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Associations of three major physiological stress systems with suicidal ideation and suicide attempts in patients with a depressive and/or anxiety disorder

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ABSTRACT

Background: People with depressive and/or anxiety disorders are at increased risk of suicidal ideation and suicide attempts, but biological correlates signaling such risk remain unclear. Independent and cumulative dysregulations in physiological stress systems, in particular the hypothalamic–pituitaryadrenal axis (HPA-axis), immune-inflammatory system, and autonomous nervous system (ANS), may contribute to this risk. However, findings have either been heterogeneous or absent thus far.

Methods: Associations between individual markers and cumulative indices of the HPA-axis (cortisol awakening response and evening cortisol), immune-inflammatory system (C-reactive protein, interleukin-6 (IL-6), and tumor necrosis factor-α), and the ANS (heart rate, respiratory sinus arrhythmia, and pre-ejection period) and the outcomes no suicide ideation with suicide attempt (SI-SA+), suicide ideation without suicide attempt (SI+SA-) and suicide ideation with suicide attempt (SI+SA+) were investigated in 1749 persons with depressive and/or anxiety disorders from the Netherlands Study of Depression and Anxiety (NESDA).

Results: High levels of CRP and IL-6 were associated with SI-SA+ and SI+SA+ respectively when compared to non-suicidal patients after adjusting for confounders and multiple testing. Also, cumulative immune-inflammatory dysregulations were positively associated with SI+SA+, suggesting a dose–response effect. No significant associations were found between HPA-axis or ANS indicators and suicide-outcomes and between immune-inflammatory system markers or cumulative stress system dysregulations and SI+SA-.

Conclusion: Although stress system markers could not differentiate between SI+SA- and non-suicidal patients, findings indicate that dysregulations of individual and cumulative immune-inflammatory markers are associated with suicide attempts in depressive and/or anxiety patients. Thus, immune-inflammatory system dysregulation may be involved in the pathophysiology of suicidal behavior, supporting further examination of the effects of anti-inflammatory interventions on suicidality.

1. Introduction

Suicide is a serious worldwide public health issue that accounts for almost 800,000 deaths per year (WHO, 2018) and often involves mental health problems (Brådvik, 2018). A depressive or anxiety disorder increases the risk for suicide twelve- and four-fold respectively in the general population (Too et al., 2019) and comorbid depression and anxiety presents a greater risk than either disorder alone (Eikelenboom et al., 2012). Although these mental disorders confer increased suicide risk, they lack specificity, since the majority will not think about suicide let alone act on suicidal thoughts via a suicide attempt (Wiebenga et al., 2021b). According to the ideation-to-action framework, the development of suicidal thoughts and suicide attempts have their own rationale and determinants (May and Klonsky, 2016). Therefore, examining these events separately is needed for earlier detection and improved treatment of high risk patients. So far, relatively little attention has been given to

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investigating contributions of underlying biological mechanisms (Wiebenga et al., 2021b).

The integrated motivational-volitional model of suicidal behavior (IMV) suggests that, besides stressors and environmental factors, a diathesis is a precondition for the development of suicide ideation and attempts (O'Connor and Kirtley, 2018). Diathesis may indeed be found, amongst other domains, in biological factors. Physiological stress systems such as the hypothalamic–pituitaryadrenal axis (HPA-axis), immune-inflammatory system, and the autonomous nervous system (ANS) are known to play a crucial role in protecting the body and helping it adapt to manage acute stress. However, these systems can contribute to physical and psychological problems when dysregulated, which is often the result of allostatic overload due to repeated exposure to physically and emotionally taxing events (McEwen, 2005). Particularly HPA-axis hyperactivity, higher levels of immune-inflammatory markers, and higher ANS tone were found to be associated with depressive and/or anxiety disorders (Dedovic and Ngiam, 2015; Mac Giollabhui et al., 2020; Vinkers et al., 2021). Therefore, it is important to investigate whether mediators of these stress systems additionally heighten risk of suicide ideation and attempts within such patients. Until now, few studies have done so.

Several recent studies found that individuals with compared to individuals without a suicide attempt history had lower baseline levels of glucocorticoid cortisol, the end product of the HPA-axis, or cortisol output in reaction to stress tests (Keilp et al., 2016; Melhem et al., 2016; Melhem et al., 2017; O'Connor et al., 2017). However, a meta-analysis by Hernandez-Diaz et al. (2020) found that cortisol levels did not significantly differ between patients with suicide ideation or suicide attempts and non-suicidal patients. Further research is therefore required, especially considering that HPA-axis dysfunctions are associated with a range of putative suicide risk factors. For example, hypercortisolism has been found to impair neurogenesis in the hippocampus, increase neural atrophy in the hippocampus and prefrontal cortex, downregulate neurotrophic factors such as brain-derived neurotrophic factor essential for neuronal plasticity, and negatively alter signaling of monoamines such as serotonin (Forget et al., 2016; Lanfumey et al., 2008; O'Connor et al., 2000; Steinberg and Mann, 2020). Besides eliciting negative effects on mood, such changes could instigate inadequate responses to stress via diminished executive functions (e.g. diminished inhibitions and cognitive flexibility), memory and learning, adaptability, and decision making. These factors are known to be clinically relevant to suicide risk (Forget et al., 2016; Lanfumey et al., 2008; McGirr et al., 2010; Steinberg and Mann, 2020).

Immune-inflammatory dysregulation, as identified by high levels of inflammatory markers such as the cytokines interleukin (IL)-6 and tumor necrosis factor (TNF-α) and C-reactive protein (CRP), is considered a potentially important mechanism in suicide (Black and Miller, 2015; Ganança et al., 2016; Melhem et al., 2017). Nonetheless, only few studies investigated associations between immune-inflammatory markers and suicide ideation and attempts over and above the presence of depression or anxiety. This is especially important considering that biological mechanisms proposed for suicidality and depression largely overlap (Brundin et al., 2017). So far, findings have been mixed. Using mood disorder patient samples, some found evidence for positive associations between IL-6, CRP and/or TNF-α and suicide ideation and attempt when compared to non-suicidal patients (Courtet et al., 2015; Dolsen et al., 2020; Janelidze et al., 2011; O'Donovan et al., 2013), whilst others did not (Bergmans et al., 2019; Coryell et al., 2018; Kim et al., 2008; Vargas et al., 2013). The manner in which higher immune-inflammatory mediators and suicidality are related remains uncertain (Sudol and Mann, 2017). A widely proposed downstream mechanism is the kynurenine pathway of tryptophan (TRP) catabolism, which may be particularly dysregulated in suicidal depressed patients (Brundin et al., 2017; Sudol and Mann, 2017; Wisłowska-Stanek et al., 2021). Excessive inflammatory cytokines could lead to more TRP conversion into kynurenine (KYN), rather than serotonin, by activating the enzyme idoleamine 2, 3-dioxygenase (IDO). Increased KYN may be converted into kynurenic acid (KYNA) and quinolinic acid which may have excitotoxic effects in the brain by activating N-methyl-D-aspartate receptors and may contribute to neurodegeneration and decreased hippocampal volume and neurotrophic factor. KYNA contributes to downregulating dopamine. Such changes could increase risk of suicidal behavior via decreased mood, anhedonia, cognitive dysfunction, impulsivity, aggression and decreased plasticity and neurogenesis.

