At mission's end: the long-term impact of deployment on mental health

Wal, S.J. van der

At mission's end

The long-term impact of deployment on mental health

De missie voorbij

De lange-termijn impact van een militaire uitzending
op mentale gezondheid

Sija Janneke van der Wal

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Cover image	'Aap in kooi' (2018) by Stef Fridael *'Monkey in cage' is a painting in which artist Stef Fridael (an Afghanistan-veteran himself) depicts the state of mind of someone who is confronted with the long-term processing of military trauma*
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"Een mensenleven is een verzameling, een enorme opeenhoping bewegingen en denkbeelden. Het meeste gaat voor altijd verloren en het kan niet anders of het geheugen begaat in de keuze van wat het vasthoudt of verliest, een wanhopige willekeur."

W.F. Hermans
'Preambule' in Paranoia

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CHAPTER 1

GENERAL INTRODUCTION

It was a day intended to bring closure. On June 24, 2021 a twenty-year period of Dutch military involvement in Afghanistan was put to an end through the transfer of two flags. One flag had flown on 'Kamp Holland' in Tarin Kowt, Uruzgan, the other one on 'Kamp Marmal' in Mazar-e-Sharif. The last deployed soldiers would return home in the coming days. It was not just a distinctive moment in Dutch military history that marked the end of an era. It was also a moment of closure and remembrance for the almost 30,000 Dutch veterans who had committed themselves to provide peace and security in a country they knew little or nothing about. This commitment was not without risk. On June 24, 2021, the sacrifices made were symbolized by 25 empty chairs. Chairs that were intended for the soldiers who did not return home safely.

First, let's go back to 2001. The United States declared the war on terrorism after the September 11, 2001 terrorist attacks. As stated by President George W. Bush, *"a war against all those who seek to export terror, and a war against those governments that support or shelter them"*[1]. The United States exerted tremendous pressure on the Afghan regime to extradite the instigators of the terror attacks. When the government in Kabul refused, the United States decided to overthrow the Taliban regime. In addition to military action, the United States and its coalition allies would provide humanitarian aid to the citizens of Afghanistan. The International Security Assistance Force (ISAF) was established pursuant to the Bonn Agreement. This agreement outlined that a peace force, mandated by the United Nations Security Council, would assist the Afghan authorities in maintaining security in Kabul and the surrounding areas by training the Afghan National Security Forces and rebuilding government institutions[2]. However, it gradually engaged in the broader war in Afghanistan and more intensive combat against the Taliban insurgency[3]. In October 2003, the United Nations Security Council authorized NATO to expand ISAF's area of operations beyond Kabul. In phase I, Provincial Reconstruction Teams (PRTs) were deployed in the northern provinces. In phase II, ISAF's area of operations was extended to the western provinces. During phase III, NATO became operational in the south. Finally, in the fall of 2006, when entering phase IV, NATO took command of the whole of Afghanistan[3].

The Dutch contribution to ISAF started when the Dutch government made an infantry company available at the end of 2001. Over time, the Dutch armed forces contributed in several ways to the ISAF mission. Of particular interest for the present dissertation is the contribution to the PRTs from June 2004 until October 2006 in the northern province of Baghlan and the contribution to Task Force Uruzgan (TFU) from August 2006 until August 2010 in the southern part of Afghanistan. The PRT assessed humanitarian needs and implemented, in cooperation with local communities, small-scale reconstruction projects, and supported the central government in its efforts to maintain and extend its

authority. TFU's task was to maintain order in the province of Uruzgan so that properly functioning public administration and reconstruction were possible[4]. In total, 24,844 Dutch soldiers contributed to ISAF and its mission[2].

Apart from the reason for the mission, its final achievements or its political sensitivity, this dissertation is above all about the military personnel who served in Afghanistan, from the infantry soldier to the military nurse or the logistics officer. Most of them described their deployment as a positive experience. They finally received the chance to perform the tasks they trained for and which may have been the reason for them to join the army in the first place. Perhaps even more importantly, they experienced a sense of comradeship that one can hardly encounter in civilian life. Despite these mostly positive memories, all of them encountered negative feelings or stressful events during their deployment. Being exposed to enemy fire, witnessing people suffering, seeing a colleague injured or even killed, or getting rejected by the local population are only a few examples of frequently reported stressors[5].

After homecoming, the majority of deployed personnel adapted relatively easily to normal life, which indicates the great remarkable of this group of individuals. Unfortunately, this was not the case for all of them. Back home, they have experienced many kinds of difficulties. Commonly reported issues are persistently re-experiencing a traumatic event, trying to avoid situation and feelings that are reminiscent of the event, having negative thoughts and feelings, and experiencing increased arousal[6]. The development of posttraumatic disorder (PTSD) symptoms is not unusual. Besides PTSD symptoms, aggressive behaviour, generalised anxiety, feelings of sadness and emptiness, sleeping problems, and unexplained physical complaints are also commonly seen. Several veterans have taken the brave step to speak publicly about their experiences within the aftermath of their deployment. This has resulted in a wide variety of valuable stories captured in books, interviews, and documentaries[7-11].

It is of great importance that the personal stories of our Afghanistan veterans are told, shared and preserved. Their stories are often shocking and gripping, but essential for our society to develop a more realistic view of war and its consequences. For this purpose, it is also of great relevance to record the impact of military missions on deployed soldiers more scientifically. And this is precisely the reason why the Prospective Research In Stress-related Military Operations (PRISMO) study was initiated in 2005. At that time, there were only very few longitudinal studies in military cohorts, and available cross-sectional studies in PTSD showed major shortcomings. The PRISMO study is a large prospective cohort study in a group of Dutch ISAF veterans with a follow-up period of ten years. The aim of this study was twofold. First, it aimed to provide

epidemiological evidence to record the long-term consequences of military deployment on mental health. This may include for example the extent of PTSD or depression symptoms in the veteran population. Epidemiological information like this can be included in the decision-making process for future military missions and may help to adapt military mental health care to the needs of veterans. Secondly, the PRISMO study aimed to map the role of different biological and psychological factors that may contribute to the development of stress-related mental health symptoms. Identification of such factors can eventually inform the development of pre-deployment screening tools or interventions to reduce the development of mental health symptoms after deployment. The combination of longitudinal research and the inclusion of biological variables made PRISMO a unique study in the field.

Prospective cohort studies in deployed military personnel have proven to be invaluable to the investigation of the consequences of deployment on mental health. Since the introduction of the diagnosis of PTSD in the third edition of the Diagnostic and Statistical Manual of Mental Disorders[12] in 1980, the long-term impact of psychological trauma has gained a more widespread recognition, also in a military context. Catalysed by society's concern regarding the mental health of military service members involved in the recent military missions in the Balkans, Iraq, and Afghanistan, several prospective military cohort studies were designed and implemented in the United Kingdom, the United States and The Netherlands. In contrast to cross-sectional studies, cohort studies allow the examination of symptom trajectories over time, the differentiation of risk factors from the consequences of developing a mental disorder, and the temporal effect of risk factors on these disorders. Cohort studies have therefore changed the research field and moved it forward. The PRISMO study was the first in the world to assess both biological and psychological measures in a large cohort of deployed military personnel using a prospective design, with measurements before and up to ten years after deployment. Later, other studies have followed this model. Other examples of important prospective longitudinal studies that address the impact of military service and deployment are Army STARRS[13], the Fort Campbell Cohort[14], the King's Cohort[15], the Marine Resilience Study[16], and the Millennium Cohort[17].

Throughout the years, the value of the PRISMO-study has been demonstrated. In addition to various individual scientific publications on a range of subjects such as health care utilization[18], impaired sleep[19], and personality[20], two dissertations have been published[21,22] that were entirely based on the PRISMO cohort. Each of them made their unique contribution to the pool of knowledge on military trauma and mental health, with the same strong conviction to identify risk factors for post-deployment mental health problems that may ultimately contribute to the prevention of severe mental

distress in future veterans. This is also true for the present dissertation. I had the privilege to conduct the final measurement in the PRISMO cohort in order to assess the long-term impact of military deployment on mental health. Using the collected data, I was able to paint a picture of the mental health of ISAF veterans ten years after they returned home from Afghanistan, and to present some initial leads for the prevention of combat-related mental health symptoms.

To guide you through these findings in the coming chapters, I will first give a detailed overview of the goals, methods, and previous scientific output of the PRISMO study (chapter 2). Next, I will describe the long-term development of respectively PTSD symptoms and agoraphobia, anxiety, depression, and hostility symptoms, and the risk factors associated with those symptoms (chapters 3 and 4). Then, I will report the findings of a study in epigenetics. This chapter describes the associations between the development of PTSD symptoms and longitudinal changes in the DNA methylome of deployed military personnel (chapter 5). Finally, I will present a random forest method to predict the development of PTSD symptoms up to ten years after deployment using pre-deployment variables (chapter 6). With this dissertation, I intended to provide a scientific basis identifying the critical components of the picture that has emerged from the personal stories of thousands of veterans: military trauma may also manifest several years after the actual exposure and may impact everyday life even longer.

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CHAPTER 2

COHORT PROFILE: THE PROSPECTIVE RESEARCH IN STRESS-RELATED MILITARY OPERATIONS (PRISMO) STUDY IN THE DUTCH ARMED FORCES

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ABSTRACT

Purpose

The Prospective Research in Stress-Related Military Operations (PRISMO) study was initiated to gain a better understanding of the long-term impact of military deployment on mental health, and to map the different biological and psychological factors that contribute to the development of stress-related mental health symptoms.

Participants

The PRISMO cohort consists of a convenience sample of Dutch military personnel deployed to Afghanistan between 2005 and 2008. Baseline data collection resulted in the recruitment of 1032 military men and women. Combat troops as well as non-combat support troops were recruited to increase the representativeness of the sample to the population as a whole.

Findings to date

The prevalence of various mental health symptoms increases after deployment in PRISMO cohort members, but symptom progression over time appears to be specific for various mental health symptoms. For post-traumatic stress disorder, we found a short-term symptom increase within 6 months after deployment (8.2%), and a long-term symptom increase at 5 years after deployment (12.9%). Several biological vulnerability factors associated with the development of stress-related conditions after deployment were identified, including predeployment glucocorticoid receptor sensitivity and predeployment testosterone level. Thus far, 34 publications have resulted from the cohort.

Future plans

Various analyses are planned that will include the prevalence of mental health symptoms at 10 years postdeployment, as well as trajectory analyses that capture the longitudinal development of symptoms. Furthermore, we will use a machine learning approach to develop predictive and network models for several mental health symptoms, incorporating biological, psychological and social factors.

INTRODUCTION

The Prospective Research In Stress-related Military Operations (PRISMO) study was initiated in 2005 by the Research Centre of the Military Mental Healthcare at the Dutch Ministry of Defence to prospectively and longitudinally study the biological underpinnings of the mental health of Dutch troops deployed to Afghanistan. At the time of the study's start, the long-term impact of deployment and exposure to traumatic events in wartime on mental health had already gained widespread recognition, as epidemiological evidence from a range of studies indicated that the incidence of mental health problems after deployment was quite substantial[1]. However, both aetiological evidence as well as biological determinants were sparse, even though they were highly warranted. We therefore facilitated prospective research on the correlation between stress-related systems and the occurrence of mental health problems that were presented in deployed troops. Considering its size and estimated duration, the Dutch participation in the International Security Assistance Force (ISAF) in Afghanistan offered a unique opportunity to gain excellent understanding of the long-term impact of military deployment on mental health, and to map the different biological and psychological factors that contributed to the development of stress-related mental health symptoms. Whereas other cohort studies have attempted to address the impact of military service and deployment on mental health, the PRISMO study is different from other cohorts in including a predeployment measurement (cf. The King's Cohort[2]), collecting biological data in addition to psychological data (cf. The Millennium Cohort[2], The Cooperative Studies Programme No. 566[3]), and including a long-term follow-up period up to 10 years after deployment (cf. The Army Study to Assess Risk & Resilience in Service members - Pre/Post Deployment Study,[4] Marine Resilience Study[5]). The findings generated by the PRISMO cohort can contribute to an outlook on vulnerability and resilience, while they are also aimed at aiding the identification of factors in order to protect the mental health of service personnel and veterans. The objective of the present paper is to provide a complete overview of the PRISMO cohort study and its most important findings to date.

COHORT DESCRIPTION

Study participants, design and follow-up

The PRISMO cohort aimed to recruit a convenience sample of 1000 military men and women who were deployed to Afghanistan between 2005 and 2008 as part of the ISAF, either as part of a Provincial Reconstruction Team or as part of Task Force Uruzgan. ISAF's most important objective was enabling the Afghan authorities to

provide national security across national territory, and building the capacity of the Afghan National Security Forces. The sample size of the PRISMO cohort was based on a desired number of 50 post-traumatic stress disorder (PTSD) cases in the cohort and an anticipated 5% prevalence of PTSD in the study population. Recruitment ran from March 2005 to May 2008 through oral presentations of the study at various army bases in the Netherlands. Both combat troops as well as non-combat support troops were recruited to increase the representativeness of the sample to the population as a whole. A financial compensation was offered in exchange for participation. After reading the study information, a total of 1032 potential participants signed up for participation prior to deployment and provided written informed consent. A total of 1007 study participants were deployed for about 4 months. The total sample represents approximately 4% of those deployed to Afghanistan as part of the Dutch contribution to ISAF. PRISMO cohort demographics and other characteristics are described in Table 1. Complete information on demographics is not available for the full cohort of Dutch ISAF veterans. Therefore we cannot be sure of the representativeness of the sample. The study was approved by the Institutional Review Board of the University Medical Centre Utrecht (Utrecht, The Netherlands).

Up to now, PRISMO has had six completed rounds of measurements spread out over 5 years (Figure 1). The seventh round of measurements (10-year follow-up) is currently carried out and planned to be completed in 2019. The baseline measurement (T_0) was carried out approximately 1 month before deployment and completed at the army base. Collection of blood samples was performed between 07:00 and 09:00 at the base. Participation also included collection of saliva samples on two consecutive days, with participants sending in their batches by mail. The first two follow-up assessments were also completed at the army base, at approximately 1 month (T_1) and 6 months (T_2) after the soldiers returned home. The 1-year (T_3), 2-year (T_4) and 5-year (T_5) assessments were completed at home. Questionnaires were sent in by mail (T_3 and T_4) or were completed online (T_5). Currently, the 10-year follow-up (T_6) is conducted at the Research Centre of the Military Mental Healthcare. Participants are invited for a face-to-face interview and for filling in questionnaires. Those participants who do not wish to partake in an interview are asked to fill out questionnaires at home. Psychiatric diagnoses derived from the structural clinical interview are lacking for this group.

Table 1. Pre-deployment characteristics of the PRISMO cohort (N=1007).

Variable	N	%
Gender		
Male	921	91.5
Female	86	8.5
Age (years)[a]		
< 21	139	13.9
21-24	327	32.7
25-29	201	20.1
30-34	118	11.8
35-39	68	6.8
40-44	64	6.4
≥ 45	83	8.3
Education level[a,b]		
Low	366	40.0
Moderate	442	48.4
High	102	11.2
Relationship[a]		
Yes	552	61.6
No	344	38.4
Rank[a]		
Private	394	40.2
Corporal	203	20.7
Non-commissioned officer	251	25.6
Staff officer	132	13.5
Previous deployments[a]		
0	479	53.3
1	229	25.5
2	104	11.6
≥ 3	87	9.7

Note: [a] sample sizes might not add up to total participants due to missing data in the descriptive values. [b] Education (ISCED levels): low=primary and lower secondary education; moderate=upper secondary, post-secondary non-tertiary, and short cycle tertiary education; high=bachelor, master, and doctoral education.

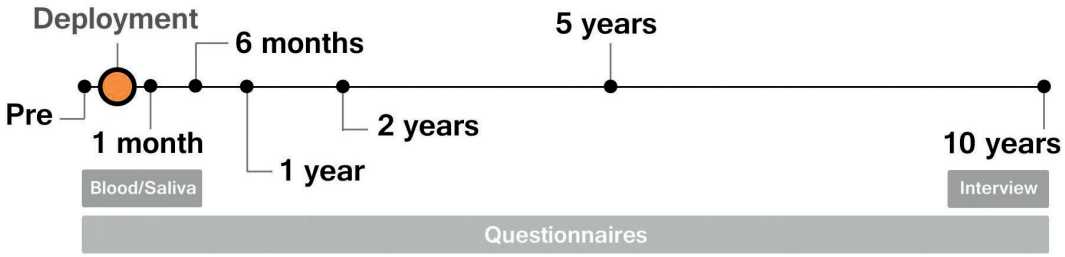

Figure 1. Design of the Prospective Research in Stress-Related Military Operations Study.

In order to minimise dropout in the follow-up assessments, all participants were repeatedly contacted (up to five times) through email, mail and/or telephone, in order to remind them to complete the questionnaires. Still, response rates dropped (Figure 2), and at the fifth follow-up measurement (5-year postdeployment), a total of 581 respondents of the original sample were retained. Detailed information on attrition can be found in Table 2, where information on differences in demographic characteristics between those remaining in the cohort at the 5-year assessment and those lost to follow-up is presented. Prior to deployment, dropouts were significantly younger, had a lower education level, were more likely to be in a relationship, had a lower rank during deployment and had less often been deployed prior to this deployment. Dropouts also more often had a function outside the military base during their deployment in comparison to participants that remained in the cohort.

Study measures

The PRISMO study contains a wide variety of measures that are listed in Table 3. All data were collected via blood samples, saliva samples, validated questionnaires and interviews. The data include the biological and psychological measures that we considered to be relevant for mental health in a military population, with special focus on stress-related mental health symptoms. Biological parameters in the field of stress regulatory systems—and related neuroendocrine and immunology systems—were determined during expert meetings at the time of study set-up. It must be noted that, since the moment of the study's design, the field of (epi)genetics has developed with much potential for prospective studies. The biological PRISMO samples have therefore been used for research opportunities that became known later on in the study.

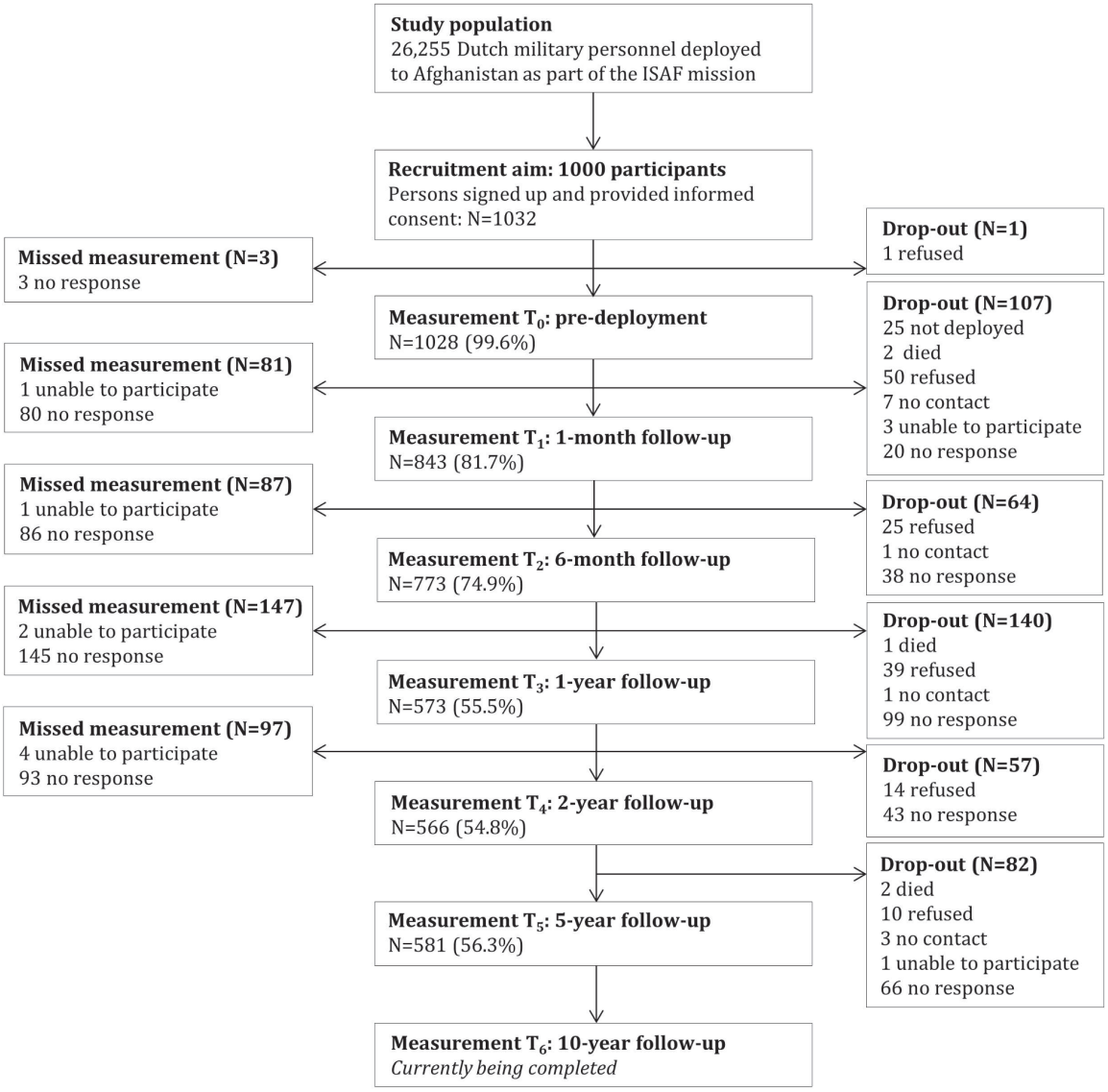

Figure 2. Participation in the Prospective Research in Stress-Related Military Operations study. 'Missed measurement' (on the left) includes participants who missed the indicated measurement, but participated again in later measurements. 'Drop-out' (on the right) includes participants who definitively dropped out of the study.

Table 2. Results of the drop-out analysis of several demographic characteristics.

	Participants remaining in the cohort until 5-year follow-up (N=581)[a] Count (%)	Participants lost to follow up until 5-year follow-up (N=451)[a] Count (%)	p-value
Gender	*(N=581)*	*(N=451)*	
Male	527 (90.7%)	412 (91.4%)	0.719
Female	54 (9.3%)	39 (8.6%)	
Age	*(N=580)*	*(N=445)*	
Mean (SD)	30.7 (9.50)	25.4 (6.95)	<0.001
Education	*(N=542)*	*(N=390)*	
Low	173 (31.9%)	202 (51.8%)	<0.001
Moderate	284 (52.4%)	168 (43.1%)	
High	85 (15.7%)	20 (5.1%)	
Relationship	*(N=539)*	*(N=379)*	
Yes	181 (33.6%)	169 (44.6%)	0.001
No	358 (66.4%)	210 (55.4%)	
Rank	*(N=578)*	*(N=424)*	
Private	169 (29.2%)	232 (54.7%)	<0.001
Corporal	113 (19.6%)	94 (22.2%)	
Non-commissioned officer	191 (33.0%	68 (16%)	
Staff officer	105 (18.2%)	30 (7.1%)	
Previous deployment	*(N=531)*	*(N=389)*	
0	246 (46.3%)	245 (63.0%)	<0.001
1	140 (26.4%)	95 (24.4%)	
≥2	145 (27.3%)	49 (12.6%)	
Function during deployment	*(N=474)*	*(N=344)*	
Inside	187 (39.5%)	68 (19.8%)	<0.001
Outside	244 (51.5%)	246 (71.5%)	
Both	43 (9.1%)	30 (8.7%)	
Deployment year	*(N=581)*	*(N=451)*	
2005/2006	152 (26.2%)	112 (24.8%)	0.628
2007/2008	429 (73.8%)	339 (75.2%)	

Note: [a] sample sizes might not add up to total participants due to missing data in the descriptive values. [b] Education (ISCED levels): low=primary and lower secondary education; moderate=upper secondary, post-secondary non-tertiary, and short cycle tertiary education; high=bachelor, master, and doctoral education. SD: standard deviation. Differences on descriptive characteristics between those remaining in the cohort and those lost to follow up were tested with a *t*-test (continuous) or χ^2-test (categorical).

Table 3. Main study measures in PRISMO over time.

	T_0: Pre-deployment	T_1: 1-month follow-up	T_2: 6-month follow-up	T_3: 1-year follow-up	T_4: 2-year follow-up	T_5: 5-year follow-up	T_6: 10-year follow-up
(Epi) Genetics							
Telomere length	Plasma	Plasma	Plasma				
DNA methylation	Plasma	Plasma	Plasma				
GR and FKBP5 SNPs	Plasma	Plasma	Plasma				
mRNA expression PBMCs	Plasma	Plasma	Plasma				
Immunology							
Leukocyte subpopulations	Plasma	Plasma	Plasma				
T-cell cytokine secretion	Plasma	Plasma	Plasma				
PBMC glucocorticoid binding	Plasma	Plasma	Plasma				
PBMC IL-1β reactivity	Plasma	Plasma	Plasma				
Neuro-endocrinology							
Testosterone	Plasma	Plasma	Plasma				
Cortisol	Plasma, Salivary	Plasma, Salivary	Plasma, Salivary				
SHBG	Plasma	Plasma	Plasma				
Oxytocin	Plasma	Plasma	Plasma				
Vasopressin	Plasma	Plasma	Plasma				
Neuropeptide Y	Plasma	Plasma	Plasma				
GABA	Plasma	Plasma	Plasma				
Demographic factors	Self-report	Self-report	Self-report	Self-report	Self-report	Self-report	Self-report, Interview

Table 3. (Continued)

	T_0: Pre-deployment	T_1: 1-month follow-up	T_2: 6-month follow-up	T_3: 1-year follow-up	T_4: 2-year follow-up	T_5: 5-year follow-up	T_6: 10-year follow-up
General health and psychological morbidity							
Physical health	Self-report	Self-report	Self-report	Self-report	Self-report		Interview
Psychological symptoms	SCL-90-R	SCL-90-R	SCL-90-R	SCL-90-R	SCL-90-R	BSI	SCL-90-R, M.I.N.I. Plus
Depression				CES-D	CES-D	CES-D	CES-D
PTSD	SRIP	SRIP	SRIP	SRIP	SRIP	SRIP	SRIP
Fatigue	CIS-20R	CIS-20R	CIS-20R	CIS-20R	CIS-20R	CIS-20R	CIS-20R
Alcohol use							AUDIT
Burnout	UBOS	UBOS	UBOS				
Quality of life							SF-36
Healthcare utilization						Self-report	Self-report
Production losses						SF-HLQ	SF-HLQ
Life events							
Life events				Self-report	Self-report	Self-report	Self-report, Interview
Early trauma	ETISR-SF						
Personality and coping							
Hostility	CMHS	CMHS	CMHS	CMHS	CMHS		
Type-D personality	DS-14	DS-14	DS-14	DS-14	DS-14	DS-14	
Temperament and character	TCI-SF	TCI-SF	TCI-SF		TCI-SF	TCI-SF	TCI-SF
Anger							STAXI-2
Coping style				Brief-COPE	Brief-COPE	Brief-COPE	

Table 3. (Continued)

	T_0: Pre-deployment	T_1: 1-month follow-up	T_2: 6-month follow-up	T_3: 1-year follow-up	T_4: 2-year follow-up	T_5: 5-year follow-up	T_6: 10-year follow-up
Social support							
General support						SSL-6	SSL-6
Deployment social support				DRRI-F	DRRI-F		
Postdeployment support				DRRI-L	DRRI-L		
Deployment experience							
Combat exposure		DES					Interview
Traumatic Blast						BTBIS	
Re-integration after deployment				PDRS	PDRS		
Moral injury							MIQ-M
Meaning							ZGL

AUDIT, Alcohol Use Disorders Identification Test[30 31]; Brief-COPE, Brief COPE Inventory[32]; BSI, Brief Symptom Inventory[4 33]; BTBIS, Brief Traumatic Brain Injury Screen[34–36]; CES-D, Centre for Epidemiologic Studies Depression Scale[37]; CIS-20R, Checklist Individual Strength[10 38]; CMHS, Cook-Medley Hostility Scale[39 40]; DES, Deployment Experience Scale[24]; DRRI, Deployment Risk and Resilience Inventory[41]; DS-14, Type-D Scale[42]; ETISR-SF, Early Trauma Inventory-Self Report[43]; GR, Glucocorticoid receptor; M.I.N.I. Plus, MINI-International Neuropsychiatric Interview-Plus[11]; MIQ-M, Moral Injury Questionnaire-Military version[44]; PBMC, Peripheral blood mononuclear cells; PDRS, Post-Deployment Reintegration Scale[45]; SCL-90-R, Symptom CheckList[8 46 47]; SF-36, Medical Outcome Study Short-Form Survey[48 49]; SF-HLQ, Short Form-Health and Labour Questionnaire[50 51]; SHBG, Sex hormone-binding globulin; SNP, Single nucleotide polymorphism; SRIP, Self-Rating Inventory for PTSD[6 7]; SSL-6, Social Support List[52 53]; STAXI-2, State-Trait Anger Expression Inventory-2[54 55]; TCI-SF, Temperament and Character Inventory-Short Form[56 57]; UBOS, Utrecht Burnout Scale[58 59]; ZGL, Zingevingslijst[60].

Outcomes

The primary outcome in PRISMO is psychological morbidity, which was measured with several validated questionnaires. Symptoms of PTSD were measured with the Dutch Self-Rating Inventory for PTSD (SRIP)[6], a questionnaire with good internal consistency, discriminant validity and concurrent validity with other PTSD measures[6,7]. Throughout the study, other mental health problems were assessed using the depression, anxiety, somatic symptoms and hostility subscales of the Dutch revised Symptom Checklist (SCL-90-R)[8] or the Dutch Brief Symptom Inventory (BSI)[9], while fatigue was measured using the Checklist Individual Strength (CIS20-R)[10].

Covariates

A wide range of covariates has been measured in PRISMO. Biological covariates included several (epi)genetic measures (e.g., telomere length, DNA methylation), immunological measures (e.g., cytokine secretion, glucocorticoid binding) and neuroendocrinological measures (e.g., hormone levels). Psychological covariates included demographic factors, deployment experience, important life events (e.g., serious illness, death of a significant other, break up, marriage, financial problems), early trauma, personality, coping style and social support. A full list of the used questionnaires and information on the validity of the instruments can be found in Table 3 and the cited references.

Cohort subsamples

In 2011, PRISMO started an additional measurement on a subsample of the cohort, PRISMO+. The aim of this substudy was to validate self-reported symptoms on questionnaires by means of comparison to reported symptoms in a structured clinical interview and anamnesis (i.e., the participant's medical history as by their own recollection). The sample was based on random sampling in four subgroups of PRISMO participants: participants with substantial PTSD symptoms, participants with substantial depressive mood symptoms, participants with substantial fatigue symptoms and participants without symptoms on previous completed questionnaires. In total, 141 participants completed the additional assessment consisting of the M.I.N.I. International Neuropsychiatric Interview Plus[11], the Clinician Administered PTSD Scale[12], an anamnesis, and the self-report measures BSI[9], SRIP[6] and CIS20-R[10]. Furthermore, a second related substudy was set up: PRISMO SCAN[13–15]. This study was performed in a small subsample (n=33) of the initial cohort supplemented with a control group of soldiers who were never deployed. It is composed of functional MRI (fMRI) scanning, both prior to deployment and twice after return home. The aim of this study was investigating the effects of severe stress on neural functioning, together with the factors that mediate individual differences in the neural sequelae of stress[13].

Patient and public involvement

The PRISMO cohort is set up in response to the increased demand for knowledge about prevalence rates and aetiology of stress-related conditions after deployment. Although we always kept the interest of veterans' mental health in mind, veterans were not involved in the design, recruitment or conduct of the study. Results of the study are disseminated to study participants by the studies website, newsletters, public summaries and individual feedback during the final follow-up measurement.

Findings to date

Research with PRISMO data covers a wide range of topics and methods for data analysis. In this section, we summarise the key findings on the most important research themes that the PRISMO cohort has contributed to. To date, a total of 34 publications have resulted from the cohort. A complete list of publications can be found online (www.prismo.nl).

The identification of single biological vulnerability factors associated with the development of stress-related conditions after deployment is one of the most important topics within PRISMO. We first focused on the glucocorticoid receptor (GR) and found that, relative to matched comparison subjects, the predeployment GR number in peripheral blood mononuclear cells was significantly higher in participants who developed a high level of PTSD symptoms postdeployment[16]. This difference in glucocorticoid sensitivity persisted until at least 6 months after the return from deployment[17]. The sensitivity of the GR also appeared to play a role in the development of depressive or fatigue symptoms postdeployment[17,18].

More recently, several peripherally measured neuroendocrine factors as potential biomarkers were studied. It was shown that a lower predeployment testosterone level was predictive for the development of PTSD symptoms at 1 and 2 years after deployment[19]. Levels of neuropeptide Y, oxytocine and arginine vasopressin were not found to be related to the level of reported PTSD symptoms over time[20,21]. In the genetic chapter of the PRISMO study it was shown that postdeployment longitudinal decreases in methylation of the SKA2 gene, a gene involved in GR transactivation, were associated with the development of PTSD symptoms after return[22]. In addition, our genome-wide blood DNA methylation analysis identified three other novel genomic regions where longitudinal decreases in DNA methylation mark PTSD susceptibility[23].

Another important part of the research using PRISMO data has concerned the prevalence and developmental trajectories of various mental health problems in the years after deployment. It showed that the prevalence of various mental health

symptoms increases after deployment, but symptom progression over time appears to be specific for various mental health symptoms (Figure 3)[24]. To assess PTSD symptom development in more detail, PTSD symptoms were longitudinally assessed up to 5 years after deployment. Besides a short-term symptom increase within the first 6 months after deployment (8.2% above cut-off on a self-report PTSD questionnaire), we found a long-term symptom increase at 5 years after deployment (12.9% above cut-off)[25]. Furthermore, three developmental trajectories were identified using a latent growth mixture model (Figure 4): a low stable trajectory of PTSD symptoms (resilient; 85.2%), a trajectory showing a moderate level of symptoms that increased strongly after 2 years postdeployment (delayed onset; 9.4%) and a trajectory with initially increasing symptoms that decreased after the first year postdeployment (recovered; 5.3%)[25].

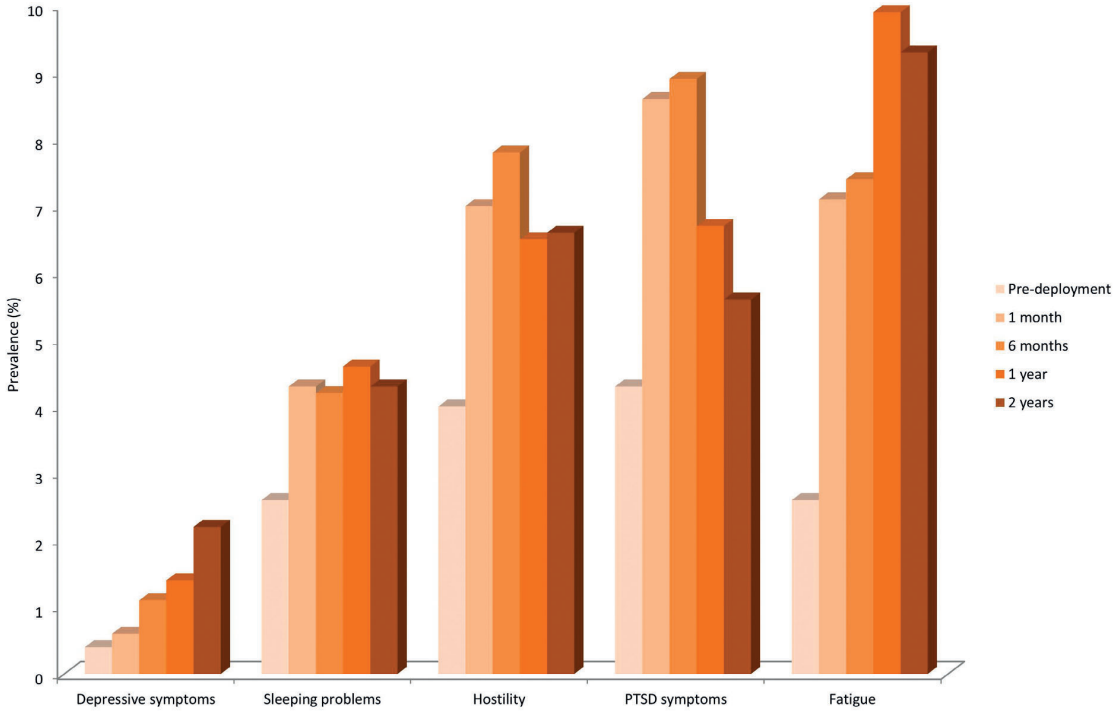

Figure 3. Prevalence of mental health symptoms in the Prospective Research in Stress-Related Military Operations cohort. Prevalence rates for all questionnaires were estimated based on 95th percentile scores as reported in the respective manuals or source publications. Changes in all prevalence rates from baseline to 1 month postdeployment were significant.

Strengths and limitations

PRISMO is unique in being the first study to assess both biological and psychological measures in a large cohort of deployed military personnel using a prospective longitudinal design, with measurements before and up to 10 years after deployment. This design enabled a differentiation of a range of vulnerability factors for the onset and course of stress-related mental health problems.

However, the large size and complexity of the cohort necessitates a discussion on some important limitations.

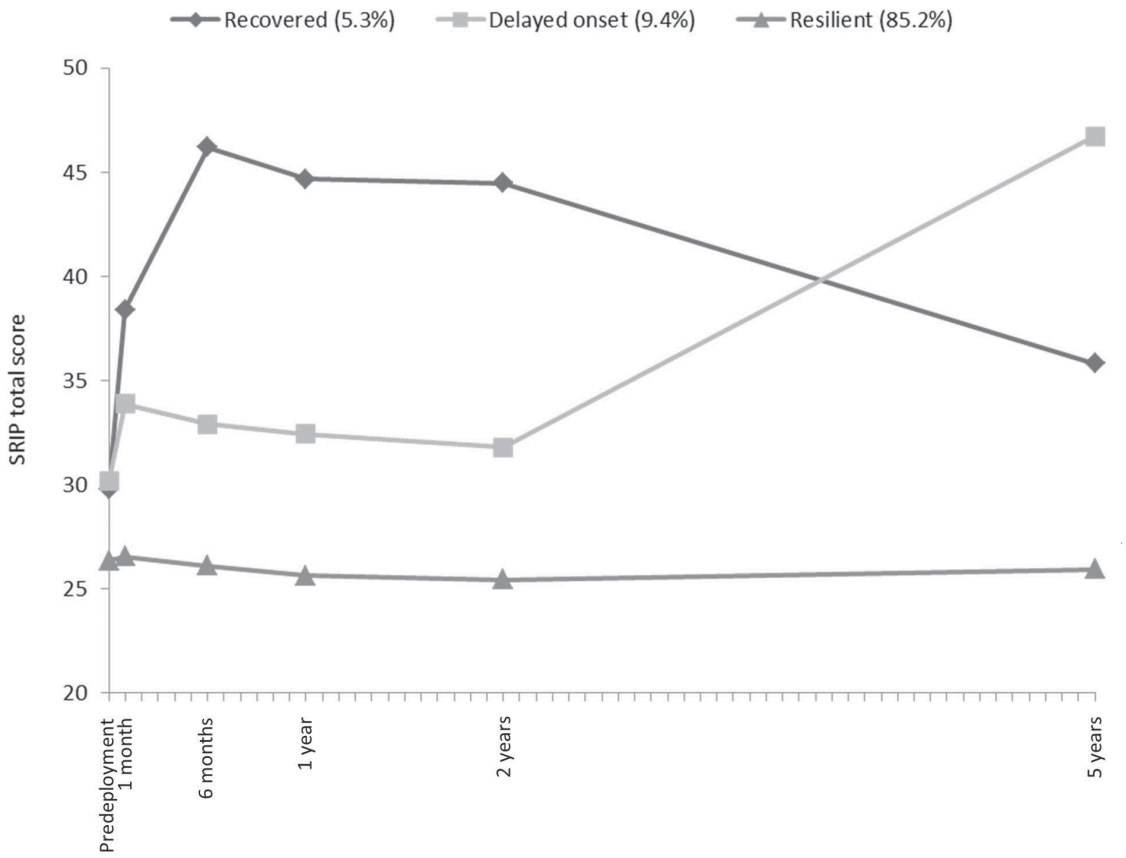

Figure 4. Latent developmental trajectories of post-traumatic stress symptoms in the Prospective Research in Stress-Related Military Operations cohort (n=960). SRIP, Self-Rating Inventory for Post-Traumatic Stress Disorder.

PRISMO largely relies on self-report measures and is therefore subject to the inherent biases associated with studies of this kind. Although standardised and validated screening instruments were used to measure the prevalence of mental health problems, it might have resulted in higher prevalence estimates compared with clinician diagnoses[26,27]. This potential source of bias can be assessed using the diagnoses derived from the clinical interview in the 10-year follow-up, which is currently being conducted. On the other hand, mental health symptoms may be under-reported given the stigma attached to mental disorders, especially within military populations[28,29]. Although attrition is inevitable in longitudinal cohort studies, it is obviously a concern. We were able to maintain approximately 55% of the original sample for the 1-, 2- and 5-year assessment. As we have showed before, dropouts differed significantly on several baseline characteristics from the respondents who remained in the cohort. Influence of non-response on the study findings can therefore not be ruled out and

might limit generalizability. However, the effects of this limitation can be reduced by use of statistical imputation techniques. Finally, there is no non-deployed control group included in this study, and the effects found therefore cannot be solely attributed to deployment. The inclusion of such a control group in future research would therefore be recommended.

