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Inflammation, depression, and anxiety disorder: A population-based study examining the association between Interleukin-6 and the experiencing of depressive and anxiety symptoms

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ABSTRACT

The uncovering of a positive association between inflammatory cytokine levels – Interkleukin-6 (IL-6) in particular – and the experiencing of depressive and anxiety symptoms is one of the most promising and enthusiastically-discussed finding in recent years. Despite considerable ambiguity in the directionality and underpinnings of this association, anti-inflammatory drugs are already being tested on mental health patients who present no physical symptoms of inflammation, risking potential adverse side effects. Researchers have thus urgently called for more rigorous empirical elucidations of this association. Based on a large, longitudinal, nationally representative sample of middle-aged adults in the United States (N = 1255), IL-6 was observed to be significantly associated with one's present experiencing of depressive and anxiety symptoms. However, IL-6 was predictive of only prospective depressive (not anxiety) symptoms measured six years later, and only when baseline number of symptoms was not accounted for. Further, evidence for IL-6's postulated role as being either a biological cause itself (augmenting HPA stress reactivity) or a biological consequence of a psychological cause (psychological stress) for depression and anxiety was not found. These findings underscore the imperativeness of more rigorous studies to be conducted in this area, and caution practitioners against the premature consideration of IL-6 levels in clinical practice.

1. Introduction

The potential role of inflammation in the pathogenesis of mental disorders has garnered substantial interest in recent years from both researchers and practitioners alike. In particular, recent studies have demonstrated a rather consistent correlation between elevated blood-circulating inflammatory cytokines and the presence of depressive and anxiety symptoms (Dantzer, 2012; Dregan et al., 2019; Salim et al., 2012; Yang et al., 2016; Zunszain et al., 2013). However, even though the directionality and underpinnings of this association remain unclear, popular media outlets have begun reporting that inflammatory cytokines may be used as a biological marker of depression and anxiety disorder and that anti-inflammatory drugs may be used in treating such disorders (Abbott, 2018; Azab, 2018; DiSalvo, 2019). Alarmingly, research clinicians have started to administer anti-inflammatory drugs, which carry risks of adverse side effects, to treat depression and anxiety disorder even when patients present no overt, physical symptoms of inflammation; such attempts have yielded equivocal results thus far (Eyre et al., 2015; Köhler et al., 2014; Köhler-Forsberg et al., 2019; Miller and Raison, 2015). Concerned researchers have thus warned against such premature consideration of inflammatory cytokines in clinical practice and called for more rigorous empirical studies to shed more light on this association (Miller and Raison, 2015). Heeding such prudent calls, this paper aims to provide a closer inspection of this association with the use of a large, longitudinal, nationally representative sample.

Inflammation is broadly defined as an immune response involving the induction of intracellular and extracellular inflammatory cytokines that mediate cellular damage; the primary target of such a response is typically an invading pathogen, but it can also erroneously target one's own body part as in the case of autoimmunity (Lindholt and Shi, 2006). Chronic autoimmune inflammation plays a central role in the etiology of chronic inflammatory diseases, such as asthma and arthritis, where elevated levels of inflammatory cytokines cause prolonged tissue damage at the affected site (Ballantyne et al., 2007; Furuzawa-Carballeda et al., 2007; Trentham et al., 1977). While mental illnesses are not traditionally deemed to be inflammatory diseases, a rather consistent positive correlation observed between blood-circulating inflammatory cytokine levels and the experiencing of depressive and anxiety symptoms has led researchers to propound that inflammation

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could play an important role in the pathogenesis of depression and anxiety disorder (Salim et al., 2012; Zunszain et al., 2013).

In particular, the inflammatory cytokine interleukin-6 (IL-6) has been consistently observed to be positively associated with increased depressive (Alesci et al., 2005; Yoshimura et al., 2009) and anxiety symptoms experienced (Murphy et al., 2015; O'Donovan et al., 2010). However, researchers are still unclear as to why and how IL-6 is related to the precipitation of such symptoms and the development of depression and anxiety disorder. Some researchers propose that IL-6 is directly involved in the etiology of these disorders, whereby inflammatory responses associated with elevated IL-6 levels trigger increased oxidative stress that influences the brain's functioning and signaling patterns (Krishnadas and Cavanagh, 2012; Lindqvist et al., 2017; Maes, 2008; Salim et al., 2011; Szuster-Ciesielska et al., 2008). Notably, it is posited that this results in the augmentation of the Hypothalamus-Pituitary-Adrenal (HPA) axis, which elevates an individual's stress reactivity and precipitate depressive and anxiety symptoms over time (Maes et al., 1993; Soygur et al., 2007). Others propound that IL-6 is a biological consequence or byproduct of increased psychological stress – the primary cause of these disorders instead; in this view, IL-6 serves merely as an early indicator of depression and anxiety disorder as opposed to being a cause itself (Butterweck et al., 2003; Lutgendorf et al., 1999; Maes et al., 1998). The former suggests both a predictive and causative role of IL-6 whereas the latter suggests only a predictive role of IL-6.