Although few studies investigated the role of ANS dysregulations in suicide risk, their involvement is probable. An adaptive response to an acute stressor entails activation of the "flight-or-fight" response via the sympathetic nervous system (SNS), effectively raising the heart rate. This is followed by modulation of this response by the parasympathetic nervous system (PNS) along the vagus nerve upon removal of the stressor, eliciting a more placid mental and bodily state and increased social engagement (Miller and Eisenlohr-Moul, 2019). However, excessive sympathetic activation and low vagal tone were found to be associated with decreased self-regulation, social engagement and executive functions (e.g. self-control, emotion regulation, and flexible thinking) and psychopathology, such as depression (Adolph et al., 2018; Penninx et al., 2013; Porges, 2001). Mentioned outcomes are characteristic of suicidal patients. For example, decreased emotion regulation ties in with the escape theory by Baumeister (1990), stating that suicide could be a flee from feeling overwhelmed by and unable to regulate emotional distress in response to stressors. Thus, heightened sympathetic activity and lowered vagal tone are hypothesized to be indicators of suicide risk. Indeed, some evidence suggests that a higher resting heart rate and lower levels of reliable non-invasive, indirect measures of vagal control such as high frequency-heart rate variability and RSA are associated with suicide risk (Adolph et al., 2018; Chang et al., 2017; Crowell et al., 2005; Tsypes et al., 2018; Wilson et al., 2016). More evidence is required due the relatively small and mostly female samples used.

It is well established that the three stress systems in question are interrelated. Inflammatory cytokines can activate secretion of glucocorticoid producing hormones corticotropin-releasing factor (CRF) and adrenocorticotropic hormone (ACTH), whereas glucocorticoids regularly have immunosuppressive effects (Steinberg and Mann, 2020). The vagus nerve has a role in regulating levels of inflammation via de cholinergic anti-inflammatory pathway (Rosas-Ballina and Tracey, 2009) and the ANS and HPA-axis are highly coordinated systems, activating one another via a positive feedback mechanism in stress responses (O'Connor et al., 2000). For instance, the catecholamine norepinephrine, an important neurotransmitter of the SNS, can stimulate cells containing CRF, activating the HPA-axis (Dunn and Swiergiel, 2008; Rotenberg and McGrath, 2016). Together, these systems aim to maintain homeostasis, but evidence suggests that dysregulations in one stress system could disrupt another. For example, increased pro-inflammatory cytokines can negatively affect glucocorticoid receptor function enabling glucocorticoid resistance. This could have detrimental effects via diminished immunosuppressive effects of glucocorticoids and continued release of CRF and ACTH in the brain (Haroon et al., 2012; Pace et al., 2007).

Cumulative stress system dysregulations are often associated with more severe physical and mental health outcomes. ANS and HPA-axis hyperactivity may have an additive adverse effect on perceived stress (Rotenberg and McGrath, 2016) and particularly cumulative indexes of dysregulations within and across stress systems in question were found to be associated with current depression and/or anxiety (Vinkers et al., 2021). Therefore, it is hypothesized that multiple stress system dysregulations could also be a stronger risk mechanism in suicide-outcomes. A few studies investigated multiple stress systems in suicidal patients simultaneously and found that dysregulations do not occur in isolation. Chang et al. (2016) found decreased vagal tone and increased pro-inflammatory cytokine levels in patients with suicide ideation compared to non-suicidal depressive patients. Melhem et al. (2017)

found higher inflammatory levels and a blunted HPA-axis in patients with suicide attempts compared to patients with suicide ideation and healthy controls. Therefore, it is plausible that cumulative stress system dysregulations could increase the likelihood of suicide-outcomes by further exacerbating earlier mentioned cognitive, behavioral and emotional problems associated with stress system dysregulations.

Overall, the role of the physiological stress systems in question in suicide processes is not clear-cut. This is due to a limited number of studies, which often present heterogeneous results and use relatively small samples and rarely differentiate between suicide ideation and attempts or investigate associations independent of the effects of psychiatric disorders. Also, studies have not applied an integrated approach to the examination of cumulative dysregulations within and across stress systems. Therefore, the first objective in the present study is to investigate association between HPA-axis (measured by cortisol awakening response and evening cortisol), immune-inflammatory (CRP, IL-6, and TNF-α), and ANS markers (HR, RSA, and PEP) and suicide ideation and attempts in a large, well-characterized cohort of patients with a depressive and/or anxiety disorder. The second objective is to investigate whether cumulative dysregulations within and across the three stress systems increase the likelihood of suicide ideation and attempts.

2. Methods

2.1. Study sample

Baseline data was used from the ongoing longitudinal cohort study NESDA. The sample included 2981 respondents between 18 and 65 years old. Objectives of this ongoing longitudinal cohort study include examining the course of depression and anxiety over time and risk factors that impact the course and development of depression and anxiety. Respondents with or without symptoms of an anxiety and/or depressive disorder were recruited across the Netherlands between September 2004 and March 2007 in various settings, including the community, primary care, and specialized mental health care. Depressive and anxiety disorders, as defined by the DSM-IV classification system (APA, 2001), were diagnosed using the Composite International Diagnostic Interview (CIDI) version 2.1. Exclusion criteria included a lack of proficiency in the Dutch language and the presence of other mental disorders as a primary clinical diagnosis such as obsessive–compulsive, bipolar, severe addiction, or psychotic disorders, since investigation of these disorders is beyond the scope of NESDA. The research ethics committees of participating centers approved the study and all respondents signed an informed consent form after receiving oral and written information about what study participation entailed. For more details about the rationale, aims, methods, and recruitment of the NESDA study, see Penninx et al. (2008) and Penninx et al. (2021). Fig. 1 presents the included and excluded individuals and number of individuals with data for each stress system marker in the final sample.