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CHAPTER 3

LONG-TERM DEVELOPMENT OF POST-TRAUMATIC STRESS SYMPTOMS AND ASSOCIATED RISK FACTORS IN MILITARY SERVICE MEMBERS DEPLOYED TO AFGHANISTAN: RESULTS FROM THE PRISMO 10-YEAR FOLLOW-UP

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ABSTRACT

Background

Symptoms of post-traumatic stress disorder (PTSD) can manifest several years after trauma exposure, and may impact everyday life even longer. Military deployment can put soldiers at increased risk for developing PTSD symptoms. Longitudinal evaluations of PTSD symptoms in deployed military personnel are essential for mapping the long-term psychological burden of recent operations on our service members, and may improve current practice in veterans' mental health care.

Methods

The current study examined PTSD symptoms and associated risk factors in a cohort of Dutch Afghanistan veterans 10 years after homecoming. Participants (N = 963) were assessed seven times from predeployment up to 10 years after deployment. Growth mixture modeling was used to identify distinct trajectories of PTSD symptom development.

Results

The probable PTSD prevalence at 10 years after deployment was 8%. Previously identified risk factors like younger age, lower rank, more deployment stressors, and less social support were still relevant 10 years after deployment. Four trajectories of PTSD symptom development were identified: resilient (85%), improved (6%), severely elevated-recovering (2%), and delayed onset (7%). Only the delayed onset group reported increasing symptom levels between 5 and 10 years postdeployment, even though 77% reported seeking help.

Conclusions

This study provides insights into the long-term burden of deployment on the psychological health of military service members. It identifies a group of veterans with further increasing PTSD symptoms that does not seem to improve from currently available mental health support, and underlines the urgent need for developing and implementing alternative treatment opportunities for this group.

INTRODUCTION

With over 25,000 troops deployed during 2005–2011, the Dutch participation in the International Security Assistance Force (ISAF) in Afghanistan was the first time the Dutch armed forces conducted a military mission of this size and complexity. In addition to the service members who lost their lives or suffered serious injuries during combat actions, the mission also left its psychological marks. As historical military conflicts teach us, signs of post-traumatic stress disorder (PTSD) can manifest several years or sometimes decades after the actual traumatic exposure, and may impact everyday life even longer[1]. Longitudinal, long-term evaluations of PTSD symptoms in this recently deployed group of military personnel are essential for mapping the psychological burden of recent operations on our service members, which may improve current practice in veterans' mental healthcare and inform policymaking in future missions.

Different coalition partners have reported on the prevalence of PTSD in their deployed troops[2,3]. The pool of longitudinal studies that assessed military personnel on multiple time points is on the other hand less extensive, and available studies often ran for a limited period of time. Studies in U.S. National Guard soldiers[4] and in U.K.[5] and Dutch[6] armed forces deployed to Iraq or Afghanistan suggest a trend of stabilizing or aggravating PTSD prevalence rates in service members deployed in recent military missions, and underline the importance of long-term monitoring of the mental health of deployed personnel. Despite the importance of prevalence rates for expressing the impact of deployment on the psychological wellbeing of a whole military population and assessing treatment demands after homecoming, prevalence rates do not reflect the large heterogeneity in symptom development that exist between individuals. This heterogeneity can be addressed with the use of latent growth mixture modeling (LGMM) techniques. Recent longitudinal studies in military populations have utilized this approach, and identified distinct but overlapping trajectories of PTSD symptom development over time. Several studies report a three-class solution, but the shape of the trajectories vary and include resilient, improving, deteriorating, or chronic trajectories[4,6,7]. U.S. studies based on data of the Millennium Cohort, a large sample of U.S. active duty and reserve forces, are consistent in reporting a four-class solution involving a resilient, decreasing, increasing, and high symptom trajectory[8-10].

Beyond the traumatic experience itself, individual vulnerability factors can contribute to changes in PTSD symptom levels and developmental trajectories. Female gender, younger age, combat exposure, or previous trauma exposure are frequently identified as risk factors for combat-related PTSD[5,6,11]. Only a few studies aimed to identify vulnerability factors related to developmental trajectories of PTSD[4,7-10]. Factors related

to increases in PTSD symptom levels after deployment can help to identify who is most at risk for developing PTSD symptoms, even after the acute phase of trauma, and target follow-up screening accordingly.

In the current study, we report on findings from the 10-year follow-up measurement in the PRISMO cohort, a large cohort of Dutch military personnel deployed to Afghanistan[12]. Previous trajectory studies did not include a predeployment measurement[10], had short follow-up times no longer than 3 years[4], or included only a few follow-up measurements[7-9]. We extended this research by studying the effects of deployment on PTSD symptoms on the long term, using a unique follow-up period of 10 years with seven consecutive measurement points. We aimed to identify trajectories of PTSD symptom development and assessed the role of different covariates on the development of PTSD symptoms. We hypothesized that the probable 10-year PTSD prevalence would significantly decline compared to 5-year after deployment. Based on the three trajectories identified in our 5-year follow-up report[6], we predicted a three-class solution with a resilient trajectory, a recovered trajectory, and a delayed onset trajectory that show symptom improvement between 5- and 10-years postdeployment.

METHODS

Study design and participants

The present study is part of a large prospective cohort study on the development of stress-related mental health symptoms in deployed Dutch military personnel, the PRISMO study, which is described in detail elsewhere[12]. Recruitment resulted in the inclusion of 1,007 study participants, who were deployed for about 4 months in behalf of ISAF between March 2005 and September 2008. The baseline measurement was carried out approximately 1 month before deployment at the army base. The first two follow-up measurements were also completed at the army base, at approximately 1 and 6 months after the soldiers returned home. The 1-, 2-, and 5-year follow-up assessments were completed at home, and the 10-year follow-up was conducted at the research facility of the Military Mental Healthcare. All measurements consisted of paper-and-pencil questionnaires, except for the 5-year follow-up, which consisted of an online questionnaire. Written informed consent was obtained from all subjects. All procedures were approved by the Institutional Review Board of the University Medical Centre Utrecht (Utrecht, The Netherlands), approval number 01/333-0.

Measures

PTSD symptoms

For all assessments symptoms of PTSD were measured with the Self-Rating Inventory for PTSD (SRIP)[13], a Dutch questionnaire to assess PTSD symptoms in the past 4 weeks based on the DSM IV criteria for PTSD. The SRIP contains 22 questions with responses measured on a Likert scale ranging from 1 (never) to 4 (very frequent). A higher sum score indicated more symptoms (range 22–88). The SRIP showed good internal consistency, discriminant validity, and concurrent validity with other commonly used PTSD measures[13,14]. As recommended in the literature, a cut-off score of 38 was used to indicate substantial PTSD symptoms[13,15].

Covariates

At baseline, participants provided information about their sex, age, educational level, rank, and previous deployments. More detailed information on the measurement scales of demographic information can be found in the Supplementary material. Potential traumatic experiences before the age of 18 were also assessed at baseline using the Early Trauma Inventory Self Report-Short Form (ETISR-SF), a questionnaire containing 27 items, of which the total sum represents the total number of different potential traumatic events experiences[16]. At the first measurement after deployment, information on the participant's role during the mission was collected and divided in three categories: inside the base (function was exclusively carried out inside the military base; for example, logistics or medical work in the field hospital), outside the base (function was carried out outside the base; e.g., patrols), and both inside and outside the base (function included activities inside the base as well as outside the base). Their exposure to traumatic stress during deployment was assessed using the Deployment Experience Scale (DES), a 19-item deployment stressors checklist[17]. At all follow-up measurements, potential new deployments after the initial deployment at study inclusion were assessed. At the 1-year follow-up, social support during and after deployment were measured with the Deployment Risk and Resilience Inventory 1 (DRRI-1), a collection of measures for studying deployment-related experiences of military veterans[18]. Part F (support from other military personnel during deployment) and part L (support from family and friends after deployment) consists respectively of 12 and 15 items with responses on a Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree), where higher scores indicated more received support.

Mental health support

The receipt of psychological care was assessed by the item "Have you ever received any care for psychological health complaints after your deployment?" at the 10-year follow-up measurement (see Supplementary material).

Statistical analysis

We assessed the change in PTSD symptom level at 10 years after deployment relative to the predeployment level in a mixed model analysis. The time variable was recoded into six dummy variables, one dummy variable for each measurement after deployment, whereby predeployment served as the reference. Continuous, longitudinal PTSD symptom scores at all seven measurements were used as the outcome variable. Covariates were included separately in the mixed models. Participants were included in the analyses if they had a PTSD assessment at one or more time points. A two-tailed *p* value of less than 0.05 was considered statistically significant.

LGMM analyses were conducted in Mplus version 8.4 to identify trajectories of PTSD symptom development. Latent class growth analysis (LCGA) as well as growth mixture modeling (GMM) were performed to identify the best performing model[19]. The models were re-fitted with a quadratic term for time to assess whether nonlinear growth curves provided better fit to the data. The models reflected the number of months between the different assessments. Missing data over time in the outcome variable was handled by full information maximum likelihood estimation. Missing values in the covariates were handled by multiple imputation. All models were compared on fit indices, entropy, class size, and interpretability. The percentage of participants that received psychological treatment was calculated for each trajectory. The effect of covariates on the trajectory assignment was investigated in adjusted multinomial regression models, in which the class assignment output from the LGMM analysis was the outcome variable. A three-step approach was used to account for the classification error of belonging to trajectory classes[20]. Details about the trajectory analysis are described in the Supplementary material.

RESULTS

Between 2005 and 2008, a total of 1,032 participants signed up for participation to the PRISMO study prior to deployment. Twenty-five participants were eventually not deployed, leaving a total of 1,007 study participants. Of those participants, 44 had no PTSD measurement at any of the time points and were excluded from the analyses. The baseline characteristics are shown in Table 1. Compared to participants without a PTSD measurement, participants with a PTSD measurement were more frequently deployed in 2007/2008 compared to 2005/2006 ($p < 0.0001$) and had a lower early trauma score ($p = 0.001$) (see Table 1).

Table 1. Demographics and other characteristics of participants in the cohort who were deployed, separated for participants included in the mixed model and latent trajectory analyses and participants with missing outcome values.

	Participants with outcome values at one or more time points (n=963)[a]	Participants without any outcome values (n=44)[a]	p-value
Sex			
Male	878 (91%)	43 (98%)	0.128
Female	85 (9%)	1 (2%)	..
Age (years)[b]			
<21	130 (14%)	9 (23%)	0.091
≥21	831 (87%)	30 (77%)	..
Educational level[c]			
Low	33 (4%)	0 (0%)	0.615
Moderate	753 (85%)	22 (88%)	..
High	99 (11%)	3 (12%)	..
Rank[d]			
Private	378 (40%)	16 (57%)	0.297
Corporal	199 (21%)	4 (14%)	..
Non-commissioned officer	245 (26%)	6 (21%)	..
Staff officer	130 (14%)	2 (7%)	..
Previous deployment(s)[e]			
Yes	417 (48%)	7 (28%)	0.053
No	460 (53%)	18 (72%)	..
Role during deployment[f]			
Inside the military base	244 (31%)	4 (31%)	0.501
Both inside and outside the military base	73 (9%)	0 (0%)	..
Outside the military base	474 (60%)	9 (69%)	..
Deployment year			
2005 or 2006	237 (25%)	24 (55%)	**<0.0001**
2007 or 2008	726 (75%)	20 (46%)	..
New deployment(s)[g]			
Yes	318 (48%)	..	..
No	344 (52%)	..	..
DES (deployment stressors) total score[h]	4.51 (3.22)	4.50 (4.95)	0.996
DDRI-F (unit social support) total score[i]	45.39 (10.19)	..	..
DDRI-L (support after deployment) total score[j]	60.43 (9.16)	..	..
ETISR-SF (early trauma) total score[k]	3.45 (3.04)	6.14 (3.32)	**0.001**

Note: data are n (%) or mean (SD). Differences in descriptive characteristics between participants with SRIP and participants without SRIP were tested with a t-test (continuous) or $\chi 2$ (categorical). Bold indicates significant relationship ($p<0.05$). Abbreviations: DES, Deployment Experience Scale; ETISR-SF, Early Trauma Inventory Self Report-Short Form; SRIP, Self-Rating Inventory for Post-Traumatic Stress Disorder. [a] Sample sizes might not add up to total because of missing data in the descriptive variables; where there is missing data, the total is indicated. Totals for participants with an SRIP measurement: [b] n=961, [c] n=885, [d] n=952, [e] n=877, [f] n=791, [g] n=662, [h] n=705, [i] n=335, [j] n=334, [k] n=874; totals for participants without an SRIP measurement: [b] n=39, [c] n=25, [d] n=28, [e] n=25, [f] n=13, [g] n=0, [h] n=2, [i] n=0, [j] n=0, [k] n=14.

PTSD symptom increase and covariates

Mean PTSD symptom levels and probable PTSD rates at each time point are reported in Table 2. A full tabulation of the results for all analyses is shown in the Supplementary material. At the 10-year follow-up measurement, 8% of the participants reported substantial PTSD symptoms, which was a significant decline compared to 5-year postdeployment ($p < 0.0001$). The mean PTSD symptom score also significantly declined at 10-year follow-up to a score of 27.35 ($p = 0.046$). The mixed model analysis with only the time points included showed a significant increase of PTSD symptoms at 10 years after deployment relative to predeployment ($\beta = 0.84$, 95% confidence intervals [CI] = 0.34–1.34).

Table 2. Dutch military personnel deployed to Afghanistan reporting post-traumatic stress symptoms at each time point.

	Total number of participants with available data	Above cutoff[a]	Mean PTSD score
Pre-deployment	680	27 (4.0%)	26.76 (5.03)
1 month	753	62 (8.2%)	27.62 (6.14)
6 months	737	63 (8.5%)	27.73 (7.07)
12 months	562	38 (6.8%)	27.02 (6.94)
2 years	528	29 (5.5%)	26.64 (5.90)
5 years	559	72 (12.9%)	28.30 (8.07)
10 years	598	48 (8.0%)	27.35 (7.20)

Note: data are n, n (%), or mean (SD). Abbreviations: PTSD, post-traumatic stress disorder; SRIP, Self-Rating Inventory for Post-Traumatic Stress Disorder. [a] A PTSD score of 38 or higher on the SRIP was used as cutoff value.

The interactions of covariates with the change in PTSD symptoms 10-year postdeployment relative to predeployment are shown in Table 3. Age was significantly related to a lower increase in PTSD symptoms at 10 years after deployment ($\beta = -0.07$, 95% CI = −0.12 to −0.01), suggesting a higher increase in PTSD symptoms for younger military personnel and a lower increase in symptoms for older military personnel relative to predeployment. As age and rank were strongly correlated ($r = 0.73$), similar confounding effects were found for rank during deployment ($\beta = -1.36$, 95% CI = −2.38 to −0.35), where the lower ranking personnel (i.e., soldier and corporal ranks) had more increased PTSD symptoms compared to higher ranking personnel (i.e., noncommissioned and staff officers). Also, educational level was related to the increase in PTSD symptoms at 10 years postdeployment ($\beta = -3.99$, 95% CI = −7.27 to −0.71), where personnel with a low educational level had greater increase in symptoms than personnel with a high educational level.

Table 3. Covariates associated with an increase in PTSD symptoms ten year after deployment relative to pre-deployment.

	Increase in PTSD symptoms 10 year post-deployment β (95% CI)	**p-value**
Age	**-0.07 (-0.12 – -0.01)**	**0.016**
Educational level		
Low	0	
Moderate	-2.48 (-5.47 – 0.52)	0.105
High	**-3.99 (-7.27 – -0.71)**	0.017
Rank		
Soldier and corporal	0	
Non-commissioned officer and staff officer	**-1.36 (-2.38 – -0.35)**	**0.009**
Previous deployment(s)		
No	0	
Yes	-0.09 (-1.12 – 0.95)	0.868
Role during deployment		
Inside	0	
Both inside and outside	**2.79 (0.79 – 4.79)**	0.006
Outside	1.10 (-0.08 – 2.28)	0.067
Deployment year		
2005/2006	0	
2007/2008	1.09 (-0.19 – 2.37)	0.095
New deployment(s)		
No	0	
Yes	0.45 (-0.56 – 1.47)	0.383
Deployment stressors	**0.28 (0.11 – 0.46)**	**0.002**
Unit social support	0.00 (-0.08 – 0.08)	0.963
Social support after deployment	**-0.12 (-0.21 – -0.03)**	**0.010**
Early general trauma	-0.06 (-0.38 – 0.25)	0.705
Early physical abuse	-0.34 (-0.78 – 0.09)	0.118
Early emotional abuse	-0.44 (-0.94 – 0.07)	0.089
Early sexual abuse	**-1.25 (-2.21 – -0.29)**	**0.011**

Note: bold indicates significant relationship (p<0.05). Abbreviations: CI, confidence interval; PTSD, post-traumatic stress disorder.

Reported previous sexual abuse was associated with a lower increase in PTSD symptoms at 10-year follow-up (β = −1.25, 95% CI = −2.21 to −0.29), whereas previous general trauma, physical abuse, and emotional abuse had no effect. Previous deployments did not have an effect on the change in PTSD symptoms. A higher level of deployment

stressors was related to a greater increase in symptoms (β = 0.28, 95% CI = 0.11–0.46). Moreover, military personnel with a role both inside and outside the base had more increased PTSD symptoms than the group that operated only inside the base (β = 2.97, 95% CI = 0.79–4.79). No difference was found between personnel that operated inside the base and personnel that operated outside the base. Year of deployment was not related to the increase in PTSD symptoms, nor was the level of unit social support during deployment. Social support after deployment was associated with a lower increase in PTSD symptoms (β = −0.12, 95% CI = −0.21 to −0.03), suggesting a lower increase in PTSD symptoms for personnel that received more social support after return. A new deployment after the main deployment was not related to the change in PTSD symptoms.

Trajectory analysis and associated factors

First, a series of LCGA were fitted, both with and without a quadratic term for time. The nonlinear growth curves provided better fit to the data in the majority of the models (see Supplementary material for fit results of the models). Next, a series of GMM were conducted. The four-class GMM including a quadratic term for time produced the best solution with respect to fit and theoretical interpretation. The five-class and six-class GMMs provided better fit indices, but consisted of multiple small groups which considerably limited theoretical justification and interpretability of the identified classes. The model with four latent trajectories (see Figure 1) consisted of one large group of 822 participants (85%) with a low and stable trajectory (i.e., resilient), a smaller group of 67 participants (7%) with a trajectory of increasing symptoms reaching cut-off for PTSD between 2 and 5 years postdeployment (i.e., delayed onset), a group of 57 participants (6%) with high symptoms predeployment and shortly after deployment, but gradual recovery after 6 months postdeployment (i.e., improved), and a group of 16 participants (2%) with heavily increasing symptoms that showed recovery after 5 years postdeployment (i.e., severely elevated-recovering). Results indicated that participants in the resilient group were the least likely to reporting receiving any mental health support (24%). Of the participants in the delayed onset group, 77% received any psychological care, compared to 43% in the improved group and 80% in the severely-elevated recovered group.

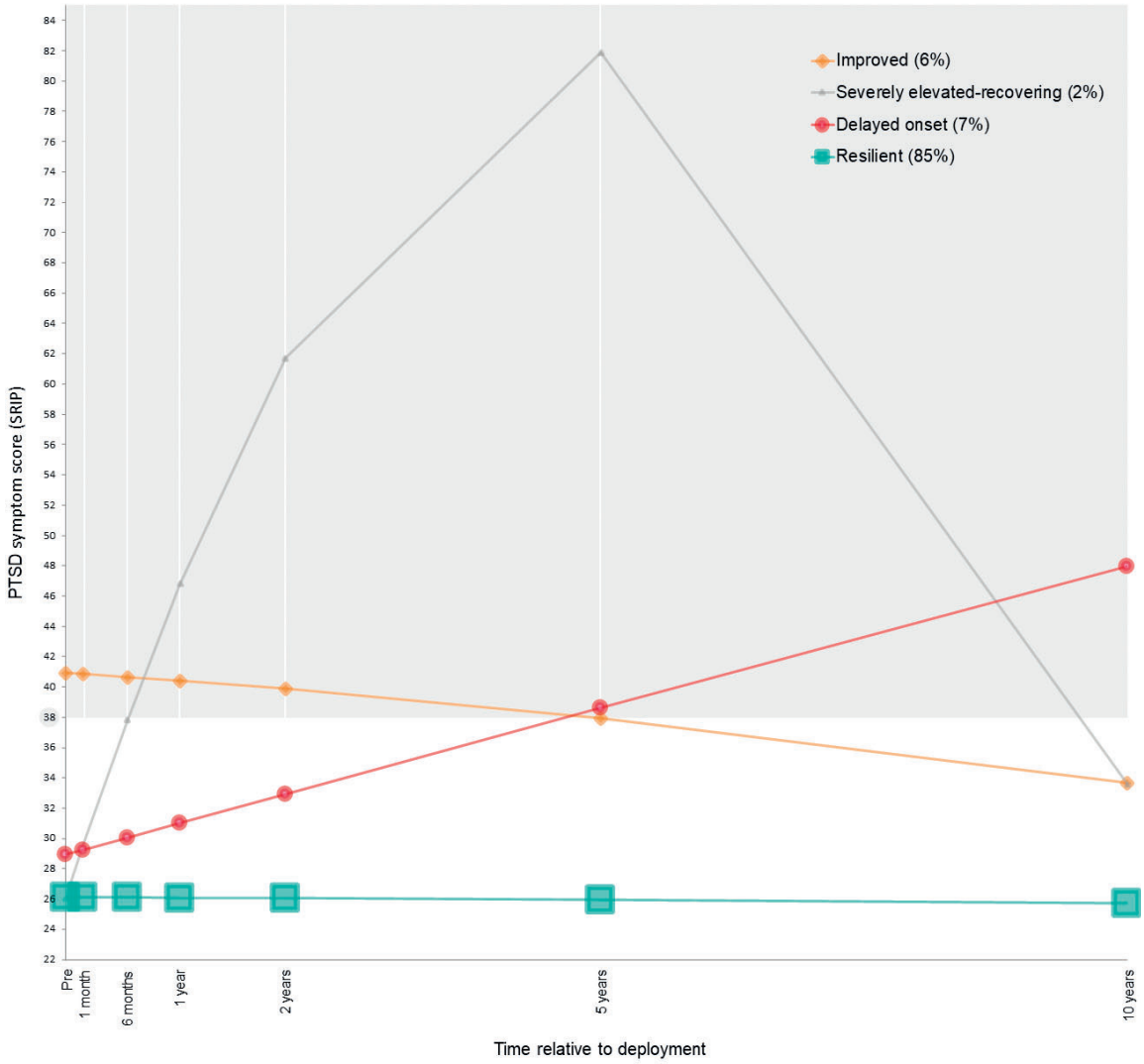

Figure 1. Latent developmental trajectories of post-traumatic stress symptoms. PTSD, post-traumatic stress disorder; SRIP, Self-Rating Inventory for Post-Traumatic Stress Disorder; A SRIP score of 38 was used as a cut-off to indicate substantial PTSD symptoms.

Table 4. Covariates associated with PTSD symptom developmental trajectories.

	Delayed onset vs. Resilient OR (95% CI)	**Improved vs. Resilient** OR (95% CI)	**Severely elevated-recovering vs. Resilient** OR (95% CI)	**Delayed onset vs. Improved** OR (95% CI)	**Severely elevated-recovering vs. Delayed onset** OR (95% CI)	**Severely elevated-recovering vs. Improved** OR (95% CI)
Age	0.96 (0.91-1.01)	0.98 (0.95-1.02)	**0.82 (0.69-0.96)**	0.97 (0.92-1.03)	0.86 (0.72-1.01)	**0.83 (0.70-0.98)**
Educational level						
Moderate vs. low	0.60 (0.18-2.05)	0.58 (0.17-1.99)	*	1.04 (0.22-5.00)	*	*
Moderate vs. high	*	0.93 (0.40-2.16)	1.55 (0.20-12.1)	*	*	1.67 (0.18-15.1)
High vs. low	*	0.62 (0.15-2.58)	*	*	*	*
Rank						
Soldier and corporal						
Non-commissioned	1.00	1.00	1.00	1.00	1.00	1.00
officer and staff officer	0.58 (0.31-1.10)	1.10 (0.63-1.92)	0.06 (0.01-2.35)	0.53 (0.23-1.21)	0.10 (0.01-4.25)	0.06 (0.01-2.24)
Previous deployment(s)						
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	0.72 (0.39-1.32)	0.88 (0.50-1.57)	0.31 (0.08-1.20)	0.81 (0.36-1.85)	0.43 (0.10-1.85)	0.35 (0.08-1.51)
Role during deployment						
Both vs. inside	**3.22 (1.21-8.55)**	1.78 (0.69-4.64)	*	1.80 (0.50-6.50)	*	*
Both vs. outside	1.84 (0.81-4.16)	1.90 (0.81-4.47)	*	0.97 (0.33-2.85)	*	*
Outside vs. inside	1.76 (0.83-3.72)	0.93 (0.48-1.79)	*	1.90 (0.70-5.12)	*	*
Deployment year						
2005/2006	1.00	1.00	1.00	1.00	1.00	1.00
2007/2008	**2.50 (1.02-6.06)**	0.99 (0.54-1.86)	5.71 (0.46-71.2)	2.50 (0.86-7.28)	2.29 (0.16-33.2)	5.73 (0.42-77.4)

Table 4. (Continued)

	Delayed onset vs. Resilient OR (95% CI)	Improved vs. Resilient OR (95% CI)	Severely elevated-recovering vs. Resilient OR (95% CI)	Delayed onset vs. Improved OR (95% CI)	Severely elevated-recovering vs. Delayed onset OR (95% CI)	Severely elevated-recovering vs. Improved OR (95% CI)
New deployment(s)						
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	0.76 (0.40-1.44)	0.68 (0.36-1.31)	1.36 (0.36-5.03)	1.11 (0.47-2.64)	1.79 (0.45-7.14)	1.99 (0.47-8.34)
Deployment stressors	**1.15 (1.05-1.26)**	**1.16 (1.06-1.28)**	**1.26 (1.07-1.50)**	0.99 (0.87-1.13)	1.10 (0.91-1.32)	1.09 (0.90-1.32)
Unit social support	0.97 (0.94-1.01)	**0.93 (0.90-0.97)**	0.94 (0.88-1.00)	1.04 (0.99-1.09)	0.97 (0.90-1.04)	1.01 (0.94-1.07)
Social support after deployment	**0.95 (0.91-0.99)**	**0.94 (0.91-0.98)**	**0.93 (0.88-0.98)**	1.01 (0.97-1.04)	0.98 (0.93-1.03)	0.98 (0.94-1.03)
Early general trauma	1.04 (0.93-1.15)	1.06 (0.93-1.21)	1.01 (0.77-1.33)	0.98 (0.92-1.04)	0.98 (0.77-1.24)	0.95 (0.76-1.20)
Early physical abuse	1.10 (0.88-1.38)	**1.23 (1.01-1.51)**	0.80 (0.34-1.89)	0.89 (0.66-1.20)	0.73 (0.30-1.78)	0.65 (0.26-1.59)
Early emotional abuse	1.23 (0.99-1.53)	**1.64 (1.40-1.91)**	1.01 (0.54-1.91)	**0.75 (0.60-0.95)**	0.82 (0.42-1.60)	0.62 (0.32-1.18)
Early sexual abuse	0.92 (0.60-1.41)	**1.59 (1.22-2.07)**	**1.54 (1.04-2.27)**	**0.58 (0.37-0.91)**	1.68 (0.96-2.91)	0.97 (0.67-1.39)

Note: bold indicates significant relationship (p<0·05). OR=odds ratio. CI=confidence interval. *Analysis could not be performed due to too small group sizes in the categorical covariates and/or trajectories.

We carried out multinomial logistic regression analyses to assess the associations between the assigned trajectories and different covariates (see Table 4). In comparison to the resilient group, the delayed onset group operated more often both inside and outside the military base compared to exclusively inside the base (OR = 3.22, 95% CI = 1.21–8.55), was more frequently deployed in 2007/2008 compared to 2005/2006 (OR = 2.50, 95% CI = 1.02–6.06), experienced more deployment stressors (OR = 1.15, 95% CI = 1.05–1.26), and received less social support after deployment (OR = 0.95, 95% CI = 0.91–0.99). The improved group experienced more deployment stressors (OR = 1.16, 95% CI = 1.06–1.28), less unit support during deployment (OR = 0.93, 95% CI = 0.90–0.97), less support after deployment (OR = 0.94, 95% CI = 0.91–0.98), and more physical (OR = 1.23, 95% CI = 1.01–1.51), emotional (OR = 1.64, 95% CI = 1.40–1.91), and sexual abuse (OR = 1.59, 95% CI = 1.22–2.07) during childhood compared to the resilient group. The severely elevated-recovering group was younger compared to the resilient group (OR = 0.82, 95% CI = 0.69–0.96), experienced more deployment stressors (OR = 1.26, 95% CI = 1.07–1.50), less support after deployment (OR = 0.93, 95% CI = 0.88–0.98), and more childhood sexual abuse (OR = 1.54, 95% CI = 1.04–2.27). Compared to the improved group, the delayed onset group experienced less emotional (OR = 0.75, 95% CI = 0.60–0.95) and sexual abuse (OR = 0.58, 95% CI = 0.37–0.91) during childhood. Finally, the severely elevated-recovering group was younger compared to the improved group (OR = 0.83, 95% CI = 0.70–0.98). The trajectories did not differ in rank, educational level, previous deployments, new deployments, or childhood general trauma score.

DISCUSSION

In the current study, we assessed the effect of deployment on post-traumatic stress symptoms 10 years postdeployment in a large sample of Dutch Afghanistan veterans that were deployed as part of the ISAF mission. During the mission, service members experienced high-intensity war-zone stressors such as exposure to enemy fire, armed combat, and seeing seriously injured colleagues and civilians[17]. Ten years after returning home, the average level of PTSD symptoms was still increased compared to the predeployment level. However, the probable 10-year PTSD prevalence of 8% and the average PTSD symptom score of 27.4 were significantly declined compared to 5-year postdeployment (respectively 12.9% and 28.3). As hypothesized, this indicates that the previously identified, subsequent increase in PTSD symptoms 5 years after deployment[6] tapers off in the following years. Our study also showed that previously identified risk factors like younger age, lower rank, more deployment stressors, and less social support are still relevant 10 years after deployment. As a combination of duties both inside and outside the military base was exclusively related to the increase in PTSD symptoms at

10-year, personnel with a combined role during deployment might be a well-defined group that could benefit from long-term monitoring to prevent worsening of symptoms between 5 and 10 years postdeployment. To our surprise, our results suggest that previous sexual abuse is associated with a lower increase in PTSD symptoms at 10-year follow-up. Paradoxically, in the literature, early sexual abuse is reported as a risk factor for developing PTSD after experiencing traumatic events in adulthood[21,22].

Using seven measurements beginning 1-month predeployment through 10 years postdeployment, we found four different trajectories of PTSD symptom development. The largest majority (85%) of deployed military personnel did not develop PTSD symptoms in the 10 years after returning home. This percentage falls into the range of identified resilient trajectory group size in similar military cohorts (range: 76–90%)[4,7-10,23,24], and supports the idea that most service members deployed to war zones show enduring resiliency despite exposure to traumatic stressors. This study provides an addition to this literature by showing that their resiliency is sustained over a long period after deployment. However, a considerable group (15%) showed symptomatic courses. Our findings regarding the number and shape of these symptomatic trajectories are comparable with several other studies, although the majority of these studies had shorter follow-up periods. Of note is the study by Porter et al.[10] using data from a mixed sample of U.S. active duty and separated military personnel of the Millennium Cohort Study with a follow-up period of 9 years. The improved trajectory (6%) has been identified in other military populations, with comparable membership rates (5%) among U.S. military service members[10], but slightly lower rates (4%) among U.K. armed force members[7] and higher rates (9%) among U.S. military personnel[8] deployed to Afghanistan and Iraq. The severely elevated-recovering trajectory (2%) is compatible with the elevated-recovering trajectory (3%) identified by Porter et al.[10] in a sample of U.S. military personnel, although their reported elevation in symptoms was not as high as in our sample. The delayed onset trajectory (7%) was also identified with a somewhat lower membership rate (5%) in the U.S. military sample by Porter et al.[10], and is consistent with prior work showing that symptoms often increase after a temporal lag relative to the exposure to a traumatic event[25]. In our previous 5-year follow-up report on the PRISMO cohort[6], we identified a resilient, recovered, and delayed onset PTSD trajectory. The four-class solution in the present 10-year follow-up probably resulted from the seperation of a small group of individuals who showed major recovery between 5 and 10 years postdeployment from the original delayed onset trajectory.

The reported decline in probable PTSD prevalence from 13% (5 years postdeployment) to 8% (10 years postdeployment) is reflected in the dynamics of the identified developmental trajectories. Obviously, the most striking drop in symptom score between 5 and 10 years

after deployment is demonstrated by the severely elevated-recovering group. Also, the improved group shows a substantial decline from probable PTSD 5 years after deployment to a mean score clearly beneath cut-off 10 years after deployment. This decrease in PTSD symptom level could be the result of successful treatment, or might reflect the natural course of the disorder. Interestingly, the delayed onset group shows increasing symptom levels between 5 and 10 years postdeployment. Healthcare professionals should be aware of this group of veterans with increasing treatment demands up to at least 10 years postdeployment, despite an average decline in symptoms of the population as a whole. Individuals belonging to the delayed onset class might in fact be a subpopulation of PTSD patients, with possibly different psychological and neurobiological underpinnings, for which targeted early interventions might be beneficial to prevent worsening of PTSD symptoms later in life. The difficulty remains, however, how veterans with an increased risk for delayed onset PTSD can be identified in an early stadium where symptoms are still subclinical or even minimally present.

Our covariate analysis demonstrated that veterans in the delayed onset trajectory experienced a higher threat level during deployment and perceived less social support after returning home compared to veterans in the resilient group. However, this also applied for the other symptomatic trajectories. Unfortunately, no differences in variables included in the present study were found between individuals in the delayed onset group and the severely elevated-recovering group. It is important to clarify why veterans in the severely elevated-recovering trajectory are able to show a striking drop in PTSD symptoms between 5 and 10 years after deployment, while the delayed onset group shows increasing symptom levels after 5 years. Differences in treatment utilization might explain this inconsistency in symptom reduction. To our surprise, our results showed that participants in the delayed onset group reported high use of mental health support (77%), similar to the severely elevated-recovering group (80%). Additional research is therefore needed to elucidate why veterans in the delayed onset group do not seem to benefit as much as the severely elevated-recovering group after seeking help, and should focus on received treatment type, timing, and outcome. Recently identified biological mechanisms in successful treatment of PTSD like DNA methylation reversal[26] and the role of underlying moral injury in treatment effectivity[27] are also of large interest and may offer new perspectives. In addition, continued effort should be put in the identification and addressment of current PTSD symptoms, as 23% of the veterans in the delayed onset group did not receive any psychological help.

Several limitations of the current study should be mentioned. First, the use of self-report measures to obtain PTSD symptom levels as a proxy for clinical diagnoses is imperfect. Although standardized and validated screening instruments were used,

it might have resulted in higher prevalence estimates compared with clinician-administered interviews[28,29]. However, its use remained consistent across time points. In addition, the reported PTSD symptoms are not necessarily the result of traumatic events during deployment. Even though we were able to maintain approximately 60% of the original sample at 10-year follow-up, the influence of nonresponse on the study findings cannot be ruled out. Another important limitation is the small group size of the "severely elevated-recovering" trajectory, which contained only 2% of our sample. The mean PTSD symptom score of this trajectory at 5 years postdeployment was near the maximum of the scale, and the variance of PTSD symptom scores in the full sample at 5 years was large compared to the other time points. The "severely elevated-recovering" trajectory might therefore be solely defined by this individual data point. Although the four-class model including this trajectory over performed the three-class model, one should be extra careful when drawing conclusions from this trajectory. Finally, the absence of information on received treatment type and timing, incurred traumatic brain injury or other types of physical injury during deployment, pre-existing psychiatric disorders, and comorbidity with other psychiatric diagnoses is a limitation of the present study. The results of this study, however, also address limitations of previous research in several ways. The predeployment measurement allowed evaluation of PTSD symptom trajectories beginning prior to deployment. We were therefore able to reveal elevated symptom levels before deployment in the improved trajectory, which would otherwise remain unobserved. Furthermore, this study has a large number of follow-up measurements during a long period of time, which enables the examination of smaller fluctuations in PTSD symptoms and the differentiation between trajectories up to 10 years after deployment.

Overall, we found a probable PTSD prevalence of 8% in a sample of Afghanistan veterans 10 years after their deployment. This implicates that the long-term symptom increase measured at 5 years postdeployment decreased partly in the following years. Of note is the delayed onset group that experienced increasing symptom levels between 5 and 10 years postdeployment, and does not seem to be able to show significant symptom reduction after seeking mental health support. These findings raise critical questions about the origin of this inconsistency in symptom reduction. Future research is therefore needed to elucidate which factors may contribute to the worsening of PTSD symptoms and probable treatment resistance in the delayed onset trajectory in order to develop and implement alternative treatment strategies for this group of veterans.

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SUPPLEMENTARY MATERIAL

Covariates

Data on education was categorized into three levels of education: low (some years of high school), medium (finished high school), and high (college or university education). Rank was divided in four categories: private, corporal, non-commissioned officer, and staff officer. Previous deployments were dichotomized (yes or no). The participant's role during the mission was stratified into 'inside the military base', 'both inside and outside the military base' and 'outside the military base'.

Mental health support

Received psychological care was assessed by the item "Have you ever received any care for psychological health complaints after your deployment?". We defined psychological care as any received care for psychological health complaints provided by a GP, social worker, psychologist, psychiatrist, or other mental health specialist. Due to the high percentage of missing values (Table S1), the psychological care variable was not imputed and therefore not tested as an associated factor for PTSD trajectories in the adjusted multinomial regression models.

Table S1. Participants reporting receiving any psychological care, separated for PTSD trajectory.

	Participants that received any psychological care	Missing data in outcome variable
All (n=963)	28.5%	35.9%
Resilient (n=845)	24.1%	35.3%
Delayed onset (n=50)	77.1%	30.0%
Improved (n=55)	43.3%	45.5%
Severely-elevated recovering (n=13)	80.0%	61.5%

Missing data analyses

The association of study drop-out with symptom levels was studied by correlating the occurrence of missing values to the posttraumatic stress symptom scores on the previous time point. The symptom level at six months after deployment was related to the occurrence of missing values at two years (r=0.113; p=0.002), five years (r=0.080; p=0.029), and ten years (r=0.086; p=0.020) after deployment. The symptom levels at one year and five years after deployment were related to the occurrence of missing values at ten years after deployment (respectively r=0.114; p=0.007 and r=0.091; p=0.031). The missing data patterns are presented in Table S2. Considering that in mixed model analysis the missing data are not assumed to be missing completely at random, and

that the results obtained from a mixed model analysis with multiple imputation can be quite unstable, no multiple imputation techniques were used prior to the mixed model analyses. For the latent trajectory growth mixture model, missing values on the potential modifying factors were handled with multiple imputation prior the analyses.

Table S2. Missing data patterns for the posttraumatic stress symptom scores at each time point.

Time points							
Pre-deployment	**1 month**	**6 months**	**1 year**	**2 years**	**5 years**	**10 years**	**n[a]**
							223
X							53
X	X						23
	X						18
			X				13
						X	30
				X			23
			X	X			16
					X		15
				X	X		16
				X	X	X	14
			X	X	X		19
			X	X	X	X	57
		X	X	X	X	X	36
X		X	X	X	X	X	18
X			X	X	X	X	27
	X	X	X	X	X	X	37
X	X	X	X	X	X	X	44

Note: X indicates a missing value for that time point. [a] n indicates the number of participants that had the corresponding missing data pattern, patterns that occurred in less than 1% of the participants were omitted.

Multiple imputation procedure

Multiple imputation was performed in SPSS version 25 using multivariate imputation by chained equations (MICE) with predictive mean matching. A total of 10 imputations were used. The imputation model included the Early Trauma Inventory Self Report-Short Form (ETISR-SF), the Self-Rated Inventory for Post-traumatic Stress Disorder (SRIP), the Deployment Experience Scale (DES), the Deployment Risk and Resilience Inventory-1

(DRRI) part F and L, and the baseline descriptive variables (i.e. age, gender, education level, rank, previous deployments, function during deployment, deployment year, and new deployments). The missing items in the ETISR-SF, DES, and DRRI were imputed at the item level. Convergence plots were used to check if the imputed values had the expected variation between the iterations. The total scores of the questionnaires were calculated by summing the imputed item scores.

Mixed model analyses

Table S3. Parameter estimates for change in posttraumatic stress symptoms over time relative to pre-deployment status without interactions with potential covariates (n=963).

	Time-effect	
	Coefficient (95% CI)	**p-value**
Intercept (pre-deployment)	26.72 (26.36 – 27.09)	<0.0001
Δ 1 month[a]	0.92 (0.46 – 1.38)	<0.0001
Δ 6 months[a]	0.99 (0.52 – 1.45)	<0.0001
Δ 1 year[a]	0.38 (-0.14 – 0.90)	0.148
Δ 2 years[a]	0.14 (-0.39 – 0.67)	0.597
Δ 5 years[a]	1.62 (1.11 – 2.14)	<0.0001
Δ 10 years[a]	0.84 (0.34 – 1.34)	0.001

Note: [a] Δ indicates the difference relative to pre-deployment status; 95% CI=95% Confidence Interval.