Adding to the ambiguity, most of these studies conducted were correlational and cross-sectional in nature (Dentino et al., 1999; Lutgendorf et al., 1999; Murphy et al., 2015; O'Donovan et al., 2010). This means that the direction of causality cannot be ascertained with confidence to begin with. When both IL-6 and symptoms of depression and anxiety disorder are measured simultaneously at a single time point, it cannot be ruled out if the mental toll from experiencing these symptoms may have resulted in an elevation of IL-6 levels instead, or if an unaccounted third variable may have been driving both the precipitation of depressive and anxiety symptoms as well as a rise in IL-6 levels (Dantzer, 2012). Even among the handful of studies that have adopted a longitudinal design, none has ever endeavored to examine IL-6 in relation to both depressive and anxiety symptoms simultaneously or to directly examine the underpinnings of IL-6's association with the precipitation of these symptoms (Gimeno et al., 2009; Khandaker et al., 2014; Valkanova et al., 2013). This severely precludes us from obtaining a holistic and nuanced understanding of the relationship between IL-6 and these implicated mental disorders that often are comorbid (Gorman, 1996; Hirschfield, 2001).

Addressing these gaps, this present study employs a longitudinal study design to examine IL-6's proposed role as a predictor of the precipitation of depressive and anxiety symptoms. Additionally, in an attempt to disambiguate current competing postulations of IL-6's role as either being a biological cause itself or a biological consequence/by-product of a psychological cause, both cortisol stress reactivity as well as psychological stress levels will be directly assessed in this study. If stress reactivity is found to significantly mediate a relationship between IL-6 and prospective depressive and anxiety symptoms experienced, it would lend support to the notion that IL-6 may be a biological cause of depressive and anxiety symptom precipitation via augmentation of HPA axis. On the other hand, if psychological stress level is found to be a significant predictor of both IL-6 levels and prospective depressive and anxiety symptoms experienced, it would lend support to the notion that IL-6 might be a biological consequence of psychological stress rather than a direct cause of depressive and anxiety symptom precipitation.

2. Methods

2.1. Subjects

Participants consisted of 1255 middle-aged adults who completed the Midlife in the United States II: Biomarker Project, which was conducted between 2004 and 2009 (Ryff et al., 2019a). The sample is a subset of a large-scale longitudinal project from the original MIDUS 1 survey that began in 1995, with 7108 noninstitutionalized adults recruited through random digit sampling from 48 contiguous states. In the Biomarker Project, participants were invited for an overnight hospital stay in one of three general clinical research centers in the United States (University of California, Los Angeles; Georgetown University; and University of Wisconsin-Madison). During which, participants underwent a physical exam that included the collection of a fasting blood sample before breakfast on the second day of their hospital stay. This will be referred to as Time 1 in this paper. A follow-up survey was subsequently, successfully conducted on 945 of these participants between 2013 and 2015 (Ryff et al., 2019b). This will be referred to as Time 2 in this paper. The average number of years elapsed between Time 1 and Time 2 is six years. Those who did not respond in MIDUS 3 as well as 2 participants with mismatching MIDUS family identification number between the waves were excluded from analyses, leaving for a final sample size of 943.

These studies were approved by the University of Wisconsin-Madison, Health Sciences Institutional Review Board. Informed consent was obtained for all participants. The data that support the findings of this study, along with detailed descriptions of the study protocol, are openly available in https://www.icpsr.umich.edu/icpsrweb/NACDA/studies/29282 (MIDUS 2 Biomarker Project) and https://www.icpsr.umich.edu/icpsrweb/NACDA/studies/36346 (MIDUS 3). All relevant descriptive statistics are summarized in Table 1.

2.2. Measures and procedures

2.2.1. Depressive and anxiety symptoms

Depressive symptoms experienced was measured using the World Health Organization composite international diagnostic interview - short form version (CIDI-SF) where participants responded, on a yes-or-no basis, to 7 questions on whether they had experienced thoughts or feelings related to depression during the past twelve months, such as losing of appetite, feeling more tired and low on energy than usual, and thinking a lot about death. All “yes” responses to these questions were then summed. Anxiety symptoms experienced was measured in the same way based on 10 questions, such as whether they were restless due to their worries or whether they had trouble remembering things due to their worries. These questions were constructed in accordance to the definitions and criteria specified in the third edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders as well as the 10th version of the Composite International Diagnostic Interview (Kessler et al., 1999).