In the present article, the analytical sample consisted of 1774 respondents with a depressive and/or anxiety disorder in the past 12 months at baseline assessment and who provided information on current (past week) suicidal ideation status and the presence of a lifetime suicide attempt. Due to the influence on stress system functioning, pregnant or breastfeeding respondents and those with less than one stress marker were also excluded. Additionally, corticosteroid use was checked as this could affect HPA-axis markers, but no participants with available HPA-axis marker data used corticosteroids. Of the remaining 1749 participants, 1231 were non-suicidal (SI-SA-), 195 had a previous attempt without current suicidal ideation (SI-SA+), 230 had current suicidal ideation and no previous attempt (SI+SA-) and 93 had current suicidal ideation and a previous attempt (SI+SA+). Some participants were excluded from specific analyses of individual stress system markers due to missing data (see Fig. 1).

2.2. Suicide ideation and suicide attempt

To measure the presence of suicidal ideation in the past week, a 5-item version of the Scale for Suicide ideation (SSI) was used. This semi-structured interview was created by Beck et al. (1979). To measure the presence of a lifetime suicide attempt, a question originally coined by the WHO/Euro multicenter study on parasuicide (Platt et al., 1992) was used. The question asks: “Have you ever made a serious attempt to end your life, for instance by harming or poisoning yourself of by getting into an accident?”.

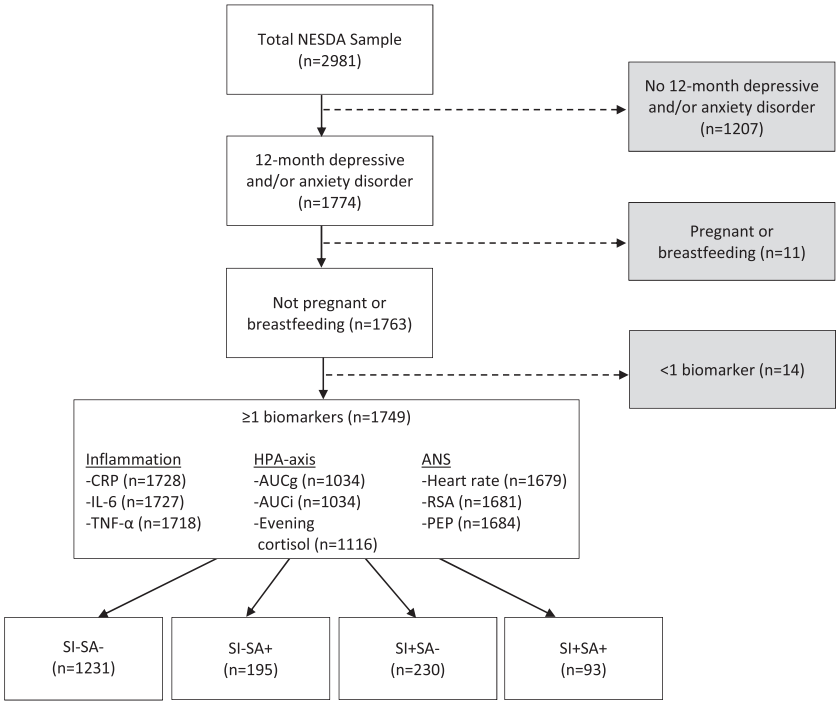

Fig. 1. Flow-diagram for included and excluded individuals and number of individuals with data per stress system marker. ANS: autonomic nervous system; AUCg: area under the curve in respect to the ground; AUCi: area under the curve in respect to the increase; CRP: C-reactive protein; HPA-axis: hypothalamic pituitary axis; IL-6: interleuking-6; NESDA: Netherlands Study of Depression and Anxiety; PEP: pre-injection period; RSA: respiratory sinus arrhythmia; SI-SA-: no current suicidal ideation and no past suicide attempt; SI-SA+: a past suicide attempt and no current suicidal ideation; SI+SA-: current suicidal ideation and no past suicide attempt; SI+SA+: current suicidal ideation and a past suicide attempt; TNF-α: tumor necrosis factor α.

2.3. HPA-axis markers, immune-inflammatory markers, and ANS markers

A full description of HPA-axis, immune-inflammatory and ANS marker measurements is presented in supplement A. Three HPA-axis markers were used based on saliva cortisol samples collected as previously described by Vreeburg et al. (2009). The cortisol awakening response (CAR) was measured by calculating the area under the curve with respect to the ground (AUCg) and with respect to increase (AUCi) (Pruessner et al., 2003). The AUCg represents the amount of cortisol released within one hour after awakening and AUCi represents the level of cortisol increase in the hour after awakening (Pruessner et al., 2003). Evening cortisol was used to give an indication of basal cortisol release. Saliva samples were deemed missing if the saliva sample was taken 5 min outside of the time-protocol (before or after) or improperly returned, which is also the main reason why a large portion of the sample was missing.

Determining circulating plasma levels of inflammatory markers CRP, IL-6, and TNF-α occurred as previously described by Vogelzangs et al. (2012).

ANS markers used were the HR, which represents the interplay between sympathetic and parasympathetic activity (Thesing et al., 2018), and the RSA and the pre-ejection period (PEP), which are indices of cardiac parasympathetic activity and sympathetic control respectively (Licht et al., 2010). ANS marker data collection and calculation of the HR, RSA and PEP were described previously by Licht et al. (2010) and Black et al. (2017).

2.4. Cumulative indices of stress systems

Cumulative indices consisting of the number of dysregulated markers per stress system (ranging from 0 to 3) were made a priori for each of the three stress systems (Thesing et al., 2018). To create these indices, dichotomous variables were made for each stress system marker, split according to the categories 'dysregulated' (high risk quartile) and 'non-dysregulated' (other quartiles). In accordance with previous NESDA articles, high risk quartiles for inflammatory and HPA-axis markers and the ANS marker HR were defined as the 4th (highest) quartile. The high risk quartiles for ANS markers PEP and RSA were defined as the 1st (lowest) quartile, since for these markers lower scores have shown higher somatic and psychopathological impairment. Participant data was only used for each cumulative index within a stress system if a participant had complete data for all markers of the respective stress system. Furthermore, another cumulative index was created for the number of stress systems containing ≥ 1 dysregulated marker (ranging from 0 to 3). The latter cumulative index was only calculated for participants with complete data for all markers across all stress systems.