Table S4. Parameter estimates for change in posttraumatic stress symptoms over time relative to pre-deployment status with age as covariate (n=963).

	Effect		Interaction time x age	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**
Intercept (pre-deployment)	27.83 (26.58 – 29.07)	<0.0001		
Δ 1 month[a]	2.09 (0.52 – 3.65)	0.009	-0.04 (-0.09 – 0.01)	0.126
Δ 6 months[a]	2.15 (0.59 – 3.71)	0.007	-0.04 (-0.09 – 0.01)	0.124
Δ 1 year[a]	2.08 (0.35 – 3.82)	0.018	-0.06 (-0.11 – -0.01)	0.044
Δ 2 years[a]	0.27 (-1.53 – 2.08)	0.767	-0.01(-0.06 – 0.05)	0.846
Δ 5 years[a]	4.64 (2.88 – 6.40)	<0.0001	-0.10 (-0.15 – -0.04)	0.001
Δ 10 years[a]	2.84 (1.14 – 4.53)	0.001	-0.07 (-0.12 – -0.01)	0.016
Age	-0.04 (-0.08 – 0.01)	0.076		

Note: [a] Δ indicates the difference relative to pre-deployment status; 95% CI=95% Confidence Interval.

Table S5. Parameter estimates for change in posttraumatic stress symptoms over time relative to pre-deployment status with educational level as covariate (n=963).

	Effect		**Interaction time x education$_{medium}$[b]**		**Interaction time x education$_{high}$[b]**	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**	**Coefficient (95%CI)**	**p-value**
Intercept (pre-deployment)	28.04 (26.09 – 29.99)	<0.0001				
Δ 1 month[a]	0.95 (-1.43 – 3.32)	0.434	-0.07 (-2.49 – 2.36)	0.955	-0.44 (-3.21 – 2.33)	0.755
Δ 6 months[a]	1.10 (-1.33 – 3.53)	0.374	-0.15 (-2.63 – 2.33)	0.903	-0.78 (-3.58 – 2.02)	0.584
Δ 1 year[a]	0.29 (-2.88 – 3.47)	0.857	0.07 (-3.16 – 3.29)	0.968	-0.54 (-4.03 – 2.93)	0.758
Δ 2 years[a]	-2.29 (-5.89 – 1.32)	0.214	2.50 (-1.15 – 6.16)	0.179	2.17 (-1.69 – 6.04)	0.270
Δ 5 years[a]	-1.00 (-4.62 – 2.61)	0.587	2.61 (-1.05 – 6.27)	0.162	2.01 (-1.88 – 5.89)	0.311
Δ 10 years[a]	3.34 (0.40 – 6.28)	0.026	-2.48 (-5.47 – 0.52)	0.105	-3.99 (-7.27 – -0.71)	0.017
Education$_{medium}$[b]	-1.30 (-3.29 – 0.69)	0.092				
Education$_{high}$[b]	-1.95 (-4.21 – 0.32)	0.201				

Note: [a] Δ indicates the difference relative to pre-deployment status; [b] reference category is the group with a low educational level; 95% CI=95% Confidence Interval; Education$_{medium}$=medium educational level; Education$_{high}$=high educational level.

Table S6. Parameter estimates for change in posttraumatic stress symptoms over time relative to pre-deployment status with military rank as covariate (n=963).

	Effect		Interaction time x rank[b]	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**
Intercept (pre-deployment)	26.90 (26.44 – 27.37)	<0.0001		
Δ 1 month[a]	1.07 (0.48 – 1.66)	<0.0001	-0.39 (-1.33 – 0.55)	0.413
Δ 6 months[a]	1.22 (0.61 – 1.83)	<0.0001	-0.59 (-1.53 – 0.36)	0.224
Δ 1 year[a]	0.62 (-0.10 – 1.34)	0.091	-0.54 (-1.58 – 0.50)	0.308
Δ 2 years[a]	0.17 (-0.60 – 0.93)	0.668	-0.08 (-1.15 – 0.98)	0.879
Δ 5 years[a]	2.54 (1.81 – 3.26)	<0.0001	-1.81 (-2.85 – -0.77)	0.001
Δ 10 years[a]	1.48 (0.80 – 2.17)	<0.0001	-1.36 (-2.38 – -0.35)	0.009
Rank[b]	-0.44 (-1.19 – 0.31)	0.253		

Note: [a] Δ indicates the difference relative to pre-deployment status; [b] the rank parameter indicates the differences between non-commissioned officer and staff officer ranks versus soldier and corporal ranks (reference category); 95% CI=95% Confidence Interval.

Table S7. Parameter estimates for change in posttraumatic stress symptoms over time relative to pre-deployment status with previous deployment(s) as covariate (n=963).

	Effect		Interaction time x previous deployments[b]	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**
Intercept (pre-deployment)	26.84 (26.33 – 27.35)	<0.0001		
Δ 1 month[a]	0.90 (0.25 – 1.56)	0.007	0.00 (-0.94 – 0.94)	0.999
Δ 6 months[a]	1.14 (0.47 – 1.81)	0.001	-0.41 (-1.36 – 0.54)	0.398
Δ 1 year[a]	0.75 (-0.01 – 1.51)	0.055	-0.71 (-1.76 – 0.35)	0.188
Δ 2 years[a]	0.05 (-0.75 – 0.85)	0.905	0.22 (-0.87 – 1.31)	0.695
Δ 5 years[a]	1.73 (0.96 – 2.50)	<0.0001	-0.41 (-1.47 – 0.65)	0.449
Δ 10 years[a]	0.84 (0.10 – 1.57)	0.027	-0.09 (-1.12 – 0.95)	0.868
Previous deployments[b]	-0.42 (-1.16 – 0.32)	0.263		

Note: [a] Δ indicates the difference relative to pre-deployment status; [b] reference category is the group without previous deployments; 95% CI=95% Confidence Interval.

Table S8. Parameter estimates for change in posttraumatic stress symptoms over time relative to pre-deployment status with role during deployment as covariate (n=963).

	Effect		Interaction time x $role_{both}$ [b]		Interaction time x $role_{outside}$ [b]	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**	**Coefficient (95%CI)**	**p-value**
Intercept (pre-deployment)	26.61 (25.90 – 27.31)	<0.0001				
Δ 1 month[a]	0.53 (-0.36 – 1.42)	0.241	0.77 (-1.03 – 2.56)	0.403	0.61 (-0.48 – 1.70)	0.274
Δ 6 months[a]	0.40 (-0.46 – 1.27)	0.362	0.86 (-0.91 – 2.64)	0.340	0.97 (-0.13 – 2.06)	0.083
Δ 1 year[a]	-0.36 (-1.27 – 0.55)	0.438	-0.04 (-1.97 – 1.89)	0.967	1.19 (0.00 – 2.38)	0.049
Δ 2 years[a]	-0.16 (-1.07 – 0.75)	0.732	-0.38 (-2.51 – 1.75)	0.725	0.57 (-0.66 – 1.80)	0.362
Δ 5 years[a]	0.70 (-0.21 – 1.61)	0.133	1.42 (-0.63 – 3.47)	0.175	1.86 (0.66 – 3.06)	0.002
Δ 10 years[a]	0.18 (-0.72 – 1.09)	0.691	2.79 (0.79 – 4.79)	0.006	1.10 (-0.08 – 2.28)	0.067
$Role_{both}$ [b]	0.35 (-0.52 – 1.21)	0.434				
$Role_{outside}$ [b]	0.72 (-0.73 – 2.17)	0.331				

Note: [a] Δ indicates the difference relative to pre-deployment status; [b] reference category is the group with a role inside the military base; 95% CI=95% Confidence Interval; $Role_{both}$=role both inside and outside the military base; $Role_{outside}$=role outside the military base.

Table S9. Parameter estimates for change in posttraumatic stress symptoms over time relative to pre-deployment status with deployment year as covariate (n=963).

	Effect		Interaction time x year$_{2007/2008}$[b]	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**
Intercept (pre-deployment)	25.12 (23.26 – 26.99)	<0.0001		
Δ 1 month[a]	-0.05 (-2.47 – 2.36)	0.965	0.54 (-0.75 – 1.82)	0.413
Δ 6 months[a]	0.82 (-1.48 – 3.13)	0.484	0.10 (-1.14 – 1.33)	0.879
Δ 1 year[a]	2.07 (-0.43 – 4.56)	0.104	-0.94 (-2.28 – 0.40)	0.169
Δ 2 years[a]	1.20 (-1.19 – 3.59)	0.324	-0.61 (-1.91 – 0.70)	0.362
Δ 5 years[a]	-1.05 (-3.43 – 1.32)	0.385	1.55 (0.26 – 2.84)	0.019
Δ 10 years[a]	-1.05 (-3.42 – 1.31)	0.382	1.09 (-0.19 – 2.37)	0.095
Year$_{2007/2008}$[b]	0.91 (-0.09 – 1.90)	0.074		

Note: [a] Δ indicates the difference relative to pre-deployment status; [b] reference category is the group deployed in 2005 and 2006; 95% CI=95% Confidence Interval.

Table S10. Parameter estimates for change in posttraumatic stress symptoms over time relative to pre-deployment status with new deployment(s) as covariate (n=963).

	Effect		Interaction time x new deployments[b]	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**
Intercept (pre-deployment)	27.43 (26.83 – 28.02)	<0.0001		
Δ 1 month[a]	0.49 (-0.25 – 1.22)	0.189	0.11 (-0.95 – 1.17)	0.841
Δ 6 months[a]	0.20 (-0.52 – 0.92)	0.588	0.84 (-0.20 – 1.89)	0.113
Δ 1 year[a]	-0.26 (-1.02 – 0.51)	0.512	0.45 (-0.65 – 1.55)	0.422
Δ 2 years[a]	-0.55 (-1.31 – 0.22)	0.162	0.71 (-0.42 – 1.83)	0.218
Δ 5 years[a]	1.59 (0.83 – 2.36)	<0.0001	-0.59 (-1.67 – 0.50)	0.288
Δ 10 years[a]	0.41 (-0.29 – 1.11)	0.254	0.45 (-0.56 – 1.47)	0.383
New deployments[b]	-1.34 (-2.18 – -0.49)	0.002		

Note: [a] Δ indicates the difference relative to pre-deployment status; [b] reference category is the group without new deployments; 95% CI=95% Confidence Interval.

Table S11. Parameter estimates for change in posttraumatic stress symptoms over time relative to pre-deployment status with deployment experience total score as covariate (n=963).

	Effect		Interaction time x DES	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**
Intercept (pre-deployment)	25.71 (24.97 – 26.44)	<0.0001		
Δ 1 month[a]	-0.37 (-1.22 – 0.48)	0.394	0.25 (0.10 – 0.40)	0.001
Δ 6 months[a]	-0.55 (-1.44 – 0.35)	0.229	0.27 (0.11 – 0.43)	0.001
Δ 1 year[a]	-1.26 (-2.24 – -0.29)	0.011	0.33 (0.15 – 0.51)	<0.0001
Δ 2 years[a]	-0.61 (-1.61 – 0.39)	0.230	0.09 (-0.09 – 0.28)	0.317
Δ 5 years[a]	0.38 (-0.60 – 1.36)	0.451	0.27 (0.09 – 0.45)	0.003
Δ 10 years[a]	-0.39 (-1.34 – 0.56)	0.426	0.28 (0.11 – 0.46)	0.002
DES total score	0.24 (0.11 – 0.37)	<0.0001		

Note: [a] Δ indicates the difference relative to pre-deployment status; DES=Deployment Experience Scale; 95% CI=95% Confidence Interval.

Table S12. Parameter estimates for change in posttraumatic stress symptoms over time relative to pre-deployment status with unit social support as covariate (n=963).

	Effect		Interaction time x DDRI-F	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**
Intercept (pre-deployment)	32.52 (29.75 – 35.28)	<0.0001		
Δ 1 month[a]	1.05 (-2.28 – 4.39)	0.535	0.00 (-0.07 – 0.07)	0.932
Δ 6 months[a]	4.73 (1.35 – 8.11)	0.006	-0.09 (-0.16 – -0.01)	0.020
Δ 1 year[a]	-0.71 (-3.99 – 2.57)	0.670	0.01 (-0.06 – 0.08)	0.771
Δ 2 years[a]	-1.60 (-5.27 – 2.07)	0.392	0.02 (-0.06 – 0.10)	0.575
Δ 5 years[a]	1.38 (-2.24 – 5.01)	0.455	0.00 (-0.07 – 0.08)	0.923
Δ 10 years[a]	0.95 (-2.80 – 4.70)	0.621	0.00 (-0.08 – 0.08)	0.963
DDRI-F total score	-0.12 (-0.18 – -0.06)	<0.0001		

Note: [a] Δ indicates the difference relative to pre-deployment status; DDRI-F=Deployment Risk and Resilience Inventory-1 Section F; 95% CI=95% Confidence Interval.

Table S13. Parameter estimates for change in posttraumatic stress symptoms over time relative to pre-deployment status with social support after deployment as covariate (n=963).

	Effect		Interaction time x DDRI-L	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**
Intercept (pre-deployment)	37.85 (33.94 – 41.76)	<0.0001		
Δ 1 month[a]	2.21 (-2.64 – 7.07)	0.371	-0.02 (-0.10 – 0.06)	0.645
Δ 6 months[a]	10.79 (6.00 – 15.58)	<0.0001	-0.16 (-0.24 – -0.08)	<0.0001
Δ 1 year[a]	6.99 (2.11 – 11.88)	0.005	-0.12 (-0.20 – -0.04)	0.004
Δ 2 years[a]	3.35 (-1.79 – 8.49)	0.201	-0.06 (-0.15 – 0.02)	0.147
Δ 5 years[a]	10.95 (5.60 – 16.30)	<0.0001	-0.15 (-0.24 – -0.06)	0.001
Δ 10 years[a]	8.00 (2.56 – 13.44)	0.004	-0.12 (-0.21 – -0.03)	0.010
DDRI-L total score	-0.18 (-0.24 – -0.12)	<0.0001		

Note: [a] Δ indicates the difference relative to pre-deployment status; DDRI-L=Deployment Risk and Resilience Inventory-1 Section L; 95% CI=95% Confidence Interval.

Table S14. Parameter estimates for change in posttraumatic stress symptoms over time relative to pre-deployment status with early general trauma score as covariate (n=963).

	Effect		Interaction time x ETISR-SF general trauma	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**
Intercept (pre-deployment)	25.90 (25.32 – 26.48)	<0.0001		
Δ 1 month[a]	1.03 (0.30 – 1.76)	0.006	-0.06 (-0.35 – 0.22)	0.670
Δ 6 months[a]	0.45 (-0.29 – 1.20)	0.233	0.26 (-0.03 – 0.55)	0.083
Δ 1 year[a]	0.68 (-0.13 – 1.50)	0.100	-0.16 (-0.48 – 0.16)	0.330
Δ 2 years[a]	0.25 (-0.59 – 1.09)	0.554	-0.04 (-0.37 – 0.29)	0.821
Δ 5 years[a]	1.61 (0.80 – 2.43)	<0.0001	0.01 (-0.31 – 0.33)	0.959
Δ 10 years[a]	0.98 (0.18 – 1.78)	0.016	-0.06 (-0.38 – 0.25)	0.705
ETISR-SF general trauma score	0.42 (0.19 – 1.78)	<0.0001		

Note: [a] Δ indicates the difference relative to pre-deployment status; ETISR-SF=Early Trauma Inventory Self-Report-Short Form; 95% CI=95% Confidence Interval.

Table S15. Parameter estimates for change in posttraumatic stress symptoms over time relative to pre-deployment status with early physical abuse score as covariate (n=963).

	Effect		Interaction time x ETISR-SF physical abuse	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**
Intercept (pre-deployment)	26.19 (25.74 – 26.63)	<0.0001		
Δ 1 month[a]	1.18 (0.62 – 1.74)	<0.0001	-0.29 (-0.69 – 0.11)	0.149
Δ 6 months[a]	1.21 (0.64 – 1.78)	<0.0001	-0.25 (-0.64 – 0.14)	0.201
Δ 1 year[a]	0.58 (-0.05 – 1.22)	0.070	-0.28 (-0.71 – 0.16)	0.215
Δ 2 years[a]	0.29 (-0.37 – 0.94)	0.389	-0.10 (-0.54 – 0.33)	0.640
Δ 5 years[a]	1.40 (0.76 – 2.04)	<0.0001	0.21 (-0.22 – 0.64)	0.344
Δ 10 years[a]	1.09 (0.48 – 1.71)	<0.0001	-0.34 (-0.78 – 0.09)	0.118
ETISR-SF physical abuse score	0.61 (0.30 – 0.93)	<0.0001		

Note: [a] Δ indicates the difference relative to pre-deployment status; ETISR-SF=Early Trauma Inventory Self-Report-Short Form; 95% CI=95% Confidence Interval.

Table S16. Parameter estimates for change in posttraumatic stress symptoms over time relative to pre-deployment status with early emotional abuse score as covariate (n=963).

	Effect		Interaction time x ETISR-SF emotional abuse	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**
Intercept (pre-deployment)	26.16 (25.75 – 26.56)	<0.0001		
Δ 1 month[a]	0.76 (0.25 – 1.27)	0.004	0.27 (-0.19 – 0.72)	0.253
Δ 6 months[a]	0.98 (0.46 – 1.50)	<0.0001	0.03 (-0.43 – 0.50)	0.890
Δ 1 year[a]	0.50 (-0.08 – 1.08)	0.089	-0.34 (-0.84 – 0.17)	0.192
Δ 2 years[a]	0.03 (-0.56 – 0.63)	0.915	0.25 (-0.26 – 0.76)	0.333
Δ 5 years[a]	1.32 (0.74 – 1.90)	<0.0001	0.52 (0.01 – 1.02)	0.044
Δ 10 years[a]	1.09 (0.53 – 1.65)	<0.0001	-0.44 (-0.94 – 0.07)	0.089
ETISR-SF emotional abuse score	1.32 (0.95 – 1.69)	<0.0001		

Note: [a] Δ indicates the difference relative to pre-deployment status; ETISR-SF=Early Trauma Inventory Self-Report-Short Form; 95% CI=95% Confidence Interval.

Table S17. Parameter estimates for change in posttraumatic stress symptoms over time relative to pre-deployment status with early sexual abuse score as covariate (n=963).

	Effect		Interaction time x ETISR-SF sexual abuse	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**
Intercept (pre-deployment)	26.58 (26.20 – 26.96)	<0.0001		
Δ 1 month[a]	0.96 (0.48 – 1.44)	<0.0001	-0.45 (-1.39 – 0.48)	0.343
Δ 6 months[a]	1.10 (0.61 – 1.59)	<0.0001	-0.92 (-1.81 – -0.03)	0.042
Δ 1 year[a]	0.39 (-0.15 – 0.93)	0.153	-0.71 (-1.61 – 0.19)	0.122
Δ 2 years[a]	0.16 (-0.39 – 0.72)	0.566	0.14 (-0.96 – 1.23)	0.808
Δ 5 years[a]	1.64 (1.10 – 2.19)	<0.0001	-0.41 (-1.38 – 0.56)	0.411
Δ 10 years[a]	1.02 (0.49 – 1.55)	<0.0001	-1.25 (-2.21 – -0.29)	0.011
ETISR-SF sexual abuse score	1.76 (1.01 – 2.51)	<0.0001		

Note: [a] Δ indicates the difference relative to pre-deployment status; ETISR-SF=Early Trauma Inventory Self-Report-Short Form; 95% CI=95% Confidence Interval.

Latent trajectory growth mixture model analyses

The latent trajectories were extracted from the data using a growth mixture model (GMM) in Mplus version 8.4. Missing data over time in the outcome variable was handled by full information maximum likelihood estimation (FIML). Time was modeled as the actual time-points occurred (i.e. -1; 1; 6; 12; 24; 60; 120), and was fixed between subjects. The model included a linear slope. We investigated one to six class solutions and used 5000 start values and 50000 iterations. First, a series of unconditional models were fitted (latent class growth analysis). Next, the models were re-fitted with a quadratic term for time to assess whether non-linear growth curves provided better fit to the data. Finally, the variances of the intercept were freed (growth mixture model). Due to non-convergence issues, the models did not allow a cubic term for time and free estimation of the time slope parameters. All models were compared on fit indices, entropy, class size, and interpretability (see Table S18 – 21).

Table S18. Fit indices for one to six solutions of the latent class growth analysis (LCGA).

Fit indices	1 class	2 classes	3 classes	4 classes	5 classes	6 classes
AIC	29133.52	27750.31	27377.08	27208.89	27054.77	26912.05
BIC	29177.35	27808.75	27450.13	27296.55	27157.04	27028.94
Adj. BIC[a]	29148.77	27770.64	27402.49	27239.38	27090.34	26952.71
Entropy	..	0.923	0.907	0.887	0.874	0.831
Proportion of participants per class[b]	..	0.141 0.859	0.796 0.022 0.182	0.195 0.054 0.748 0.003	0.003 0.211 0.027 0.712 0.048	0.060 0.003 0.026 0.073 0.188 0.649

Note: [a] BIC adjusted for sample size; [b] class proportions based on the estimated model; AIC=Akaike Information Criteria; BIC=Bayesian Information Criteria.

Table S19. Fit indices for one to six solutions of the latent class growth analysis (LCGA) including a quadratic term for time.

Fit indices	1 class	2 classes	3 classes	4 classes	5 classes	6 classes
AIC	29134.41	27735.04	27368.68	27171.03	27015.96	26899.04
BIC	29183.11	27803.22	27456.35	27278.17	27142.58	27045.14
Adj. BIC[a]	29151.35	27758.76	27399.18	27208.30	27060.01	26949.86
Entropy	..	0.919	0.882	0.888	0.849	0.832
Proportion of participants per class[b]	..	0.143 0.857	0.192 0.775 0.033	0.048 0.750 0.198 0.004	0.064 0.227 0.030 0.676 0.004	0.191 0.069 0.023 0.645 0.005 0.067

Note: [a] BIC adjusted for sample size; [b] class proportions based on the estimated model; AIC=Akaike Information Criteria; BIC=Bayesian Information Criteria.

Table S20. Fit indices for one to six solutions of growth mixture models (GMM).

Fit indices	1 class	2 classes	3 classes	4 classes	5 classes	6 classes
AIC	27633.53	27278.15	27102.49	26947.24	26816.43	26715.28
BIC	27682.23	27341.46	27180.41	27039.77	26923.57	26837.04
Adj. BIC[a]	27650.47	27300.18	27129.60	26979.43	26853.67	26757.64
Entropy	..	0.934	0.909	0.894	0.887	0.887
Proportion of participants per class[b]	..	0.054 0.946	0.013 0.920 0.068	0.062 0.067 0.011 0.860	0.096 0.020 0.814 0.058 0.011	0.020 0.100 0.009 0.792 0.075 0.004

Note: [a] BIC adjusted for sample size; [b] class proportions based on the estimated model; AIC=Akaike Information Criteria; BIC=Bayesian Information Criteria.

Table S21. Fit indices for one to six solutions of growth mixture models (GMM) including a quadratic term for time.

Fit indices	1 class	2 classes	3 classes	4 classes	5 classes	6 classes
AIC	27633.99	27280.36	27078.01	26920.19	26783.42	26674.48
BIC	27687.56	27353.41	27170.54	27032.20	26914.91	26825.45
Adj. BIC[a]	27652.62	27305.77	27110.20	26969.15	26829.16	26726.99
Entropy	..	0.932	0.900	0.890	0.882	0.860
Proportion of participants per class[b]	..	0.055 0.945	0.070 0.910 0.020	0.059 0.070 0.854 0.017	0.015 0.088 0.015 0.801 0.081	0.032 0.012 0.793 0.083 0.058 0.022

Note: [a] BIC adjusted for sample size; [b] class proportions based on the estimated model; AIC=Akaike Information Criteria; BIC=Bayesian Information Criteria.

CHAPTER 4

LONG-TERM RISK FOR MENTAL HEALTH SYMPTOMS IN DUTCH ISAF VETERANS: THE ROLE OF PERCEIVED SOCIAL SUPPORT

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ABSTRACT

Background

Military personnel deployed to combat and peacekeeping missions are exposed to high rates of traumatic events. Accumulating evidence suggests an important association between deployment and the development of other mental health symptoms beyond post-traumatic stress disorder.

Methods

This study examined the prevalence of agoraphobia, anxiety, depression, and hostility symptoms in a cohort of Dutch ISAF veterans (N = 978) from pre-deployment up to 10 years after homecoming. The interaction of potential moderating factors with the change in mental health symptoms relative to pre-deployment was investigated at each time point.

Results

The probable prevalence of agoraphobia, anxiety, depression, and hostility symptoms significantly increased over time to respectively 6.5, 2.7, 3.5, and 6.2% at 10 years after deployment. Except for hostility symptoms, the probable prevalence at 10 years after deployment was the highest compared to all previous follow-up assessments. Importantly, less perceived social support after returning from deployment was found as a risk factor for all different mental health symptoms. Unit support was not associated with the development of mental health problems.

Conclusions

This study suggests a probable broad and long-term impact of deployment on the mental health of military service members. Due to the lack of a non-deployed control group, causal effects of deployment could not be demonstrated. Continued effort should nevertheless be made in the diagnosis and treatment of a wide range of mental health symptoms, even a decade after deployment. The findings also underscore the importance of social support after homecoming and its potential for the prevention of long-term mental health problems.

INTRODUCTION

Military deployment to combat and peacekeeping missions can offer individuals an opportunity to increase personal growth, to build skills, and to gain new perspectives of the world around them. Extensive military training prepares service members for handling all kinds of stressful situations that might be encountered during their mission. However, when witnessing people suffer, seeing a colleague killed, or being held at gunpoint, psychological scars may appear. 'After all, we are only ordinary men' (Pink Floyd, 1973). Continued effort should therefore be put in identifying and addressing of mental health problems in deployed military personnel returning home.

With the recent involvement in the Balkan, Iraq, and Afghanistan wars, the society's concern regarding the mental health of military service members is growing. This concern is endorsed by several publications reporting on prevalence rates of a wide range of mental health disorders in returning military personnel. The largest amount of literature is almost exclusively focused on the development of post-traumatic stress disorder (PTSD) symptoms[1-6]. Although the amount of literature focusing on other types of mental health problems is less extensive, the relation with deployment-related stressors is well documented[7-12]. For example, combat exposed US service members deployed to Iraq and Afghanistan were at increased risk for new depression onset compared to their non-deployed colleagues[12]. Another study in US service members returning from Iraq showed depression concerns in 4.7–10.3% of the active component soldiers[13]. More recently, a study in service members of the Australian Defence Force deployed to Afghanistan found probable prevalence rates of 4.5% for anxiety, 4.6% for depression, and 7.9% for any mental disorder within 4-month post-deployment[14]. Except for anxiety, this was a significant increase compared to pre-deployment.

The direct effect of deployment on mental health symptoms is probably moderated by several factors. Besides often identified risk factors for stress-related disorders such as younger age, female gender, combat exposure, or previous traumatic experiences, social support may play an important role in military service member's mental health[15-18]. Social support can be defined as the perceived availability of support, affection, and instrumental aid from significant social partners[19]. Having a perception of a good quality of social support, for example by experiencing a strong family support system, may lead to a sense of purpose and a more robust mental health during and following deployment[18]. In comparison, if service members perceive less support from family, friends, colleagues, or even society, contact moments may diminish or act as demanding stressors, and may initiate or excite the development of mental health symptoms after returning home[18].

As a follow-up on our previous study[10], in the current study we examined the prevalence of a high level of agoraphobia, anxiety, depression, and hostility symptoms in Dutch military personnel deployed to Afghanistan up to 10 years after deployment. Moreover, we assessed the role of different covariates on the development of these mental health symptoms after homecoming. This study addresses limitations of previous research by including a pre-deployment measurement allowing evaluation of mental health symptoms prior to deployment and five consecutive follow-up measurements during a long period of time. In our report on the development of PTSD in this cohort, we identified a higher prevalence of PTSD symptoms at 10-years post-deployment compared to all previous measurements up to 2-years after deployment[20]. Also, in a previous report on the prevalence of other mental health symptoms, we identified increases in the prevalence of agoraphobia-, anxiety-, and depression symptoms up to 2-years post-deployment. The prevalence of hostility symptoms, on the other hand decreased after 6 months[10]. Based on these findings, we hypothesize that agoraphobia-, anxiety-, and depression, symptoms will be further increased at the 10-year follow-up measurement, while hostility symptoms will be further decreased.

METHODS

Study population

The present study reports on findings from the PRISMO-study, a large prospective cohort study on the development of stress-related mental health symptoms in Dutch military personnel deployed to Afghanistan, which is described in detail elsewhere[21]. A total of 1007 study participants who were deployed for about 4 months to Afghanistan on behalf of the International Security Assistance Force (ISAF) between 2005 and 2008 were included in the study. Written informed consent was obtained from all subjects. Approximately 1 month prior to their deployment, participants completed the baseline measurement at the army base. At approximately 1 and 6 months after returning home, the first two follow-up measurements were also completed at the army base. The 1-, 2-year, and 5-year follow-up assessment were completed at home, and the 10-year follow-up was conducted at the research facility of the Military Mental Healthcare. Except for the 5-year measurement which was completed online, all measurements consisted of paper-and-pencil questionnaires. In order to minimize dropout in the follow-up assessments, all participants were repeatedly contacted (up to five times) through email, mail and/or telephone, in order to remind them to complete the questionnaires. Still, response rates dropped to 843 respondents at 1 month, 773 at 6 months, 573 at 1 year, 566 at 2 years, 581 at 5 years, and 598 at 10 years. The current study used data from all measurement points, except from the 5-year measurement. At this measurement point, mental health symptoms were measured with a different assessment tool, and therefore not included

in the present analyses. All procedures were approved by the Institutional Review Board of the University Medical Center Utrecht (Utrecht, The Netherlands).

Measures

Mental health symptoms

For all assessments, mental health symptoms were measured with the agoraphobia (7 items), anxiety (10 items), depression (16 items), and hostility (6 items) subscales of the Dutch revised Symptom Checklist (SCL-90-R)[22]. The agoraphobia subscale measures a disproportional reaction of fear in open spaces, public spaces, or other certain places where a person feels weak, is afraid not to be able to rely on a trusted other, or is afraid of losing control of his or her presence. The anxiety subscale measures increased arousal and more general symptoms such as nervousness, tension, as well as more specific symptoms such as panic attacks and restlessness. Also cognitive components of anxiety-like feelings of misfortune and anxious thoughts and imaginations are assessed. The depression subscale assesses depressed mood, inability to feel pleasure, decreased self-esteem, and thoughts of guilt, helplessness, death, and suicide. This subscale also includes physical symptoms like a loss of appetite, lack of energy, and loss of sexual interest. Finally, the hostility subscale measures thoughts, feelings, or behaviors characteristic for a negative state of mind of anger. The SCL-90 contains 90 items with responses measured on a Likert scale ranging from 1 (not at all) to 5 (very much). The SCL-90 has good internal consistency, discriminant validity, and concurrent validity[23-25]. A cut-off value of ⩾11 was used for agoraphobia, ⩾22 for anxiety, ⩾36 for depression, and ⩾11 for hostility. Cut-off values for all subscales were based on the 95th percentile scores of a sample from the general population as reported in the Dutch manual of the SCL-90-R[10,26]. The receipt of psychological care was assessed by the item 'Have you ever received any care for psychological health complaints after your deployment?' at the 10-year follow-up measurement. We defined psychological care as any received care for psychological health complaints provided by a GP, social worker, psychologist, psychiatrist, or other mental health specialist. Due to the fact that we had no information on the timing, type, and length of the psychological care, this variable was not tested as a covariate in our analyses and only used as a descriptive.

Covariates

At baseline, participants provided information about their sex, age, educational level, rank, and the number of previous deployments. Potential traumatic experiences before the age of 18 were assessed using the Early Trauma Inventory Self Report-Short Form (ETISR-SF)[27]. The ETISR-SF contains 27 items measured on a five-point frequency scale, and included four domains of childhood traumatic events: general trauma, physical-, emotional-, and sexual abuse. At the first measurement after deployment, information on the participant's role during the mission was collected and divided

in three categories: inside the base, outside the base, and both inside and outside the base. Exposure to potentially traumatic and combat-related stressors during deployment was assessed with the Deployment Experience Scale (DES), a 19-item deployment stressors checklist[10]. At the 1-year follow-up assessment, participants completed part F (support from other military personnel during deployment; 12 items) and part L (support from family and friends after deployment; 17 items) of the Deployment Risk and Resilience Inventory 1 (DRRI-1)[28], a collection of measures assessing deployment-related experiences of military veterans. Although the DRRI-1 was administered at the 1-year follow-up assessment, the questionnaire assessed the perceived support during deployment (part F) or the perceived support in the period directly after deployment (part L). Responses were measured on a Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). Potential new deployments after the initial deployment were assessed at each follow-up assessment. All tested covariates were selected before analysis. We included the covariates that we, based on the existing literature, considered to be relevant for mental health in a military population, with special focus on stress-related mental health symptoms.

Statistical analysis

The change in agoraphobia, anxiety, depression, and hostility symptom levels at 1 month, 6 months, 1 year, 2 years, and 10 years after deployment, relative to the pre-deployment level, were assessed in four separate linear mixed-effects models with repeated measures. The time variable was recoded into five dummy variables (one dummy variable for each measurement after deployment), whereby pre-deployment served as the reference. All five dummy variables for time were included in the models. Continuous, longitudinal symptom scores were used as the outcome variable. The coefficients and associated p values of the dummy variables for time were reported. After running these four 'initial' mixed models, the interaction of the potential moderating factors (i.e. demographic factors, early trauma, deployment characteristics, social support; see covariates) with the change in mental health symptoms relative to pre-deployment was investigated at each time point. In each initial model, the covariate itself as well as the interaction terms between the covariate and all five dummy variables for time were now added as fixed effects. The different covariates were included separately in the initial mixed models. We did not use a multivariate approach due to model stability issues and correlation between some of the covariates. Coefficients and associated p values of the interaction terms were used as the effect size for the covariates, and only reported for time points with a significant change in symptoms relative to pre-deployment. Participants were excluded from the analysis if they had no SCL-90-R assessment at any time point. A two-tailed p value of less than 0.05 was considered statistically significant.

Missing data analysis

Considering that in mixed model analysis the missing data are not assumed to be missing completely at random, and that the results obtained from a mixed model analysis with multiple imputation can be quite unstable[29], no multiple imputation techniques were used prior to the mixed model analyses. Detailed information on missing data can be found in Table S2 in the Supplementary material.

RESULTS

At baseline, a total of 1007 participants were included in the PRISMO cohort. Twenty-nine of them had no valid SCL-90-R measurement at any of the time points including the pre-deployment measurement (referred to as participants without a SCL-90-R measurement) and were excluded from the analyses. A total of 978 participants with at least one valid SCL-90-R measurement at any of the time points (referred to as participants with a SCL-90-R measurement) were therefore included in the present analyses. The baseline characteristics are shown in Table 1. No significant differences in demographics were found between participants with and without a SCL-90-R measurement. Differences in demographics between responders and non-responders at the 10-year follow-up measurement can be found in Table S1 in the Supplementary material. In short, participants that did not complete the 10-year follow-up measurement had a lower educational level and a lower rank, were more often previously deployed, had more often a role outside the military base, and experienced more deployment stressors. Mean agoraphobia, anxiety, depression, and hostility symptom levels and probable prevalence rates at each time point are shown in Figure 1 and Table 2. A full tabulation of the results for the analyses are shown in the Supplementary material. The interactions of covariates with the change in mental health symptoms are shown in Table 3. Reported patterns of comorbidity between the mental health symptoms at all time points are shown in Table S2 in the Supplementary material. The percentage of military personnel that did not report any of the assessed mental health symptoms (i.e. that did not score above cut-off for agoraphobia, anxiety, depression, and hostility symptoms) was 92.5% at 1 month, 91.5% at 6 months, 90.7% at 1 year, 91.9% at 2 years, and 89.0% at 10 years post-deployment (Supplementary Table S3). 28.5% of the participants indicated to have received any psychological care for mental health symptoms. Of the participants that did report any of the assessed mental health symptoms at any of the time points (i.e. that did score above cut-off for agoraphobia, anxiety, depression, and/or hostility symptoms at any time point), 55% received any psychological care.

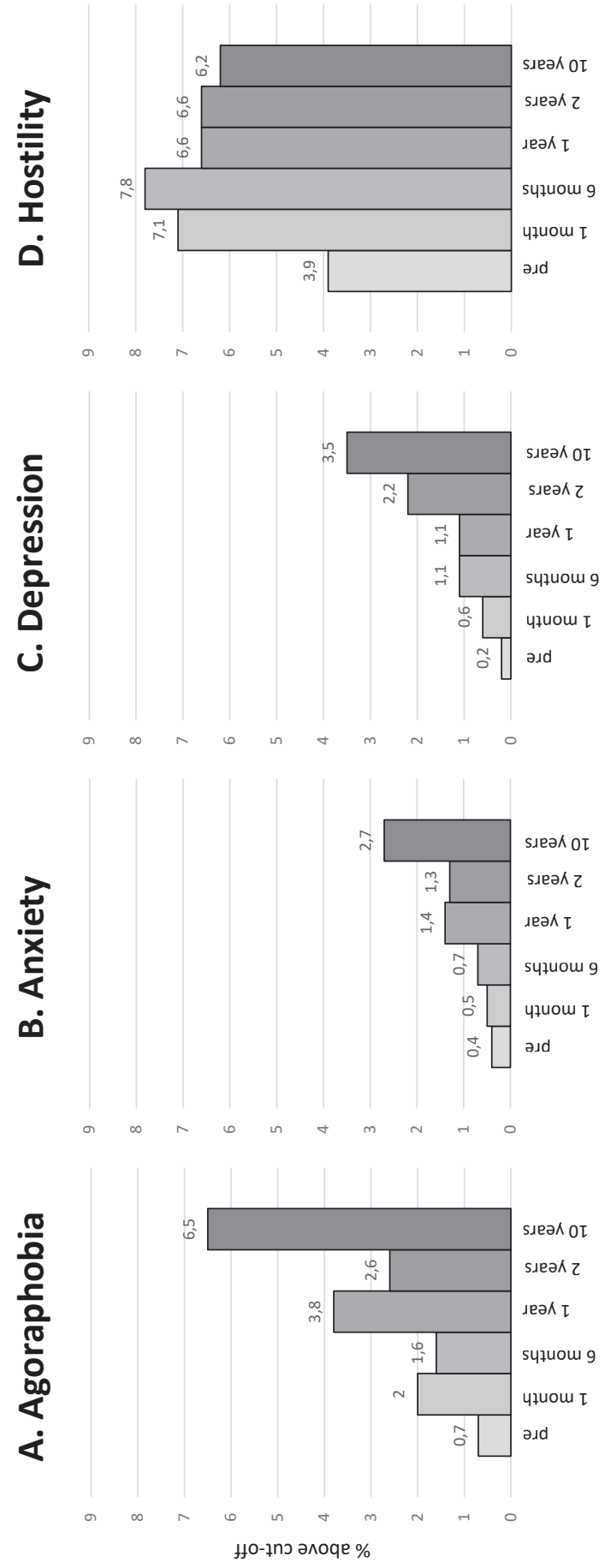

Figure 1. Reported agoraphobia (a), anxiety (b), depression (c), and hostility (d) symptoms over time in Dutch ISAF veterans. Prevalence rates were based on the Symptom Checklist (SCL-90-R). Cut-off values for all subscales were based on the 95th percentile scores of a sample from the general population as reported in the respective questionnaire manual. Cut-off values: agoraphobia: ⩾11; anxiety: ⩾22; depression: ⩾36; hostility: ⩾11.

Table 1. Demographics and other characteristics of participants in the cohort who were deployed, separated for participants included in the analyses and participants without any outcome value.

	Participants with outcome values at one or more time points (n=978)[a]	Participants without any outcome value (n=29)[a]	p-value
Sex			
Male	893 (91%)	28 (97%)	
Female	85 (9%)	1 (3%)	0.319
Age (years)[b]			
<21	136 (14%)	3 (13%)	
≥21	840 (86%)	21 (88%)	0.841
Educational level[c]			
Low	362 (40%)	4 (33%)	
Moderate	435 (48%)	7 (58%)	
High	101 (11%)	1 (8%)	0.790
Rank[d]			
Private	388 (40%)	6 (50%)	
Corporal	199 (21%)	4 (33%)	
Non-commissioned officer	250 (26%)	1 (8%)	
Staff officer	131 (14%)	1 (8%)	0.411
Previous deployment(s)[e]			
Yes	417 (47%)	3 (25%)	
No	470 (53%)	9 (75%)	0.129
Role during deployment[f]			
Inside the military base	244 (31%)	4 (36%)	
Both inside and outside the military base	73 (9%)	0 (0%)	
Outside the military base	476 (60%)	7 (64%)	0.564
Deployment year			
2005 or 2006	251 (26%)	10 (35%)	
2007 or 2008	727 (74%)	19 (66%)	0.286
New deployment(s)[g]			
Yes	285 (45%)	..	..
No	348 (55%)	..	..
DES (deployment stressors) total score[h]	4.51 (3.22)	..	..
DDRI-F (unit social support) total score[i]	45.39 (10.19)	..	..
DDRI-L (support after deployment) total score[j]	60.35 (9.07)	..	..
ETISR-SF (early trauma) total score[k]	3.49 (3.06)	..	..