2.2.2. Interleukin-6

To assess IL-6 levels, fasting blood samples were collected from each participant and stored in a −60 °C to −80 °C freezer, which were subsequently shipped in a dry ice container to the MIDUS Biocore laboratory. Serum-level IL-6 was measured using the Quantikine® high-sensitivity enzyme-linked immunosorbent assay (ELISA) kit #HS600B (R&D Systems, Minneapolis, MN). The assay range and reference range were 0.156–10 pg/mL and 0.45–9.96 pg/mL respectively. The laboratory inter-assay coefficient of variance was 12.31% and the intra-assay coefficient of variance was 3.25%, which were within an established acceptable range (Desilva et al., 2003).

2.2.3. Stress reactivity

Consistent with past studies, stress reactivity was assessed by subtracting baseline, resting salivary cortisol levels from salivary cortisol levels after engaging in stressful cognitive tasks (Neupert et al., 2006). An established stress reactivity protocol was adopted from (Fuller-Rowell et al., 2013), whereby participants were first allowed to rest for 11 min before a sample of their saliva was obtained (baseline cortisol level). Next, participants engaged in a stressful cognitive task for 6 min,

Table 1
Descriptive statistics.

	Time 1			Time 2		
	n	*M (SD)*	*Range*	*n*	*M (SD)*	*Range*
Demographic						
Age	943	57.18 (10.95)	35–86	943	63.46 (11.08)	43–92
Sex (% of male)	943	44.4%				
Marital Status (% of married)	942	73.20%		943	66.80%	
Citizenship (% US citizen)	943	99.7%				
Education Level	941	7.80 (2.45)	1–12	943	7.80 (2.43)	1–12
Income	907	2.53 (1.12)	1–4	857	2.86 (1.10)	1–4
Personality						
Openness to Experience	936	2.98 (0.52)	1.00–4.00	893	2.95 (0.54)	1.43–4.00
Conscientiousness	940	3.42 (0.44)	1.80–4.00	893	3.42 (0.46)	1.60–4.00
Extraversion	940	3.14 (0.57)	1.20–4.00	893	3.12 (0.56)	1.20–4.00
Agreeableness	940	3.44 (0.50)	1.20–4.00	893	3.43 (0.51)	2.00–4.00
Neuroticism	940	2.03 (0.63)	1.00–4.00	893	2.02 (0.62)	1.00–4.00
Physical Health Status and Medication Use						
Body Mass Index (BMI)	942	29.05 (5.91)	16.49–60.39	871	28.19 (5.96)	16.14–56.82
Blood Pressure (Systolic, mmHg)	942	130.64 (17.64)	83–191		–	
Number of Physical Comorbidities	943	3.89 (2.87)	0–20	894	3.21 (3.03)	0–20
Use of Sedatives (% of yes)	941	3.3%		895	3.0%	
User of Tranquilizers (% of yes)	941	2.7%		895	2.0%	
Use of Stimulants (% of yes)	940	1.0%		893	0.2%	
Use of Anti-Depressants (% of yes)	940	1.5%		894	1.6%	
Use of Oral Anti-Inflammatory Drug (% of yes)	864	45.8%				
Predictor Variables						
Serum Interleukin-6 (IL-6)	934	2.57 (2.34)	0.16–21.68			
Psychological Stress	941	21.42 (6.11)	10–48			
Stress Reactivity	889	1.35 (7.82)	−55.14–40.25			
Criterion Variables						
Number of Depressive Symptoms	943	0.65 (1.78)	0–7	943	0.61 (1.74)	0–7
Number of Anxiety Symptoms	943	0.11 (0.81)	0–10	943	0.12 (0.85)	0–10

Note. Education was assessed on a scale of 1 (No school) to 12 (Ph.D, ED. D, MD, LLB, LLD, JD, or other professional degree).

followed by 6 min of rest. Participants then engaged in another stressful cognitive task for 6 min followed by another 6 min of rest, before a sample of their saliva was collected again (post-stress cortisol level). The stressful cognitive tasks administered were the Morgan And Turner Hewitt (MATH) arithmetic task and the Stroop Color-Word task (order of presentation counterbalanced). A detailed description of the tasks is available at http://www.midus.wisc.edu/midus2/.