2.5. Covariates

Sociodemographic variables included in analyses were age (years) and sex. Also, potential covariates specific to each stress system were included. Analyses of inflammatory markers were adjusted for anti-inflammatory medication use (Vogelzangs et al., 2012) and blood sample collection location. Additionally, potential confounding effects of lifestyle variables smoking status and alcohol consumption were controlled for in separate analyses of inflammatory markers (O'Connor et al., 2009). Analyses of HPA-axis markers were adjusted for awakening time, working status on day of sampling, and season on day of sampling (Vreeburg et al., 2009). Analyses of all ANS markers included adjustments for the use of cardiac medication, whilst analyses including RSA were also adjusted for respiratory rate and analyses including PEP were additionally adjusted for mean arterial pressure (Houtveen et al., 2005; Licht et al., 2010). Furthermore, significant associations between ANS markers and suicide-outcomes were additionally controlled for antidepressant use, considering that they particularly affect ANS markers in previous NESDA research (Licht et al., 2012). Relevant covariates were also adjusted for in analyses of cumulative dysregulations. Moreover, significant associations were adjusted for body mass index (BMI) in a sensitivity model, although this could be considered an overcorrection, especially with regards to immune-inflammatory markers. A significant amount of IL-6, TNF-α and CRP results from adipose tissue (Ellulu et al., 2017; Fontana et al., 2007; Palaniswamy et al., 2020; Timpson et al., 2011). This indicates that these inflammatory markers might mediate a relationship between BMI and suicide-outcomes and that BMI should therefore not be treated as a confounder (Twisk, 2016). The role of included inflammatory markers as mediators of the association between BMI and suicide-outcomes was therefore also investigated for any inflammatory markers found to be significantly associated with suicide-outcomes. Lastly, a sensitivity analysis was performed investigating associations between inflammatory markers and suicide-outcomes excluding anti-inflammatory medication users (n = 79), considering the direct impact of anti-inflammatory medication on inflammatory levels.

2.6. Statistical analyses

Baseline characteristics of patients with a depressive and/or anxiety disorder in the past year were split according to suicidal status and described in terms of percentages, means, and standard deviations. Group differences were evaluated using chi-square tests for categorical variables and analyses of variance (ANOVA) for continuous variables. Since the variables CRP, IL-6, TNF-α, evening cortisol, RSA, and mean arterial pressure were not normally distributed, natural logarithm-transformations were performed prior to analyses. The variables were presented back-transformed in the tables. To improve comparability of results, all stress system markers were standardized in the subsequent analyses.

To investigate associations between the (continuous and dichotomous) individual stress system markers and suicidal status, multinomial logistic regression analyses were performed, with suicidal status (four-level factor variable with non-suicidal as the reference category) as dependent variable and level of an individual stress system marker as independent variable. Next, multinomial logistic regression analyses was used to investigate associations between cumulative dysregulated markers within a stress system and cumulative dysregulations across stress systems and suicide-outcomes. Covariates were adjusted for after performing univariate analyses as described in section '2.5. Covariates'. Also, the potential mediating role of inflammatory markers in the association between BMI and suicide-outcomes was investigated using the 'change in coefficient method' (Rijnhart et al., 2021).

Results with a p value < 0.05 were considered statistically significant. Corrections were made for multiple testing using the Benjamini-Hochberg False Discovery Rate method (Benjamini and Hochberg, 1995) (FDR p value < 0.05) in logistic regression analyses. Statistical analyses were performed using IBM SPSS version 26 for Mac.

3. Results

3.1. Clinical characteristics

The analytic sample (N = 1749) consisted of participants with a mean age of 41.3 (SD = 12.4) and 67.5% of the participants were female. Participants in the SI-SA+ and SI+SA+ group had an average of 1.7 (SD = 1.3) and 2.0 (SD = 1.7) previous suicide attempts respectively with a median number of years since the last attempt of 10.0 (IQR = 16.0) and 4.0 (IQR = 11.5) years respectively. 13.8% and 28.0% of the individuals in the SI-SA+ and SI+SA+ groups respectively reported a suicide attempt in the past year. Clinical characteristics split according to the outcome suicidal status can be found in Table 1. With regards to clinical severity, the groups with suicide ideation and/or a past attempt had a higher clinical severity than the non-suicidal group as indicated by more

Table 1
Sociodemographic, psychiatric, lifestyle and health characteristics and specific stress system covariates of patients with a depressive and/or anxiety disorder in the past 12 months according to suicidal status (n = 1749).

	SI-SA- (n = 1231)	SI-SA+ (n = 195)	SI+SA- (n = 230)	SI+SA+ (n = 93)	P[a]
Sociodemographic variables					
Age (years), mean (SD)	41.2 (12.6)	43.1 (11.9)	40.8 (12.0)	40.2 (12.1)	0.149
Women, %	68.4	69.7	59.6	69.9	0.052
Psychiatric disorder characteristics					
Psychiatric status in past 12 months					<0.001
Pure depression, %	24.5	20.5	23.9	14.0	
Pure anxiety, %	35.4	16.9	10.4	7.5	
Comorbid depression-anxiety, %	40.1	62.6	65.7	78.5	
Severity of depression, mean (SD)	25.0 (11.0)	31.3 (12.0)	37.1 (10.6)	41.5 (10.3)	<0.001
Use of antidepressants, %	34.2	49.2	49.1	47.3	<0.001
Lifestyle and health variables					
Smoking, %	40.9	51.8	48.3	61.3	<0.001
Alcohol consumption, mean (SD)	6.9 (10.2)	6.3 (11.5)	8.5 (12.6)	4.6 (9.7)	0.02
BMI (kg/m^2), mean (SD)	25.5 (5.2)	26.8 (6.1)	24.9 (4.8)	26.6 (5.9)	<0.001
Specific stress system covariates					
Inflammation					
Use of anti-inflammatory medication, %	3.9	8.2	3.5	7.5	0.021
Blood sample collection area					0.011
Amsterdam, %	43.4	36.1	34.1	38.0	
Leiden, %	29.9	33.5	39.7	41.3	
Groningen, %	26.7	30.4	26.2	20.7	
Hypothalamic Pituitary Adrenal axis					
Awakening time, mean (SD)	7.5 (1.2)	7.2 (1.4)	7.7 (1.3)	7.7 (1.3)	0.007
Working on day of cortisol sampling, %	55.9	53.8	55.2	42.6	0.355
Season of sampling					0.384
October-February (less daylight), %	46.7	51.8	44.3	43.0	
March-September (more daylight), %	53.3	48.2	55.7	57.0	
Autonomous Nervous System					
Use of cardiac medication, %	12.2	14.4	10.0	14.0	0.541
Respiratory rate, mean (SD)	17.6 (1.7)	18.0 (1.8)	17.8 (1.8)	17.8 (1.7)	0.015
Mean arterial pressure, mean (SD)[b]	99.7 (13.8)	101.0 (12.2)	99.1 (13.4)	99.8 (11.9)	0.468

Abbreviations: BMI = body mass index (weight in kg divided by height in meters squared); SI-SA- = Non-suicidal; SI-SA+ = lifetime attempt and no current suicidal ideation; SD = Standard deviation; SI+SA- = Current suicidal ideation without lifetime attempt; SI+SA+ = Current suicidal ideation with lifetime attempt.
[a] Based on ANOVA (for continuous indicators) or chi-square test (for categorical indicators) statistics.
[b] Variables that were natural logarithm-transformed are presented back-transformed.

comorbid depression and anxiety, greater severity of depression and antidepressant use. The SI+SA+ group also appeared to be more clinically severe than the SI-SA+ and SI+SA- groups as indicated by more comorbid depression and anxiety and a higher severity of depression. The mean levels of individual stress system markers can be found in Table 2.