Note: data are n (%) or mean (SD). Differences in descriptive characteristics between participants with and without any outcome value were tested with a $\chi 2$-test (categorical). DES, Deployment Experience Scale; DDRI-F, Deployment Risk and Resilience Inventory part F; DDRI-L, Deployment Risk and Resilience Inventory part L; ETISR-SF, Early Trauma Inventory Self Report-Short Form. Education (ISCED levels): low=primary and lower secondary education; moderate=upper secondary, post-secondary non-tertiary, and short cycle tertiary education; high=bachelor, master, and doctoral education.

[a] Sample sizes might not add up to total because of missing data in the descriptive variables; where there is missing data, the total is indicated. Totals for participants included in the analyses: [b] n=976, [c] n=898, [d] n=968, [e] n=887, [f] n=793, [g] n=633, [h] n=706, [i] n=335, [j] n=333, [k] n=888; totals for participants without any outcome value: [b] n=24, [c] n=12, [d] n=12, [e] n=12, [f] n=11, [g] n=0, [h] n=0, [i] n=0, [j] n=0, [k] n=0.

Table 2. Reported agoraphobia, anxiety, depression, and hostility symptoms over time in Dutch ISAF veterans.

	Total number of participants with available data	Above cut-off[a]	Mean SCL-90 subscore	Range SCL-90 subscore[b]
Agoraphobia				
Pre-deployment	829	6	7.19 (0.69)	7 - 16
1 month	807	16	7.32 (1.08)	7 - 19
6 months	731	12	7.30 (1.14)	7 - 23
1 year	558	21	7.41 (1.54)	7 - 28
2 years	544	14	7.40 (1.45)	7 - 24
10 years	600	39	7.77 (2.37)	7 - 30
Anxiety				
Pre-deployment	818	3	11.01 (1.78)	10 - 22
1 month	798	4	11.05 (2.16)	10 - 39
6 months	724	5	11.07 (2.29)	10 - 32
1 year	553	8	11.15 (2.77)	10 - 39
2 years	531	7	11.18 (2.64)	10 - 37
10 years	595	16	11.50 (3.81)	10 - 50
Depression				
Pre-deployment	823	2	17.97 (2.97)	16 - 38
1 month	800	5	18.28 (3.83)	16 - 50
6 months	729	8	18.33 (4.13)	16 - 46
1 year	552	8	19.08 (5.71)	16 - 64
2 years	544	12	19.25 (5.65)	16 - 63
10 years	595	21	19.30 (6.11)	16 - 60
Hostility				
Pre-deployment	828	32	6.96 (1.58)	6 - 22
1 month	808	57	7.29 (2.15)	6 - 21
6 months	732	57	7.21 (2.29)	6 - 24
1 year	558	37	7.21 (2.41)	6 - 29
2 years	547	36	7.26 (2.34)	6 - 27
10 years	598	37	7.07 (2.28)	6 - 26

Note: data are n or mean (SD). SCL-90, Symptom Checklist-90. [a] Used cut-off values for subscales: agoraphobia: ≥11; anxiety: ≥22; depression: ≥36; hostility: ≥11. [b] Minimum and maximum scores for subscales: agoraphobia: 7-35; anxiety: 10-50; depression: 16-80; hostility: 6-30.

Table 3. Significant effect sizes of risk factors for an increase in psychological symptoms over time relative to pre-deployment.

	Age	Education	Rank[a]	Previous deployment	Role during deployment[b]	Deployment experience	Social support	Unit support	Early general trauma	Early emotional abuse	Physical abuse	Early sexual abuse
Agoraphobia												
Δ 1 month	..	..	..	..	..	0.044*	..	..	..	..	..	..
Δ 1 year	..	..	..	..	0.286*	0.077**	-0.036***	..	..	..	..	..
Δ 2 years	..	..	..	..	..	..	..	..	..	..	..	..
Δ 10 years	-0.026***	..	-0.598***	0.286*	0.665**	0.091***	-0.054***	..	..	..	..	..
Anxiety												
Δ 10 years	-0.045***	..	-0.970***	..	0.917**	0.163***	-0.094***	..	..	..	..	..
Depression												
Δ 1 year	..	..	..	..	..	0.141*	-0.227***	..	..	..	..	1.131*
Δ 2 years	..	..	..	..	..	..	-0.152***	..	..	0.623*	..	..
Δ 10 years	-0.086***	..	1.547***	1.000*	1.041*	0.211*	-0.166***	..	..	..	..	..
Hostility												
Δ 1 month	..	..	..	..	..	0.090**	-0.053**	..	..	0.204*	..	..
Δ 6 months	..	..	..	..	..	0.083*	-0.069***	..	..	..	..	..
Δ 1 year	..	..	..	..	..	0.076*	-0.090***	..	..	..	..	..
Δ 2 years	..	..	..	..	..	..	-0.043*	..	..	..	..	..
Δ 10 years	..	..	..	..	..	..	-0.050*	..	..	..	..	..

Note: Δ indicates the significant difference in symptom score relative to pre-deployment status, when there was no significant difference in symptom score relative to pre-deployment at a time-point, no covariates were tested; effect sizes are β-values; .. indicates no significant effect size; * p<0.05; ** p<0.001; *** p<0.0001; [a] the rank parameter indicates the difference between non-commissioned officer and staff officer ranks versus private and corporal ranks (reference category); [b] the role during deployment parameter indicates the difference between the group with a role outside the military base versus the group with a role inside the military base (reference category).

Agoraphobia

The percentage of participants scoring above cut-off on agoraphobia symptoms at 10 years after deployment was 6.5%. This was a much higher percentage compared to all earlier follow-up measurements, with a probable prevalence rates ranging from 1.6% at 6 months post-deployment to 3.8% at 1 year post-deployment. The mixed model analysis with only the time points included showed that, relative to pre-deployment, agoraphobia symptoms were increased at 1 month, 1 year, 2 years and 10 years after deployment (Supplementary Table S4).

Age was significantly related to a lower increase in agoraphobia symptoms at 10 years after deployment (β = %95 ;0.026− confidence interval (CI) 0.038− to 0.015−), suggesting a higher increase in agoraphobia symptoms relative to pre-deployment for younger military personnel. Similar moderating effects were found for rank during deployment (β = −0.598; 95% CI −0.824 to −0.373), where the lower-ranking personnel had more increased agoraphobia symptoms at 10-year post-deployment compared to higher-ranking personnel. Also, military personnel with one or more previous deployments had a lower increase (β = 0.286; 95% CI 0.055–0.516) in symptoms at 10 years after deployment relative to pre-deployment. Military personnel with a role outside the base had more increased agoraphobia symptoms at 1 year (β = 0.286; 95% CI 0.010–0.562) and 10 years (β = 0.665; 95% CI 0.383–0.927) after deployment than the group that operated only inside the base. Moreover, a higher level of deployment stressors was related to a greater increase in agoraphobia symptoms at 1 month (β = 0.044; 95% CI 0.011–0.077), 1 year (β = 0.077; 95% CI 0.036–0.118), and 10 year (β = 0.091; 95% CI 0.052–0.131) post-deployment. Social support after deployment was associated with a lower increase in agoraphobia symptoms at 1 year (β = −0.036; 95% CI −0.054 to −0.018) and 10 years (β = −0.054; 95% CI −0.075 to −0.034) after deployment, suggesting a lower increase in agoraphobia symptoms for personnel that perceived more social support after a return.

Anxiety

Ten years after deployment, 2.7% of all participants scored above cut-off on anxiety symptoms. This was an increase compared to the probable prevalence rates on previous follow-up measurements, ranging from 0.5% (1-month post-deployment) to 1.3% (2 years post-deployment). The mixed model showed that anxiety symptoms were only significantly increased at 10-years after deployment relative to pre-deployment (Supplementary Table S5).

At 10 years post-deployment, age (β = −0.045; 95% CI −0.066 to −0.023) and rank (β = −0.970; 95% CI −1.378 to −0.563) were associated with a lower increase in anxiety

symptoms, suggesting that younger and lower-ranking personnel had a higher increase in anxiety symptoms relative to pre-deployment. A role outside the base compared to a role inside the base was related to a larger increase in anxiety symptoms at 10 years after deployment (β = 0.917; 95% CI 0.428–1.407). Personnel that experienced a higher level of deployment stressors also had more increased anxiety symptoms 10 years post-deployment relative to pre-deployment (β = 0.163; 95% CI 0.092–0.233). Furthermore, a higher level of social support after deployment was related to a lower increase in anxiety symptoms at 10 years after deployment (β = −0.094; 95% CI −0.131 to −0.057).

Depression

The prevalence of a high level of depression symptoms 10 years after deployment was 3.5%. This percentage was higher compared to previous follow-up measurements that ranged from 0.6% at 1-month post-deployment to 1.3% at 2 years post-deployment. The mixed model revealed that depression symptoms were only elevated at 1 year, 2 years, and 10 years relative to the level before deployment (Supplementary Table S6).

Age (β = −0.086; 95% CI −0.124 to −0.048) and rank (β = −1.547; 95% CI −2.271 to −0.822) were significantly related to a lower increase in depressive symptoms relative to pre-deployment at 10 years post-deployment, suggesting a higher increase in depression symptoms for younger and lower-ranking personnel. Having participated in one or more previous deployments was related to a higher increase in depression symptoms 10 years after deployment relative to pre-deployment (β = 1.000; 95% CI 0.257–1.744). A role outside the base compared to a role inside the base was also associated with a higher increase in depression symptoms at 10 years after deployment (β = 1.041; 95% CI 0.424–2.108). A higher level of deployment stressors was related to a greater increase in depression symptoms at 1 year (β = 0.141; 95% CI 0.010–0.272) and 10 years (β = 0.211; 95% CI 0.085–0.338) post-deployment relative to pre-deployment. Social support after deployment was associated with a lower increase in depression symptoms compared to pre-deployment at 1 year (β = −0.227; 95% CI −0.285 to −0.168), 2 years (β = −0.152; 95% CI −0.213 to −0.091), and 10 years (β = −0.166; 95% CI −0.232 to −0.100) after deployment, suggesting a lower increase in depression symptoms for personnel that perceived more social support after homecoming. Finally, reported childhood emotional abuse was related to a greater increase in depression symptoms at 2 years after deployment compared to pre-deployment (β = 0.623; 95% CI 0.270–0.976), while childhood sexual abuse was related to a greater increase in depression symptoms at 1 year after deployment (β = 1.131; 95% CI 0.393–1.869).

Hostility

In total, 6.2% of all participants scored above cut-off for hostility symptoms at 10 years after deployment. This was a decrease compared to all previous follow-up assessments, ranging from 6.6% at 1 and 2-year follow-up to 7.8% at 6 months follow-up. The mixed model showed that hostility symptoms were increased at all follow-up assessments relative to the pre-deployment level (Supplementary Table S7).

For hostility symptoms, only three covariates were associated with the increase in symptoms after deployment. Personnel that experienced a higher level of deployment stressors had a higher increase in hostility symptoms relative to pre-deployment at 1 month (β = 0.090; 95% CI 0.041–0.140), 6 months (β = 0.083; 95% CI 0.029–0.136), and 1 year (β = 0.076; 95% CI 0.015–0.138) post-deployment. Social support after deployment was related to a lower increase in hostility symptoms relative to pre-deployment at 1 month (β = −0.053; 95% CI −0.080 to −0.025), 6 months (β = −0.069; 95% CI −0.097 to −0.041), 1 year (β = −0.090; 95% CI −0.118 to −0.062), 2 years (β = −0.043; 95% CI −0.073 to −0.014), and 10 years (β = −0.050; 95% CI −0.082 to −0.019) after returning home, suggesting a lower increase in hostility symptoms in personnel that received more social support after homecoming. Childhood emotional abuse was associated with a higher increase in hostility symptoms at 1 month after deployment compared to pre-deployment (β = 0.204; 95% CI 0.059–0.349).

DISCUSSION

This paper suggests a long-term effect of deployment on the mental health of Dutch military personnel deployed to Afghanistan. Although the large majority of deployed service members showed low levels of mental health symptoms, the average levels of agoraphobia, anxiety, depression and hostility symptoms were still increased at 10 years after deployment compared to the pre-deployment level. The identified prevalence of a high level of anxiety (2.7%) and depression (3.5%) symptoms was quite low in comparison to a US sample of military personnel deployed to Iraq and Afghanistan in which a current prevalence of 36% was found for anxiety disorder and 25% for depression 7.5 years after deployment[7]. However, these prevalence rates were based on diagnoses derived from clinical interviews. A one-to-one comparison with the prevalence rates based on a self-report measure as in the current study is therefore not possible. Except for hostility symptoms, the probable prevalence of all mental health problems at 10 years after deployment was the highest compared to all previous follow-up assessments in our sample. To our knowledge, this is the first study to report the prevalence of a wide range of mental health symptoms (beyond PTSD) in military

personnel up to 10 years after deployment. The results have implications for current monitoring policies that usually include routine screenings that stop after 1 or 2 years.

For agoraphobia, anxiety, and depression symptoms, there was an increase in the percentage of the participants scoring above cut-off between 2 and 10 years post-deployment. This suggests a long-term deterioration in mental health symptoms in deployed personnel over time. Interestingly, a large study on ageing and the prevalence of mental health symptoms in a general population sample from the UK showed that the risk of developing a common mental disorder remained almost constant up to age 55[30]. Also, the NEMESIS-2 study, a large Dutch nationally representative survey on the prevalence of mental health disorders, found a higher 12-month prevalence of mood disorders and anxiety disorder in the 18–24 age category compared to the 25–34 and 35–44 age categories[31]. It can therefore be suggested that the identified increase in mental health symptoms in the present study is related to deployment rather than a result of the ageing of the sample. However, as the cut-off values used to calculate the probable prevalence rates in our sample were based on the 95th percentile score of a representative sample from the general Dutch population[26] (i.e. 5% of the general population scored above this cut-off value), it is important to note that although deployed military personnel reported high levels of agoraphobia, anxiety, and depression symptoms more frequently over time; as a group, they experience better mental health compared to the general population. Only the prevalence of a high level of agoraphobia symptoms at 10 years after deployment (6.5%) was higher compared to the prevalence in the general population. When studying a cohort of military personnel that is going to be deployed, you are dealing with a psychologically healthy population at baseline. Psychological testing before one is joining the army selects psychologically fit individuals, and extensive military training prepares service members for handling all kinds of stressful situations. Together with the observation that a substantial portion of the participants did not report high deployment stressors, it seems plausible that even after deployment our cohort experiences better mental health compared to the general population. For hostility symptoms, the prevalence was higher in comparison to the general population at all measurements after deployment. To our surprise, this was not the case pre-deployment (3.9%). Military personnel in our sample thus experienced high levels of hostility less frequently before their deployment, even less frequently than individuals in the general population, but develop hostility rates after deployment that transcend the rates in the general population.

In our report on the development of PTSD symptoms that included a measurement at 5 years post-deployment, we found a higher probable PTSD prevalence at 5 years after deployment that significantly declined at 10 years after deployment[20]. This subsequent

increase in symptom level at 5 years post-deployment could well be the case for other mental health symptoms, suggesting a decline in symptoms after 5 years instead of a long-term symptom deterioration over time. Although no SCL-90-R measure was available at the 5-year assessment, participants completed an online version of the Brief Symptom Inventory (BSI)[32], the short version of the SCL-90-R which also includes a subscale for depression, anxiety, and hostility symptoms. When using the BSI, we found a prevalence of a high level of symptoms at 5 years after the deployment of 8.8% for anxiety, 4.8% for depression, and 14.9% for hostility (see Supplementary Figure S1), supporting the hypothesis of a prevalence peak at 5 years post-deployment that tapers off in the following years. However, it is important to emphasize that these prevalence rates are based on a different psychopathology assessment tool that was administered as an online questionnaire instead of a paper-and-pencil questionnaire.

Our study also identified several factors that moderated the relation between deployment and the development of mental health symptoms afterwards. Previously identified risk factors for mental health problems in deployed military personnel like younger age, lower rank, combat stress exposure, or childhood trauma[2,14,33,34] were also found relevant in the present study. Besides the level of combat stress exposure, the level of perceived social support after returning home was the only tested covariate that was identified as a risk factor for all different mental health symptoms on several points in time. Its relationship with the development of depression symptoms at 1, 2, and 10 years after deployment was especially prominent.

The importance of social support in the mental health of military service members has been widely described in the literature[15,16,18,35,36], although with limited follow-up periods. It has been proposed that receiving social support can decrease the perception of a traumatic or stressful event. This will constrain the psychological difficulties following the event, and provides emotional resources that can lessen the burden of these experiences[18]. For example, social support can improve coping strategies and thereby enables military personnel to express their feelings and thoughts which in turn can be conducive for processing a threatening event[18,37]. In addition, several physiological mechanisms or pathways have been proposed to explain the buffering effect of social support on stress responsiveness. For instance, positive social support is suggested to suppress glucocorticoid concentrations[38] and cortisol levels[39], while negative social exchanges may instead increase the risk of HPA axis hyperactivity[38]. Also, oxytocin is frequently named as an important underlying biological mechanism for the stress-protective effects of positive social support [39-41]. On the other hand, some research suggested that social support does not influence subsequent mental health symptoms. Instead, the perception of received social support might change in relation to the

severity of mental health symptoms[35,42]. However, in the present study perceived social support after homecoming was measured 1 year after deployment, and was still found to be associated with the increase in agoraphobia, anxiety, depression, and hostility symptoms 10 years after deployment. As we showed that social support after deployment turned out to be an important factor even 10 years after deployment for a wide range of mental health symptoms, interventions that enhance social support may protect deployed personnel against post-deployment mental health problems. Continued effort should therefore be put in the addressment and monitoring of social support during family briefings and post-deployment screenings.

Besides social support from family and friends after deployment, unit cohesion, which includes emotional safety, bonding, and support between soldiers and with unit leaders[43], has received substantial attention in the literature[36,44-47]. These studies all show that service members who report high unit cohesion exhibit less mental health problems. It was therefore to our surprise that we did not find such a clear effect for unit support in our study. In fact, unit support was not significantly associated with any of the assessed mental health symptoms at any point in time. As previous research on unit cohesion was predominantly performed in US military personnel, the role of unit cohesion in mental health symptom development might be mission or unit-specific, or may be influenced by cultural factors. In addition, the use of different questionnaires to measure unit cohesion across studies, and the fact that unit cohesion was assessed 1 year after deployment in the present study might also partly explain the found inconsistency in results.

The results of the current study must be interpreted in the context of its limitations. Most important, it is not known whether the reported increase in mental health symptoms is exclusively the result of deployment, as we did not examine prevalence rates of mental health symptoms in a non-deployed military cohort. Therefore, we can not rule out that this increase is a result of military life itself. Secondly, we used self-report measurements to obtain mental health symptom levels. The results might therefore be subject to the biases associated with the use of self-report assessments. Our prevalence rates were based on cut-off values on a questionnaire, which are more or less arbitrary. This approach excludes participants with a comparable level of symptoms as participants scoring just above the cut-off. Although we used the SCL-90-R, a validated and often used instrument to measure psychopathology, it may also have resulted in higher prevalence rates compared to clinician diagnoses[48,49]. Moreover, the absence of an SCL-90-R measurement at 5 years after deployment might have left a high increase in symptom levels unnoted. Also, unit support and social support after deployment were exclusively assessed 1 year after deployment,

increasing the risk for recall bias. Furthermore, due to the explorative nature of the analyses, we did not adjust for multiple testing. The adjustment would render a few of the effects non-significant, and is a point of concern. Although inevitable in longitudinal studies, attrition is also a significant concern and the influence of non-response on the study findings cannot be ruled out. Finally, the variability in symptom scores in our cohort was relatively small. Therefore, we were not able to examine potentially heterogeneous trajectories of symptom development, which would be highly interesting and clinically relevant information. On the other hand, the present study possessed several strengths and addresses the limitations of previous research. For example, the pre-deployment measurement enabled us to determine whether symptom levels were significantly increased compared to pre-deployment. Furthermore, the five follow-up measurements over a period of 10 years following deployment offered a unique opportunity to assess the potential long-term impact of deployment on several mental health problems, and made differences in symptom progression over time noticeable for the various mental health symptoms.

In conclusion, the present study provides insights into the potential long-term impact of deployment by showing that the level of agoraphobia, anxiety, depression, and hostility symptoms was still increased at 10 years after returning home from deployment compared to pre-deployment. For agoraphobia, anxiety, and depression, the prevalence of a high level of symptoms at 10 years after deployment was even higher than the prevalence rates at all previous follow-up moments. However, prevalence rates of agoraphobia, anxiety, and hostility symptoms derived from a comparable questionnaire at 5-year follow-up suggest a prevalence peak at 5 years post-deployment that tapers off in the following year. Society should be aware of long-term increases in mental health problems in deployed service members, and monitoring policies must be adapted accordingly. Furthermore, this study underscores the importance of a high level of perceived social support from friends and family for more robust mental health in deployed personnel. Given that social support is potentially modifiable, it serves as a good candidate for intervention programs in deployed military personnel and their families that can target a wide range of mental health outcomes over a long period of time.

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SUPPLEMENTARY MATERIAL

Table S1. Demographics and other characteristics of participants with a 10-year follow-up measurement versus participants without a 10-year follow-up measurement.

	Participants with a 10-year follow-up measurement (n=598)[a]	Participants without a 10-year follow-up measurement (n=409)[a]	p-value
Sex			
Male	543 (91%)	378 (92%)	0.367
Female	55 (9%)	31 (8%)	
Age (years)[b]			
<21	76 (13%)	63 (16%)	0.193
≥21	521 (87%)	340 (84%)	
Educational level[c]			
Low	194 (35%)	172 (48%)	**<0.001**
Moderate	280 (51%)	162 (45%)	
High	77 (14%)	25 (7%)	
Rank[d]			
Private	198 (33%)	196 (51%)	**<0.001**
Corporal	117 (20%)	86 (22%)	
Non-commissioned officer	176 (30%)	75 (19%)	
Staff officer	102 (17%)	30 (8%)	
Previous deployment(s)[e]			
Yes	284 (52%)	136 (62%)	**<0.001**
No	260 (48%)	219 (38%)	
Role during deployment[f]			
Inside the military base	186 (38%)	62 (20%)	**<0.001**
Both inside and outside the military base	42 (9%)	31 (10%)	
Outside the military base	258 (53%)	225 (71%)	
Deployment year			
2005 or 2006	153 (26%)	108 (26%)	0.770
2007 or 2008	445 (74%)	301 (74%)	
New deployment(s)[g]			
Yes	271 (46%)	..	..
No	325 (55%)	..	..
DES (deployment stressors) total score[h]	4.30 (3.15)	4.91 (3.31)	**0.016**
DDRI-F (unit social support) total score[i]	45.95 (9.80)	43.48 (11.26)	0.063
DDRI-L (support after deployment) total score[j]	60.77 (8.33)	58.92 (11.22)	0.188
ETISR-SF (early trauma) total score[k]	3.35 (3.13)	3.72 (2.93)	0.081

Note: data are n (%) or mean (SD). Differences in descriptive characteristics between participants with and without a ten-year follow-up measurement were tested with a $\chi 2$-test (categorical) or an independent samples t-test (continuous). DES=Deployment Experience Scale. DDRI-F=Deployment Risk and Resilience Inventory part F. DDRI-L=Deployment Risk and Resilience Inventory part L. ETISR-SF=Early Trauma Inventory Self Report-Short Form. Education (ISCED levels): low=primary and lower secondary education; moderate=upper secondary, post-secondary non-tertiary, and short cycle tertiary education; high=bachelor, master, and doctoral education. [a] Sample sizes might not add up to total because of missing data in the descriptive variables; where there is missing data, the total is indicated. Totals for participants with a ten-year follow-up measurement: [b] n=597, [c] n=551, [d] n=593, [e] n=544, [f] n=486, [g] n=596, [h] n=461, [i] n=259, [j] n=258, [k] n=546; totals for participants without a ten-year follow-up measurement: [b] n=403, [c] n=359, [d] n=387, [e]n=355, [f] n=318, [g] n=0, [h] n=246, [i] n=76, [j]n=75, [k] n=342.

Table S2. Number of valid responses on variables included in the analyses (total sample = 978).

	Pre	1 month	6 months	1 year	2 years	10 years
Agoraphobia	829	807	731	558	544	600
Anxiety	818	798	724	553	531	595
Depression	823	800	729	552	544	595
Hostility	828	808	732	558	547	598
Age	976	-	-	-	-	-
Rank	968	-	-	-	-	-
Previous deployment(s)	887	-	-	-	-	-
Role during deployment	-	793	-	-	-	-
Deployment experience	-	706	-	-	-	-
Unit support	-	-	-	335	-	-
Social support	-	-	-	333	-	-
Early general trauma	921	-	-	-	-	-
Early physical abuse	925	-	-	-	-	-
Early emotional abuse	912	-	-	-	-	-
Early sexual abuse	909	-	-	-	-	-

Note: data are n (%); n indicates the number of participants with valid data on the specific variable.

Table S3. Reported mental health symptom patterns for each time point.

agoraphobia	anxiety	depression	hostility	Pre N=801	1 month N=782	6 months N=720	1 year N=546	2 years N=529	10 years N=580
				768 (95.9%)	723 (92.5%)	659 (91.5%)	495 (90.7%)	486 (91.9%)	516 (89.0%)
●				1 (0.1%)	3 (0.4%)	3 (0.4%)	11 (2.0%)	5 (1.0%)	19 (3.3%)
	●			1 (0.1%)	0	0	0	0	2 (0.3%)
		●		0	2 (0.3%)	2 (0.3%)	2 (0.4%)	2 (0.4%)	3 (0.5%)
			●	25 (3.1%)	41 (5.2%)	43 (6.0%)	25 (4.6%)	24 (4.5%)	17 (2.9%)
●	●			1 (0.1%)	2 (0.3%)	0	2 (0.4%)	0	2 (0.3%)
●		●		0	0	1 (0.1%)	0	0	0
●			●	2 (0.2%)	8 (1.0%)	6 (0.8%)	3 (0.5%)	3 (0.6%)	2 (0.3%)
	●	●		0	0	1 (0.1%)	0	0	0
	●		●	1 (0.1%)	0	0	2 (0.4%)	0	0
		●	●	2 (0.2%)	1 (0.1%)	1 (0.1%)	2 (0.4%)	2 (0.4%)	3 (0.5%)
●	●	●		0	0	0	0	0	2 (0.3%)
●	●		●	0	0	2 (0.3%)	0	0	1 (0.2%)
	●	●	●	0	0	2 (0.3%)	0	3 (0.6%)	1 (0.2%)
●		●	●	0	0	0	0	0	4 (0.7%)
●	●	●	●	0	2 (0.3%)	0	4 (0.7%)	4 (0.8%)	8 (1.4%)

Note: data are n (%); prevalence based on the Symptom Checklist-90 (SCL-90); used cut-off values for symptoms: agoraphobia: ≥11; anxiety: ≥22; depression: ≥36; hostility: ≥11.

Table S4. Parameter estimates for change in agoraphobia symptoms over time relative to pre-deployment status without interactions with potential moderators (n=978).

	Time-effect	
	Coefficient (95% CI)	**p-value**
Intercept (pre-deployment)	7.20 (7.12 – 7.28)	<0.0001
Δ 1 month[a]	0.11 (0.01 – 0.21)	**0.026**
Δ 6 months[a]	0.09 (-0.01 – 0.19)	0.093
Δ 1 year[a]	0.23 (0.11 – 0.34)	**<0.001**
Δ 2 years[a]	0.20 (0.09 – 0.32)	**0.001**
Δ 10 years[a]	0.60 (0.48 – 0.71)	**<0.0001**

Note: [a] Δ indicates the difference relative to pre-deployment status; 95% CI=95% Confidence Interval.

Table S5. Parameter estimates for change in anxiety symptoms over time relative to pre-deployment status without interactions with potential moderators (n=978).

	Time-effect	
	Coefficient (95% CI)	**p-value**
Intercept (pre-deployment)	11.03 (10.89 – 11.17)	<0.0001
Δ 1 month[a]	0.01 (-0.18 – 0.19)	0.950
Δ 6 months[a]	0.03 (-0.16 – 0.22)	0.773
Δ 1 year[a]	0.15 (-0.06 – 0.36)	0.169
Δ 2 years[a]	0.16 (-0.05 – 0.37)	0.137
Δ 10 years[a]	0.52 (0.32 – 0.72)	**<0.0001**

Note: [a] Δ indicates the difference relative to pre-deployment status; 95% CI=95% Confidence Interval.

Table S6. Parameter estimates for change in depression symptoms over time relative to pre-deployment status without interactions with potential moderators (n=978).

	Time-effect	
	Coefficient (95% CI)	**p-value**
Intercept (pre-deployment)	17.98 (17.72 – 18.23)	<0.0001
Δ 1 month[a]	0.28 (-0.04 – 0.61)	0.083
Δ 6 months[a]	0.32 (-0.02 – 0.65)	0.062
Δ 1 year[a]	1.06 (0.70 – 1.44)	**<0.0001**
Δ 2 years[a]	1.33 (0.96 – 1.71)	**<0.0001**
Δ 10 years[a]	1.41 (1.05 – 1.77)	**<0.0001**

Note: [a] Δ indicates the difference relative to pre-deployment status; 95% CI=95% Confidence Interval.

Table S7. Parameter estimates for change in hostility over time relative to pre-deployment status without interactions with potential moderators (n=978).

	Time-effect	
	Coefficient (95% CI)	**p-value**
Intercept (pre-deployment)	6.98 (6.86 – 7.10)	<0.0001
Δ 1 month[a]	0.31 (0.16 – 0.46)	**<0.0001**
Δ 6 months[a]	0.23 (0.08 – 0.39)	**0.003**
Δ 1 year[a]	0.33 (0.15 – 0.50)	**<0.001**
Δ 2 years[a]	0.40 (0.23 – 0.58)	**<0.0001**
Δ 10 years[a]	0.21 (0.04 – 0.37)	**0.015**

Note: [a] Δ indicates the difference relative to pre-deployment status; 95% CI=95% Confidence Interval.

Table S8. Parameter estimates for change in agoraphobia symptoms over time relative to pre-deployment status with different moderators (n=978).

	Interaction time x moderator variable	
	Coefficient (95% CI)	**p-value**
Age		
Δ 1 month[a]	-0.009 (-0.020 – 0.002)	0.106
Δ 1 year[a]	-0.007 (-0.019 – 0.005)	0.271
Δ 2 years[a]	-0.004 (-0.016 – 0.008)	0.547
Δ 10 years[a]	-0.026 (-0.038 – -0.015)	**<0.0001**
Rank[b]		
Δ 1 month[a]	-0.130 (-0.333 – 0.073)	0.208
Δ 1 year[a]	-0.143 (-0.375 – 0.088)	0.224
Δ 2 years[a]	-0.127 (-0.361 – 0.107)	0.288
Δ 10 years[a]	-0.598 (-0.824 – -0.373)	**<0.0001**
Previous deployment(s)[c]		
Δ 1 month[a]	0.096 (-0.109 – 0.300)	0.359
Δ 1 year[a]	0.073 (-0.163 – 0.309)	0.544
Δ 2 years[a]	0.014 (-0.226 – 0.254)	0.909
Δ 10 years[a]	0.286 (0.055 – 0.516)	**0.015**
Role during deployment[d]		
Both inside and outside the base		
Δ 1 month[a]	0.077 (-0.341 – 0.495)	0.717
Δ 1 year[a]	0.056 (-0.399 – 0.511)	0.809
Δ 2 years[a]	-0.145 (-0.635 – 0.346)	0.564
Δ 10 years[a]	0.424 (-0.055 – 0.903)	0.082
Outside the base		
Δ 1 month[a]	0.087 (-0.162 – 0.336)	0.492
Δ 1 year[a]	0.286 (0.010 – 0.562)	**0.042**
Δ 2 years[a]	0.165 (-0.117 – 0.447)	0.252
Δ 10 years[a]	0.665 (0.383 – 0.927)	**<0.001**
Deployment experience[e]		
Δ 1 month[a]	0.044 (0.011 – 0.077)	**0.010**
Δ 1 year[a]	0.077 (0.036 – 0.118)	**<0.001**
Δ 2 years[a]	0.040 (-0.001 – 0.081)	0.059
Δ 10 years[a]	0.091 (0.052 – 0.131)	**<0.0001**
Unit support[f]		
Δ 1 month[a]	0.005 (-0.011 – 0.022)	0.534
Δ 1 year[a]	-0.006 (-0.022 – 0.010)	0.470
Δ 2 years[a]	0.002 (-0.016 – 0.021)	0.786
Δ 10 years[a]	0.013 (-0.006 – 0.031)	0.159

Table S8. (Continued)

	Interaction time x moderator variable	
	Coefficient (95% CI)	**p-value**
Social support[g]		
Δ 1 month[a]	-0.013 (-0.031 – 0.005)	0.152
Δ 1 year[a]	-0.036 (-0.054 – -0.018)	**<0.0001**
Δ 2 years[a]	-0.018 (-0.037 – 0.001)	0.070
Δ 10 years[a]	-0.054 (-0.075 – -0.034)	**<0.0001**
Early general trauma[h]		
Δ 1 month[a]	-0.007 (-0.068 – 0.055)	0.831
Δ 1 year[a]	0.061 (-0.010 – 0.133)	0.093
Δ 2 years[a]	0.045 (-0.027 – 0.117)	0.225
Δ 10 years[a]	0.026 (-0.044 – 0.095)	0.470
Early physical abuse[h]		
Δ 1 month[a]	-0.011 (-0.088 – 0.066)	0.780
Δ 1 year[a]	0.021 (-0.071 – 0.112)	0.659
Δ 2 years[a]	-0.075 (-0.163 – 0.013)	0.097
Δ 10 years[a]	-0.088 (-0.177 – 0.002)	0.055
Early emotional abuse[h]		
Δ 1 month[a]	0.071 (-0.027 – 0.169)	0.156
Δ 1 year[a]	0.016 (-0.097 – 0.130)	0.777
Δ 2 years[a]	0.031 (-0.080 – 0.142)	0.581
Δ 10 years[a]	-0.028 (-0.139 – 0.082)	0.616
Early sexual abuse[h]		
Δ 1 month[a]	-0.022 (-0.207 – 0.163)	0.814
Δ 1 year[a]	-0.061 (-0.269 – 0.148)	0.568
Δ 2 years[a]	-0.151 (-0.346 – 0.043)	0.127
Δ 10 years[a]	-0.132 (-0.334 – 0.070)	0.200

Note: [a] Δ indicates the difference relative to pre-deployment status, when there was no significant difference in symptom score relative to pre-deployment at a time-point, no covariates were reported; 95% CI=95% Confidence Interval; [b] the rank parameter indicates the difference between non-commissioned officer and staff officer ranks versus private and corporal ranks (reference category); [c] reference category is the group with one or more previous deployments; [d] reference category is the group with a role inside the military base; [e] deployment experience was measured with the Deployment Experience Scale (DES); [f] unit support during deployment was measured with the Deployment Risk and Resilience Inventory-1 Section F (DRRI-F); [g] social support after deployment was measured with the Deployment Risk and Resilience Inventory-1 Section L (DRRI-L); [h] early trauma was measured with the Early Trauma Inventory Self-Report-Short Form (ETISR-SF).

Table S9. Parameter estimates for change in anxiety symptoms over time relative to pre-deployment status with different moderators (n=978).

	Interaction time x moderator variable	
	Coefficient (95% CI)	**p-value**
Age		
Δ 10 years[a]	-0.045 (-0.066 – -0.023)	**<0.0001**
Rank[b]		
Δ 10 years[a]	-0.970 (-1.378 – 0.563)	**<0.0001**
Previous deployment(s)[c]		
Δ 10 years[a]	0.391 (-0.022 – 0.804)	0.064
Role during deployment[d]		
Both inside and outside the base		
Δ 10 years[a]	0.753 (-0.107 – 1.614)	0.086
Outside the base		
Δ 10 years[a]	0.917 (0.428 – 1.407)	**<0.0001**
Deployment experience[e]		
Δ 10 years[a]	0.163 (0.092 – 0.233)	**<0.0001**
Unit support[f]		
Δ 10 years[a]	0.026 (-0.007 – 0.059)	0.125
Social support[g]		
Δ 10 years[a]	-0.094 (-0.131 – -0.057)	**<0.0001**
Early general trauma[h]		
Δ 10 years[a]	-0.026 (-0.151 – 0.100)	0.690
Early physical abuse[h]		
Δ 10 years[a]	-0.027 (-0.191 – 0.137)	0.746
Early emotional abuse[h]		
Δ 10 years[a]	-0.132 (-0.332 – 0.068)	0.196
Early sexual abuse[h]		
Δ 10 years[a]	0.105 (-0.261 – 0.471)	0.573

Note: [a] Δ indicates the difference relative to pre-deployment status, when there was no significant difference in symptom score relative to pre-deployment at a time-point, no covariates were reported; 95% CI=95% Confidence Interval; [b] the rank parameter indicates the difference between non-commissioned officer and staff officer ranks versus private and corporal ranks (reference category); [c] reference category is the group with one or more previous deployments; [d] reference category is the group with a role inside the military base; [e] deployment experience was measured with the Deployment Experience Scale (DES); [f] unit support during deployment was measured with the Deployment Risk and Resilience Inventory-1 Section F (DRRI-F); [g] social support after deployment was measured with the Deployment Risk and Resilience Inventory-1 Section L (DRRI-L); [h] early trauma was measured with the Early Trauma Inventory Self-Report-Short Form (ETISR-SF).

Table S10. Parameter estimates for change in depression symptoms over time relative to pre-deployment status with different moderators (n=978).

	Interaction time x moderator variable	
	Coefficient (95% CI)	**p-value**
Age		
Δ 1 year[a]	-0.005 (-0.044 – 0.033)	0.786
Δ 2 years[a]	-0.004 (-0.043 – 0.035)	0.849
Δ 10 years[a]	-0.086 (-0.124 – -0.048)	**<0.0001**
Rank[b]		
Δ 1 year[a]	-0.185 (-0.930 – 0.560)	0.626
Δ 2 years[a]	-0.383 (-1.134 – 0.368)	0.317
Δ 10 years[a]	-1.547 (-2.271 – -0.822)	**<0.0001**
Previous deployment(s)[c]		
Δ 1 year[a]	0.183 (-0.580 – 0.947)	0.638
Δ 2 years[a]	-0.575 (-1.347 – 0.197)	0.145
Δ 10 years[a]	1.000 (0.257 – 1.744)	**0.008**
Role during deployment[d]		
Both inside and outside the base		
Δ 1 year[a]	0.007 (-1.396 – 1.409)	0.993
Δ 2 years[a]	-0.593 (-2.100 – 0.914)	0.441
Δ 10 years[a]	1.041 (-0.428 – 2.510)	0.165
Outside the base		
Δ 1 year[a]	0.122 (-0.731 – 0.975)	0.779
Δ 2 years[a]	-0.374 (-1.243 – 0.495)	0.398
Δ 10 years[a]	1.041 (0.424 – 2.108)	**0.003**
Deployment experience[e]		
Δ 1 year[a]	0.141 (0.010 – 0.272)	**0.035**
Δ 2 years[a]	-0.017 (-0.149 – 0.115)	0.803
Δ 10 years[a]	0.211 (0.085 – 0.338)	**0.001**
Unit support[f]		
Δ 1 year[a]	-0.034 (-0.087 – 0.019)	0.207
Δ 2 years[a]	-0.066 (-0.126 – -0.006)	0.030
Δ 10 years[a]	-0.006 (-0.066 – 0.054)	0.838
Social support[g]		

Table S10. (Continued)

	Interaction time x moderator variable	
	Coefficient (95% CI)	**p-value**
Δ 1 year[a]	-0.227 (-0.285 – -0.168)	**<0.0001**
Δ 2 years[a]	-0.152 (-0.213 – -0.091)	**<0.0001**
Δ 10 years[a]	-0.166 (-0.232 – -0.100)	**<0.0001**
Early general trauma[h]		
Δ 1 year[a]	0.096 (-0.131 – 0.323)	0.408
Δ 2 years[a]	0.223 (-0.002 – 0.454)	0.052
Δ 10 years[a]	0.018 (-0.202 – 0.238)	0.872
Early physical abuse[h]		
Δ 1 year[a]	0.193 (-0.103 – 0.488)	0.201
Δ 2 years[a]	0.271 (-0.013 – 0.556)	0.062
Δ 10 years[a]	-0.022 (-0.311 – 0.267)	0.882
Early emotional abuse[h]		
Δ 1 year[a]	0.230 (-0.133 – 0.592)	0.214
Δ 2 years[a]	0.623 (0.270 – 0.976)	**0.001**
Δ 10 years[a]	-0.091 (-0.449 – 0.267)	0.619
Early sexual abuse[h]		
Δ 1 year[a]	1.131 (0.393 – 1.869)	**0.003**
Δ 2 years[a]	0.360 (-0.261 – 0.981)	0.256
Δ 10 years[a]	0.211 (-0.440 – 0.861)	0.526

Note: [a] Δ indicates the difference relative to pre-deployment status, when there was no significant difference in symptom score relative to pre-deployment at a time-point, no covariates were reported; 95% CI=95% Confidence Interval; [b] the rank parameter indicates the difference between non-commissioned officer and staff officer ranks versus private and corporal ranks (reference category); [c] reference category is the group with one or more previous deployments; [d] reference category is the group with a role inside the military base; [e] deployment experience was measured with the Deployment Experience Scale (DES); [f] unit support during deployment was measured with the Deployment Risk and Resilience Inventory-1 Section F (DRRI-F); [g] social support after deployment was measured with the Deployment Risk and Resilience Inventory-1 Section L (DRRI-L); [h] early trauma was measured with the Early Trauma Inventory Self-Report-Short Form (ETISR-SF).