Saliva samples were collected via cottons swabs from Salivette®. Participants were instructed to place the cotton swab in their mouth, chew it until saturated with saliva, then put it back in the provided tube and recap it. These samples were stored in a −80 °F freezer and sent to the Technical University of Dresden for cortisol assay by immunochemical luminescence at the end of the session. Two saliva samples were collected from each participant at each phase (baseline and post-cognitive task) and the average between each set of two were taken. One data was dropped from analyses as it was an extreme outlier (more than 3 standard deviations from the mean) that was possibly a result of measurement errors. It had a mean baseline salivary cortisol level of 1889.311 nmol/L and a mean post-cognitive task salivary cortisol level of 480.448 nmol/L, both of which are more than double the normal human range of cortisol levels (Laudat et al., 1988; Ljubijankić et al., 2008). All other data were within expected normal ranges.

2.2.4. Psychological stress

Level of psychological stress experienced was measured using the established 10-item Perceived Stress Scale (PSS; Cohen, 1988; Cohen, Kamarck, & Mermelstein, 1983). On a scale of 1 being *never* to 5 being *very often*, participants were tasked to indicate how often they experienced certain stress-related thoughts or feelings, such as “felt difficulties were piling up so high that you couldn't overcome them” or “found that you could not cope with all the things that you had to do”. Past studies have rigorously evaluated the scale and deemed it to be a valid and reliable measure of psychological stress experienced (Lee, 2012; Roberti et al., 2006).

2.2.5. Covariates

A set of variables were also controlled for due to their potential confounding effects. For demographics, age, sex, marital status, and socioeconomic status (education level and income) were accounted for. Consistent with past studies (Braveman, 2001; Hartanto et al., 2019), income was stratified into quartiles and operationalized as a continuous variable (Q1: less than $16,000; Q2: $17,000–$34,000; Q3: $34,750–$61,250; Q4: more than $62,500). Personality trait was also accounted for due to their established association with depressive and anxiety symptoms (Bolger and Eckenrode, 1991; Lara et al., 1997; Matsudaira and Kitamura, 2006). Personality was assessed under the Big Five framework using participants’ responses to a 25-item adjective-based measure, indicating how much each adjective described themselves on a scale of 1 being *not at all* to 4 being *a lot*. The scale was developed for use in MIDUS through a combination of existing personality inventories and has been validated in a study of 1000 participants (Lachman and Weaver, 1997).

Participants’ physical health status and medication use were also accounted for. Based on the suggestions of past studies (Dregan et al., 2019), BMI, systolic blood pressure, and number of physical comorbidities (e.g., chronic heart disease, cancer, arthritis) were assessed. Additionally, use of medications that may impact either IL-6 levels or depressive/anxiety symptoms experienced were accounted for; this included use of oral anti-inflammatory medications, sedatives, tranquilizers, stimulants, and anti-depressants.

3. Results

All analyses were conducted using Poisson regression, because both dependent variables are count data (Coxe et al., 2009; Hutchinson and Holtman, 2005). The first set of analyses tested whether IL-6 was associated with number of depressive and anxiety symptoms experienced

Table 2
Predicting number of depressive symptoms experienced in Time 1.

	Model 1 *B* (*SE*)	Model 2 *B* (*SE*)	Model 3 *B* (*SE*)
Predictor			
Serum Interleukin-6 (IL-6)	0.07 (0.01)***	0.07 (0.01)***	0.05 (0.01)**
Covariates			
Age		−0.02 (0.004)***	−0.03 (0.01)***
Sex		−0.59 (0.11)***	−0.50 (0.11)***
Marital status		−0.55 (0.09)***	−0.54 (0.09)***
Education Level		−0.07 (0.02)***	−0.07 (0.02)**
Income		0.01 (0.04)	0.12 (0.04)**
Openness to experience		0.39 (0.10)***	0.27 (0.11)*
Conscientiousness		−0.21 (0.10)*	−0.09 (0.11)
Extraversion		−0.40 (0.09)***	−0.46 (0.10)***
Agreeableness		0.29 (0.10)**	0.30 (0.11)**
Neuroticism		1.05 (0.07)***	0.93 (0.08)***
Body Mass Index			0.003 (0.007)
Blood Pressure			0.01 (0.002)**
Number of Physical Comorbidities			0.12 (0.01)***
Use of Sedatives			−0.61 (0.24)*
User of Tranquilizers			0.18 (0.21)
Use of Stimulants			1.20 (0.33)***
Use of Anti-Depressants			0.32 (0.24)
Use of Oral Anti-Inflammatory Drug			−0.03 (0.09)

Note: Sex was dummy coded with "female" as reference. Marital status was dummy coded with "currently unmarried" as reference. Use of medications was dummy coded with "no" as reference.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

Table 3
Predicting number of anxiety symptoms experienced in Time 1.

