants within a similar window of time (before 10AM). Utilizing a very large, population-representative sample increases power and generalizability; however, a cross-sectional study design precludes causal inference. Nonetheless, despite the cross-sectional nature of these data, we believe that examining the relationship between depression, inflammation, and cognitive functioning in a population-representative sample that uses reliable and well-validated measures is important, given the dearth of high-quality data examining this question. Importantly, Lifelines recruited a substantial proportion of northern Netherlands (10%) and implemented a recruitment strategy designed to incorporate multiple generations of the same family. As such, over 67% of participants in Lifelines have at least one family member enrolled in the study and the assumption that all observations are independent consequently has been violated, which reduces confidence in the parameters estimated because contributory factors have not been modelled (e.g., genetic commonalities, living in same home, etc.). Finally, although we used a reliable and valid measure of executive functioning, it is possible that differences in executive functioning actually reflect generalized cognitive dysfunction, rather than specific difficulties in executive functioning.

This paper showed that low-grade inflammation and depression are both independently associated with worse executive functioning and their combination exerts a small cumulative increase in the strength of the association. There is urgent need for stronger theory describing the role that inflammatory processes play in the etiology of cognitive dysfunction in depression and for well-powered, prospective studies in youth to establish the causal relationships between related risk factors, such as poor diet, adiposity, and stress so that we can better understand and maintain brain health at a population level.

## Declaration of Competing Interest

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

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bbi.2021.05.022>.

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