Table S11. Parameter estimates for change in hostility over time relative to pre-deployment status with different moderators (n=978).

	Interaction time x moderator variable	
	Coefficient (95% CI)	**p-value**
Age		
Δ 1 month[a]	-0.011 (-0.027 – 0.005)	0.184
Δ 6 months[a]	-0.005 (-0.022 – 0.011)	0.529
Δ 1 year[a]	-0.014 (-0.031 – 0.004)	0.135
Δ 2 years[a]	-0.006 (-0.024 – 0.012)	0.514
Δ 10 years[a]	-0.008 (-0.025 – 0.010)	0.387
Rank[b]		
Δ 1 month[a]	0.045 (-0.256 – 0.347)	0.768
Δ 6 months[a]	0.070 (-0.242 – 0.381)	0.661
Δ 1 year[a]	-0.227 (-0.571 – 0.117)	0.195
Δ 2 years[a]	-0.113 (-0.460 – 0.234)	0.523
Δ 10 years[a]	-0.109 (-0.444 – 0.226)	0.523
Previous deployment(s)[c]		
Δ 1 month[a]	-0.075 (-0.381 – 0.231)	0.630
Δ 6 months[a]	0.182 (-0.135 – 0.499)	0.260
Δ 1 year[a]	0.246 (-0.107 – 0.599)	0.171
Δ 2 years[a]	-0.004 (-0.362 – 0.354)	0.983
Δ 10 years[a]	-0.252 (-0.596 – 0.093)	0.152
Role during deployment[d]		
Both inside and outside the base		
Δ 1 month[a]	0.146 (-0.470 – 0.762)	0.643
Δ 6 months[a]	0.276 (-0.347 – 0.899)	0.385
Δ 1 year[a]	-0.115 (-0.787 – 0.557)	0.737
Δ 2 years[a]	0.416 (-0.309 – 1.142)	0.260
Δ 10 years[a]	0.372 (-0.341 – 1.084)	0.307
Outside the base		
Δ 1 month[a]	0.052 (-0.317 – 0.421)	0.783
Δ 6 months[a]	0.233 (-0.141 – 0.607)	0.222
Δ 1 year[a]	0.249 (-0.160 – 0.658)	0.233
Δ 2 years[a]	0.119 (-0.298 – 0.536)	0.576

Table S11. (Continued)

	Interaction time x moderator variable	
	Coefficient (95% CI)	**p-value**
Δ 10 years[a]	0.372 (-0.111 – 0.697)	0.155
Deployment experience[e]		
Δ 1 month[a]	0.090 (0.041 – 0.140)	**<0.001**
Δ 6 months[a]	0.083 (0.029 – 0.136)	**0.002**
Δ 1 year[a]	0.076 (0.015 – 0.138)	**0.015**
Δ 2 years[a]	-0.037 (-0.099 – 0.025)	0.237
Δ 10 years[a]	0.041 (-0.019 – 0.100)	0.179
Unit support[f]		
Δ 1 month[a]	-0.001 (-0.025 – 0.025)	0.990
Δ 6 months[a]	-0.008 (-0.033 – 0.018)	0.554
Δ 1 year[a]	-0.004 (-0.029 – 0.021)	0.768
Δ 2 years[a]	-0.001 (-0.028 – 0.027)	0.969
Δ 10 years[a]	0.015 (-0.013 – 0.043)	0.308
Social support[g]		
Δ 1 month[a]	-0.053 (-0.080 – -0.025)	**<0.001**
Δ 6 months[a]	-0.069 (-0.097 – -0.041)	**<0.0001**
Δ 1 year[a]	-0.090 (-0.118 – -0.062)	**<0.0001**
Δ 2 years[a]	-0.043 (-0.073 – -0.014)	**0.0040**
Δ 10 years[a]	-0.050 (-0.082 – -0.019)	**0.002**
Early general trauma[h]		
Δ 1 month[a]	0.009 (-0.081 – 0.100)	0.842
Δ 6 months[a]	0.162 (0.065 – 0.258)	0.100
Δ 1 year[a]	0.055 (-0.050 – 0.160)	0.305
Δ 2 years[a]	0.050 (-0.056 – 0.155)	0.359
Δ 10 years[a]	0.072 (-0.031 – 0.174)	0.170
Early physical abuse[h]		
Δ 1 month[a]	-0.030 (-0.144 – 0.085)	0.613
Δ 6 months[a]	-0.034 (-0.155 – 0.087)	0.578
Δ 1 year[a]	-0.010 (-0.147 – 0.127)	0.889
Δ 2 years[a]	0.041 (-0.091 – 0.173)	0.540
Δ 10 years[a]	-0.124 (-0.258 – 0.011)	0.072

Table S11. (Continued)

	Interaction time x moderator variable	
	Coefficient (95% CI)	**p-value**
Early emotional abuse[h]		
Δ 1 month[a]	0.204 (0.059 – 0.349)	**0.006**
Δ 6 months[a]	0.061 (-0.092 – 0.214)	0.432
Δ 1 year[a]	-0.011 (-0.178 – 0.156)	0.896
Δ 2 years[a]	-0.015 (-0.178 – 0.148)	0.858
Δ 10 years[a]	-0.134 (-0.299 – 0.030)	0.110
Early sexual abuse[h]		
Δ 1 month[a]	0.230 (-0.044 – 0.504)	0.100
Δ 6 months[a]	0.169 (-0.106 – 0.444)	0.227
Δ 1 year[a]	0.162 (-0.147 – 0.471)	0.304
Δ 2 years[a]	0.153 (-0.135 – 0.441)	0.297
Δ 10 years[a]	0.004 (-0.297 – 0.306)	0.978

Note: [a] Δ indicates the difference relative to pre-deployment status; 95% CI=95% Confidence Interval; [b] the rank parameter indicates the difference between non-commissioned officer and staff officer ranks versus private and corporal ranks (reference category); [c] reference category is the group with one or more previous deployments; [d] reference category is the group with a role inside the military base; [e] deployment experience was measured with the Deployment Experience Scale (DES); [f] unit support during deployment was measured with the Deployment Risk and Resilience Inventory-1 Section F (DRRI-F); [g] social support after deployment was measured with the Deployment Risk and Resilience Inventory-1 Section L (DRRI-L); [h] early trauma wasmeasured with the Early Trauma Inventory Self-Report-Short Form (ETISR-SF).

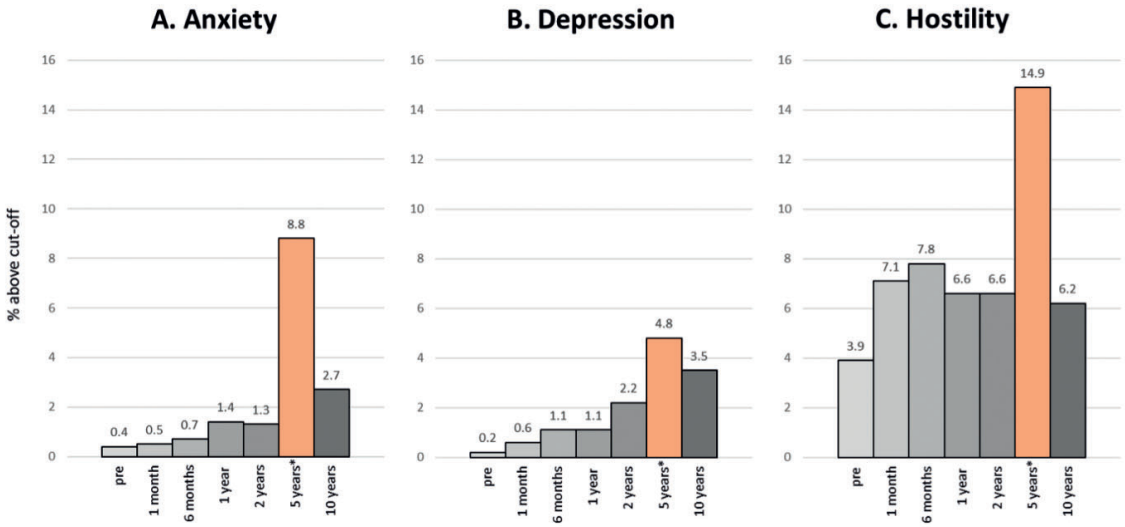

Figure S1. Reported anxiety (A), depression (B), and hostility (C) symptoms over time in Dutch ISAF veterans including a five-year follow-up measurement. Prevalence rates pre-deployment, and one month, six months, one year, two years, and ten years post-deployment were based on the Symptom Checklist (SCL-90-R); prevalence rates at five years post-deployment were based on the Brief Symptom Inventory (BSI). Cut-off values for all subscales were based on the 95th percentile scores of a sample from the general population as reported in the respective questionnaire manual (SCL: anxiety: ≥22; depression: ≥36; hostility: ≥11; BSI: anxiety: ≥1.33; depression: ≥1.67; hostility: ≥1.20). * Five year measurement was administered as an online questionnaire instead of a paper-and-pencil questionnaire.

CHAPTER 5

ASSOCIATIONS BETWEEN THE DEVELOPMENT OF PTSD SYMPTOMS AND LONGITUDINAL CHANGES IN THE DNA METHYLOME OF DEPLOYED MILITARY SERVICEMEN: A COMPARISON WITH POLYGENIC RISK SCORES

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ABSTRACT

Objective

Military servicemen deployed to war zones are at increased risk of developing posttraumatic stress disorder (PTSD) and successful adaptation to stress is important. Epigenetic alterations in response to trauma have been identified as mechanism of adaptation and may therefore predict deployment-related PTSD symptoms. To date, human studies of epigenetic marks for traumatic stress have been largely constrained by short-term analyses of one or two time points.

Method

This study in a prospective Dutch military cohort (N = 125) examined longitudinal changes of DNA methylation profiles before, as well as one and six months after deployment-related combat exposure in relation to the development of PTSD symptoms over a period of up to five years after deployment. We investigated the predictive value of specific methylation changes for immediate and delayed-onset PTSD symptoms and recovery. This epigenetic prediction was compared to polygenic risk score predictions obtained from the currently available largest genome-wide association study of PTSD.

Results

A total of fourteen genomic regions were identified in which PTSD symptom levels were associated with methylation changes over time (pre-deployment, one, and six months post-deployment). Of these regions, four were significant determinants of longitudinal development of PTSD symptoms. In addition, we observed that, together with risk level during deployment (operating inside or outside the military base) and physical childhood trauma, post-deployment decreases in methylation at a genomic region in *EP300/miRNA1281* was associated with a delayed onset of PTSD compared to a resilient profile. Polygenic risk, in contrast, was related to PTSD onset within six months after deployment but was not associated with long term outcomes.

Conclusion

The present study suggests predictive utility of changes in DNA methylation for the subsequent development of PTSD symptoms and showed that the currently available measure of polygenic risk is primarily related to non-delayed disease onset.

INTRODUCTION

Epigenetic modifications in response to trauma or severe stress may be a critical factor in risk or resilience to stress-related disorders. They reflect the complex interplay between environment and genes, and could therefore be one of the mechanisms in the pathway between trauma and the development of posttraumatic stress disorder (PTSD). This interplay is particularly relevant for military populations, as they regularly encounter stressful events during deployment and show a high burden of PTSD following deployment[1-3]. One of the best characterized mechanisms of epigenetic regulation is DNA methylation, and mounting evidence from animal models and human clinical studies suggests that changes to DNA methylation resulting from trauma are associated with PTSD (reviewed in:[4-6]). Candidate gene as well as epigenome-wide studies have highlighted genes involved in the immune system and HPA axis that are involved in PTSD[5]. However, human studies have been largely constrained by relatively short-term analyses of post-trauma symptoms, generally up to six to twelve months after deployment.

Moreover, genome-wide epigenetic studies in PTSD that use longitudinal data are scarce. The largest study on methylation changes so far suggests the implication of immune-related genes in the human leukocyte antigen region, *HEXDC*, and *MAD1L1*, a gene previously associated with PTSD[7]. A genome-wide DNA methylation study of our group in a Dutch military sample pinpointed novel genomic regions where decreases in blood DNA methylation across a period of exposure to combat trauma were related to increasing levels of PTSD symptoms over a six-month period. Targeted analyses of these findings replicated the observed association at the genomic regions in *ZFP57*, *RNF39*, and *HIST1H2APS2* in an independent prospective military cohort of US marines[8]. *ZFP57* methylation was also shown to reverse following successful PTSD treatment, which provides further support for the association of decreased methylation of *ZFP57* to symptoms of PTSD[9].

There are good reasons to investigate the relation between DNA methylation changes in more intervals around the trauma exposure and development of PTSD symptoms in the short term and longer follow up. Firstly, it has the potential to capture the dynamics of DNA methylation changes during deployment and immediately after return for the identification of genes and genetic pathways that are related to PTSD and response to trauma. Secondly, it enables study of how these dynamic changes are related to short and longer term outcomes. A third reason is the potential for the prediction of PTSD, since there are currently no clear biological measures that can be used to screen individuals for an increased vulnerability to develop PTSD symptoms after deployment.

Studies by others and our group show that PTSD can develop with a latency of months to several years, as demonstrated by identification of a delayed onset PTSD developmental trajectory in addition to resilient and recovery trajectories[1,10,11]. Routine screening for PTSD usually discontinues after one or two years post-deployment. Identification of biological markers reflecting vulnerability for delayed onset PTSD may therefore have an important role for prevention and early intervention. Another relevant question is how such epigenetic changes compare to genetic prediction for PTSD. In the past years substantial progress has been made to illuminate the role of genes in PTSD susceptibility leading to genome wide significant identification of risk genes[12]. The question remains, however, how these risk genes are related to longer term PTSD outcomes.

The current study is, to our knowledge, the first to investigate longitudinal changes of DNA methylation profiles across a period of combat exposure using three time points (pre-deployment, one month- and six months post-deployment) in relation to the development of PTSD symptoms in a cohort of deployed military servicemen. In order to assess the predictive value of methylation patterns for the development of PTSD symptoms over time, we identified genetic regions where methylation changes are related to changes in PTSD symptoms and used these to predict developmental trajectories over a five-year follow-up period. Because of the higher clinical relevance of identifying a predictive biomarker for the development of PTSD symptoms before PTSD symptomatology is present and the limitation that methylation changes can only be determined after deployment, the focus in these analyses was on predicting delayed onset of PTSD symptoms years after deployment. Identification of such a biomarker for late-onset PTSD may be very useful for targeted screening and early intervention. Finally, we compared predictions based on methylation changes to that of polygenic risk scores (PRS), a measure for one's genetic liability to PTSD.

MATERIALS AND METHODS

Discovery data set

Participants

Samples are from a subset of participants from the Prospective Research in Stress-related Military Operations (PRISMO study). PRISMO is a large prospective cohort study on the development and biological underpinnings of stress-related mental health symptoms in Dutch military personnel deployed to Afghanistan for at least four months between 2005 and 2008[13]. The current study draws on peripheral blood samples from 125 PRISMO participants obtained one month before deployment and

one and six months after the deployment period, and survey data obtained at six different time points spread out over five years (Figure 1). No blood samples were available for the one year-, two year-, and five year follow-up measurement. A subset of PRISMO study participants was pre-selected based on two criteria: 1) available DNA, and 2) prioritization of participants who developed PTSD at any of the time points.

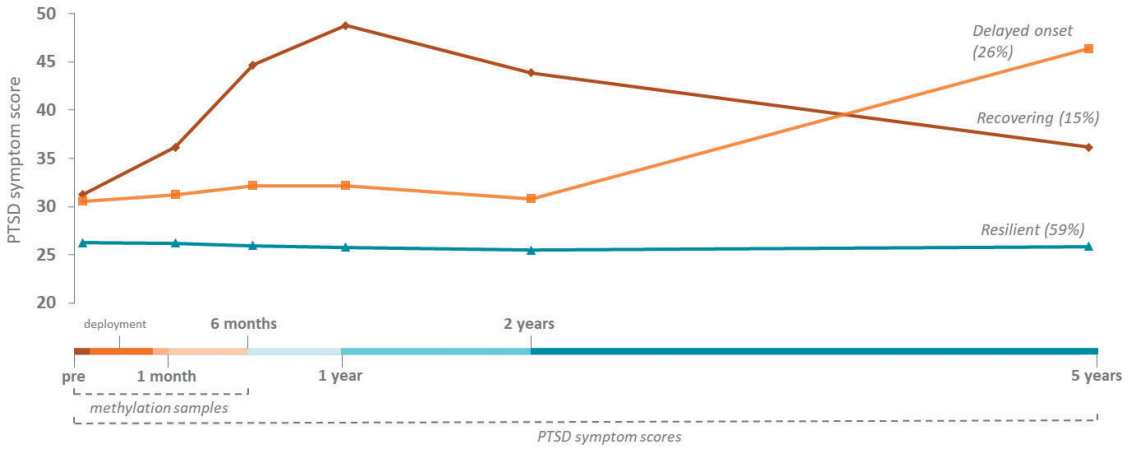

Figure 1. Schematic illustration of the overall study design and the latent developmental trajectories of self-reported posttraumatic stress symptoms as measured by the Self-Report Inventory for PTSD (SRIP) over the study's time period. Note: Latent developmental trajectories and symptom scores are based on the full PRISMO sample as described in[1]; trajectory membership percentages are based on the sample of the present study; PTSD = posttraumatic stress disorder; methylation samples were available at the first three measurement points, PTSD symptom scores were available at all measurement points (pre-deployment up to five years post-deployment).

PTSD symptoms were assessed at six different time points (pre-deployment, one month-, six month-, one year-, two year- and five year post-deployment) using the Self-Report Inventory for PTSD (SRIP), a questionnaire with good internal consistency, discriminant validity and concurrent validity with other PTSD measures[14,15]. As recommended in the literature, a cut-off score of 38 was used to indicate substantial PTSD symptoms[15]. No subjects scored above cut-off pre-deployment. At the follow-up measurements at one and six months post-deployment, respectively, 29 subjects and 30 subjects scored above cut-off. Three trajectories of posttraumatic stress symptoms (resilient, recovering, and delayed onset, see Figure 1) from pre-deployment up to five year post-deployment were previously identified in a latent growth mixture model using the full PRISMO sample (N = 960), as described in[1]. The model included a group with a low and stable PTSD trajectory (i.e. resilient), a group that had a moderate level of PTSD symptoms that increased heavily in the last time period (i.e. delayed onset), and a group that had increasing symptoms in the first year after deployment and then showed a

recovery process (i.e. recovering) (Figure 1). Of note are the elevated symptom levels pre-deployment in the delayed onset and recovering trajectory.

Exposure to traumatic stress during deployment was measured with a 19-item deployment experience checklist, the Deployment Experience Scale (DES), which covered a range of potentially traumatic experiences that can occur during deployment[16]. Childhood trauma was assessed using the Dutch version of the Early Trauma Inventory Self Report-Short Form (ETISR-SF)[17]. Demographics and other characteristics of the participants are described in Table 1. Participants received financial compensation for participation. Written informed consent was obtained from all participants in accordance with procedures approved by the Institutional Review Board of the University Medical Center Utrecht.

DNA isolation genotyping and methylation quantification

Genotyping was conducted using Illumina Human OmniExpress 24 v1.1. DNA for the methylation assay was quantified fluorescently prior to bisulfite conversion (Zymo Research, CA, USA). Genome-wide DNA methylation was interrogated using the Infinium Methylation EPIC BeadChip (Illumina, Inc., CA, USA). Batches were minimized by putting the three time points of one participant on the same array and equally distributing PTSD status over the arrays. Also, batches were minimized using information from the control probes as implemented in the functional normalization procedure of Meffil[18]. The dataset was preprocessed in R version 3.3.3 with the meffil package[18], using functional normalization[19]. There were no samples with fewer than three beads in 20% of the probes. Single nucleotide polymorphism (SNP) profile included on the array matched their genetic identity. Nine samples had to be removed, five because of failed hybridization as indicated by outliers (3 SD from the methylation mean), one outside the predefined boundaries of the control probe, one for gender mismatch, and two for gender estimate outlier. 1152 probes with a detection p-value greater than 0.01 were removed. Non-specific probes and those with SNPs in the probe sequence were removed[20,21]. After quality control, 864,528 CpGs in 361 samples and 133 different individuals were left for further analysis. The level of DNA methylation is expressed as a 'beta' value ranging from 0 (no cytosine methylation) to 1 (complete cytosine methylation). Analyses were performed using M-values (log2 ratio of beta values)[22].

Table 1. Demographics and clinical characteristics of the full PRISMO sample and the different PTSD developmental trajectories.

	All (N=125)	Resilient (N=74)	Recovering (N=19)	Delayed onset (N=32)	p-value
Gender (%)	92.8	94.6	89.5	90.6	0.559
Male	7.2	5.4	10.5	9.4	
Female					
Age (SD)	27.3 (8.9)	27.1 (8.7)	26.6 (8.5)	28.2 (9.7)	0.797
Educational level (%)[a]	40.0	38.4	41.2	43.3	0.622
Low	52.5	56.2	52.9	43.3	
Moderate	7.5	5.5	5.9	13.3	
High					
Rank (%)	44.0	44.6	47.4	40.6	0.897
Private	23.2	24.3	26.3	18.8	
Corporal	24.8	24.3	15.8	31.3	
Non-commissioned officer	8.0	6.8	10.5	9.4	
Staff officer					
Previous deployment(s) (% yes)	46.2	45.1	44.4	50.0	0.899
Function (%)	21.6	17.1	17.6	34.5	0.045
Inside the military base	67.2	75.7	70.6	44.8	
Outside the military base	11.2	7.1	11.8	20.7	
Both inside and outside the military base					
Deployment year (%)	13.6	13.5	15.8	12.5	0.936
2005 or 2006	86.4	86.5	84.2	87.5	
2007 or 2008					
New deployment(s) (% yes)	22.1	22.0	22.2	22.2	1.000
Deployment stressor score (SD)[b]	6.4 (3.6)	6.5 (3.5)	7.7 (3.0)	5.5 (3.9)	0.142
Childhood trauma score (SD)c	3.9 (3.4)	3.6 (2.9)	4.1 (3.5)	4.8 (4.3)	0.270

Note: data are % or mean (SD). Differences in descriptive characteristics between participants in the different trajectories were tested with one-way ANOVA (continuous) or Fisher's Exact (categorical). [a] Education (International Standard Classification of Education levels): low=primary and lower secondary education; moderate=upper secondary, postsecondary non-tertiary, and short cycle tertiary education; high=bachelor, master, and doctoral education; [b] Deployment stressor score measured with the Deployment Experience Scale; [c] Childhood trauma score measured with the Early Trauma Inventory Self Report-Short Form; SD=standard deviation.

Replication data set

Replication of the identified DMRs was sought in the Marine Resiliency Study (MRS)[23]. MRS is a large prospective PTSD study with a longitudinal follow-up in a cohort of 2599 marines deployed to either Iraq or Afghanistan. Measurements were obtained approximately one month pre-deployment and one week, three months and six months post-deployment. PTSD symptoms were measured using a structured diagnostic interview and the Clinician Administered PTSD Scale (CAPS)[24]. Peripheral blood samples were collected pre-deployment and three and six months post-deployment. A subset of 128 men was selected for DNA methylation analysis, with a mean age at baseline of 22 years. The participants showed no PTSD diagnoses (CAPS ≤ 25) pre-deployment. In the follow-up measurements at three months and six months post-deployment, respectively 51 and 36 participants were diagnosed with PTSD. The institutional review boards of the University of California San Diego, VA San Diego Research Service, and Naval Health Research Center approved the study. Written informed consent was obtained from all participants.

Genome-wide DNA methylation levels were assessed in DNA extracted from whole blood using the Infinium HumanMethylation450 array. Baseline and follow-up samples were positioned differently between studies. Methylation level βs were calculated using the Minfi package and normalized to correct for type-I and II probe design bias using the BMIQ procedure implemented in watermelon. Batch and plate effects were removed using COMBAT. Relative proportions of cell compositions were estimated to account for cellular heterogeneity in blood-derived samples using the Minfi package.

Polygenic risk scores

PRS of PTSD were calculated for each subject based on the Psychiatric Genomics Consortium PTSD (PGC-PTSD) Freeze 2 European ancestry GWAS[12], using PRSice version 2.2.11.b[25], but with the PRISMO samples being left out of the GWAS meta-analysis. We selected SNPs associated at the optimal p-value threshold of 0.45 or lower.

Statistical analysis

An overview of the statistical analyses can be found in Table 2. For the methylation analysis, independent surrogate variables (ISVA) were calculated as implemented in Meffil to adjust for technical batch effects. Cell type composition was estimated using the Houseman algorithm[26]. Inspection of the potential confounding was performed using the surrogate variables and their correlation to known confounders (genetic ancestry, cell type composition, age, smoking, and gender). Optimal fit was obtained based on qq-plotting to avoid type I error inflation. In the optimal model, three ISVA's were included that effectively accounted for technical batches (see Supplementary

Figure S1) alongside five cell types, age, smoking, gender, and two genetic principal components. To identify differentially methylated positions (DMPs), longitudinal analyses were conducted using DNA methylation levels (one month pre-deployment (T0) and one (T1) and six months (T2) post-deployment) as the outcome and SRIP scores (T0, T1 and T2) as a determinant in a mixed model. Baseline SRIP score (T0), the time variable, an interaction term between time and SRIP scores, and the known confounders were included in the model. The interaction term was included to assess whether the association between methylation level and PTSD scores significantly changed over time. A random intercept was used to account for the variance between participants. The QQ-plot of the expected p-values versus the observed values and a lambda of 0.989 (see Supplementary Figure S2) indicated absence of type-I error inflation and no artificial differences between groups. False discovery rate p-values were calculated according to the Benjamini-Hochberg method ($p < 0.05$). The assumptions of the linear regression mixed models were evaluated by inspecting the distribution of residuals for the identified loci. Differentially methylated regions (DMRs) were calculated based on the p-values for each methylation locus using the DMRcate package[27]. A DMR consists of a strongly associated locus ($p < 0.0001$) and several other significantly associated loci within the proximity of 1000 base pairs. The furthest loci define the borders (start and stop location) of a DMR.

Standardized methylation levels (z-values) at T0, T1, and T2 of identified DMRs of the first set of analyses were then used as determinants of longitudinal development of PTSD symptom scores over the three time points in a mixed model. Goodness of fit of the models was determined using loglikelihood-ratio-tests. The optimal fitting models included a random intercept and random slope, and assumed a quadratic development over time. Genetic ancestry (two genetic principal components), cell type composition (five cell types), age, smoking, and gender were used as covariates. To assess methylation scores as determinant for PTSD symptom development, a model with and without interaction terms between time and methylation scores and time^2 and methylation scores were compared on goodness of fit using a loglikelihood-ratio-test. A p-value < 0.05 was considered statistically significant. A similar procedure was followed to assess PRS as a determinant of PTSD symptom scores over time in a separate model; age and gender were used as covariates in the mixed model, and goodness of fit was compared between the models with and without interactions between time and PRS.

Table 2. Overview statistical analyses.

Analysis	Variables	Statistical model	Cohort/ data set
1. Discovery DMPs	Outcome: DNA methylation levels (T_0, T_1, T_2) Predictor: PTSD score (T_0, T_1, T_2)	Mixed model	PRISMO
2. Identification DMRs and PRS as determinants	Outcome: PTSD score (T_0, T_1, T_2) Predictor: a. DMR methylation levels (T_0, T_1, T_2) b. PRS	Mixed model	PRISMO
3. Replication DMRs	Outcome: PTSD score (T_0, T_1, T_2) Predictor: DMR methylation levels (T_0, T_1, T_2)	Mixed model	MRS
4. Correlations DMRs, PRS, and PTSD symptoms	a. DMR change score (T_0- T_1 or T_1-T_2) x PTSD score (T_0 to T_5) b. DMR change score x PRS c. PRS x PTSD score (T_0 to T_5)	Pearson's correlation	PRISMO
5. Association DMRs and PRS with PTSD trajectories	Outcome: PTSD trajectory Predictor: a. DMR change score b. PRS	Multinomial logistic regression	PRISMO (imputed)
6. Prediction model delayed onset PTSD	Outcome: delayed PTSD trajectory (vs. resilient trajectory) Predictors: DMR change score, variables in Table 1	Stepwise backward logistic regression model	PRISMO (imputed)

Note: DMP=differentially methylation position; PTSD=posttraumatic stress disorder; PRS=polygenic risk score.

To assess the robustness of the identified DMRs in an independent dataset, the methylation scores of the DMRs were tested as determinants of longitudinal development of PTSD symptom scores in the MRS data set using the same mixed model analysis with a quadratic term for time and a random intercept and random slope. The included covariates in the models were five cell types, three ancestry-related principal components (based on previous MRS analyses), age, and smoking. Goodness of fit was compared between the models with and without interactions between the time variables and methylation scores.

For follow up analysis of the significant DMRs in the discovery and validation analysis, DNA methylation levels at each time point were adjusted for cell type composition by computing the residuals in a linear regression model, and corresponding methylation change scores were calculated (T0-T1, T1-T2) where a positive change score indicated a decrease in methylation level, and a negative change score indicated an increase in methylation level. To assess whether DMR change scores were correlated to PTSD scores

at specific time points, Pearson's correlations between the methylation change scores and PTSD symptom scores at six time points (pre-deployment till five-year post-deployment) were calculated. In addition, correlations between PRS and PTSD symptom scores, and PRS and methylation change scores were calculated. Standardized methylation change scores and PRS were then assessed as determinants for PTSD developmental trajectories over the five-year follow-up period using separate multinomial logistic regression models in SPSS using an imputed data set (see section 2.5). To assess the potential utility of DNA methylation change scores and PRS as biological markers for a late onset of PTSD, the DMR methylation change scores and PRS that were significantly associated with the delayed PTSD trajectory were tested in a stepwise backward logistic regression model to predict a delayed onset PTSD versus a resilient profile using SAS version 9.4. Several demographic and psychological factors that are known from the literature to possibly relate to changes in post-traumatic stress symptoms (for a review:[28]) were included in the full model, and can be found in Table 1. All variables measured on a continuous scale were standardized using z-scores. Variables with a p-value > 0.10 were eliminated step-by-step. Firth correction was applied for bias-reduction of the maximum likelihood estimates. Long-term follow-up data on PTSD symptom scores and trajectories were not yet available in the MRS data set and therefore replication of the association with delayed-onset PTSD symptoms could not be obtained.

Imputation of missing data

Missing values in the PRISMO dataset were assumed to be missing at random, and were managed using data imputation (see Supplementary Table S1). As multiple imputation is not suitable for a stepwise selection approach, single Bayesian stochastic regression imputation using fifty iterations was performed in SPSS. The imputation model included all the predictor variables (and covariates) that were used in the multinomial logistic regression analyses, as well as the outcome variable (PTSD symptom trajectory).

RESULTS

Genome-wide DNA methylation and polygenic risk in relation to PTSD symptom development

Analyses identified fourteen DMRs in which PTSD symptom levels were associated with changes in DNA methylation (see Supplementary Table S2). Of these DMRs, four were significant determinants of longitudinal development of PTSD symptom scores in the optimized mixed models (DMR1, DMR2, DMR6, and DMR7; Table 3). DMR1 was located in or near the transcription start sites of the *TUBA3FP* pseudogene and *P2RX6* gene, DMR 2 in or near the *EP300* and *miRNA1281* genes, and DMR6 in or near the *IMPA1*

gene. DMR7 was not located in or near any transcription start sites. The direction of effect was negative for all loci in DMR1, DMR2, and DMR7, indicating that decreased DNA methylation levels at the DMRs were associated with increased PTSD symptom scores over time. The effect was positive for DMR6, indicating that increased methylation was associated with increased PTSD symptom scores over time. PRS was not a significant determinant of longitudinal PTSD symptom scores (p = 0.446).

Replication of DMRs related to PTSD symptom development

Replication failed for the identified DMRs in the independent MRS data set. Longitudinal changes in DNA methylation were not significantly associated with longitudinal changes in PTSD symptom scores at DMR1 (p = 0.873), DMR2 (p = 0.725), DMR6 (p = 0.085), and DMR7 (p = 0.535).

Table 3. List of differentially methylated regions (DMRs) that were significant determinants of longitudinal development of PTSD symptom score.

	Chromosomal position of DMR	Genes	Probes	p-value (Stouffer method)	p-value in determinant analysis
DMR1	chr22: 21368603, 21368765	*TUBA3FP P2RX6*	cg06912512 cg19789653 cg09481857 cg21014483 cg01038149	8.84 E-05	0.002
DMR2	chr22: 41487073, 41487283	*EP300 miR128*1	cg00500400 cg08131204	1.18 E-06	0.016
DMR6	chr8: 82598501, 82598664	*IMPA1*	cg05798523 cg23402311 cg03588978 cg04364718 cg12093930	1.87 E-06	0.033
DMR7	chr8: 144973617, 144973638	-	cg26529963 cg03000485	9.19 E-05	0.040

Note: the column on determinant analysis provides the P-values for the analyses in which methylation levels were tested as determinants of longitudinal development of PTSD symptom scores; PTSD=posttraumatic stress disorder; DMR=differentially methylated region.

Correlation DNA methylation, polygenic risk, and PTSD symptoms

Of the four DMRs at which changes in methylation levels were significant determinants of changes in PTSD symptom scores (section 3.1), the methylation change between

T1 (one month post-deployment) and T2 (six months post-deployment) at DMR1 was positively correlated with PTSD symptoms at T1 (one month post-deployment; r = 0.348, p = 0.001), T2 (six months post-deployment; r = 0.244, p = 0.020) and T6 (five years post-deployment; r = 0.281, p = 0.027). Methylation change between T1 and T2 at DMR2 was positively correlated with PTSD symptoms at T2 (r = 0.219, p = 0.038) and T6 (five years post-deployment; r = 0.326, p = 0.010). DMR6 methylation change between T1 and T2 was negatively correlated with PTSD symptoms at T1. Methylation changes in DMR7 were not correlated with PTSD symptoms, nor were methylation changes between T0 (pre-deployment) and T1 at any of the DMRs. PRS was only correlated with PTSD symptoms at T2 (r = 0.218, p = 0.032). There were no correlations between PRS and DMR methylation changes.

Association methylation changes and polygenic risk with PTSD trajectories

DNA methylation change between T1 and T2 at DMR1 was significantly associated with PTSD trajectory (loglikelihood-ratio-test: p = 0.010). The multinomial logistic regression model indicated an association between DMR1 methylation change between T1 and T2 and a recovering PTSD developmental trajectory compared to a resilient trajectory (OR = 2.37, p = 0.008), and a delayed trajectory compared to a recovering trajectory (OR = 0.497, p = 0.042). DMR2 methylation change between T1 and T2 was also associated with PTSD trajectory (loglikelihood-ratio-test: p = 0.001). The model indicated an association between DMR2 methylation change between T1 and T2 and a recovering trajectory compared to a resilient trajectory (OR = 1.65, p = 0.010), and a delayed onset trajectory compared to a resilient trajectory (OR = 2.73, p = 0.001). Methylation changes of DMR6 and DMR7 were not associated with PTSD developmental trajectory, nor were methylation changes between T0 and T1 in DMR1 and DMR2. PRS was not significantly associated with PTSD trajectory. Full results of the logistic regression models can be found in Supplementary Table S3. Mean methylation levels for DMR1 and DMR2 on each time point for the full sample and the different trajectories can be found in Figure 2.

Prediction model delayed onset PTSD

As only DMR2 methylation change score between T1 and T2 was associated with a delayed onset trajectory in the previous analysis, DMR2 T1-T2 methylation change (among other factors) was included in the full prediction model for a delayed onset PTSD trajectory (N = 106). The final prediction model included three variables. The first variable was one's thread level during deployment (function inside the military base vs. outside the base: OR = 4.11, p = 0.009; function both inside and outside the base vs. outside the base: OR = 6.77, p = 0.010), the second variable was physical childhood trauma (OR = 1.96, p = 0.006), and the third variable was DMR2 T1-T2 methylation change score (OR = 1.74, p = 0.029). The model had an area under the curve (AUC) of 0.79.

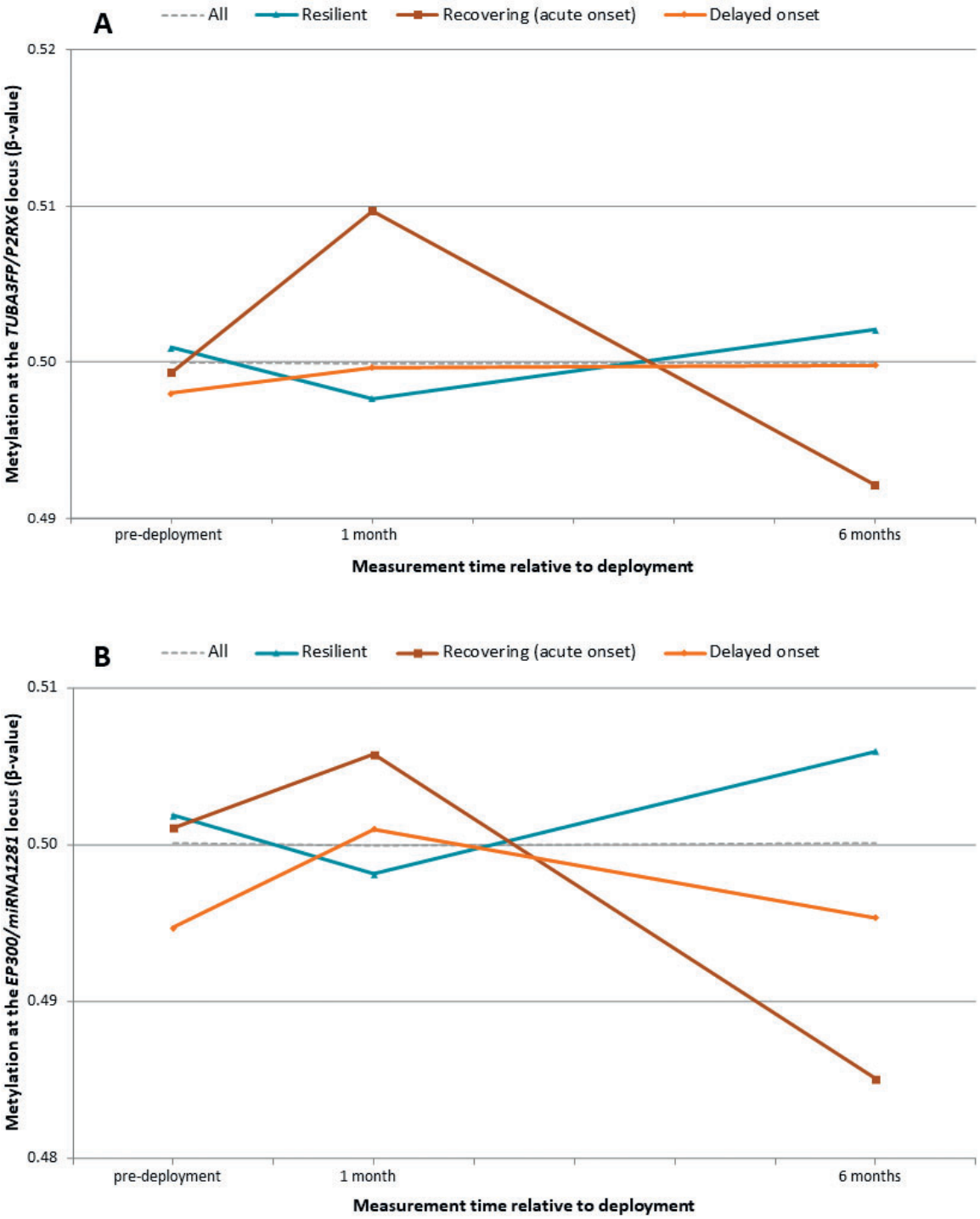

Figure 2. Mean methylation (β-value) corrected for cell type composition at the (a) DMR1 *TUBA3FP/P2RX6* and (b) DMR2 *EP300/miRNA1281* locus on each time point for the complete sample (dotted line) and separated for posttraumatic stress disorder symptom trajectories (colored lines).

DISCUSSION

In the present study in a Dutch military cohort, we investigated longitudinal changes in blood DNA methylation profiles across a period of combat exposure in relation to the development of posttraumatic stress symptoms, and studied the predictive value of these methylation changes for the delayed onset of PTSD over a follow-up period of five years. Methylation of four genomic regions served as significant determinants of the longitudinal development of PTSD symptoms. Furthermore, we found that increases in methylation between one month post-deployment and six months post-deployment within the *P2RX6* gene were associated with a delayed onset PTSD trajectory compared to a recovering trajectory, while post-deployment decreases in methylation within *EP300/miRNA1281* were associated with a delayed onset PTSD trajectory compared to a resilient profile. Our findings provide preliminary evidence for the predictive utility of DNA methylation for the late onset development of PTSD symptoms.