	Model 1 *B* (*SE*)	Model 2 *B* (*SE*)	Model 3 *B* (*SE*)
Predictor			
Interleukin-6 (IL-6) Level	0.08 (0.03)**	0.09 (0.04)*	0.03 (0.06)
Covariates			
Age		−0.04 (0.01)*	−0.05 (0.02)*
Sex		0.10 (0.31)	0.58 (0.37)
Marital status		−0.41 (0.25)	−1.05 (0.34)**
Education Level		−0.29 (0.05)***	−0.52 (0.09)***
Income		−0.17 (0.13)	0.01 (0.17)
Openness to experience		0.41 (0.30)	0.44 (0.42)
Conscientiousness		0.01 (0.29)	0.46 (0.43)
Extraversion		−1.02 (0.30)**	−1.18 (0.44)*
Agreeableness		0.95 (0.30)**	1.18 (0.39)*
Neuroticism		2.82 (0.24)***	2.89 (0.30)***
Body Mass Index			−0.01 (0.03)
Blood Pressure			−0.01 (0.01)
Number of Physical Comorbidities			0.14 (0.05)**
Use of Sedatives			−1.56 (1.06)
User of Tranquilizers			−0.97 (0.76)
Use of Stimulants			−7.93 (<0.01)
Use of Anti-Depressants			1.65 (0.65)*
Use of Oral Anti-Inflammatory Drug			−0.18 (0.36)

Note: Sex was dummy coded with "female" as reference. Marital status was dummy coded with "currently unmarried" as reference. Use of medications was dummy coded with "no" as reference.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

in Time 1. Number of depressive and anxiety symptoms experienced in Time 1 were separately regressed on IL-6 levels. IL-6 was found to be significantly, positively associated with both depressive symptoms experienced in Time 1, $B = 0.07$, $SE = 0.01$, 95% CI = [.05, 0.10], $p < .001$, and anxiety symptoms experienced in Time 1, $B = 0.08$, $SE = = 0.03$, 95% CI = [.02, 0.14], $p = .006$. As seen in Tables 2 and 3, these results held even when demographics and personality variables (Model 2) as well as physical health and medication use status (Model 3) were controlled; with the exception of the relationship between IL-6 and anxiety symptoms experienced in Time 1, which was rendered non-significant after controlling for physical health and medication use status.

The second set of analyses examined whether IL-6 levels measured in Time 1 significantly predicted number of depressive and anxiety symptoms experienced in Time 2. Number of depressive and anxiety symptoms experienced in Time 2 were separately regressed on IL-6 levels. IL-6 significantly predicted increased depressive symptoms experience in Time 2, $B = 0.05$, $SE = 0.01$, 95% CI = [.03, 0.08], $p < .001$, but was unassociated with anxiety symptoms experienced in Time 2, $B = 0.06$, $SE = 0.03$, 95% CI = [−0.01, 0.12], $p = .082$. Critically, however, as seen in Tables 4 and 5, IL-6 was not a significant predictor of depressive or anxiety symptoms experienced in Time 2 when number of symptoms experienced in Time 1 (i.e., baseline) was controlled (Model 2). These results remained non-significant after additionally controlling for demographics and personality variables (Model 3) as well as physical health and medication use status (Model 4).

The third set of analyses examined stress reactivity as a potential mediator between IL-6 levels at Time 1 and number of depressive and anxiety symptoms experienced in Time 2. A Poisson-based mediation analysis was conducted using Mplus with IL-6 specified as the predictor, stress reactivity as the mediator, and number of depressive symptoms experienced in Time 2 as the outcome variable. As shown in Table 6, IL-6 was found to be significantly, negatively associated with stress reactivity, $B = -0.29$, $SE = 0.11$, 95% CI = [−0.51, −0.07], $p = .010$, but stress reactivity was not, in turn, associated with number of depressive symptoms in Time 2, $B = -0.01$, $SE = 0.01$, 95% CI = [−0.02, 0.01], $p = .331$. Expectedly, this indirect path was found to be non-significant, $B = 0.002$, $SE = 0.002$, 95% CI = [−0.002, 0.01], $p = .363$, and remained so after number of depressive symptoms experienced in Time 1, $B = 0.001$, $SE = 0.002$, 95% CI = [−0.004, 0.01], $p = .780$, demographics and personality variables, $B = -0.002$, $SE = 0.002$, 95% CI = [−0.01, 0.002], $p = .346$, and physical health and medication use status, $B = -0.004$, $SE = 0.003$, 95% CI = [−0.01, 0.002], $p = .197$, were additionally controlled for.