3.2. Immune-inflammatory, HPA-axis, ANS activity and suicidal status

Table S1 shows unadjusted associations between individual stress system markers and suicide-outcomes. No significant associations were found between HPA-axis or ANS markers and suicide-outcomes and no inflammatory markers were significantly associated with SI+SA-. Nonetheless, inflammatory markers CRP and IL-6 were found to be significantly positively associated with both SI-SA+ and SI+SA+, and TNF-α was also significantly positively associated with SI+SA+. After additionally correcting for multiple testing, significant associations between CRP and TNF-α and the outcome SI+SA+ were lost. After subsequently adjusting the findings for sociodemographic variables, stress system specific confounders, and multiple testing, only the association between IL-6 and SI+SA+ and between CRP and SI-SA+ remained significant as shown in Table 3.

Table 2
Mean levels (SD) of stress system markers in patients with a depressive and/or anxiety disorder in the past 12 months according to suicidal status (n = 1749).

	N	SI-SA- (n = 1231)	SI-SA+ (n = 195)	SI+SA- (n = 230)	SI+SA+ (n = 93)	P[a]
Inflammation						
C-reactive protein (mg/L)[b]	1535	3.0 (5.5)	3.7 (5.2)	2.5 (3.3)	3.3 (4.4)	0.001
Interleukin-6 (pg/mL)[b]	1534	1.2 (2.7)	1.6 (4.0)	1.4 (2.5)	1.4 (1.4)	0.001
Tumor Necrosis Factor α (pg/mL)[b]	1526	1.1 (1.3)	1.1 (1.3)	1.1 (1.6)	1.6 (2.6)	0.085
HPA-axis						
AUCg (nmol/L/hr)	933	19.3 (7.3)	19.3 (9.1)	19.2 (6.3)	18.4 (6.5)	0.862
AUCi (nmol/L/hr)	933	2.5 (6.1)	2.8 (7.1)	1.9 (6.3)	2.2 (5.8)	0.69
Evening cortisol (nmol/L)[b]	1005	5.5 (3.4)	5.5 (3.9)	5.6 (3.1)	5.3 (2.5)	0.726
ANS						
Heart rate (bpm)	1497	69.0 (9.9)	70.0 (9.6)	69.2 (10.6)	71.0 (10.6)	0.309
Respiratory Sinus Arrhythmia (ms)[b]	1499	45.9 (28.4)	41.3 (24.6)	44.0 (29.5)	43.3 (29.8)	0.092
Pre-ejection period (ms)	1502	121.3 (17.1)	120.2 (19.1)	120.5 (17.8)	123.3 (19.1)	0.532

Abbreviations: ANS = autonomous nervous system; AUCg = area under the curve with respect to the ground; AUCi = area under the curve with respect to increase; HPA-axis = hypothalamic–pituitaryadrenal axis; IQR = Interquartile range; SI-SA- = Non-suicidal; SI-SA+ = lifetime attempt and no current suicidal ideation; SD = Standard deviation; SI+SA- = Current suicidal ideation without lifetime attempt; SI+SA+: Current suicidal ideation with lifetime attempt.
[a] Based on ANOVA.
[b] Variables that were natural logarithm-transformed are presented back-transformed.

Table 3
Adjusted associations between stress system markers and suicide-outcomes in patients with a depressive and/or anxiety disorder in the past 12 months (n = 1749).

	SI-SA+ [a] OR (95% CI)	P	SI+SA- [a] OR (95% CI)	P	SI+SA + [a] OR (95% CI)	P
Inflammation						
C-reactive protein						
Continuous	1.25 (1.08–1.46)	0.004*	0.95 (0.82–1.09)	0.44	1.25 (1.02–1.55)	0.04
Highest quartile	1.75 (1.27–2.32)	0.001*	1.17 (0.85–1.61)	0.344	1.71 (1.10–2.70)	0.019
Interleukin-6						
Continuous	1.21 (1.03–1.43)	0.022	1.11 (0.95–1.28)	0.19	1.45 (1.15–1.82)	0.001*
Highest quartile	1.55 (1.11–2.15)	0.010	1.23 (0.89–1.70)	0.22	2.27 (1.45–3.54)	<0.001*
Tumor Necrosis Factor α						
Continuous	1.07 (0.92–1.24)	0.392	0.96 (0.83–1.11)	0.59	1.24 (1.03–1.50)	0.02
Highest quartile	1.15 (0.81–1.64)	0.438	0.83 (0.58–1.18)	0.297	1.11 (0.67–1.83)	0.685
# of high risk IF markers (0–3)	1.34 (1.13–1.59)	0.001*	1.05 (0.88–1.24)	0.589	1.49 (1.18–1.88)	0.001*
HPA-axis						
AUCg						
Continuous	0.92 (0.74–1.14)	0.447	0.99 (0.81–1.20)	0.896	1.01 (0.73–1.41)	0.95
Highest quartile	0.78 (0.48–1.27)	0.320	0.92 (0.59–1.43)	0.70	0.91 (0.44–1.89)	0.806
AUCi						
Continuous	1.03 (0.83–1.28)	0.802	0.93 (0.76–1.14)	0.93	1.02 (0.73–1.44)	0.909
Highest quartile	0.98 (0.62–1.57)	0.941	1.05 (0.68–1.62)	0.82	1.09 (0.54–2.19)	0.821
Evening cortisol						
Continuous	0.85 (0.69–1.05)	0.138	1.04 (0.85–1.27)	0.699	0.90 (0.64–1.26)	0.529
Highest quartile	0.85 (0.52–1.39)	0.519	1.38 (0.91–2.09)	0.13	0.32 (0.11-0.91)	0.03
# of high risk HPA-axis markers (0–3)	1.30 (0.83–2.05)	0.250	1.11 (0.90–1.38)	0.33	0.99 (0.67–1.46)	0.95
ANS						
Heart rate						
Continuous	1.09 (0.94–1.27)	0.262	1.03 (0.90–1.19)	0.65	1.20 (0.98–1.48)	0.084
Highest quartile	1.26 (0.90–1.77)	0.182	1.04 (0.75–1.45)	0.808	1.23 (0.77–1.96)	0.392
Respiratory Sinus Arrhythmia						
Continuous	0.96 (0.80–1.17)	0.705	0.89 (0.75–1.06)	0.20	0.82 (0.63–1.07)	0.135
Lowest quartile	0.98 (0.66–1.44)	0.902	1.28 (0.89–1.83)	0.186	1.13 (0.64–1.98)	0.681
Pre-ejection period						
Continuous	0.95 (0.82–1.12)	0.558	0.95 (0.82–1.10)	0.504	1.13 (0.90–1.42)	0.297
Lowest quartile	1.13 (0.78–1.62)	0.527	1.07 (0.76–1.52)	0.704	1.13 (0.67–1.91)	0.65
# of high risk ANS markers (0–3)	1.08 (0.90–1.30)	0.389	1.07 (0.90–1.27)	0.45	1.09 (0.84–1.42)	0.502
Overall						
# of high risk stress systems (0–3)	1.16 (0.87–1.55)	0.311	1.07 (0.84–1.38)	0.58	1.20 (0.76–1.91)	0.431