Evidence was found for an association of DNA methylation changes with PTSD symptom levels for DMRs that were located in or near the transcription start sites of the Purinergic Receptor P2X6 (*P2RX6*) gene, E1A binding protein p300 (*EP300*) and microRNA 1281 (*miRNA1281*) genes, and the Inositol Monophosphatase 1 (*IMPA1*) gene. *P2RX6* belongs to the family of P2X receptors, which are ligand-gated ion channels. Interestingly, the related functional gene cluster (a group of functionally highly related genes) includes *RYR2* and *CACNA1C*[29], previously implicated in PTSD pathogenesis[30,31]. Moreover, *P2RX6* expression is suggested to be associated with anxiety behavior, schizophrenia, and alcohol and drug dependence[29,32,33].

EP300 (also referred to as *p300*) encodes a histone acetyltransferase that regulates transcription via chromatin remodeling[34]. It also acts as a scaffold for transcription factors to activate gene transcription[35]. Modifications in chromatin structure have been widely implicated in memory and cognition, and more specifically in contextual fear memory[36]. *EP300* is suggested to be required for newly acquired and reactivated fear memories in the amygdala, as inhibition of *EP300* impairs fear memory consolidation, reconsolidation and synaptic plasticity in the lateral amygdala in rodents[37]. As it has often been proposed that in PTSD the traumatic memory has been over-consolidated and reconsolidated, these findings suggest a mediating role for *EP300* in the development of PTSD symptoms. However, in the present study DNA methylation was assessed in blood, and due to likely tissue specific differences, it is difficult to infer causality from these findings. Less is known about the *miRNA1281* in relation to PTSD development. One microRNA expression study found a downregulation in *miRNA1281* expression in

combat veterans with PTSD compared to combat-exposed controls, but this result has not yet been replicated in other expression studies[38].

IMPA1 encodes a modulator of intracellular signal transduction, and is proposed as a physiologically relevant target for lithium administered to bipolar disorder patients[39-41]. So far, no direct associations with PTSD have been reported. However, *IMPA1* is a putative target of microRNA 135, a regulatory element in serotonergic activity associated with stress-related neuropsychiatric disorders[42].

Both CpGs in the *EP300/miRNA1281* locus were involved in methylation-quantitative trait loci (mQTL) based on the mQTL Database[43]. All indicated SNPs were located in intergenic sequences on chromosome 5 and 10, and their clinical relevance is unknown. However, the clustered SNPs on chromosome 5 were proximate to the *ADAMTS16* gene, a gene previously indicated in functional impairment in psychiatric disorders[44]. For the other loci, no clustered SNPs were identified. Based on the iMethyl database[45], the *P2RX6* locus included an expression quantitative trait methylation (eQTM) pointing to an association with transcription of the phosphatase-coding gene *PPM1F*. This gene plays a broad role in both the stress response and serotonergic signaling, and is suggested to moderate the association between PTSD and cortical thickness[46,47]. The *EP300/miRNA1281* locus included an eQTM pointing to the protease-coding gene *DES11*. How these specific correlations between methylation level and gene expression could relate to PTSD development in unclear.

We attempted to replicate our identified loci in an independent prospective military cohort, but the associations between methylation of the *P2RX6*, *EP300/miRNA1281*, and *IMPA1* loci and PTSD symptoms up to six months after deployment were not significant in this replication dataset. Moreover, this study identifies different loci compared to previous methylome wide PTSD studies. This may indicate false-positive findings but may also be related to vast differences in methodology and populations between studies. Several confounders are at play such as genetic ancestry, personality, culture, environmental and combat exposures, and nutrition. Specific to the replication data set, differences in PTSD assessment (self-report vs. clinical diagnoses) and the use of different arrays (850 k vs. 450 k) might explain any discrepancy between the results of the separate data sets. However, we also did not find overlap in our results and the results reported by[8]; despite our samples were drawn from the same cohort of military personnel. Putative reasons for that are the fact that overlap is only partial, and more importantly, changes over three time points pose a very different concept of DNA methylation changes. In the current analysis only the most versatile loci are identified.

Unique to this study is that besides the association between DNA methylation changes and PTSD symptom development shortly after deployment, we also studied the relationship between DNA methylation changes and longer term PTSD outcomes using PTSD symptom trajectories. Our study suggests predictive utility of DNA methylation at *EP300/miRNA1281* for a delayed onset of PTSD symptoms between two and five years after the original trauma exposure. Most research addresses prevalence rates and risk factors for acute development of PTSD symptoms after trauma exposure, and thereby overlooks those who seem well initially but develop symptoms later in time. A challenge is to identify who is most at risk for developing symptomatology after the acute phase, and target follow-up screening and monitoring accordingly [48]. In our prediction model we observed that, together with thread level during deployment and physical childhood trauma, decreases in methylation within *EP300/miRNA1281* between one month and six months post-deployment were most strongly associated with the development of a delayed onset of PTSD symptoms. Although the results need to be interpreted with caution given the low number of participants represented in the delayed onset trajectory, this study suggests possible utility of DNA methylation measures for screening trauma-exposed individuals for an increased risk to develop a delayed onset of PTSD. This could be useful for prevention and early intervention in this group. Increased methylation changes at the *P2RX6* locus between one month and six months post-deployment also predicted a delayed onset trajectory but was only able to distinct that from a recovering trajectory. Although the clinical utility of this finding is lower, it does suggest that individuals with an acute and delayed onset of PTSD differ in epigenetic response after deployment. Long-term follow-up data on symptom scores were not available in the replication dataset and therefore we were not able to validate these findings in an independent cohort.

It is noteworthy that not the initial change in methylation level (pre-deployment to one month post-deployment) but the change after deployment was associated with PTSD trajectory. Compared to pre-deployment, the trajectories with substantial PTSD symptom development (either acute or delayed) show an initial increase in methylation level, whereas methylation levels drop in the resilient trajectory. However, these initial methylation responses at *P2RX6* and *EP300/miRNA1281* were not significantly different between trajectories. This suggests that, at least for the identified genomic regions, the initial epigenetic response following trauma is similar for both PTSD cases and controls, while they differ in their ability to reverse their methylation levels during the aftermath of trauma, and that such reversal is protective for PTSD.

We also compared the association between PTSD symptoms and epigenetic measures with the association between PTSD symptoms and individual genetic liability to PTSD

(PRS). PRS showed a significant correlation with acute onset PTSD within six months but had no relation with later onset (in contrast to the DNA methylation prediction). This suggests that discovery of the genetic risk is driven by onset soon after deployment, and that different (genetic) processes may underlie delayed onset. It also points to the possibility that sampling practice within the PGC in other PTSD developmental trajectories lead to underrepresentation of delayed onset PTSD. In this study, DNA methylation performed better as predictor of PTSD compared to genetic risk. The findings open a new perspective on the role of genetic risk to PTSD and the potential role of DNA methylation. Despite the documented relation between genetic vulnerability and epigenetic regulation, our data underscore the vast differences between the two and in this small dataset no common outcomes were present. Further studies that for instance investigate genetic risk for late onset or interrogate the relationship between PRS and DNA methylation are of interest to unravel the complex interplay between genetic predisposition and environmental exposures that impact on transcriptional regulation.

The current study possessed several strengths, including the prospective sampling, the use of an unbiased epigenome-wide approach, methylation measures at three consecutive time points, and a follow-up period of five years. Nonetheless, the study's results should be interpreted in the context of its limitations. The size of our sample was relatively small, and predominantly consisted of European males. It may therefore be difficult to extrapolate the findings to other samples and populations. In addition, DNA methylation was assessed in blood, and due to tissue specificity, it is difficult to infer causality from these findings. Regarding the analyses using the PTSD trajectories, the elevated pre-deployment scores of the delayed onset and recovering trajectory may limit the extent to which the analyses can truly predict the development of PTSD symptoms, as individuals in these trajectories already experienced a certain amount of PTSD symptoms before deployment. Furthermore, the use of backward regression might have introduced additional bias and therefore limit the generalizability of the findings from the prediction model. Also, the reported effect sizes are small. Due to the explorative nature of the analyses we did not adjust for the multiple prediction analysis. Adjustment for multiple testing would render the effects non-significant, and is obviously a point of concern. Finally, as in most DNA methylation studies, the actual DNA methylation differences driving the associations were small. Although these differences are likely to be biologically relevant for transcript length[49] and count[50], the field is only in the early stages of understanding the complexity of transcriptional regulation[51].

Overall this study provided new insights into the potential relationships between epigenetic alterations at different time periods and the development of PTSD symptoms up to five years post-deployment. In addition, a possible epigenetic mark was identified with the potential to contribute to successful classification of individuals with increased risk for developing a delayed onset of PTSD symptomatology. Finally, the results suggest that the current genetic background is most strongly related to acute disease onset, and that different processes may be at play in those individuals that develop PTSD after years of delay.

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SUPPLEMENTARY MATERIAL

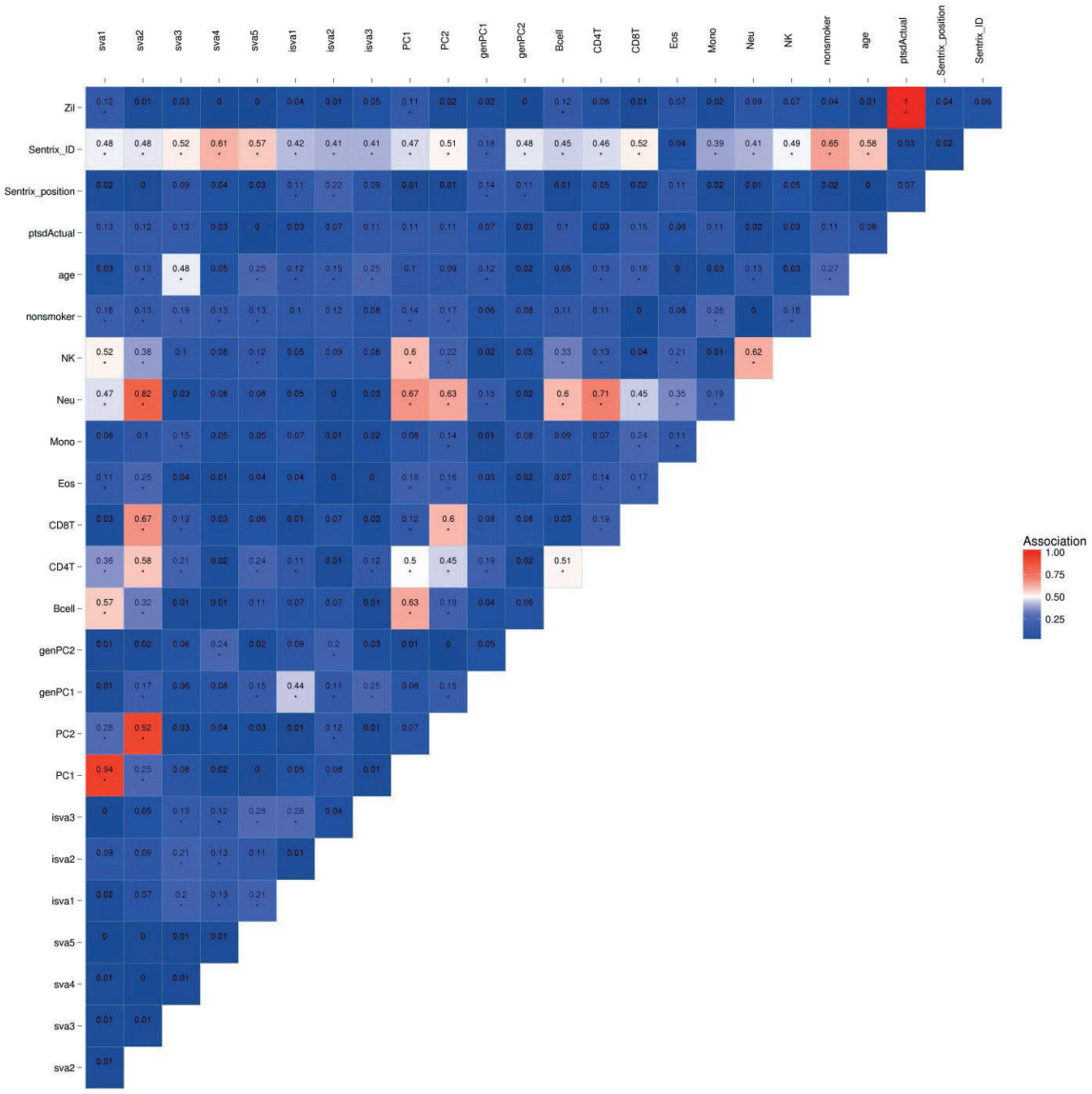

Figure S1. Correlation plot showing the relation of the SVA with potential confounders.

Note: PC=principal components; SVA=surrogate variables.

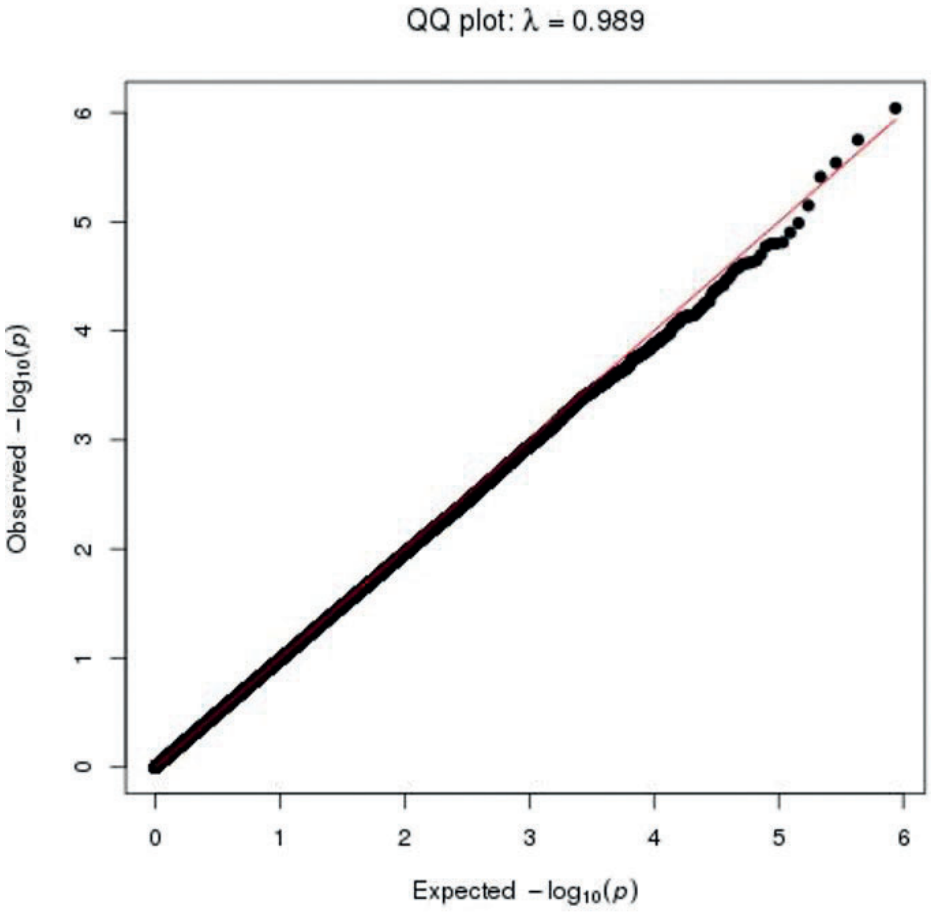

Figure S2. QQ-plot of the robust error analysis.

Table S1. Details on missing values in the outcome variable and the variables included in the single Bayesian stochastic regression imputation model.

Non-imputed variables	**Missing values N (%)**
PTSD score at baseline	18 (14.4)
PTSD score at 1 month	11 (8.8)
PTSD score at 6 months	8 (6.4)
PTSD score at 1 year	37 (29.6)
PTSD score at 2 years	48 (38.4)
PTSD score at 5 years	41 (32.8)
Imputed variables	**Missing/imputed values N (%)**
DMR1 methylation at baseline	8 (6.4)
DMR1 methylation at 1 month	17 (13.6)
DMR1 methylation at 6 months	16 (12.8)
DMR2 methylation at baseline	13 (10.4)
DMR2 methylation at 1 month	18 (14.4)
DMR2 methylation at 6 months	16 (12.8)
DMR6 methylation at baseline	13 (10.4)
DMR6 methylation at baseline	18 (14.4)
DMR6 methylation at 1 month	16 (12.8)
DMR7 methylation at baseline	13 (10.4)
DMR7 methylation at 1 month	18 (14.4)
DMR7 methylation at 6 months	16 (12.8)
New deployment(s)	39 (31.2)
Childhood general trauma score	1 (0.8)
Childhood physical trauma score	1 (0.8)
Childhood emotional trauma score	2 (1.6)
Childhood sexual trauma score	2 (1.6)

Note: PTSD=posttraumatic stress disorder; DMR=differentially methylated region.

Table S2. Genome-wide significant differentially methylated regions (DMRs) in the PRISMO sample.

	Chromosomal position of DMR	Genes	Probes	M-value per timepoint	p-value (Stouffer method)
DMR1	chr22: 21368603, 21368765	*TUBA3FP P2RX6*	cg06912515	T_0: -6.11253 T_1: -6.10767 T_2: -6.08259	8.84 E-05
			cg19789653	T_0: -6.02660 T_1: -5.98451 T_2: -5.98876	
			cg09481857	T_0: -6.13618 T_1: -6.09909 T_2: -6.11143	
			cg21014483	T_0: -5.58381 T_1: -5.54866 T_2: -5.55620	
			cg01038149	T_0: -4.84318 T_1: -4.81578 T_2: -4.74708	
DMR2	chr22: 41487073, 41487283	*EP300 miR1281*	cg08131204	T_0: -3.12842 T_1: -3.01123 T_2: -3.05542	1.18 E-06
			cg00500400	T_0: -4.54530 T_1: -4.49676 T_2: -4.51763	
DMR3	chr20: 57463265, 57463357	*RP1-309F20.3 GNAS*	cg22741626	T_0: 1.09991 T_1: 1.11214 T_2: 1.12866	9.84 E-04
			cg18997188	T_0: 0.64609 T_1: 0.62023 T_2: 0.65643	
			cg20213508	T_0: 0.74252 T_1: 0.74046 T_2: 0.72923	
			cg26791489	T_0: 0.81432 T_1: 0.82604 T_2: 0.84242	
			cg04779428	T_0: 0.66349 T_1: 0.61870 T_2: 0.65497	
			cg04019914	T_0: 1.04222 T_1: 1.01672 T_2: 1.03912	

Table S2. (Continued)

	Chromosomal position of DMR	Genes	Probes	M-value per timepoint	p-value (Stouffer method)
DMR4	chr19: 51774377, 51774666	*CTD-3187F8.11* *CTD-3187F8.2*	cg15497724	T_0: 1.90534 T_1: 1.88825 T_2: 1.83039	1.21 E-05
			cg01718065	T_0: 1.68837 T_1: 1.64132 T_2: 1.65797	
			cg14884932	T_0: 1.65318 T_1: 1.57792 T_2: 1.65894	
			cg14724749	T_0: 1.01138 T_1: 0.96431 T_2: 1.05977	
			cg13749314	T_0: 0.31032 T_1: 0.31886 T_2: 0.34482	
DMR5	chr12: 12878428, 12878440	*APOLD1* *RP11-180M15.4*	cg09462578	T_0: -4.12678 T_1: -4.11350 T_2: -4.13727	1.13 E-05
			cg04607235	T_0: -4.97590 T_1: -5.00137 T_2: -5.01364	
DMR6	chr8: 82598501, 82598664	*IMPA1*	cg05798523	T_0: -5.26660 T_1: -5.26110 T_2: -5.24939	1.87 E-06
			cg23402311	T_0: -5.38898 T_1: -5.37957 T_2: -5.35563	
			cg03588978	T_0: -3.99517 T_1: -4.03742 T_2: -4.02731	
			cg04364718	T_0: -4.34152 T_1: -4.33815 T_2: -4.29553	
			cg12093930	T_0: -3.80685 T_1: -3.83977 T_2: -3.84049	
DMR7	chr8: 144973617, 144973638	-	cg26529963	T_0: 3.16448 T_1: 3.12878 T_2: 3.13937	9.19 E-05
			cg03000485	T_0: 4.08064 T_1: 4.05300 T_2: 4.03901	

Table S2. (Continued)

	Chromosomal position of DMR	Genes	Probes	M-value per timepoint	p-value (Stouffer method)
DMR8	chr6: 33284488, 33284646	*ZBTB22*	cg04810660	T_0: 3.20113 T_1: 3.19972 T_2: 3.16011	7.68 E-04
			cg08277746	T_0: 3.74881 T_1: 3.68120 T_2: 3.69285	
			cg08421271	T_0: -0.73371 T_1: -0.70736 T_2: -0.72112	
DMR9	chr5: 101119084, 101119128	-	cg17598923	T_0: 0.17186 T_1: 0.11530 T_2: 0.19588	8.03 E-06
			cg05545777	T_0: -0.75757 T_1: -0.74531 T_2: -0.76296	
DMR10	chr5: 138713897, 138713954	*SLC23A1*	cg00697057	T_0: 3.06206 T_1: 3.05007 T_2: 3.00003	5.65 E-03
			cg00976381	T_0: 3.09307 T_1: 3.04942 T_2: 3.03631	
DMR11	chr4: 99064459, 99064746	*STPG2*	cg10515332	T_0: -4.45823 T_1: -4.44725 T_2: -4.43517	1.95 E-07
			cg25414656	T_0: -4.04009 T_1: -3.94427 T_2: -3.98976	
			cg00999950	T_0: -4.96032 T_1: -4.94016 T_2: -4.93127	
			cg18180107	T_0: -4.27786 T_1: -4.26749 T_2: -4.24284	
			cg03467027	T_0: -4.77078 T_1: -4.80223 T_2: -4.76779	
			cg07917127	T_0: -3.97715 T_1: -3.97837 T_2: -3.97150	

Table S2. (Continued)

	Chromosomal position of DMR	Genes	Probes	M-value per timepoint	p-value (Stouffer method)
DMR12	chr4: 118007206, 118007342	*TRAM1L1*	cg22155281	T_0: 2.55812 T_1: 2.56540 T_2: 2.55645	4.13 E-07
			cg03345976	T_0: 3.30031 T_1: 3.30940 T_2: 3.30381	
			cg25548984	T_0: 2.02421 T_1: 1.99190 T_2: 1.95923	
DMR13	chr2: 180872053, 180872164	*CWC22*	cg00460911	T_0: -4.58714 T_1: -4.57924 T_2: -4.58118	1.15 E-05
			cg20057831	T_0: -4.64359 T_1: -4.59443 T_2: -4.63647	
			cg01881094	T_0: -3.94919 T_1: -3.88086 T_2: -3.89682	
			cg18778932	T_0: -4.58004 T_1: -4.55757 T_2: -4.61858	
			cg04967250	T_0: -4.40511 T_1: -4.40451 T_2: -4.41391	
DMR14	chr1: 7844446, 7844471	*PER3*	cg05803631	T_0: -4.91736 T_1: -4.86505 T_2: -4.88813	2.62 E-06
			cg01444397	T_0: -5.08050 T_1: -5.06171 T_2: -5.09185	
			cg06338235	T_0: -4.96257 T_1: -4.93527 T_2: -4.93220	
			cg16456870	T_0: -4.83361 T_1: -4.73638 T_2: -4.70705	

Note: DMR=differentially methylated region; T_0=pre-deployment; T_1=1 month post-deployment; T_2=6 months post-deployment.

Table S3. Parameter estimates for the association between PTSD developmental trajectories and DNA methylation changes or polygenic risk scores in the imputed and non-imputed datasets.

Imputed dataset	**DNA methylation change baseline – 1 month Odds-ratio(95%-CI)**	**DNA methylation change 1 month – 6 months Odds-ratio(95%-CI)**
DMR1		
Delayed vs. Resilient	0.859 (0.552-1.338)	1.155 (0.705-1.894)
Recovering vs. Resilient	0.649 (0.397-1.061)	**2.374**** (1.248-4.516)
Delayed vs. Recovering	1.324 (0.773-2.268)	**0.487*** (0.243-0.973)
DMR2		
Delayed vs. Resilient	0.759 (0.497-1.160)	**1.653*** (1.033-2.644)
Recovering vs. Resilient	0.613 (0.371-1.014)	**2.734**** (1.509-4.956)
Delayed vs. Recovering	1.238 (0.717-2.137)	0.605 (0.328-1.114)
DMR6		
Delayed vs. Resilient	1.155 (0.767-1.740)	1.095 (0.715-1.675)
Recovering vs. Resilient	0.877 (0.527-1.457)	0.673 (0.400-1.133)
Delayed vs. Recovering	1.317 (0.744-2.331)	1.627 (0.902-2.937)
DMR7		
Delayed vs. Resilient	1.216 (0.803-1.841)	0.983 (0.645-1.498)
Recovering vs. Resilient	1.239 (0.752-2.041)	0.927 (0.554-1.550)
Delayed vs. Recovering	0.981 (0.565-1.703)	1.061 (0.595-1.891)
Non-imputed dataset	**DNA methylation change baseline – 1 month Odds-ratio(95%-CI)**	**DNA methylation change 1 month – 6 months Odds-ratio(95%-CI)**
DMR1		
Delayed vs. Resilient	0.800 (0.490-1.306)	1.406 (0.772-2.563)
Recovering vs. Resilient	0.639 (0.370-1.103)	**2.065*** (1.050-4.060)
Delayed vs. Recovering	1.252 (0.694-2.260)	0.681 (0.342-1.357)
DMR2		
Delayed vs. Resilient	0.838 (0.524-1.341)	1.708 (0.988-2.953)
Recovering vs. Resilient	0.892 (0.499-1.594)	**1.938*** (1.029-3.651)
Delayed vs. Recovering	0.940 (0.490-1.802)	0.881 (0.445-1.744)
DMR6		
Delayed vs. Resilient	1.066 (0.665-1.709)	1.155 (0.686-1.943)
Recovering vs. Resilient	0.794 (0.435-1.448)	0.742 (0.415-1.328)
Delayed vs. Recovering	1.342 (0.681-2.647)	1.556 (0.781-3.097)
DMR7		
Delayed vs. Resilient	1.310 (0.818-2.098)	0.912 (0.549-1.514
Recovering vs. Resilient	1.124 (0.623-2.028)	1.106 (0.614-1.992)
Delayed vs. Recovering	1.165 (0.607-2.237)	0.824 (0.416-1.632)
Polygenic risk score[a]		
Delayed vs. Resilient	0.700 (0.094-5.212)	
Recovering vs. Resilient	5.530 (0.554-55.24)	
Delayed vs. Recovering	0.127 (0.008-1.900)	

Note: * p-value <0.05; ** p-value <0.01; [a] Variable polygenic risk score had no missing values and was therefore not imputed; PTSD=Posttraumatic stress disorder; CI=confidence interval; DMR=differentially methylated region.

CHAPTER 6

THE PREDICTION OF LONG-TERM PTSD SYMPTOM DEVELOPMENT IN MILITARY PERSONNEL: APPLYING MACHINE LEARNING TO PRE-DEPLOYMENT RISK FACTORS

Authors

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Submitted

ABSTRACT

Active-duty army personnel are frequently exposed to traumatic events during deployments, yet only a minority of them develop mental health disorders such as posttraumatic stress disorder (PTSD). Why some are at increased risk for developing PTSD after deployment is still not fully understood. A large amount of literature has been published on the identification of risk factors for PTSD, but have not yet led to the development of effective pre-deployment screening tools. Machine learning might be a promising approach for developing better prediction models. The present study utilized a random forest method to predict the development of PTSD symptoms up to ten years after deployment in a cohort of Dutch Afghanistan veterans. The dataset consisted of both psychological and biological pre-deployment variables. The predictive model had a performance well above chance (AUC = 0.71, sensitivity = 0.63, specificity = 0.69). Among the top five highest-ranked predictive features were self-reported symptoms (depression, anxiety and distrust and personal sensitivity) and lab markers (vasopressin and DEX-sensitivity). A random forest model using a dataset with only psychological predictors performed as well as the random forest model based on both psychological and biological information. The results suggest that a random forest approach can be effective in the identification of important predictive markers to define novel risk mitigation interventions. As the model performance in the present study was modest and no external validation could be performed, more research is needed to increase the usability for pre-deployment screening.

INTRODUCTION

The military operations in Iraq and Afghanistan raise important questions about the consequences of combat and peacekeeping missions on the mental health of deployed soldiers. Research has shown that exposure to deployment stressors results in considerable incidence of posttraumatic stress disorder (PTSD)[1–4] that transcends the prevalence in the general population[5]. After each mission, a significant number of soldiers returns home facing a post-deployment life with PTSD symptoms and common comorbid disorders that will impact their daily social and occupational functioning. These burdens to the individual and society call for a better understanding of risk factors in order to develop effective pre-deployment screening tools and risk mitigation strategies.

Although the recent operations in Iraq and Afghanistan have led to an expansion of pre-deployment screening and resilience-building initiatives, programs have not proven very successful[6,7]. One reason for this lack of success might be the use of traditional methodological approaches in the development of predictive models for post-deployment PTSD which might not be able to capture non-linear and multidimensional relationships between predictors and the outcome of interest[7,8]. In recent years, machine learning has shown promise to address these complexities. In supervised machine learning, an algorithm is trained on a labeled dataset to learn data distributions and patterns, for example with the aim to categorize individuals as belonging to one or another predefined category[9]. It has proved to be effective in predictive modeling in a medical setting[10,11], and is now increasingly implemented in psychiatric conditions[12]. A review based on 15 studies found that the use of machine learning algorithms to integrate high-dimensional data leads to improvement in PTSD risk prediction, even when the sources of data are similar to those used in traditional prognostic models[7].

In a military context, machine learning algorithms have been used to identify PTSD subtypes[13], predict suicide[14], and to predict psychiatric disorder symptoms[8,15–19] in military personnel, and have found to significantly outperform traditional regression models.[19] Of particular interest is the study by Schultebraucks and colleagues, which utilized a machine learning approach to examine the value of a multidimensional pre-deployment dataset for predicting 90-180 days post-deployment PTSD status in Afghanistan veterans.[18] This study showed that pre-deployment PTSD risk can be predicted with high sensitivity and specificity based on the combination of biomarkers, self-reports, and neurocognitive functioning.[18] Other studies on prognostic factors for deployment-related PTSD are often cross-sectional, which makes it difficult to

distinguish risk factors from the consequences of developing PTSD. As there are only a few large prospective longitudinal studies on the development of PTSD in military personnel, the possibilities to train and validate machine learning algorithms utilizing multidimensional pre-deployment data for predicting PTSD risk are limited.

This prospective longitudinal cohort study, the Prospective Research in Stress-related Military Operations (PRISMO) study, examined whether a dataset consisting of pre-deployment biological markers and clinical and personality self-reports can predict PTSD symptom development over the course of ten years after a four-month deployment period to Afghanistan. A random forest of ensembles of decision trees[20] was used to build a classification algorithm for predicting membership in a PTSD symptom trajectory and to detect the variables that are most predictive of post-deployment PTSD symptom development. To our knowledge, this is the first study that applies a machine learning method to predict PTSD symptoms development with a long-term follow-up period up to ten years after deployment. This approach has the potential to discover novel risk factors for PTSD, and its results can potentially be used for the development of more effective pre-deployment screening and risk mitigation interventions.

METHODS

Study population

The sample utilized in the random forest approach comprised 963 Dutch veterans deployed to Afghanistan on behalf of the International Security Assistance Force (ISAF) between 2005 and 2008. All participants took part in the PRISMO-study, a large prospective cohort study on the development of stress-related mental health symptoms in Dutch military personnel deployed to Afghanistan, which is described in detail elsewhere[21]. Participants were assessed approximately one month prior to a four-month deployment, and one month, six months, one year, two years, five years and ten years after returning home. Assessments were completed at the army base for the baseline measurement and first two follow-up measurements. The 1-, 2-, and 5-year follow-up assessments were completed at home, and the 10-year follow-up measurement was completed at home or at the research facility of the Military Mental Healthcare. Written informed consent was obtained from all subjects. The PRISMO-study was conducted in accordance with the ethical principles for the conduct of human research as specified in the Declaration of Helsinki, and approved by the Institutional Review Board of the University Medical Center Utrecht (Utrecht, The Netherlands).

Procedure

This longitudinal study included a total of seven time points of data collection. A complete overview of the data collection phases and measured variables is presented in Supplementary Table S1. Participants in the PRISMO-study were included in the present analysis if they had an available score of the Self-Rating Inventory for PTSD (SRIP)[22] at one or more of the data collection time points. Table 1 displays the baseline characteristics of the sample. Differences between the participants with and without a SRIP-measurement are shown in Supplementary Table S2.

Variables

Outcome measure: clinical items for identifying PTSD trajectories

Items of the SRIP[22], a Dutch questionnaire to assess PTSD symptoms in the past four weeks based on the DSM-IV criteria for PTSD, were used to identify trajectories of PTSD symptom development. The SRIP contains 22 questions with responses measured on a Likert scale ranging from 1 (never) to 4 (very frequent). The SRIP showed good internal consistency and discriminant validity with other commonly used PTSD measures[22,23].

Clinical predictors: psychological symptoms and personality

All psychological markers used for predicting PTSD symptom development were assessed by self-reports. Mental health symptoms were measured with the agoraphobia, anxiety, depression, somatization, hostility, sleeping problems, insufficiency of thinking and acting, and distrust and interpersonal sensitivity subscales of the Dutch revised Symptom Checklist (SCL-90-R)[24]. Fatigue was assessed using the fatigue severity, concentration problems, reduced motivation, and reduced activity subscales of the Checklist of Individual Strength (CIS)[25]. Burnout symptoms were measured with the emotional exhaustion, depersonalization, and professional accomplishment subscales of the Utrecht Burnout Scale (UBOS).[26] The personality dimensions novelty seeking, harm avoidance, reward dependence, persistence, self-directedness, cooperativeness, and self-transcendence were assessed with the short-form Temperament and Character Inventory (TCI-SF)[27]. Potential traumatic experiences before the age of 18 were assessed using the general trauma, physical abuse, and emotional abuse subscale of the Early Trauma Inventory Self Report-Short Form (ETISR-SF)[28]. Due to near-zero variance values, the sexual abuse subscale of the ETISR-SF was not included as a predictor in the model. Finally, exposure to potentially traumatic and combat-related stressors during deployment was measured with the Deployment Experience Scale (DES)[29].

Table 1. Baseline characteristics of participants included into the analysis.

Variables	Participants (n=963)*
Sex	
Male	878 (91%)
Female	85 (9%)
Age (years)	
<21	130 (14%)
≥21	831 (87%)
Educational level	
Low	33 (4%)
Moderate	753 (85%)
High	99 (11%)
Rank	
Private	378 (40%)
Corporal	199 (21%)
Non-commissioned officer	245 (26%)
Staff officer	130 (14%)
Previous deployment(s)	
Yes	417 (48%)
No	460 (53%)
Role during deployment	
Inside the military base	244 (31%)
Both inside and outside the military base	73 (9%)
Outside the military base	474 (60%)
Deployment year	
2005 or 2006	237 (25%)
2007 or 2008	726 (75%)
New deployment(s)	
Yes	318 (48%)
No	344 (52%)
DES (deployment stressors) total score	4.51 (3.22)

Note: data are n (%) or mean (SD). SRIP=Self-Rating Inventory for Post-traumatic Stress Disorder. DES=Deployment Experience Scale. *Sample sizes might not add up to total because of missing data in the descriptive variables.

Biological predictors: blood measures

The blood-markers used for predicting PTSD symptom development were based on previous publications from the PRISMO-study and included plasma neuropeptide Y[30], arginine vasopressin[31], oxytocin[31], testosterone[32], sex-hormone binding globulin (SHBG)[32], dehydroepiandrosterone (DHEA)[32], GABA[33], and dexamethasone (DEX)

sensitivity of peripheral blood cells[34]. Detailed methodology is described in the cited publications. In addition, age was also included as a variable in the analysis.

Statistical analysis

Latent growth mixture modeling (LGMM)

LGMM was conducted to identify distinct trajectories of PTSD development in the PRISMO sample using PTSD scores at seven consecutive time points, and is described in detail in a previous publication on this cohort[2]. In short, latent class growth analysis (LCGA) models as well as growth mixture modeling (GMM) models were performed and re-fitted with a quadratic term for time to assess whether non-linear growth curves provided better fit to the data. Missing data was handled by full information maximum likelihood estimation. All models were compared on fit indices, entropy, class size, and interpretability. The outcome variable for classification was membership to any PTSD trajectory (i.e. a non-resilient trajectory) as identified in the best performing LGMM model.

Data preprocessing

All steps of data preprocessing and analysis were performed using R version 4.1.0 in Rstudio 1.4.1106. Missing values in the predictor variables (see Supplementary Table S3) were imputed using random forest imputation in the R package 'mice'[35]. The dependent variable was removed from the dataset prior to imputation. Random undersampling of subjects belonging to the resilient trajectory was used to counter high class imbalance in the outcome variable. Five datasets were generated that each included 1) all subjects belonging to a PTSD trajectory and 2) a unique random subset of subjects belonging to a resilient trajectory so that the datasets were perfectly balanced. Despite a loss in information, undersampling was preferred above oversampling techniques like synthetic minority oversampling technique (SMOTE) as oversampling of the subject belonging to a PTSD trajectory resulted in overfitting of the model and seriously inflated model performance estimates in the present dataset.

Random forests

Random forests of classification trees were constructed in the R package 'caret'[36] and evaluated using the 'MLeval'[37] package. First, the number of trees (ntree) and the number of variables sampled as split candidates at each node (mtry) were fine-tuned by examining random combinations to determine the optimal parameter settings (ntree = 500 and mtry = 6 for all random forests). As internal validation the bootstrap method was used to select a sample from the dataset to train the decision tree and the remaining sample to estimate the prediction error, and was repeated 10 times. Area under the receiver operating curve (AUC), sensitivity, and specificity were used

to evaluate classification accuracy of the final model. A variable importance score, the importance of each predictor to the random forest, was determined for each predictor variable. This approach was executed for each of the five balanced datasets. AUC, sensitivity, specificity and scaled variable importance scores of the five models were averaged to achieve a mean performance score of the predictive power of the random forest. The approach was repeated with only the top ten highest-ranked predictive values included (ntree = 500 and mtry =3). Finally, each balanced dataset was split in a dataset with exclusively biological predictors included and a dataset with exclusively psychological predictors included. Random forests were constructed as described above with adjusted parameter settings for the datasets with psychological predictors (ntree = 500 and mtry = 5) and biological predictors (ntree = 500 and mtry = 3).

RESULTS

Overall performance

The best performing LGMM model consisted of four latent trajectories: one resilient trajectory and three PTSD trajectories (a delayed onset trajectory, an improving trajectory, and a severely elevated-recovering trajectory); see[2] for details on the trajectories. In total, 118 participants belonged to one of the PTSD trajectories and 845 participants belonged to the resilient trajectory. Five balanced datasets were created with 118 PTSD trajectory cases and 118 unique randomly selected resilient trajectory cases.

The random forests based on five balanced datasets including psychological symptom self-reports, personality dimensions, and biomarker information all performed well above chance in predicting PTSD symptom development in the ten years post-deployment. The average performance was AUC = 0.71, sensitivity = 0.63, and specificity = 0.69. Table 2 summarizes the predictive performance of the five random forest models. Random forest models with only the top ten highest-ranked predictor variables included performed equally well (AUC = 0.72; sensitivity = 0.63; specificity = 0.68). The random forests based on psychological predictors also performed well above chance (AUC = 0.71; sensitivity = 0.63; specificity = 0.68), while the models based on biological predictors had poor performances (AUC = 0.54; sensitivity = 0.54; specificity = 0.54) (see Supplementary Table S4).

Table 2. Performance of the final models based on five balanced datasets.

	AUC	Sensitivity	Specificity
Dataset 1	0.74 (0.68-0.80)	0.64 (0.55-0.72)	0.72 (0.63-0.79)
Dataset 2	0.68 (0.61-0.75)	0.57 (0.48-0.65)	0.70 (0.62-0.78)
Dataset 3	0.71 (0.64-0.78)	0.61 (0.52-0.69)	0.68 (0.59-0.76)
Dataset 4	0.71 (0.64-0.78)	0.63 (0.54-0.71)	0.63 (0.54-0.71)
Dataset 5	0.73 (0.67-0.79)	0.64 (0.55-0.72)	0.72 (0.63-0.79)
Average	*0.71*	*0.63*	*0.69*

Variable importance ranking

Figure 1 displays the average variable importance scores of all variables for predicting PTSD symptom development using the complete dataset. Scores were scaled to range from 0 to 100. The top five highest-ranked predictive features included depression, anxiety, plasma arginine vasopressin level, DEX-sensitivity of peripheral blood cells, and distrust and interpersonal sensitivity. The variable importance scores per model are shown in Supplementary Figures S1-S5. Supplementary Table S4 lists the variables that appeared at least once in the top five predictors of any of the models. Figure 2 displays the scaled average variable importance scores of all psychological variables using the dataset with only psychological predictors included. The top five highest-ranked predictive variables in the psychological dataset included depression, anxiety, concentration problems, professional accomplishment, and deployment experience. The variable importance scores per model are shown in Supplementary Figures S6-S10.