A separate analysis was then conducted with number of anxiety symptoms experienced in Time 2 specified as the outcome variable instead. As shown in Table 7, IL-6 was found to be significantly, negatively associated with stress reactivity, $B = -0.31$, $SE = 0.11$, 95% CI = [−0.53, −0.09], $p = .006$, and stress reactivity, in turn, significantly predicted decreased number of anxiety symptoms experienced in Time 2, $B = -0.07$, $SE = 0.01$, 95% CI = [−0.08, −0.05], $p < .001$. This indirect path was found to be statistically significant, $B = 0.02$, $SE = 0.01$, 95% CI = [.01, 0.04], $p = .010$, and remained so even after controlling for number of anxiety symptoms experienced in Time 1, $B = 0.02$, $SE = 0.01$, 95% CI = [.001, 0.03], $p = .034$. This indirect path, however, was rendered non-significant after demographics and personality variables, $B = 0.01$, $SE = 0.01$, 95% CI = [−0.01, 0.02], $p = .322$, and physical health and medication use status, $B = 0.02$, $SE = 0.01$, 95% CI = [−0.001, 0.04], $p = .059$, were

Table 4
Predicting number of depressive symptoms experienced in Time 2.

	Model 1 *B* (*SE*)	Model 2 *B* (*SE*)	Model 3 *B* (*SE*)	Model 4 *B* (*SE*)
Predictor				
Serum Interleukin-6 (IL-6)	0.05 (0.01)***	0.02 (0.02)	0.02 (0.02)	0.001 (0.02)
Covariates				
Depressive Symptoms (Time 1)		0.32 (0.01)***	0.24 (0.02)***	0.20 (0.02)***
Age			−0.03 (0.01)***	−0.03 (0.01)***
Sex			−0.11 (0.11)	−0.09 (0.11)
Marital status			−0.05 (0.10)	−0.05 (0.10)
Education Level			−0.04 (0.02)*	−0.04 (0.02)
Income			−0.11 (0.04)*	−0.07 (0.05)
Openness to experience			0.21 (0.11)*	0.20 (0.11)
Conscientiousness			−0.16 (0.11)	−0.15 (0.11)
Extraversion			−0.22 (0.10)*	−0.26 (0.11)*
Agreeableness			0.16 (0.11)	0.11 (0.12)
Neuroticism			0.20 (0.08)**	0.15 (0.09)
Body Mass Index				0.02 (0.01)*
Blood Pressure				−0.01 (0.003)*
Number of Physical Comorbidities				0.06 (0.01)***
Use of Sedatives				0.10 (0.22)
User of Tranquilizers				0.65 (0.20)**
Use of Stimulants				0.82 (0.32)*
Use of Anti-Depressants				−0.55 (0.30)
Use of Oral Anti-Inflammatory Drug				0.29 (0.10)**

Note: Sex was dummy coded with "female" as reference. Marital status was dummy coded with "currently unmarried" as reference. Use of medications was dummy coded with "no" as reference.

* $p < .05$.
** $p < .01$.
*** $p < .001$.

additionally controlled for.

The final set of analyses examined psychological stress as a simultaneous predictor of both IL-6 levels in Time 1 and number of depressive and anxiety symptoms experienced in Time 2. A Poisson-based path analysis was conducted using Mplus, with psychological stress specified as a predictor of both IL-6 levels at Time 1 and number of depressive symptoms experienced in Time 2. Psychological stress was not found to be significantly associated with IL-6 levels, $B = 0.001$, $SE = 0.01$, 95% CI = [−0.02, 0.03], $p = .938$, even though psychological stress levels significantly predicted increased number of depressive symptoms experienced in Time 2, $B = 0\ 0.11$, $SE = 0.01$, 95% CI = [.10, 0.13], $p < .001$. These results held even after controlling for

Table 5
Predicting number of anxiety symptoms experienced in Time 2.