Abbreviations: # = number; ANS = autonomous nervous system; AUCg = area under the curve with respect to the ground; AUCi = area under the curve with respect to increase; HPA-axis = hypothalamic–pituitaryadrenal axis; IF = inflammation; SI-SA+ = lifetime attempt and no current suicidal ideation; SI+SA- = Current suicidal ideation without lifetime attempt; SI+SA+ = Current suicidal ideation with lifetime attempt.
Note. Adjustment for age, sex, and stress system specific confounders: use of anti-inflammatory medication (yes/no) and blood sample collection area for inflammation, awakening time (00:00–23:59), working on day of sampling (yes/no), and season of sampling (light/dark) for HPA-axis, use of cardiac medication (yes/no) for ANS, and additionally respiratory rate for respiratory sinus arrhythmia and mean arterial pressure for pre-ejection period.
*Significant after correction for multiple testing using the False Discovery Rate (Benjamini and Hochberg, 1995) based on 66 tests.
[a] Reference group consists of non-suicidal patients with a depressive and/or anxiety disorder in the past 12 months.

Adjusted associations between inflammatory markers and suicide-outcomes found in Table 3 were largely unaffected after additionally correcting for lifestyle variables smoking and alcohol consumption (Table S2) or BMI (Table S3) in sensitivity models. Only the association between CRP as a continuous variable and SI-SA+ was no longer significant. A sensitivity analysis in which anti-inflammatory medication users were excluded from analyses investigating associations between inflammatory markers and suicide-outcomes indicated that anti-inflammatory medication did not affect associations found (Table S4).

Furthermore, the role of inflammatory markers significantly associated with suicide-outcomes as mediators in the associations between BMI and suicide-outcomes was investigated. Firstly, the association between BMI and SI-SA+ was positive and significant (OR = 1.24, 95% CI: 1.09–1.42, p = .002) and the association between BMI and SI+SA+ was positive and approached significance (OR = 1.20, 95% CI: 1.00–1.45, p = .05). After adjusting the association between BMI and the suicide-outcomes for CRP and IL-6, 15% and 39% of the effect was mediated by CRP and 14% and 39% of the effect was mediated by IL-6 for SI-SA+ and SI+SA+ respectively. This further strengthens the argument that BMI and inflammation partly lie on the same causal pathway. Therefore, the results of analyses correcting for BMI should be interpreted cautiously.

3.3. Cumulative indices within/across biological stress systems and suicidal status

Unadjusted associations between cumulative indices within and across stress system markers and suicide-outcomes can be found in Table S1. No significant associations were found between the number of dysregulated HPA-axis or ANS markers and the suicide-outcomes. However, a significant association was found between a higher number of inflammatory markers within a high risk quartile (as a continuous variable) and the outcomes SI-SA+ and SI+SA+, but not with SI+SA-. The mentioned results remained largely unaffected after adjusting for sociodemographics, stress system specific confounders, and multiple corrections (Table 3). The results remained similar after performing additional sensitivity analyses in which associations between inflammatory markers and suicide-outcomes were also corrected for lifestyle variables smoking and alcohol consumption (Table S2) and BMI (Table S3).

The number of inflammatory markers within a high risk quartile variable was also turned into a categorical variable to test whether there was a dose–response effect. Fig. 2 shows that, after adjusting for sociodemographics and stress system specific confounders, the likelihood only increases with each additional inflammatory marker within a high risk quartile for the outcome SI+SA+. This dose–response effect remains in sensitivity models additionally adjusting for lifestyle variables

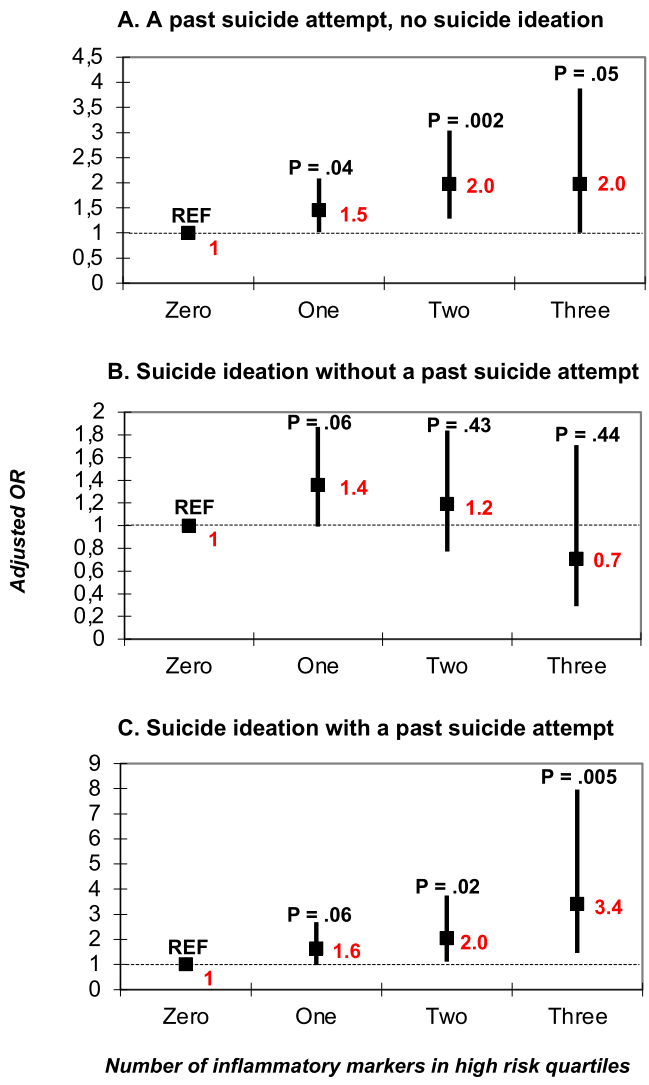

Fig. 2. Adjusted associations between the number of inflammatory markers in high risk quartiles (0–3) and suicidal status in patients with a depressive and/or anxiety disorder in the past 12 months (n = 1749). Adjustments were made for age, sex, blood sample collection area, and use of anti-inflammatory medication (yes/no).

smoking and alcohol consumption and health variable BMI (Table S5).