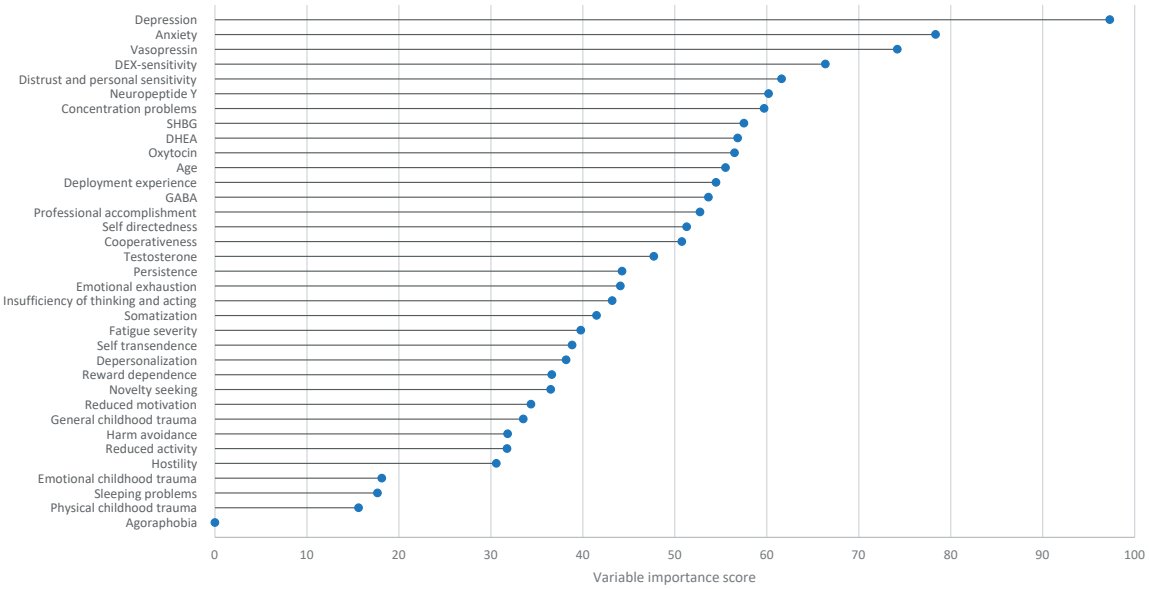

Figure 1. Average variable importance scores of all predictor variables for predicting PTSD symptom development. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled to range 0-100.

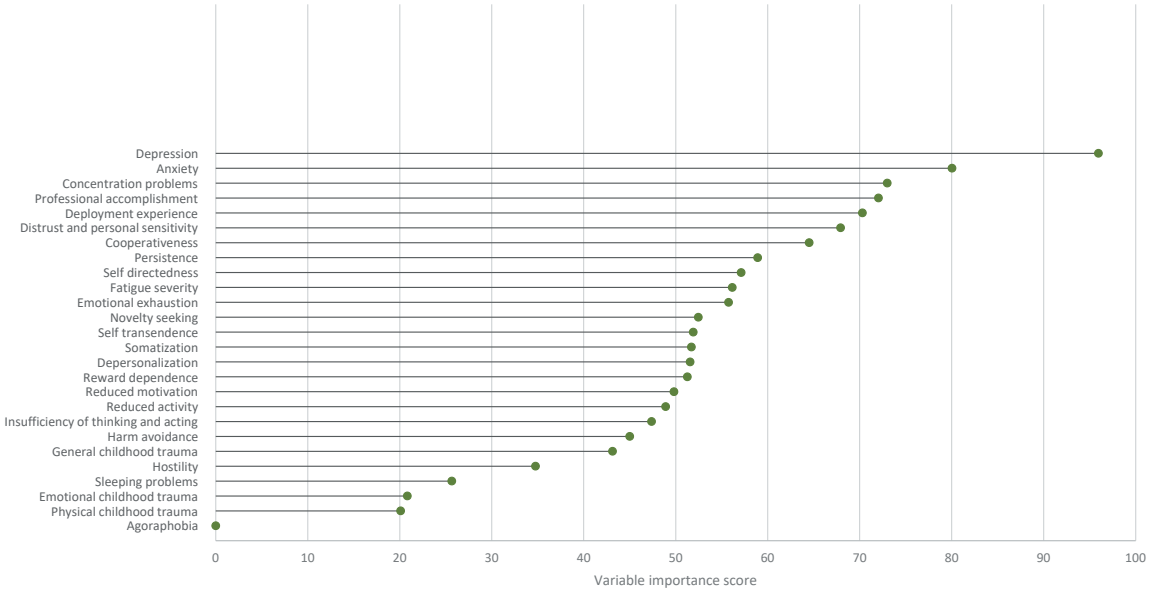

Figure 2. Average variable importance scores of all psychological predictor variables for predicting PTSD symptom development using datasets with only psychological predictors included. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled to range 0-100.

DISCUSSION

In the present paper we developed a random forest model using pre-deployment measures to predict the development of PTSD symptoms as reflected in LGMM trajectories in military personnel up to ten years after returning from deployment to Afghanistan. The model based on psychological and biological information performed with an average AUC of 0.71 well above chance in distinguishing military personnel in a PTSD trajectory from personnel in a resilient trajectory. The model with only the top ten highest-ranked predictor variables included showed similar performance scores, which offers opportunities in terms of generalizability and practical implementation of the prediction model. The top five most powerful predictors in the algorithm included psychological symptom self-reports and blood markers. Surprisingly, the random forest model based on exclusively psychological variables performed as well as the model based on both psychological and biological factors. This is not consistent with previous findings indicating that PTSD risk can best be predicted based on a combination of biomarkers and psychological factors[18,38,39].

As previous studies on PTSD prediction are mainly cross-sectional, and therefore diagnostic instead of predictive of PTSD status, possibilities of direct comparison of the present findings are limited. Similar to the PRISMO-study, the Fort Campbell Cohort study analyzed pre-deployment risk factors for PTSD development in military personnel[40,41]. Using data of this prospective, longitudinal naturalistic cohort, Schultebraucks et al. utilized a random forest approach to analyze multivariate predictors for discriminating LGMM trajectories 90-180 days post-deployment.[18] Their results provided evidence that the combination of psychological self-reports, biomarkers, and neurocognitive function is best predictive for pre-deployment PTSD risk, and thus outperformed random forests based on these variable types in isolation. We were not able to replicate a similar finding in our cohort. However, a larger number and more diverse types of biomarkers (e.g. metabolic, lipid panel, inflammatory markers, liver functioning tests, metabolomics, methylation marks, and polygenic risk score) were used in the study by Schultebraucks et al. compared to the blood measures used in our model. In addition, they included cognitive assessments for attention, emotion, regulation, and executive function, of which two measures were among the top 5 highest ranked predictive features. As their random forest to predict LGMM trajectories had a performance of AUC = 0.85 compared to a performance of AUC = 0.71 of our model, future research to develop effective predictive models should test a broader range of biomarkers and neurocognitive assessments in combination as well as in isolation. However, it should be noted that the study by Schultebraucks et al. predicted PTSD symptoms shortly after deployment, while the present study predicted PTSD symptom development

up to ten years after deployment. Psychological factors might therefore perform well in predicting short-term as well as long-term symptom development, while biological factors are particularly relevant for short-term prediction. In addition, the predictive power of pre-deployment risk factors for long-term prediction could be reduced due to the increasing importance of post-deployment factors such as perceived social support[42,43].

In the present study, self-report measures of depression and anxiety symptoms were found to be the strongest predictors for the development of PTSD symptoms in the ten years after deployment. Soldiers who suffer from depressive and anxiety symptoms before deployment might thus be more susceptible to develop substantial PTSD symptoms when they are exposed to combat environments.

This fits previous findings indicating the importance of pre-deployment self-reported psychological symptoms as risk factors for PTSD[44–46], and matches the findings by Schultebraucks et al[18]. In addition to depressive and anxiety symptoms, distrust and interpersonal sensitivity was also found to be an important predictor. Feelings of personal inferiority were identified as mediator in the relationship between trauma and PTSD symptoms in war-exposed civilian populations in cross-sectional studies[47,48], but are to our knowledge not previously identified as a risk factor for the development of PTSD symptoms in deployed military cohorts. Distrust towards others or paranoid cognition has been linked to PTSD in veterans[49] and civilians[50]. However, due to the cross-sectional methodology of these studies, distrust could also be explained as a consequence of the development of PTSD instead of a vulnerability factor. Besides psychological symptom self-reports, our dataset also included information on personality and childhood trauma. Various personality factors[51,52] and reported childhood abuse[53,54] have repeatedly been associated with the development of PTSD in military samples. To our surprise, these variables were not identified as high-ranked predictors in our model. Only the personality dimensions cooperativeness, persistence and self-directedness were among the top 10 predictive variables in the psychological dataset.

Biomarkers in the blood, such as arginine vasopressin and neuropeptide Y, were also important predictors for PTSD symptom development. Arginine vasopressin is a nonapeptide produced by the hypothalamus, and of potential interest because of its role in the regulation of stress and anxiety[55]. There is doubt in the literature whether peripherally measured vasopressin levels reflect the level of central activity, and whether this measure can therefore serve as a valuable biological marker for PTSD[31,55]. So far, vasopressin has not been strongly implicated in PTSD[56]. However, our

results suggest that plasma vasopressin is of predictive value, which fits prior findings that associated elevated plasma vasopressin levels to PTSD status in male veterans[57]. In a previous report on the PRISMO-cohort, the relation between plasma vasopressin levels and the development of PTSD was studied using linear mixed modeling[31]. Here, no significant association was found between vasopressin levels and the development of PTSD symptoms over time. As the same data were used in both studies, these findings highlight the differences between the use of machine learning and traditional methodological approaches in predictive modeling. A similar result was found for plasma neuropeptide Y levels. Neuropeptide Y is a peptide neurotransmitter that is associated with modulation of the stress response[58]. There is some evidence that levels of neuropeptide Y are altered in PTSD patients, although the results are mixed[59,60]. In our model, peripheral neuropeptide Y was identified as a predictor for PTSD symptoms. We did not find this association in a previous study in the same cohort when using linear mixed modeling[30]. Moreover, there is evidence about the association between glucocorticoid alterations and PTSD[61], although hypocortisolism is not a consistent finding in PTSD.[62] We found that leukocyte sensitivity to glucocorticoids (measured as high DEX-sensitivity of T-cell proliferation) contributes to the prediction of post-deployment PTSD symptoms, which is in line with previous research that indicate that the presence of PTSD is associated with changes in the sensitivity of leukocytes for regulation by glucocorticoids[63–65].

Limitations

This prospective, longitudinal cohort study provides the possibility to study pre-deployment risk for developing PTSD symptoms in the ten years after deployment. The available dataset included a range of psychological variables as well as biomarkers to assess the predictive performance of a random forest model. The results should nevertheless be interpreted in the context of its limitations. We used self-report scores to identify trajectories of PTSD development, and PTSD diagnosis was not verified using clinical interviews. Also, different trajectories of PTSD symptom development were combined into one outcome value. We cannot rule out that different trajectories of symptom development (e.g. early onset vs. late onset) have different sets of predictive variables. Unfortunately, our dataset was too modest in size to distinguish between PTSD trajectories. Future research using larger sample sizes should investigate this hypothesis. Furthermore, due to serious overfitting issues when using oversampling methods, we chose to utilize undersampling techniques to achieve class balance in the dataset. Although this approach avoided inflated model performance estimates, it has limited our sample size and the power of the analysis. While considering a large set of predictive variables, we did not include methylation, inflammatory, neurocognitive or neuroimaging markers, as these were only available in a smaller subset of the

participants. If these had been available for all participants, this might have increased the classification accuracy of the model. External validation in independent datasets is necessary to assess the generalizability of the model.

CONCLUSION

Our findings suggest that pre-deployment psychological and biological information has predictive value in distinguishing between Afghanistan veterans that develop PTSD symptoms and veterans that show resilience up to ten years after returning home. In particular it shows the importance of self-reported psychological symptoms and biomarkers involved in regulation of the stress response for predicting combat-related PTSD risk. However, the model performance on the present dataset was modest, and usability of the model for pre-deployment screening is therefore limited. This study nevertheless shows that a random forest approach can be effective in the identification of predictive markers to define novel interventions for targeting deployment-related PTSD.

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SUPPLEMENTARY MATERIAL

Table S1. Overview of the data collection phases and measured variables.

Measurement time	Category	Variable	Assessment tool
Pre-deployment	Mental health symptoms	PTSD	Self-Rating Inventory for PTSD (SRIP)[1]
		Agoraphobia	Symptom Checklist (SCL-90-R)[2]
		Anxiety	Symptom Checklist (SCL-90-R)
		Depression	Symptom Checklist (SCL-90-R)
		Somatization	Symptom Checklist (SCL-90-R)
		Hostility	Symptom Checklist (SCL-90-R)
		Sleeping problems	Symptom Checklist (SCL-90-R)
		Insufficiency of thinking and acting	Symptom Checklist (SCL-90-R)
		Distrust and interpersonal sensitivity	Symptom Checklist (SCL-90-R)
	Fatigue	Fatigue severity	Checklist of Individual Strength (CIS)[3]
		Concentration problems	Checklist of Individual Strength (CIS)
		Reduced motivation	Checklist of Individual Strength (CIS)
		Reduced activity	Checklist of Individual Strength (CIS)
	Burnout	Emotional exhaustion	Utrecht Burnout Scale (UBOS)[4]
		Depersonalization	Utrecht Burnout Scale (UBOS)
		Professional accomplishment	Utrecht Burnout Scale (UBOS)
	Personality	Novelty seeking	Temperament and Character Inventory - short form (TCI-SF)[5]
		Harm avoidance	Temperament and Character Inventory - short form (TCI-SF)
		Reward dependence	Temperament and Character Inventory - short form (TCI-SF)
		Persistence	Temperament and Character Inventory - short form (TCI-SF)
		Self-directedness	Temperament and Character Inventory - short form (TCI-SF)
		Cooperativeness	Temperament and Character Inventory - short form (TCI-SF)

Table S1. (Continued)

Measurement time	Category	Variable	Assessment tool
		Self-transcendence	Temperament and Character Inventory - short form (TCI-SF)
	Trauma exposure	General childhood trauma	Early Trauma Inventory Self Report-Short Form (ETISR-SF)[6]
		Physical childhood abuse	Early Trauma Inventory Self Report-Short Form (ETISR-SF)
		Emotional childhood abuse	Early Trauma Inventory Self Report-Short Form (ETISR-SF)
	Lab markers	Neuropeptide Y	Blood draw
		Arginine vasopressin	Blood draw
		Oxytocin	Blood draw
		Testosterone	Blood draw
		Sex-hormone binding globulin	Blood draw
		Dehydroepiandrosterone	Blood draw
		GABA	Blood draw
		Dexamethasone sensitivity	Blood draw
1 month post-deployment	Mental health symptoms	PTSD	Self-Rating Inventory for PTSD (SRIP)
	Trauma exposure	Deployment stressors	Deployment Experience Scale (DES)[7]
6 months post-deployment	Mental health symptoms	PTSD	Self-Rating Inventory for PTSD (SRIP)
1 year post-deployment	Mental health symptoms	PTSD	Self-Rating Inventory for PTSD (SRIP)
2 years post-deployment	Mental health symptoms	PTSD	Self-Rating Inventory for PTSD (SRIP)
5 years post-deployment	Mental health symptoms	PTSD	Self-Rating Inventory for PTSD (SRIP)
10 years post-deployment	Mental health symptoms	PTSD	Self-Rating Inventory for PTSD (SRIP)

Table S2. Demographics and other characteristics of participants in the PRISMO cohort separated for participants included in the analyses and participants with missing outcome values.

	Participants with outcome values at one or more time points (n=963)*	**Participants without any outcome values (n=44)***	**p-value**
Sex			0.128
Male	878 (91%)	43 (98%)	..
Female	85 (9%)	1 (2%)	
Age (years)			0.091
<21	130 (14%)	9 (23%)	..
≥21	831 (87%)	30 (77%)	
Educational level			0.615
Low	33 (4%)	0 (0%)	..
Moderate	753 (85%)	22 (88%)	..
High	99 (11%)	3 (12%)	
Rank			0.297
Private	378 (40%)	16 (57%)	..
Corporal	199 (21%)	4 (14%)	..
Non-commissioned officer	245 (26%)	6 (21%)	..
Staff officer	130 (14%)	2 (7%)	
Previous deployment(s)			0.053
Yes	417 (48%)	7 (28%)	..
No	460 (53%)	18 (72%)	
Role during deployment			0.501
Inside the military base	244 (31%)	4 (31%)	..
Both inside and outside the military base	73 (9%)	0 (0%)	..
Outside the military base	474 (60%)	9 (69%)	
Deployment year			**<0.0001**
2005 or 2006	237 (25%)	24 (55%)	..
2007 or 2008	726 (75%)	20 (46%)	
New deployment(s)			..
Yes	318 (48%)	..	..
No	344 (52%)	..	
DES (deployment stressors) total score	4.51 (3.22)	4.50 (4.95)	0.996

Note: data are n (%) or mean (SD). Differences in descriptive characteristics between participants with SRIP and participants without SRIP were tested with a t-test (continuous) or $\chi 2$ (categorical). Bold indicates significant relationship ($p<0.05$). SRIP=Self-Rating Inventory for Post-traumatic Stress Disorder. DES=Deployment Experience Scale. ETISR-SF=Early Trauma Inventory Self Report-Short Form. *Sample sizes might not add up to total because of missing data in the descriptive variables.

Table S3. Number of missing responses on the variables included in the analysis (n=963).

Variable	Missing
Age	0 (0.0%)
PTSD symptoms T_0*	283 (29.4%)
PTSD symptoms T_1*	210 (21.8%)
PTSD symptoms T_2*	226 (23.5%)
PTSD symptoms T_3*	401 (41.6%)
PTSD symptoms T_4*	435 (45.2%)
PTSD symptoms T_5*	404 (42.0%)
PTSD symptoms T_6*	365 (37.9%)
Agoraphobia symptoms	147 (15.3%)
Anxiety symptoms	157 (16.3%)
Depression symptoms	153 (15.9%)
Somatization	151 (15.7%)
Hostility	148 (15.4%)
Sleeping problems	138 (14.3%)
Insufficiency of thinking and acting	152 (15.8%)
Distrust and interpersonal sensitivity	159 (16.5%)
Fatigue severity	139 (14.4%)
Concentration problems	134 (13.9%)
Reduced motivation	134 (13.9%)
Reduced activity	140 (14.5%)
Emotional exhaustion	139 (14.4%)
Depersonalization	165 (17.1%)
Professional accomplishment	147 (15.3%)
Novelty seeking	206 (21.4%)
Harm avoidance	204 (21.2%)
Reward dependence	208 (21.6%)
Persistence	202 (21.0%)
Self-directedness	171 (17.8%)
Cooperativeness	196 (20.4%)
Self-transcendence	185 (19.2%)
General childhood trauma	56 (5.8%)
Physical childhood abuse	52 (5.4%)

Table S3. (Continued)

Variable	Missing
Emotional childhood abuse	65 (6.7%)
Deployment stressors	258 (26.8%)
Neuropeptide Y	37 (3.8%)
Vasopressin	195 (20.2%)
Oxytocin	40 (4.2%)
Testosterone	31 (3.2%)
SHBG	31 (3.2%)
DHEA	31 (3.2%)
GABA	37 (3.8%)
DEX-sensitivity	460 (47.8%)

Note: * PTSD symptom scores at T0-T6 were used in the LGMM analysis to compute the outcome variable (membership to any PTSD trajectory). Missing values in PTSD symptom scores were handled by full information maximum likelihood estimation during LGMM. Missing values in all other variables were imputed using random forests imputation.

Table S4. Variables that appeared in the top 5 predictors of any of the models.

Predictor	Number of appearances
Depression	5
Vasopressin	4
Anxiety	3
Distrust and interpersonal sensitivity	2
DEX-sensitivity	2
Age	1
Somatization	1
Insufficiency of thinking and acting	1
Cooperativeness	1
Deployment experience	1
Neuropeptide Y	1
Oxytocin	1
DHEA	1

Table S5. Performances of the final models based on psychological and biological predictors.

	AUC	Sensitivity	Specificity
Psychological			
Dataset 1	0.74 (0.68-0.80)	0.65 (0.56-0.73)	0.70 (0.61-0.77)
Dataset 2	0.69 (0.62-0.76)	0.59 (0.50-0.68)	0.68 (0.59-0.76)
Dataset 3	0.69 (0.62-0.76)	0.64 (0.55-0.72)	0.69 (0.60-0.76)
Dataset 4	0.71 (0.64-0.78)	0.59 (0.49-0.67)	0.63 (0.54-0.71)
Dataset 5	0.73 (0.64-0.80)	0.66 (0.57-0.71)	0.73 (0.64-0.80)
Average	*0.71*	*0.63*	*0.68*
Biological			
Dataset 1	0.57 (0.50-0.64)	0.58 (0.49-0.66)	0.58 (0.49-0.66)
Dataset 2	0.49 (0.42-0.56)	0.52 (0.43-0.61)	0.49 (0.40-0.58)
Dataset 3	0.52 (0.45-0.59)	0.51 (0.42-0.60)	0.50 (0.41-0.59)
Dataset 4	0.51 (0.44-0.58)	0.51 (0.42-0.69)	0.53 (0.44-0.62)
Dataset 5	0.58 (0.51-0.69)	0.54 (0.45-0.63)	0.60 (0.51-0.69)
Average	*0.54*	*0.54*	*0.54*

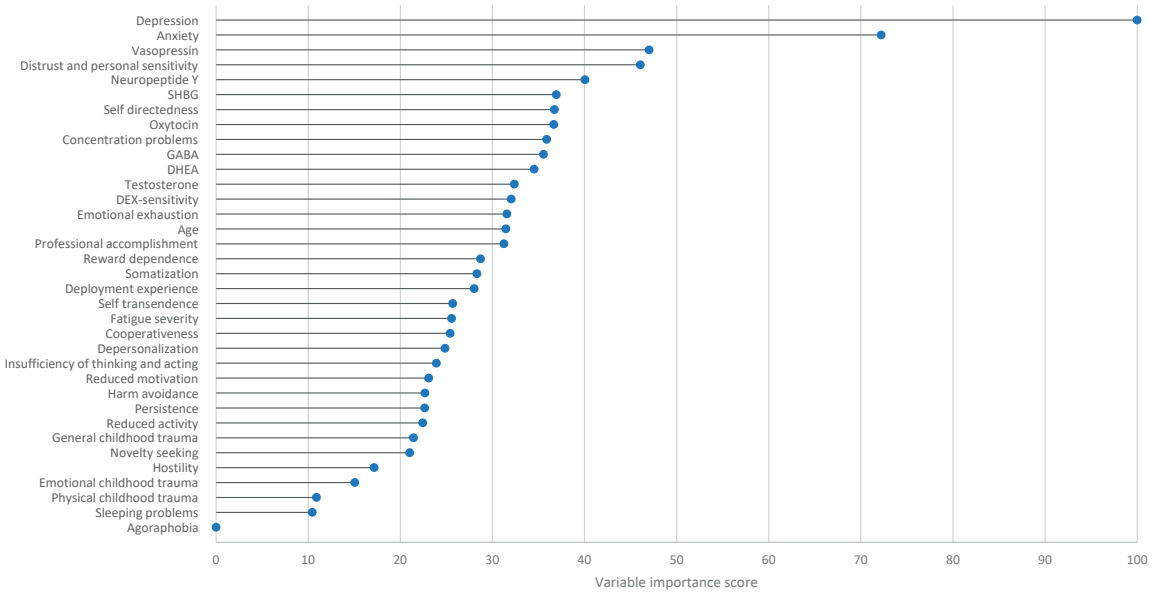

Figure S1. Variable importance scores of all predictor variables for predicting PTSD symptom development in dataset 1. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled to range 0-100.

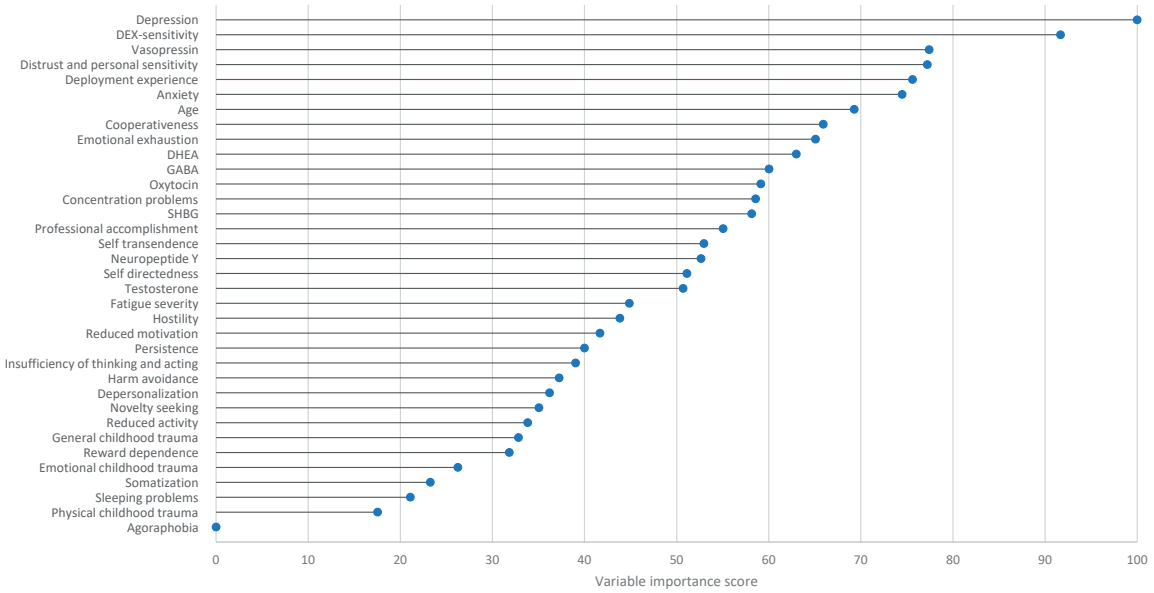

Figure S2. Variable importance scores of all predictor variables for predicting PTSD symptom development in dataset 2. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled to range 0-100.

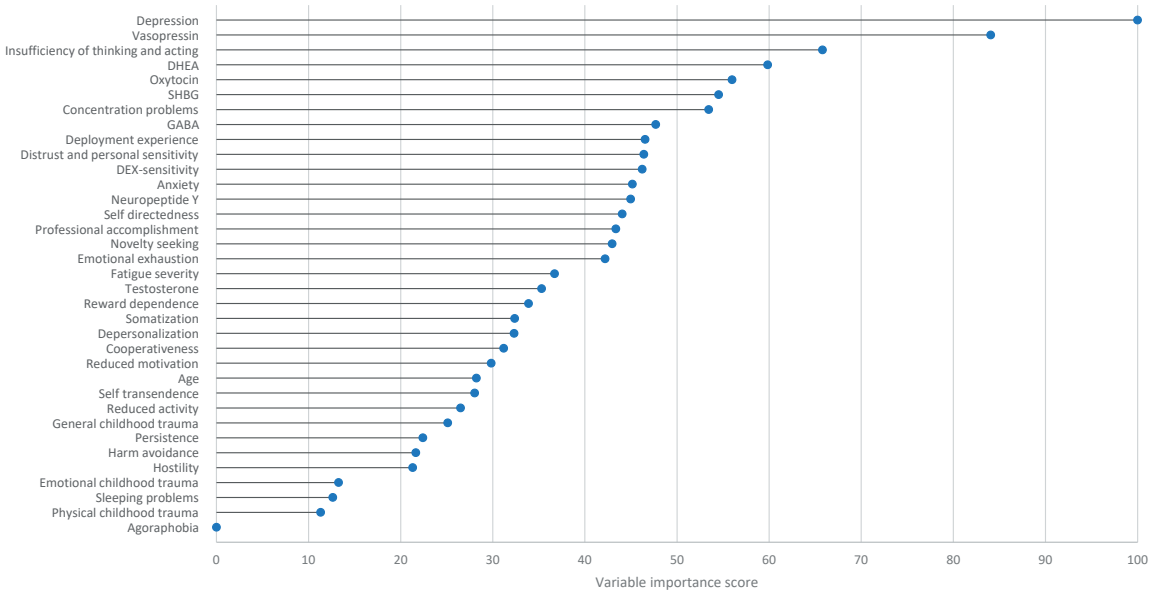

Figure S3. Variable importance scores of all predictor variables for predicting PTSD symptom development in dataset 3. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled to range 0-100.

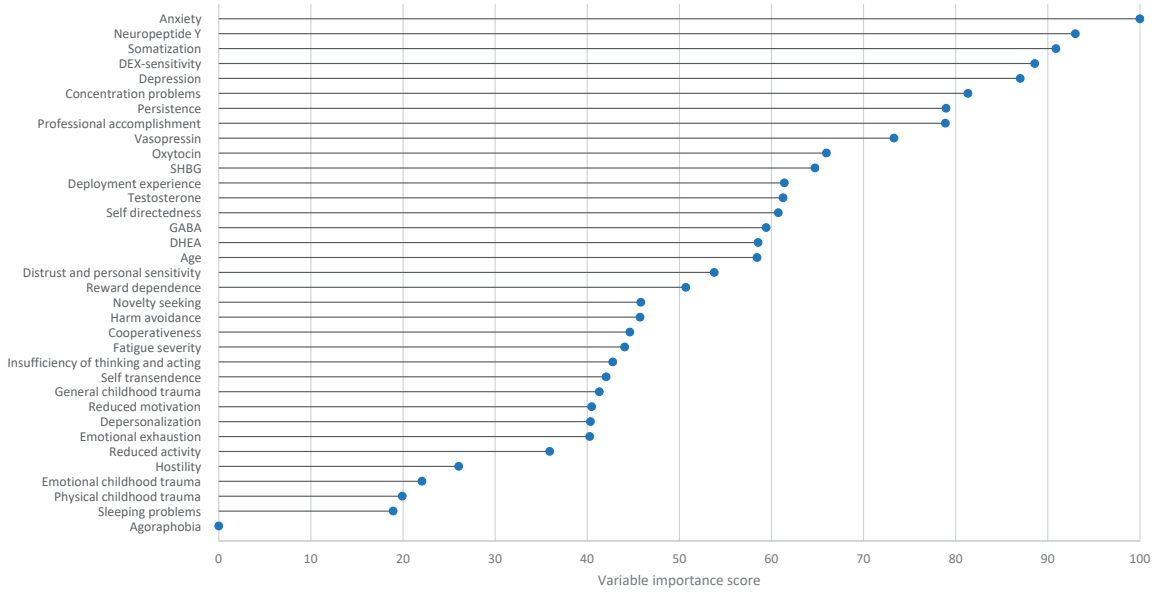

Figure S4. Variable importance scores of all predictor variables for predicting PTSD symptom development in dataset 4. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled to range 0-100.

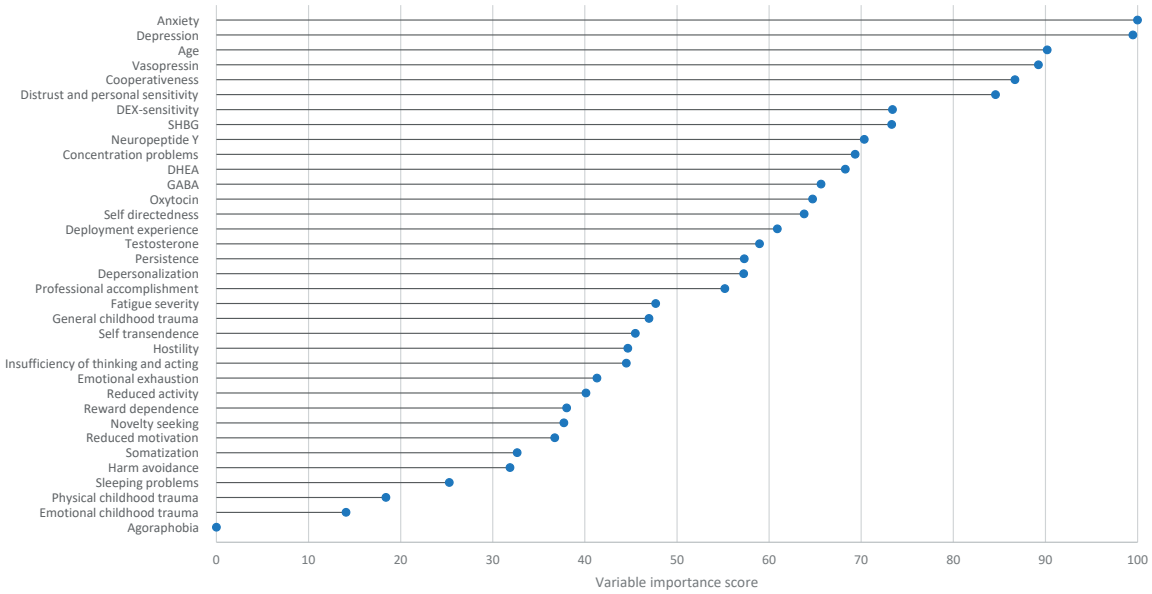

Figure S5. Variable importance scores of all predictor variables for predicting PTSD symptom development in dataset 5. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled to range 0-100.

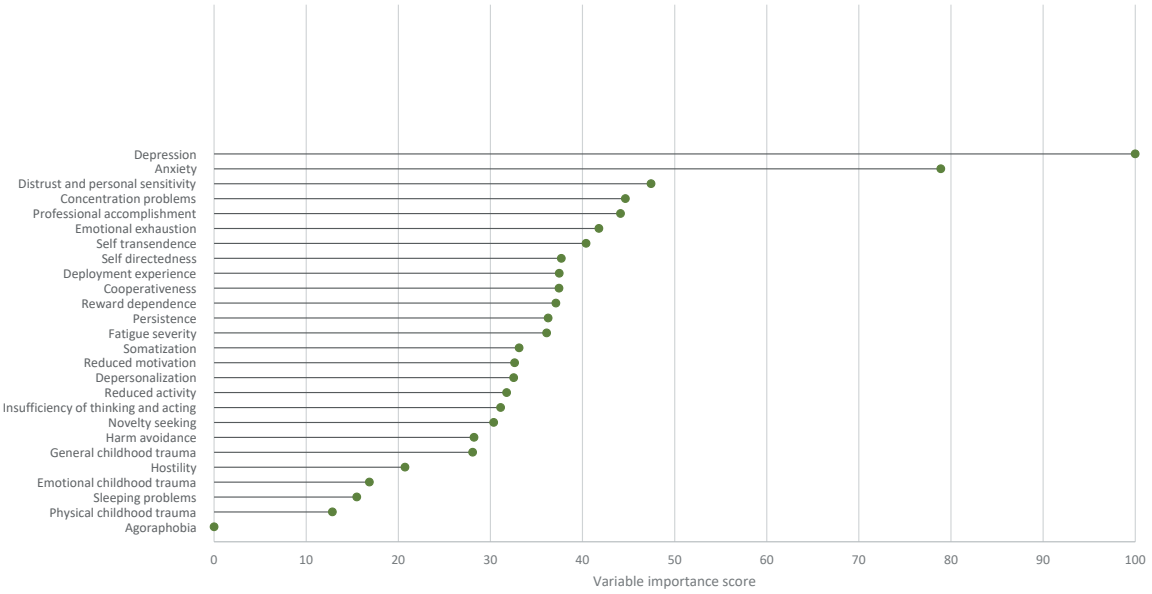

Figure S6. Variable importance scores of predictor variables for predicting PTSD symptom development in dataset 1 with only psychological variables included. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled to range 0-100.

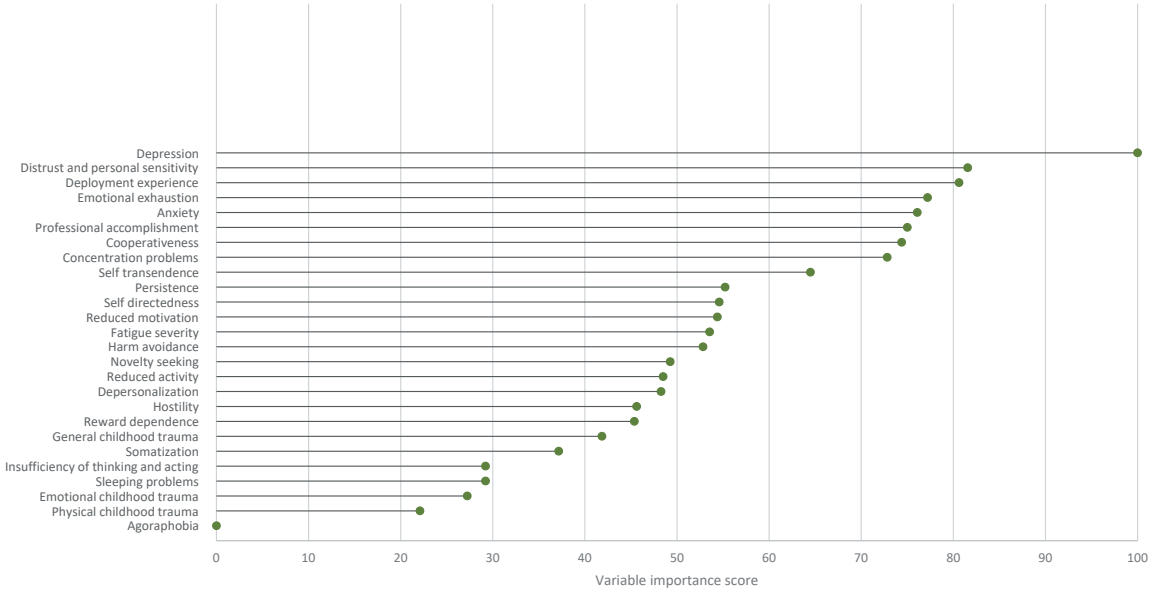

Figure S7. Variable importance scores of predictor variables for predicting PTSD symptom development in dataset 2 with only psychological variables included. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled to range 0-100.

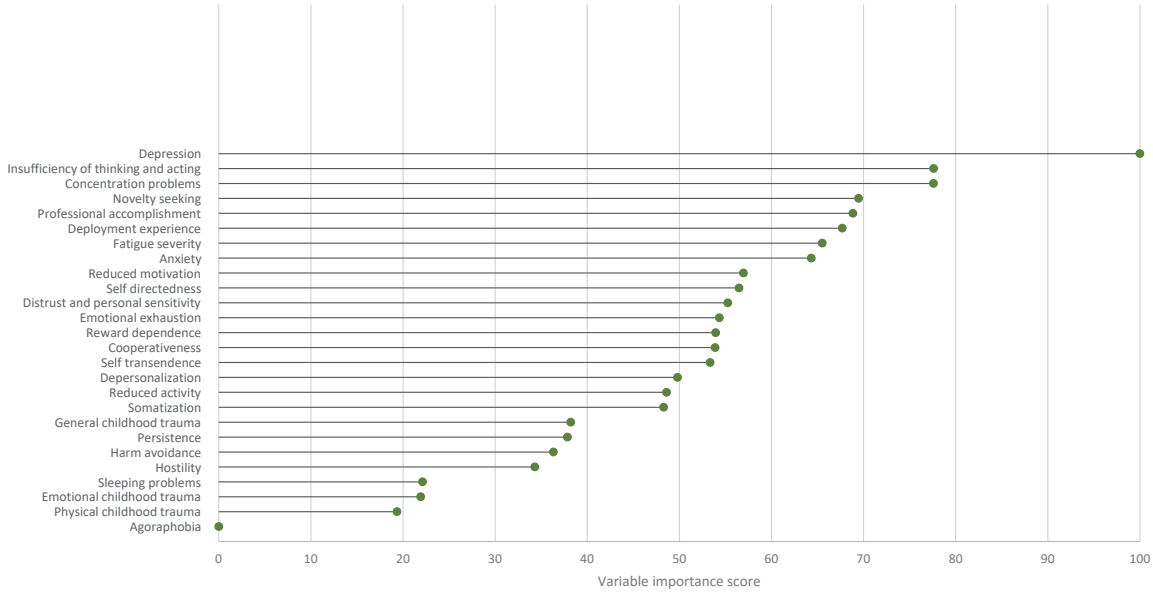

Figure S8. Variable importance scores of predictor variables for predicting PTSD symptom development in dataset 3 with only psychological variables included. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled to range 0-100.

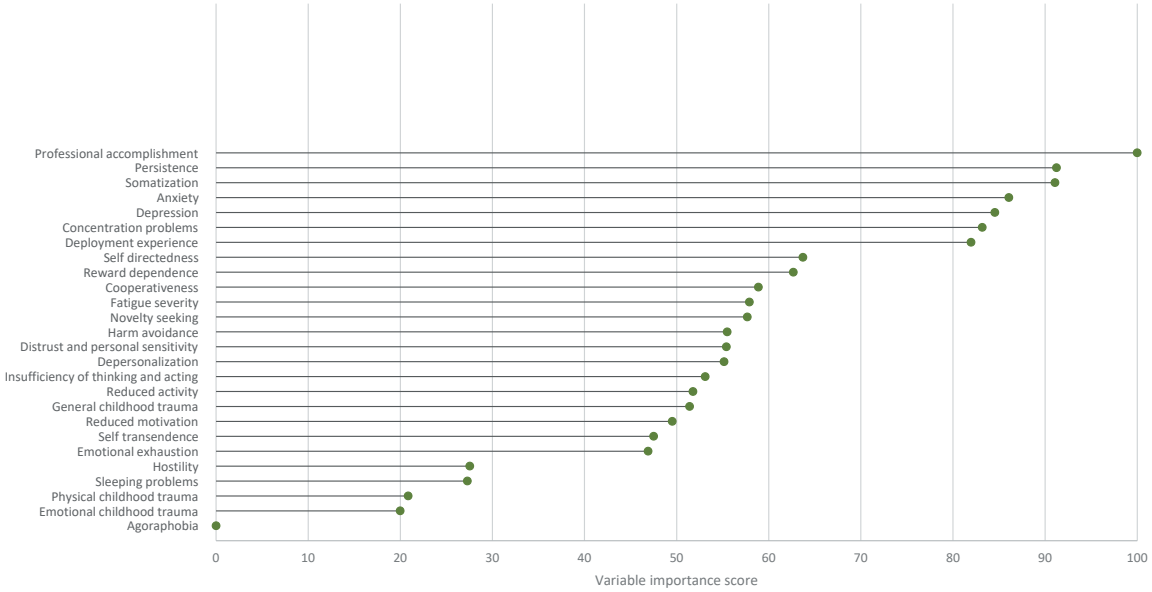

Figure S9. Variable importance scores of predictor variables for predicting PTSD symptom development in dataset 4 with only psychological variables included. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled to range 0-100.