	Model 1 *B* (*SE*)	Model 2 *B* (*SE*)	Model 3 *B* (*SE*)	Model 4 *B* (*SE*)
Predictor				
Serum Interleukin-6 (IL-6)	0.06 (0.03)	−0.08 (0.05)	−0.06 (0.05)	−0.07 (0.06)
Covariates				
Anxiety Symptoms (Time 1)		0.57 (0.03)***	0.26 (0.05)***	0.19 (0.06)**
Age			−0.01 (0.01)	−0.02 (0.06)
Sex			−0.54 (0.33)	−0.44 (0.35)
Marital status			−0.35 (0.24)	−0.43 (0.29)
Education Level			−0.16 (0.06)**	−0.11 (0.07)
Income			−0.11 (0.13)	0.01 (0.14)
Openness to experience			0.24 (0.28)	0.09 (0.33)
Conscientiousness			−1.23 (0.27)***	−0.93 (0.32)**
Extraversion			−0.41 (0.28)	−0.24 (0.33)
Agreeableness			1.28 (0.34)***	1.40 (0.42)**
Neuroticism			0.89 (0.21)***	1.05 (0.25)***
Body Mass Index				0.05 (0.02)*
Blood Pressure				−0.003 (0.01)
Number of Physical Comorbidities				0.11 (0.04)**
Use of Sedatives				1.10 (0.48)*
User of Tranquilizers				−0.52 (0.47)
Use of Stimulants				1.83 (0.73)*
Use of Anti-Depressants				1.27 (0.51)*
Use of Oral Anti-Inflammatory Drug				0.61 (0.29)*

Note: Sex was dummy coded with "female" as reference. Marital status was dummy coded with "currently unmarried" as reference. Use of medications was dummy coded with "no" as reference.

* $p < .05$.
** $p < .01$.
*** $p < .001$.

Table 6
Stress reactivity as a mediator between IL-6 and depressive symptoms (Time 2).

Model	*B*	*SE (B)*	95% CI	*p*
Outcome: Stress Reactivity				
IL-6	−0.29	0.11	[−0.51, −0.07]	.010
Outcome: Depressive Symptoms (Time 2)				
IL-6	0.05	0.01	[.02, 0.08]	<.001
Stress Reactivity	−0.01	0.01	[−0.02, 0.01]	.331

Table 7
Stress reactivity as a mediator between il-6 and anxiety symptoms (Time 2).

Model	*B*	*SE (B)*	95% CI	*p*
Outcome: Stress Reactivity				
IL-6	−0.31	0.11	[−0.53, −0.09]	.006
Outcome: Anxiety Symptoms (Time 2)				
IL-6	0.05	0.03	[−0.02, 0.11]	.166
Stress Reactivity	−0.07	0.01	[−0.08, −0.05]	<.001

number of depressive symptoms experienced in Time 1, demographics and personality variables, and physical health and medication use status.

A separate analysis was then conducted with number of anxiety symptoms experienced in Time 2 specified as the outcome variable instead. Psychological stress was not found to be significantly associated with IL-6 levels, $B = 0\ 0.001$, $SE = 0.01$, 95% CI = [−0.02, 0.03], $p = .938$, even though psychological stress levels significantly predicted increased number of anxiety symptoms experienced in Time 2, $B = 0\ 0.16$, $SE = 0.01$, 95% CI = [.14, 0.18], $p < .001$. These results held even after controlling for number of anxiety symptoms experienced in Time 1, demographics and personality variables, and physical health and medication use status.

4. Discussion

Based on a large, nationally representative sample of middle-aged adults in the United States, blood serum interkeukin-6 (IL-6) level was found to be significantly, positively associated with one's present number of depressive and anxiety symptoms experienced (i.e., measured at Time 1). This is consistent with the findings of past correlational, cross-sectional studies that make up the bulk of the current literature in this area of research (Dentino et al., 1999; Lutgendorf et al., 1999; Murphy et al., 2015; O'Donovan et al., 2010). It should, however, be noted that the association between IL-6 and number of anxiety symptoms experienced was rendered non-significant when physical health and medication use status were controlled, suggesting for the possibility that one's physical health and medication use status may serve as a third-variable responsible for the simultaneous fluctuations in levels of IL-6 and anxiety symptoms experienced.

Critically, IL-6 was not found to be a significant predictor of number of depressive or anxiety symptoms measured at Time 2 when number of symptoms assessed at Time 1 (i.e., baseline) was controlled; though, without controlling for baseline, IL-6 was a significant predictor of number of depressive symptoms experienced in Time 2 (but not number of anxiety symptoms). However, given that this association was rendered non-significant after controlling for baseline, it can be said that IL-6 provides no incremental predictive validity over one's current number of depressive symptoms experienced, such that it rendered a non-significant predictor when the latter is controlled for. This suggests that the observed association between IL-6 and one's prospective number of depressive symptoms is likely driven by the former's sheer association with one's current number of depressive symptoms rather than it being a possible cause of prospective depressive symptoms experienced itself. As demonstrated in past studies, early depression levels in-particular are significantly predictive of future depression levels (e.g., Chassin et al., 1999; Nolen-Hoeksema et al., 1992).