4. Discussion

The present study investigated whether individual markers and cumulative indices of important physiological stress systems (i.e. the immune system, HPA-axis, and ANS) are associated with suicide ideation and attempts in a large depressive and/or anxiety patient cohort. Results indicate that stress system markers could not differentiate individuals with suicide ideation without a past attempt from non-suicidal individuals. However, high levels of individual and cumulative markers of the immune-inflammatory system significantly differentiated individuals with a past suicide attempt from non-suicidal individuals.

The significant positive relationships between pro-inflammatory markers CRP and IL-6 and SI-SA+ and SI+SA+ respectively were most robust. These inflammatory markers were found to distinguish between patients with and without a suicide attempt in multiple previous studies (Black and Miller, 2015; Courtet et al., 2015; Gibbs et al., 2016; Janelidze et al., 2011; Melhem et al., 2017). Conversely, Dolsen et al. (2020) only found a positive association between IL-6 and current suicide ideation and not with a past suicide attempt in depressive and/or anxiety disorder patients using NESDA data. However, in contrast to the present paper, Dolsen et al. (2020) used a sample also containing individuals with remitted depressive and/or anxiety disorders and one suicide attempt group containing individuals with and without current suicide ideation. Recency of psychopathology symptoms may affect associations with stress systems (Vinkers et al., 2021; Vogelzangs et al., 2016), hampering comparability of results. In the present article, trending associations were also found between higher CRP and TNF-α levels and SI+SA+ and between higher IL-6 levels and SI-SA+. Heightened inflammation across multiple immune-inflammatory markers in both suicide attempt groups is also reflected in the significant associations between the cumulative index of inflammatory marker dysregulations and the suicide attempt groups. However, cumulative effects appear to be mainly driven by CRP in the SI-SA+ group and IL-6 in the SI+SA+ group.

Furthermore, in line with most previous studies, we found no significant associations between TNF-α and CRP and SI+SA- when compared to a patient control group (Bergmans et al., 2019; Courtet et al., 2015; Dolsen et al., 2020; Gibbs et al., 2016; Melhem et al., 2017). Also, no significant association was found between IL-6 and SI+SA- and so far there is little evidence for such an association when compared to a non-suicidal patient control group (Serafini et al., 2020). Dolsen et al. (2020) found the suicide ideation group to have higher IL-6 than the non-suicidal group in lifetime depressed and/or anxious individuals, but the control group had significantly more remitted individuals, which could explain the difference. Melhem et al. (2017) compared a suicide ideation and non-suicidal group in a heterogeneous inpatient sample, but found no significant difference in IL-6 levels.

Various mechanisms might explain heightened levels of immune-inflammatory levels in depressive and/or anxiety patients with a past suicide attempt. One may be the presence of higher clinical severity in the SI+SA+ group. The present findings indicate that the SI+SA+ group has more comorbid depression and anxiety and a greater severity of depression. Earlier research finds that the latter variables are predictive of a more chronic course of depressive and anxiety symptoms (Penninx et al., 2011). Considering that IL-6 is predictive of a chronic course of depression and that higher depression severity is predictive of higher IL-6 (Lamers et al., 2019), this bidirectional relationship could result in sustained, low-grade inflammation. However, clinical severity was actually lower in the SI-SA+ group compared to the other suicidal groups, suggesting heightened inflammatory levels are not just reflecting clinical severity or a current crisis. Since significantly higher levels of IL-6 were only found in SI+SA+, IL-6 could be an indicator of acute suicide risk and higher clinical severity in patients capable of attempting suicide. Previous studies indeed found that IL-6 was more elevated in patients with more recent and violent attempts and higher suicide severity (Fernández-Sevillano et al., 2021; Sudol and Mann, 2017; Wisłowska-Stanek et al., 2021). Meanwhile, CRP might be elevated in patients with suicide attempts regardless of recency and severity of attempts or severity of suicidality, as was found by Courtet et al. (2015). In that regard, CRP may have a trait-like presentation. If and how specific inflammatory markers such as CRP and IL-6, as opposed to heightened inflammation in general, may differentially affect nervous system functioning and subsequently affect depression and suicidal behavior requires further study. Little is yet known about this (Valkanova et al., 2013).

Also, we have previously shown that depressive and/or anxiety patients with a previous attempt experienced more childhood trauma than the non-suicidal and suicidal ideation group (Wiebenga et al., 2021a). Childhood trauma may increase the likelihood of (chronically) higher inflammation levels due to constant exposure to psychosocial stress from an early age. This may have long-lasting dysregulating effects on levels of inflammatory markers and inflammatory responses to stressors (Ganança et al., 2016; Kuzminskaite et al., 2020; Müller et al., 2019). Indeed, Schiweck et al. (2020) have shown that upregulated monocyte

inflammation-related gene expression in patients with a major depressive disorder (MDD) is associated with both childhood adversity and high suicide risk. Conversely, MDD patients not exposed to childhood adversity and without suicide risk or low suicide risk had predominantly downregulated inflammatory gene expression.

So far, only few biological mechanisms have been implicated in the association between heightened levels of inflammation and suicidal behavior. Dysregulated tryptophan metabolism via the kynurenine pathway may be an important downstream mechanism as a result of excessive inflammatory cytokines leading TRP away from serotonin production and towards a neurotoxic pathway via KYN by stimulating IDO (Sudol and Mann, 2017). In turn, this could elicit cognitive, behavioral and emotional outcomes known to be associated with suicidal behavior (Brundin et al., 2017; Serafini et al., 2013). Considering that this mechanism has also been implicated in depression, our results suggest that it may be of particular importance to depressed patients with suicide attempts. It has also previously been shown that, in depressed patients, the suicide attempt group indeed had higher KYN levels than non-suicidal patients (Sublette et al., 2011). Furthermore, the association between dysregulated inflammatory markers and suicide attempts may also be explained by an association between heightened inflammation and reward dysfunction. Anhedonia, i.e. decreased motivation to pursue rewards and experience of pleasure, has been found to be associated with increased suicide risk independent of depression and to be more severe in depressed patients that attempt suicide than patients with suicide ideation (Auerbach et al., 2015; Ducasse et al., 2018). This association may be driven by heightened inflammation, since Felger et al. (2016) found higher CRP levels to be associated with decreased connectivity between ventral striatum and ventromedial prefrontal cortex in depressed patients. This decrease of neural activity in reward-related areas of the brain was also found to be associated with higher anhedonia. Nevertheless, further examination is required to determine whether this mechanism is specific to or more pronounced in depressed suicide attempt patients compared to non-suicidal depressed patients.