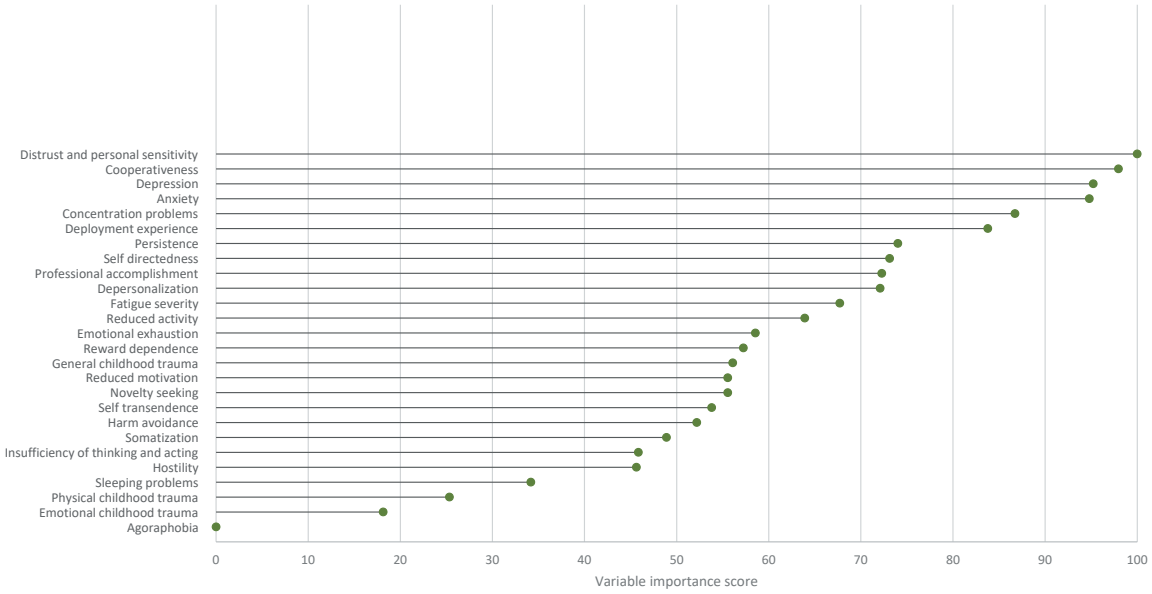

Figure S10 Variable importance scores of predictor variables for predicting PTSD symptom development in dataset 5 with only psychological variables included. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled to range 0-100.

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CHAPTER 7

SUMMARY AND GENERAL INTRODUCTION

"*I have seen things that have changed me forever. I decided that I didn't want to look back. I didn't want to bother my loved ones and I pushed the people away who kept asking questions. I thought, if I work hard enough, I'll forget it.*"[1]. From June till September 2007, veteran Erik worked as a military operating assistant in a NATO hospital in Kandahar, Afghanistan. Six years later, when Erik underwent surgery, it went wrong. *"That was a strong trigger. Suddenly I saw the operating room in Afghanistan"* In the weeks that followed, he got worse. Finally, he called the Veterans Institute. *"Asking for help was the hardest part for me. I had to admit I couldn't do it alone".* Within days, Erik received psychological help and was diagnosed with PTSD[1].

Prevalence and trajectories of post-deployment mental health symptoms

As the story of Erik shows, deployment-related mental health symptoms do not have to manifest immediately after trauma exposure. In the case of Erik, an event six years later reminded him of his time in Afghanistan and mentally returned him to the military hospital in Kandahar, which served as the trigger for the onset of his PTSD symptoms. However, posttraumatic stress can manifest at any time in a person's life. In the PRISMO cohort, a short-term PTSD symptom increase within the first six months after deployment was found. Six months post-deployment, 9% of the cohort indicated a high level of PTSD symptoms (probable PTSD prevalence). Besides this short-term effect, a long-term increase in symptoms five years after deployment was also revealed, with a probable PTSD prevalence of 13%[2]. In the present dissertation, a probable PTSD prevalence of 8% ten years after deployment was found (chapter 3). Although the prevalence of PTSD was still elevated compared to pre-deployment, it was a significant decline compared to five years post-deployment. This indicates that the subsequent increase in PTSD symptoms five years after deployment tapers off in the following years. Of course, this interesting finding is good news. But it also indicates that around 8% of the Dutch veterans who served in Afghanistan still suffer from substantial PTSD symptoms ten years after returning home. And that is a less optimistic message.

The risk of developing PTSD symptoms after homecoming from recent military missions has also been shown in several studies from different coalition partners (for a review, see:[3,4]). Longitudinal studies suggest a trend of stabilizing or aggravating PTSD prevalence rates[5,6]. Altogether, it underlines the importance of long-term monitoring of the mental health of deployed soldiers after a mission ends. Besides prevalence rates of PTSD, chapter 3 also shows the heterogeneity in symptom development among individuals. By using a latent growth mixture modeling technique, we identified four different trajectories of PTSD symptom development over the ten years after deployment: resilient (85%), improved (6%), severely elevated-recovering (2%), and delayed onset (7%). Although the majority of comparable studies had shorter follow-up

periods, the number and shape of these trajectories are very similar across studies[7-9], resulting in a solid scientific basis for the description of different trajectories of PTSD symptom development after deployment.

As the focus is often on veterans who struggle with post-deployment problems, it is worth highlighting that the large majority of deployed personnel, approximately 85% in the case of Dutch ISAF veterans, did not develop any PTSD symptoms in the ten years after deployment. Thus most service members deployed to war zones show enduring resilience despite exposure to traumatic stressors. Apart from individual risk- and protective factors, extensive military training and psychological preparation to handle all kinds of stressful situations that might be encountered during deployment will probably have contributed to the high degree of resiliency in Dutch military service members. Nevertheless, a considerable group (15%) did show symptomatic trajectories after homecoming. The individuals in the improved trajectory showed high symptoms pre-deployment and shortly after deployment, but gradual recovery after six months post-deployment. The individuals in the severely elevated-recovering trajectory had heavily increasing symptoms that showed recovery after five years post-deployment. Fortunately, the veterans in these trajectories show recovery after a period with moderate to severe PTSD symptoms. This does not apply to all veterans that showed PTSD symptoms. 7% of the veterans in our sample showed a delayed trajectory of increasing symptoms that reached the cut-off for PTSD between two and five years. Between five and ten years post-deployment, their symptoms were still increasing, although 77% of this group received some form of psychological care in the years after deployment. A decade after their deployments, we should especially be aware of this group of veterans.

Although other mental health symptoms beyond PTSD are more difficult to link to deployment directly, they can control the lives of veterans just as much and should therefore not be overlooked. In the present dissertation, we found that the probable prevalence of agoraphobia, anxiety, depression, and hostility symptoms significantly increased over time to respectively 7%, 3%, 4%, and 6% at ten years after deployment (chapter 4). Except for hostility symptoms, the probable prevalence at ten years after deployment was the highest compared to all previous follow-up measurements (although no probable prevalence is available at five years post-deployment). Up to two years post-deployment, the probable prevalence rates were quite low. Especially the increase in agoraphobia symptoms, from 3% at two years post-deployment to 7% at ten years post-deployment, is notable and a potential cause for concern. Based on large studies on aging and mental health symptoms in the general population[10,11], it can be suggested that the increase in mental health symptoms is related to deployment rather

than a result of the aging of the population. Therefore, these types of mental health symptoms may take longer to develop than PTSD symptoms within the aftermath of a significant stressful period such as a deployment. It is important to note that, despite this stressful period in their lives, as a group Dutch ISAF veterans still experience better mental health in terms of depression and anxiety compared to the general population. This seems plausible because we are dealing with a psychological healthy population pre-deployment that is psychologically tested before joining the army and extensively trained for military operations.

Risk factors for post-deployment mental health symptoms

Beyond the traumatic experience itself, individual vulnerability factors can contribute to developing mental health symptoms and developmental trajectories. Although military personnel are often seen by society as a very homogenous group of individuals that differ as a group from the general population, there is a lot of variation between service members in their childhood experiences, personality, military experience and social environment. Assessing which factors are related to increases in PTSD symptoms levels after deployment can help to identify who is most at risk. In chapter 3, we found that previously identified risk factors like younger age, lower rank, more deployment stressors, and less social support[2,6,12] were still relevant risk factors for the development of PTSD symptoms ten years after deployment. For the other mental health symptoms, we identified perceived social support from family and friends after returning home from deployment as the most important risk factor (chapter 4). Surprisingly, unit cohesion was not associated with any of the assessed mental health symptoms. Given that social support is potentially modifiable by providing intervention programs for military personnel and their family and friends, a wide range of mental health outcomes over a long period of time could be targeted in this way.

As targeted early interventions might especially be beneficial for veterans in the delayed onset PTSD trajectory to prevent worsening of their symptoms later in life, assessing risk factors for this trajectory might help identify these veterans when symptoms are still subclinical. We found that veterans in the delayed onset trajectory experienced a higher threat level during deployment and perceived less social support after returning home compared to veterans in the resilient group, but these risk factors also applied for the other symptomatic trajectories (chapter 3). Assessing differences in variables between individuals in the delayed onset group and individuals in the severely elevated-recovering trajectory would be highly informative to clarify why veterans in the latter trajectory were able to show a striking decline in PTSD symptoms between five and ten years after deployment as opposed to veterans in the delayed onset trajectory. However, no differences in the included variables were found. As a next step it would

be imperative to compare treatment history between these groups. In addition, recently identified biological mechanisms in the development and treatment of PTSD could be of considerable interest and may offer new perspectives.

One of these biological mechanisms of interest is DNA methylation. As epigenetic modification like DNA methylation reflects the complex interplay between environment and genes, it could be an underlying mechanism in the pathway from trauma to the development of mental health symptoms. In chapter 5, we studied longitudinal changes of DNA methylation profiles from pre-deployment to six months after deployment in relation to the development of PTSD symptoms up to five years after deployment. In line with previous research (for a review, see:[13,14]) we found evidence for associations between methylation changes and PTSD in our cohort. We identified four genetic regions with methylation changes over time that were significant determinants of the longitudinal development of PTSD symptoms. In addition, we also found initial evidence that post-deployment decreases in methylation at a genomic region in *EP300/miRNA1281* were also associated with the delayed onset trajectory compared to the resilient trajectory. This shows the potential of epigenetic marks to contribute to the successful identification of veterans with increased risk for developing delayed onset of PTSD in an early stadium where symptoms are still subclinical or even minimally present.

Predicting PTSD development

The identification of risk factors for PTSD, as also described in this dissertation, has not yet led to the development of effective pre-deployment screening tools or resilience-building initiatives[15]. It is common practice to study risk factors for PTSD by using traditional statistical methods. However, these methods are not able to capture non-linear and multidimensional relationships between predictors and the outcome of interest. Therefore, machine learning methods such as random forest modeling are increasingly implemented in psychiatric conditions to develop prognostic models[16]. In chapter 6, we trained a random forest model on pre-deployment variables, psychological as well as biological variables, to predict the development of PTSD symptoms up to ten years after deployment. The model performed well above chance (AUC = 0.71), and among the top five highest-ranked predicted features were self-reported symptoms (depression, anxiety and distrust and personal sensitivity) and biological markers (vasopressin and DEX-sensitivity). Some of the biological factors did not show significant associations with PTSD symptom development in the PRISMO cohort in previous studies that used linear mixed modeling, but were found to be important contributing variables in the present prediction modeling. This highlights the differences between machine learning and traditional statistical methods. As the

model performance on the current dataset was modest, the usability of the model as a ready-to-use pre-deployment screening tool is limited. However, the model offers important leads for the identification of risk factors for PTSD now that those factors have been analysed in conjunction, because as we know, factors never operate in isolation in something as complex as the development of a mental health disorder.

A perspective on delayed onset PTSD

When we speak about the impact of deployment on the mental health of service members, we usually do not look far ahead. We think about the problems that a veteran has to adapt to everyday life again, or about the prevalence rates of PTSD in the first few years after deployment. With this dissertation, I hope that I have convinced the reader to look beyond those first few years by showing the long-term impact that deployment can have on our service members. This long-term impact is represented by the identified group of approximately 7% of the Dutch ISAF veterans with a delayed onset PTSD. Ten years after their deployment, these veterans still suffer from increasing symptom levels. Health care professionals should be aware of this group of veterans with increasing treatment demands up to at least ten years after deployment, despite an average decline in symptoms in the population as a whole. However, the awareness of this group and its growing treatment needs alone does not seem to be enough. We know that even though the majority of this group seeks help, they do not seem to benefit from it. What are their perspectives in the current healthcare system? What needs to be changed to help them?

One theory for this group of veterans with a delayed onset of PTSD symptoms is that they might be a subpopulation of PTSD patients: a subpopulation with possibly different psychological and (neuro)biological underpinnings. Suggestions for distinct subtypes of PTSD have already been made on internalizing and externalization symptoms[17] and for a dissociative subtype[18,19]. Interestingly, the dissociative subtype which additionally suffered from depersonalization and derealization symptoms, was also distinguished by a delayed onset of symptoms. To date, only a few studies succeeded in characterizing PTSD subtypes in terms of biological correlates[20]. For example, the dissociative subtype was found to be related to altered subcortical white matter connectivity[21] and altered resting-state functional connectivity of the amygdala[22].

Biological and psychological correlates for delayed onset PTSD could be studied in a machine learning approach such as described in chapter 6, by comparing veterans with a delayed onset of PTSD symptoms to veterans with an early-onset of symptoms. The utilization of a machine learning approach for identifying military-related PTSD subtypes and their correlates has already been successfully demonstrated by Siegel and

colleagues[20]. In this study, two symptom severity PTSD subtypes were identified that could be distinguished by methylation, micro RNA and lactate markers[20]. Unfortunately, the sample sizes in the present study were too small to be able to make a comparison between a short-term and delayed onset of PTSD on the included risk factors. For future research, making this comparison could be an interesting starting point, as variation in psychological and (neuro)biological underpinnings may be a reason why veterans with a delayed onset of PTSD symptoms do not seem to respond adequately to available treatments[23].

Because we do not have a clear insight into the treatment history of veterans in the PRISMO study, it should first be sorted out whether treatment type and timing differ between veterans who show recovery between five and ten years after deployment (severely elevated-recovering) and veterans who do not show recovery in this period (delayed onset). There are several novel and interesting new perspectives on the treatment resistance of PTSD that are well worth exploring. In chapter 5, we demonstrated that changes in the DNA methylome were associated with the development of PTSD symptoms. However, there is also evidence that successful trauma-focused psychotherapy for PTSD restores these epigenetic marks[24]. Therefore it might be of interest to map and compare these methylation changes in veterans in a delayed onset trajectory and veterans in a severely elevated-recovering trajectory.

Another interesting perspective is that veterans with a delayed onset PTSD might suffer from another type of trauma. They might be exposed to traumatic events that violated their moral values, and therefore experience distress and functional impairments or 'moral injuries'[25,26]. Although it is still under debate whether veterans with underlying moral injury might or might not respond to evidence-based treatments for PTSD[26], novel treatment models that directly address moral injuries and their recovery might be more beneficial for veterans with a delayed onset of PTSD symptoms compared to the predominantly cognitive-behavioral based 'treatment-as-usual'. Another promising new approach that might demonstrate better efficiency in this group of veterans with suspected treatment resistance is using psychedelic drugs as adjuncts to facilitate psychotherapeutic treatments[27,28]. The treatment of sustained PTSD symptom severity might benefit from improvements in the capacity to engage with traumatic experiences in therapy induced by psychoactive substances[27,29]. This engagement in the processing of traumatic memories, for example in exposure-based therapies, might be particularly difficult for veterans with guilt and shame associated with the trauma. Integrating psychoactive substances within the psychotherapeutic treatment that specifically targets acts of commission, omission or betrayal[30] may address these challenges, and

could therefore catalyze the psychotherapeutic process and lead to better treatment outcomes in these veterans[27,31].

In addition to the hypothesis of possibly different psychological and biological underpinnings of their unresolved symptoms and the outlook for new treatment strategies for veterans in the delayed onset group, continued effort should be put into the identification and assessment of current PTSD symptoms in the veteran population. 23% of the veterans in the delayed onset group did not receive any psychological help in the ten years after deployment, although they experienced substantial levels of PTSD symptoms. In the face of the current monitoring policies that usually include routine screenings that stop after one or two years, there is still a lot to gain with more targeted and prolonged monitoring approaches.

Ethical considerations of prediction models

In the second part of this dissertation, I focused on the risk factors for post-deployment mental health symptoms and the development of a prediction model for long-term PTSD symptoms. The ultimate goal for this type of research is to develop a screening tool that can be used pre-deployment to get an accurate estimate of the PTSD risk for each service member that is listed to be deployed. For this purpose, service members will need to fill out specific questionnaires, blood would be taken, and a few neurocognitive tests would be taken. A trained algorithm would then evaluate this information, and after a few seconds, the commander in charge would know whether this service member will be deployed. This sounds like the newest episode of the Netflix-series *Black Mirror*, a scenario we don't see as realistic. Although there are a lot of remaining obstacles in the development of such a screening tool and error-free prediction will never be achieved, it is something we are working on in the research field. Of course, the goal of screening approaches to prevent PTSD development is noble and there are apparent positive consequences no one will debate. However, there are ethical implications of the pre-deployment identification of individuals that are at risk for developing PTSD after homecoming that should be discussed.

First, there is a risk of oversimplistic understanding and applications of predictive models for post-deployment PTSD symptoms[32,33]. As described in the fictional example above, it will be straightforward for the commander in charge to overvalue the model's classification output (PTSD: yes/no) by not taking the false positive and false negative rates into account. Algorithms for predictive models should therefore always be accompanied by clear information and education. But can we expect a user to fully understand a predictive model based on machine learning and to make an adequate assessment of the meaning and value of its outcomes? Especially in an

environment where so many interests play a role. And if we assume that the user is able to understand the model and its outcomes, how much should the presence of an increased risk for PTSD influence decisions about who can go to war or even who can stay in military service[32]? Will they simply exclude all candidates that screen positive? And how ethical is it if this decision is influenced by external factors like staff shortages? Are model outcomes suddenly assessed differently? Although prediction models for PTSD may protect some service members and their families from the psychological costs of mental health problems and the Ministry of Defence from long-term financial costs associated with mental health care and compensation claims, screening may lead to individual restrictions on someone's opportunity to be deployed based on an outcome that may not occur[32]. It therefore raises concerns of discrimination. Besides that, mandatory screening also raises questions about the confidentiality of highly privacy-sensitive data[34]. Are you obliged to provide this information to your employer? And if you do so, which persons within the military organization have access to your data?

If we take the perspective of the screened service member: what does it mean for an individual to know that you are at increased risk for developing PTSD after your deployment? First, it is almost impossible for a layperson to understand what the outcome of a classification model means. If you are not able to properly estimate the size of the risk, how can you then make the decision whether you should go on deployment or not? In addition, the knowledge that you are more vulnerable to develop mental health symptoms can negatively affect self-esteem and the relationships within a unit. One can imagine that it raises concerns in individuals about how they are perceived by their colleagues and commanders, or how it affects their military career. Merely the realisation that you are at increased risk could already lead to psychological problems. Furthermore, excluding service members with an increased risk for PTSD, whether it is on their own initiative or on the initiative of the organization, increases homogeneity within units and might even weaken them. For example, the identified risk factor 'distrust' that was incorporated in our predictive model, could also make an individual more alert to signs of danger and might thereby increase the safety of the unit in a warzone.

All these open questions and ethical concerns indicate that, as the development of predictive models for PTSD continues, a parallel and ongoing discussion on the moral implications is highly needed. Also, we should think about whether we want to invest in pre-deployment screening approaches or in the psychological support afterwards. A systematic review on pre-deployment psychological screening for disaster relief workers showed that, despite the attractiveness of screening for pre-deployment

indicators of resilience, the evidence base is very weak and does not support the use of pre-deployment screening as a method to protect the psychological health of disaster workers[35]. Of course, prediction models for PTSD are far from fully developed, and the inclusion of biological and neurocognitive measures can make a significant contribution to the predictive value of the models. But it is not inconceivable that these models will never be successful in preventing mental health problems. Investing in psychological support after homecoming from deployment, including appreciation and recognition which the Ministry of Defence is already strongly committed to, remains very important and worthwhile to keep improving.

Limitations

Although the PRISMO cohort enabled the differentiation of a range of vulnerability factors for the onset and long-term course of stress-related mental health problems in deployed military personnel and thereby makes an important contribution to the literature, the findings in the present dissertation should be interpreted in the context of its limitations. One of the most important limitations is the lack of a non-deployed military control group. For example, we are not able to compare the prevalence rates of mental health symptoms in our deployed cohort to the prevalence rates in a non-deployed control group. Therefore, it is not known whether the reported increase in symptom levels is exclusively the result of deployment. Furthermore, as frequently discussed in the previous chapters, we used self-report assessments of mental health symptoms which makes the results subject to the biases associated with the use of self-reports. Also, attrition is a significant concern and influence of non-response on the study results cannot be ruled out. However, we tried to minimize this effect by taking into account missing values in our analyses.

In the light of gender disparity in our scientific and medical knowledge base[36], there is a large underrepresentation of women in the PRISMO cohort. And although this is representative for the military, it is of high importance to study whether women respond differently to combat exposure. Also, deployment experiences may differ between men and women, as well as post-deployment factors like perception of family support or stigmatization. Due to the low percentage of women in the PRISMO cohort, we were not able to make comparisons between male and female veterans. Fortunately, research initiatives are emerging that specifically study the impact of deployment in military women (e.g.[37-39]). A final important limitation of the present dissertation is its focus on the individual. In the previous chapters we studied a range of risk factors for the development of mental health symptoms, but almost all of these factors relate to the individual. One important exception to this is social support. We identified decreased social support from family and friends after returning home from

deployment as one of the most important risk factors for developing mental health symptoms. It would therefore be of great interest for future research to elucidate the role of the partner, family and the military environment in the support system of veterans, and to investigate their influence on (preventing) development of mental health problems after homecoming.

CONCLUDING REMARK

This dissertation falls within a large body of data and literature on the development of mental health problems after deployment. However, it is unique in the fact that it provides evidence for, and a description of, the long-term impact of deployment on service members up to ten years after deployment, with the ability to make comparisons to pre-deployment psychological health. With the ten-year measurement that formed the solid basis of this dissertation, the regular scheduled follow-up of the PRISMO cohort has come to an end. This does not mean that his cohort will not face difficulties in the future. Although it was not studied in the present dissertation, events later in life may serve as a trigger for the onset or worsening of mental health symptoms. Unfortunately, this concept has now painfully been tested by the recent events in Afghanistan. On August 15, 2021, the Taliban reached Kabul and the government crumbled. Afghanistan fell once again into the hands of the Taliban. As they watch the casualties inflicted on civilians, many Afghanistan veterans are feeling devastation and anger: *"It touches you because you've been there. You tried to change something. It looks like it didn't work out"*[40]. Significant events like the fall of Afghanistan bring back memories in many veterans that weren't present for a long time. As positive appraisals of service, or meaningful military engagement, might function as an aspect of psychological resilience[41], this event poses another substantial risk for the mental health of ISAF veterans. It teaches us that we must continue to commit ourselves to the psychological wellbeing of our veterans, even years after a mission's end. I hope this dissertation has contributed to that.

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APPENDICES

NEDERLANDSE SAMENVATTING

LIST OF PUBLICATIONS

CURRICULUM VITAE

DANKWOORD

NEDERLANDSE SAMENVATTING

De prevalentie en ontwikkeling van psychische klachten na uitzending

Met dit proefschrift heb ik een wetenschappelijke onderbouwing geprobeerd te geven voor het beeld dat al naar voren is gekomen uit de persoonlijke verhalen van duizenden veteranen: militair trauma kan een psychologisch litteken veroorzaken dat zich pas jaren na de feitelijke traumablootstelling manifesteert en het dagelijks leven nog veel langer kan beïnvloeden. Alle resultaten die in dit proefschrift besproken worden zijn afkomstig uit het PRISMO-onderzoek. Het PRISMO-onderzoek is een grote prospectieve cohortstudie onder zo'n duizend Nederlandse ISAF-veteranen. Zowel een maand voor hun uitzending naar Afghanistan als in de tien jaar na thuiskomst hebben deze militairen deelgenomen aan verschillende meetmomenten. Tijdens deze meetmomenten hebben de deelnemers onder andere vragenlijsten ingevuld en bloedsamples afgestaan. Het doel van het PRISMO-onderzoek was tweeledig. Ten eerste was het onderzoek bedoeld om epidemiologisch bewijs te verzamelen om meer inzicht te krijgen in de langetermijngevolgen van militaire inzet voor de geestelijke gezondheid van uitgezonden militairen. Daarnaast was het onderzoek erop gericht om de rol van verschillende biologische en psychologische factoren in kaart te brengen die kunnen bijdragen aan de ontwikkeling van stress-gerelateerde psychische klachten. De combinatie van langlopend onderzoek en het meenemen van zowel biologische als psychologische variabelen maakt de PRISMO-studie tot een uniek onderzoek in het veld.

In het PRISMO-onderzoek vonden we al eerder een korte-termijn toename van posttraumatische stress stoornis (PTSS) symptomen waarbij 9% van het cohort ISAF-veteranen een hoog niveau van PTSS-symptomen ervaart op zes maanden na uitzending. Ook vonden we een lange-termijn toename op vijf jaar na uitzending, waarbij 13% van de veteranen een hoog niveau van PTSS-symptomen ervaart. Uit dit proefschrift blijkt dat op tien jaar na uitzending nog steeds zo'n 8% van de Nederlandse ISAF-veteranen kampt met ernstige PTSS-klachten (hoofdstuk 3). Dit is een daling ten opzichte van de prevalentie op vijf jaar na uitzending. Deze bevinding is natuurlijk goed nieuws. Het geeft echter ook aan dat ongeveer 8% van de Nederlandse Afghanistan-veteranen na tien jaar nog steeds lijdt aan substantiële PTSS-klachten, wat een minder optimistische boodschap is.

Dit proefschrift laat ook zien dat er tussen veteranen veel verschil bestaat in de ontwikkeling en het beloop (traject) van PTSS-symptomen (hoofdstuk 3). Ongeveer 85% van de PRISMO-deelnemers ontwikkelt geen PTSS-symptomen in de tien jaar na uitzending ('weerbaar' traject). De meeste veteranen laten dus een blijvende

weerbaarheid zien ondanks blootstelling aan potentieel traumatische stressoren tijdens uitzending. Een aanzienlijke groep van zo'n 15% van de PRISMO-deelnemers ontwikkelt op enig moment substantiële PTSS-symptomen in de jaren na uitzending, en maakt dus een symptomatisch traject door. Zo is er een groep veteranen die zowel voor uitzending als kort na uitzending een hoog aantal PTSS-symptomen ervaart, maar waarbij deze klachten over de tijd verminderen ('verbeterend' traject). Een andere groep veteranen rapporteert na uitzending een zeer sterke stijging in PTSS-symptomen, waarbij deze symptomen na vijf jaar weer sterk afnemen ('sterk verhoogd-herstellend' traject). De veteranen in deze trajecten laten herstel zien na een periode met middelhoge tot ernstige PTSS-klachten. Dit geldt niet voor alle veteranen met PTSS-symptomen. 7% van de veteranen in ons cohort laat een traject zien waarbij PTSS-symptomen langzaamaan steeds verder toenemen en tussen twee en vijf jaar het gestelde afkappunt bereiken voor een hoog aantal klachten ('vertraagd' traject). Ook na vijf jaar laat deze groep geen herstel zien in hun symptomen, hoewel 77% van deze veteranen enige vorm van psychologische hulp heeft ontvangen in de jaren na uitzending. Deze groep veteranen verdient onze aandacht. Aandacht alleen is echter niet voldoende. We moeten ons afvragen wat de perspectieven zijn voor deze veteranen in ons huidige zorgsysteem, en wat er zou moeten veranderen om hen verder te kunnen helpen.

Naast PTSS-symptomen rapporteren veteranen in het PRISMO-cohort ook een verhoging van andere psychische klachten ten opzichte van voor hun uitzending (hoofdstuk 4). Zo kampt 7% van de veteranen met substantiële agorafobie symptomen (pleinvrees), 3% met angstsymptomen, 4% met depressieve symptomen en 6% met hostiliteit (agressie). Met uitzondering van hostiliteit is de prevalentie van deze typen psychische klachten op tien jaar na uitzending het hoogst van alle meetmomenten. Hierbij is het belangrijk om te vermelden dat er geen prevalentiecijfers van deze psychische klachten beschikbaar zijn op vijf jaar na uitzending. Tot twee jaar na uitzending was de prevalentie van agorafobie symptomen, angstsymptomen en depressieve symptomen relatief laag. Vooral de toename van agorafobie symptomen van 3% op twee jaar na uitzending tot 7% op tien jaar na uitzending is opvallend en een mogelijke reden tot zorg. Op basis van omvangrijke studies over veroudering en psychische klachten in de algemene populatie kan gesuggereerd worden dat de toename van psychische klachten in het PRISMO-cohort eerder gerelateerd is aan de uitzending dan dat het simpelweg een resultaat is van het ouder worden. Het lijkt er daarom op dat agorafobie symptomen, angstsymptomen en depressieve symptomen langer nodig hebben om zich te uiten als gevolg van een uitzending dan PTSS-klachten. Het is echter belangrijk om te benadrukken dat ondanks deze stressvolle periode in hun leven, Nederlandse ISAF-veteranen als een groep in vergelijking met de algemene populatie nog steeds een betere mentale gezondheid heeft wat betreft depressie

en angst. Dit lijkt plausibel als we ons realiseren dat we te maken hebben met een psychologische gezonde populatie voorafgaand aan uitzending. Daarnaast zijn deze militairen psychologisch getest voor zij in dienst kwamen en uitgebreid getraind om te kunnen omgaan met stressvolle militaire uitdagingen.

Risicofactoren voor psychische klachten na uitzending

Naast de traumatische ervaring zelf kunnen ook individuele kwetsbaarheidsfactoren (risicofactoren) bijdragen aan de ontwikkeling van psychische klachten. Hoewel militairen door de samenleving vaak worden gezien als een homogene groep individuen, is er veel variatie tussen militairen in hun jeugdervaringen, persoonlijkheid, militaire ervaring en sociale omgeving. Uit dit proefschrift wordt duidelijk dat eerder geïdentificeerde risicofactoren zoals een jongere leeftijd, lagere rang, meer stressoren tijdens uitzending en minder sociale steun na uitzending nog steeds relevante risicofactoren zijn voor het ervaren van PTSS-symptomen op tien jaar na uitzending (hoofdstuk 3). Voor de andere typen psychische klachten identificeerden we ervaren sociale steun van familie en vrienden na thuiskomst als de belangrijkste risicofactor (hoofdstuk 4). Verrassend genoeg was sociale steun vanuit de eenheid tijdens uitzending in onze studie niet gerelateerd aan de ontwikkeling van psychische klachten na uitzending. Omdat sociale steun mogelijk versterkt kan worden door het aanbieden van interventieprogramma's voor militair personeel en hun familie en vrienden, zou de ontwikkeling van een breed spectrum aan psychische klachten op deze manier voorkomen of verminderd kunnen worden.

Vroeg ingezette interventieprogramma's zouden in het bijzonder effectief kunnen zijn voor veteranen in het 'vertraagde' traject om te voorkomen dat sluimerende PTSS-klachten later in het leven verergeren. Het bestuderen van specifieke risicofactoren voor dit traject kan helpen om kort na uitzending veteranen te identificeren die op dat moment nog weinig tot geen PTSS-symptomen ervaren, maar wel een verhoogde kans hebben om deze later te ontwikkelen. Uit de PRISMO-studie blijkt dat veteranen in dit traject meer stressvolle gebeurtenissen hebben meegemaakt tijdens uitzending en minder sociale steun hebben ontvangen na uitzending in vergelijking tot veteranen die geen PTSS-symptomen hebben ontwikkeld (hoofdstuk 3). Deze risicofactoren zijn echter ook van toepassing op de andere symptomatische trajecten, waardoor er in dit proefschrift nog geen duidelijk onderscheid gemaakt kan worden in de risicofactoren voor deze verschillende PTSS-trajecten. De identificatie van verschillen in variabelen tussen veteranen die wel en veteranen die geen herstel van ernstige PTSS-symptomen laten zien tussen vijf en tien jaar na uitzending, zou ook meer inzicht kunnen geven in de vraag waarom sommige veteranen in staat zijn om zo'n sterke afname in hun PTSS-symptomen te laten zien. Onder andere gedetailleerde behandelingsgeschiedenis en

informatie over biologische mechanismen in de ontwikkeling en behandeling van PTSS kunnen hierbij nieuwe inzichten bieden.

Eén van de biologische mechanismen die in dit proefschrift onderzocht is en van belang zou kunnen zijn voor de ontwikkeling van PTSS-symptomen is DNA-methylering (hoofdstuk 5). DNA-methylering is het proces waarbij een methylgroep aan een DNA-molecuul wordt toegevoegd. Hierdoor verandert de structuur van het DNA, waardoor het DNA anders afgelezen wordt en processen in een cel aangepast kunnen worden. In het PRISMO-cohort hebben we vier genetische regio's kunnen identificeren waarbij veranderingen in de methylering van voor uitzending tot zes maanden na uitzending geassocieerd zijn met de ontwikkeling van PTSS-symptomen in deze periode. Ook vonden we een eerste aanwijzing dat afname in DNA-methylering in de maanden na uitzending in de genetische regio *EP300/miRNA1281* geassocieerd is met het 'vertraagde' PTSS-traject ten opzichte van het 'weerbare' traject. Deze veranderingen in methylering vinden dus plaats in het stadium waarin de veteranen in dit traject geen of subklinische PTSS-symptomen ervaren. Deze bevinding demonstreert het potentieel van methylering-veranderingen voor het in een vroeg stadium identificeren van veteranen die een verhoogd risico hebben op het ontwikkelen van PTSS later in hun leven.

Het voorspellen van PTSS-ontwikkeling

De identificatie van risicofactoren voor PTSS, zoals ook beschreven in dit proefschrift, heeft op dit moment nog niet geleid tot de ontwikkeling van effectieve screeningsmethoden die voorafgaand aan uitzending ingezet kunnen worden. Het is gebruikelijk om risicofactoren te bestuderen door gebruik te maken van klassieke statistische methoden, maar deze methoden laten meerdere tekortkomingen zien. Machine learning methoden, een vorm van kunstmatige intelligentie, zouden deze tekortkomingen kunnen overkomen. In dit proefschrift hebben we een vorm van machine learning (random forest) gebruikt om met vóór uitzending gemeten psychologische en biologische variabelen het ontwikkelen van PTSS-symptomen tot tien jaar na uitzending te voorspellen (hoofdstuk 6). Het model presteerde redelijk en identificeerde depressieve symptomen, angstsymptomen, wantrouwen en persoonlijke sensitiviteit, vasopressine en DEX-sensitiviteit als de belangrijkste voorspellende factoren voor het ontwikkelen van een symptomatisch PTSS-traject. Omdat dit model op de huidige dataset niet optimaal presteert, is de bruikbaarheid als kant-en-klaar screeningsinstrument zeer beperkt. Wel biedt dit model belangrijke aanknopingspunten voor de identificatie van risicofactoren voor PTSS nu deze factoren in samenhang geanalyseerd zijn. Want zoals we weten, risicofactoren opereren nooit in isolement in iets complex als de ontwikkeling van een psychische aandoening.

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van der Wal, S. J., Geuze, E., & Vermetten, E. (2022). Long-term risk for mental health symptoms in Dutch ISAF veterans: the role of perceived social support. *Psychological Medicine,* 1-11.

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CURRICULUM VITAE

Sija Janneke (Sanne) van der Wal was born on October 9th, 1992, in Gorinchem, The Netherlands. Sanne completed VWO at the Merewade College in Gorinchem. After high school, she started a Bachelor in Dutch Language and Culture, but after one year she discovered that literature was more of a hobby and that her heart was in bio(medical)- and health sciences. She then pursued a Bachelor in Health and Life Sciences at the Vrije Universiteit Amsterdam, where her fascination for the human mind, and in particular the pathology of the mind, arose. Her educational path therefore continued with a Research Master in Clinical and Developmental Psychopathology at the same university. During her studies, Sanne gained research experience in the field of psychiatry through internships focusing on the relatively unknown condition Body Integrity Identity Disorder (Psychiatry Department of the Academical Medical Center Amsterdam, supervised by Dr. Rianne Blom) and an internship abroad focusing on depression and personality disorders (Psychiatry Department of the Johns Hopkins Hospital in Baltimore, U.S.A., supervised by Prof. dr. Gerald Nestadt). After obtaining her Master's degree in 2017, Sanne worked at the Brain Research and Innovation Centre of the Dutch Ministry of Defence in collaboration with the Psychiatry Departments of the Leiden University Medical Center and the University Medical Center Utrecht. Here, she got the opportunity to study the long-term effects of military deployment on mental health that resulted in the present dissertation. After finishing her PhD and working temporarily as an epidemiologist at the Gemeente Utrecht, Sanne is continuing her scientific carrier as a post-doctoral researcher within the Sleep and Cognition lab of the Netherlands Institute for Neuroscience under supervision of Prof. dr. Eus van Someren.

Sija Janneke (Sanne) van der Wal is geboren op 9 oktober 1992 in Gorinchem, Nederland. Sanne volgde het VWO op het Merewade College in Gorinchem. Na de middelbare school begon ze aan een Bachelor Nederlandse Taal en Cultuur, maar na een jaar kwam ze erachter dat literatuur meer een hobby was en dat haar hart lag in de (bio)medische- en gezondheidswetenschappen. Ze volgde daarom een Bachelor in Gezondheid- en Levenswetenschappen aan de Vrije Universiteit Amsterdam, waar haar fascinatie voor de menselijke geest, en in het bijzonder pathologie van de geest, ontstond. Haar opleiding vervolgde ze daarom met een Research Master Clinical and Developmental Psychopathology aan dezelfde universiteit. Tijdens haar opleiding heeft Sanne onderzoekservaring binnen de psychiatrie opgedaan tijdens stages die zich richtten op de relatief onbekende aandoening Body Integrity Identity Disorder (Afdeling Psychiatrie, Academisch Medisch Centrum Amsterdam, onder begeleiding van Dr. Rianne Blom) en een buitenlandse stage gericht op depressie en persoonlijkheidsstoornissen (Psychiatry Department, Johns Hopkins Hospital, Baltimore, Verenigde Staten, onder begeleiding

van Prof. dr. Gerald Nestadt). Na het behalen van haar masterdiploma in 2017 is Sanne gaan werken bij het Expertisecentrum van de Militaire GGZ, in samenwerking met de psychiatrie afdelingen van het Leids Universitair Medisch Centrum en het Universitair Medisch Centrum Utrecht. Hier kreeg ze de mogelijkheid om onderzoek te doen naar de lange-termijn effecten van een militaire uitzending op de mentale gezondheid, wat resulteerde in dit proefschrift. Na het afronden van haar promotieonderzoek en tijdelijk gewerkt te hebben als epidemioloog bij de Gemeente Utrecht, heeft Sanne haar wetenschappelijke carrière voortgezet als postdoctoraal onderzoeker in het Slaap en Cognitie lab van het Nederlands Herseninstituut onder begeleiding van Prof. dr. Eus van Someren.

DANKWOORD

Een proefschrift schrijf je niet alleen. Ik ben daarom erg dankbaar voor alle hulp, steun en afleiding die ik tijdens dit proces heb mogen ontvangen uit mijn omgeving. In het bijzonder wil ik een aantal mensen bedanken voor hun unieke en waardevolle bijdrage.

Afghanistan-veteranen
Zonder namen te kunnen noemen van deelnemers, dit proefschrift is voor en door jullie. Ik kan jullie niet genoeg bedanken voor jullie jarenlange inzet en toewijding aan het PRISMO-onderzoek. Jullie openheid tijdens onze gesprekken tijdens de 10-jaars meting is bewonderenswaardig en heeft mij ook buiten de inhoud van dit proefschrift ontzettend veel geleerd.

Los van het onderzoek, Stef, dankjewel voor het delen van je verhaal en het ter beschikkingstellen van je werk voor de omslag van dit proefschrift. Hoe vaak ik ook naar je schilderij kijk, ik ben nog elke keer onder de indruk hoe de boodschap van dit proefschrift hier zo treffend in gevangen is. Ik ben blij dat onze wegen op deze manier hebben mogen kruisen, en dankbaar dat je dit proefschrift van zo'n waardevolle beeltenis hebt kunnen en willen voorzien.

Supervisors
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Stef Fridael | Kunstenaar en Afghanistan-veteraan