Taken together, these findings suggest that IL-6 levels may simply be fluctuating with one's current experiencing of depressive and anxiety symptoms and may not be directly involved in the pathogenesis and development of depression and anxiety disorder; though IL-6 may still potentially be used as a predictor of future depression levels due to its sheer association with one's current depression levels and the established predictive validity of the latter.

Further corroborating the proposition that IL-6 may not play a causative role in the pathogenesis and development of depression and anxiety disorder, evidence for IL-6 serving as either a direct biological base for the precipitation of depressive and anxiety symptoms (via augmenting HPA stress reactivity) or a biological consequence/by-product of a psychological base (psychological stress experienced) was not found. Specifically, mediation analyses did not support the existence of an indirect relationship between IL-6 and number of depressive and anxiety symptoms experienced in Time 2 via stress reactivity levels (with one exception discussed below). Separately, path analyses revealed that while psychological stress levels experienced in Time 1 significantly predicted increased depressive and anxiety symptoms experienced in Time 2, psychological stress levels were not significantly associated with IL-6 levels.

Interestingly, IL-6 was observed to exert a significant, positive indirect effect on anxiety symptoms experienced in Time 2 via stress reactivity in an unexpected manner when demographics and personality variables as well as physical health and medication use were not controlled for. Specifically, it was observed that higher levels of IL-6 was associated with lower levels of stress reactivity, which, in turn, was negatively associated with anxiety symptoms experienced in Time 2. This goes against our current understanding that stress reactivity would precipitate anxiety symptoms (e.g., Dorn et al., 2003), and that IL-6 may precipitate such symptoms by increasing stress reactivity. Further empirical studies are needed to validate and explicate this unexpected finding. It should, however, be noted that these associations were rendered non-significant when covariates such as demographics and personality variables as well as physical health and medication use were controlled for, indicating that it is highly likely that this finding may have been confounded.

Collectively, results of this study suggest that IL-6 is only robustly related to one's current experiencing of depressive and anxiety symptoms. While some evidence supporting the predictive validity of IL-6 for prospective depressive symptoms was obtained, evidence of its predictive validity for prospective anxiety symptoms was not found. Furthermore, evidence for IL-6 as being either a direct biological cause (augmenting HPA stress reactivity) or a biological consequence of a psychological cause (psychological stress) was not found. It is plausible that IL-6 may instead be a consequence or byproduct of depression and anxiety, such that its level fluctuates with an individual's concurrent depressive and anxiety symptoms experienced, but in itself does not substantively influence the trajectory or development of depression and anxiety. Overall, these findings cast reasonable doubt with regard to our current understanding of IL-6's role in the pathogenesis of depression and anxiety disorder and caution practitioners against the premature consideration of IL-6 in clinical practice.

4.1. Limitations and future directions

Although the current study employed a longitudinal study design and a large nationally representative sample which enabled us to rule out a number of confounding factors, some limitations exist. Firstly, the current study was conducted solely in the U.S., which potentially limits the generalizability of these findings. Thus, it is important that future studies attempt to replicate these findings with samples from other countries to assess the generalizability of these findings. Secondly, IL-6, psychological stress, and stress reactivity were only measured in Time 1. While this does not compromise the main purpose and analyses of

this study, as these variables are proposed to be predictive of prospective depressive and anxiety symptoms, it precludes us from making any assessment with regards to changes in these variables between the two time points and how they may concurrently relate to the number of depressive and anxiety symptoms at Time 2. Such an assessment would have provided additional empirical information to evaluate the possibility that IL-6 may instead be a consequence or byproduct of depression and anxiety, as postulated in the discussion section. As this limitation stem primarily from resource constraints, others with greater means are encouraged to measure these implicated variables at two time points to assess the validity of this postulation.

4.2. Conclusion

The present study replicates past findings on the positive relationship between IL-6 and concurrent depressive and anxiety symptoms experienced. However, evidence to support a causative role of IL-6 in the precipitation of depressive and anxiety symptoms was not found. On the other hand, evidence for a predictive role of IL-6 was only limited to prospective depressive symptoms, and only when baseline number of symptoms is not accounted for. These findings underscore the imperativeness of more rigorous studies to be conducted in this area, and caution practitioners against the premature consideration of IL-6 levels in clinical practice.

Author statement

The author confirms being the sole contributor of this work.

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Declaration of Competing Interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2020.112809.

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