Similar to results found in the meta-analysis by Hernandez-Diaz et al. (2020), we did not find differences in levels of HPA-axis markers between patients with suicide ideation and attempts and non-suicidal patients. Therefore, it appears that resting state cortisol levels offer little discriminatory value with regards to distinguishing patients with suicide ideation or attempts from non-suicidal individuals with a depressive and/or anxiety disorder. Rather, it is possible that resting state cortisol dysregulation is mainly a risk mechanism for the development of psychopathology in general (Vinkers et al., 2021). Future research using more dynamic measurements of cortisol changes in response to an acute stressor might be more beneficial in identifying elevated risk of suicide ideation and attempt within individuals with a depressive and/or anxiety disorder. For example, O'Connor et al. (2017) found lower levels of cortisol in participants from the community with a previous suicide attempt when compared to healthy controls in response to an acute stress test.

Associations between ANS markers and suicide-outcomes were also not found in the present study. So far, very few studies have investigated this relationship. A higher resting HR was shown to be associated with death by suicide in a large Taiwanese and Norwegian cohort consisting of participants from the general population (Chang et al., 2016), but no studies have previously investigated HR in depressive and/or anxiety patients with suicide ideation or attempts. Positive, negative, and a lack of associations have been found between RSA functioning and suicide ideation and attempts, although several studies have relied on small female samples and in one instance also lacked a control group (Crowell et al., 2005; Lin et al., 2015; Tsypes et al., 2018; Wilson et al., 2016). Furthermore, no differences were found with regards to levels of PEP between adolescent girls that do and do not perform any nonfatal acts of intentional self-harm (Crowell et al., 2005). Given our findings and the mixed results and limitations in previous studies, it appears unlikely that dysregulation of basal ANS functioning is a principal mechanism in suicide ideation and attempts in depressive and/or anxiety patients. Nevertheless, as with the HPA-axis, dynamic measurements of the ANS may hold more promise and remain to be investigated in a large sample. So far, Adolph et al. (2018) and Wilson et al. (2016) found indications of lower vagal control in response to a stressor in patients with suicide ideation and suicide attempts respectively.

Finally, although multiple stress system dysregulations may occur in depressive or anxiety patients in general (Penninx et al., 2013), only inflammatory marker dysregulations were more pronounced in depressive or anxiety patients with a suicide attempt history compared to patient controls. Considering that heightened inflammatory markers can negatively affect HPA-axis and ANS functioning, one could expect multiple stress system dysregulations, as some studies previously indicated (Chang et al., 2017; Melhem et al., 2017). However, this might not have been found for several reasons. Firstly, HPA-axis and ANS hyper- and hypoactivity have been found to be associated with suicide-outcomes (Hernandez-Diaz et al., 2020; Lin et al., 2015) and the presence of both types of suicidal patients in our sample may have led to an overall equilibrium. Secondly, sustained low-grade inflammation may make other stress systems more habituated to inflammatory effects. For example, individuals with rheumatoid arthritis with constantly elevated levels of inflammation did not significantly differ with regard to basal HPA-axis marker levels when compared to healthy respondents (Eijsbouts et al., 2005) and Black et al. (2017), using NESDA data, found no association between heightened cortisol and inflammatory markers. Thirdly, a ceiling effect may have occurred for HPA-axis and ANS measures, considering that it was previously found, using NESDA data, that depressive and/or anxiety disorders were associated with HPA-axis hyperactivity and higher ANS tone (Vinkers et al., 2021).

Despite the use of a large, well characterized patient cohort, some limitations should be taken into account. First, within the present cross-sectional study, causality cannot be inferred, therefore associations found between individual as well as cumulative inflammatory markers and the suicide attempt groups should be further investigated longitudinally and/or experimentally. Second, recall bias may be an issue when asking participants about the presence of a previous suicide attempt. Reporting errors have been shown to occur (Eikelenboom et al., 2014). Another limitation of retrospective reporting of factors such as suicide ideation and attempts, is the difficulty of capturing state changes in real-time in the natural environment prior to their onset. Ecological momentary assessment is able to overcome such limitations using modern technology such as smartphones and wearable devices and should be applied to investigate physiological activity and its role in the onset of suicidality. So far this technology has been underutilized in suicide research and only minimally applied in studying depressive patients (Colombo et al., 2019; Davidson et al., 2017). Third, the suicide attempt group was not split according to single or multiple attempts, lethality of suicide attempts, or intensity of suicidal ideation, since this would lead to underpowered subgroups and some of this information was not available. Some research suggests that risk profiles may differ depending on aforementioned factors (Aaltonen et al., 2016; Oquendo et al., 2009). Fourth, although the immune-inflammatory markers used in the present study are among the most frequently investigated in depression and suicide research (Lamers et al., 2019; Serafini et al., 2020), the cytokine profile is limited. Cytokines such as IL-1β, IL-2, interferon-gamma (IFN)-γ, IL-4, and IL-10 are promising (Serafini et al., 2020). More studies are required to investigate such cytokines and establish elaborate biological profiles taking into account distinct suicidal processes and examining their effects on suicidal status beyond the presence of psychiatric disorders.

Altogether, findings indicate that individual as well as cumulative immune-inflammatory marker dysregulations are associated with suicide attempt outcomes when compared to non-suicidal individuals within a depressive and/or anxiety disorder sample. Thus, immune system dysregulation may be involved in the pathophysiology of suicidal

behavior and results support further examination of the effects of anti-inflammatory interventions on decreasing suicidal behavior as summarized by Brundin et al. (2017). Independent and cumulative HPA-axis and ANS markers, however, were not related to suicide ideation or attempts independent of a depressive and/or anxiety disorder and no associations were found between immune system indicators or cumulative stress system dysregulations and suicide ideation without a past suicide attempt.

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Data availability statement

According to European law (GDPR) data containing potentially identifying or sensitive patient information are restricted; our data involving clinical participants are not freely available in a public repository. However, data are – under some specifications - available upon request via the NESDA Data Access Committee (nesda@ggzingeest.nl). See also our website: www.nesda.nl.

Declaration of Competing Interest

B. Penninx received (non-related) research funding from Boehringer Ingelheim and Jansen Research. The other authors declare that they have no conflict of interest.

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Supplementary data

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