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

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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.

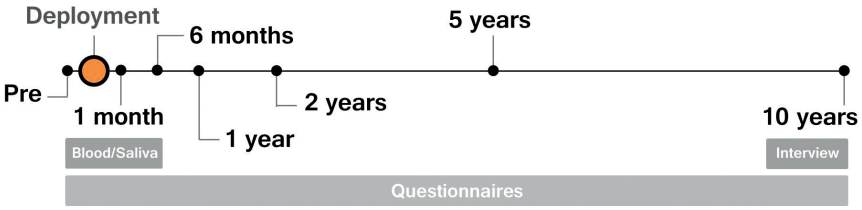

Figure 1. Design of the Prospective Research in Stress-Related Military Operations Study.

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.

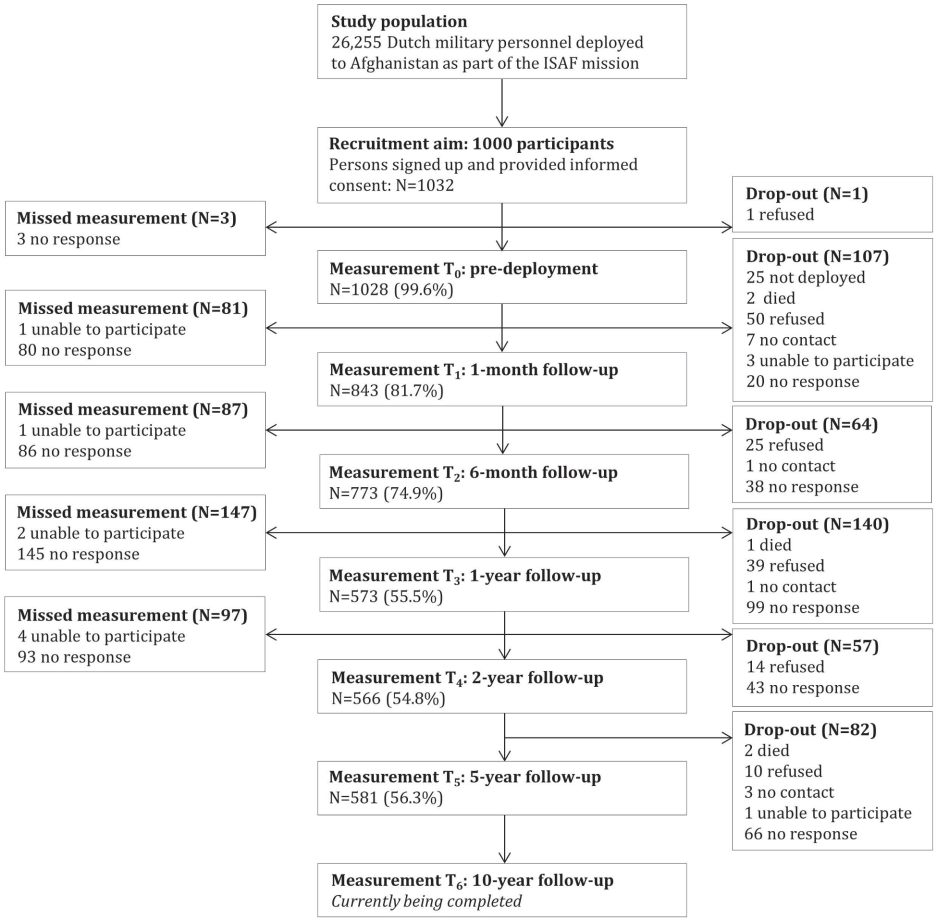

Figure 2. Participation in the Prospective Research in Stress-Related Military Operations study. 'Missed measurement' (on the left) includes participants who missed the indicated measurement, but participated again in later measurements. 'Drop-out' (on the right) includes participants who definitively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

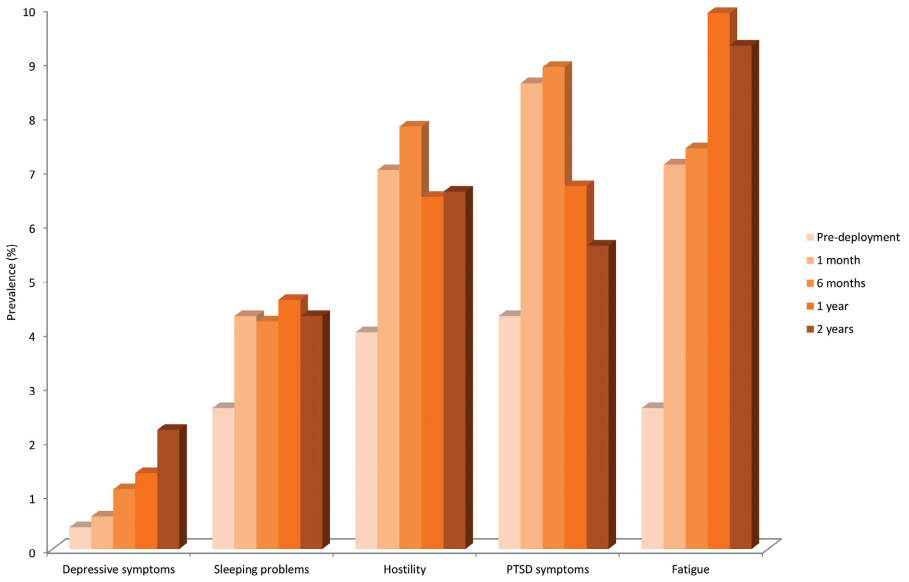

Figure 3. Prevalence of mental health symptoms in the Prospective Research in Stress-Related Military Operations cohort. Prevalence rates for all questionnaires were estimated based on 95th percentile scores as reported in the respective manuals or source publications. Changes in all prevalence rates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

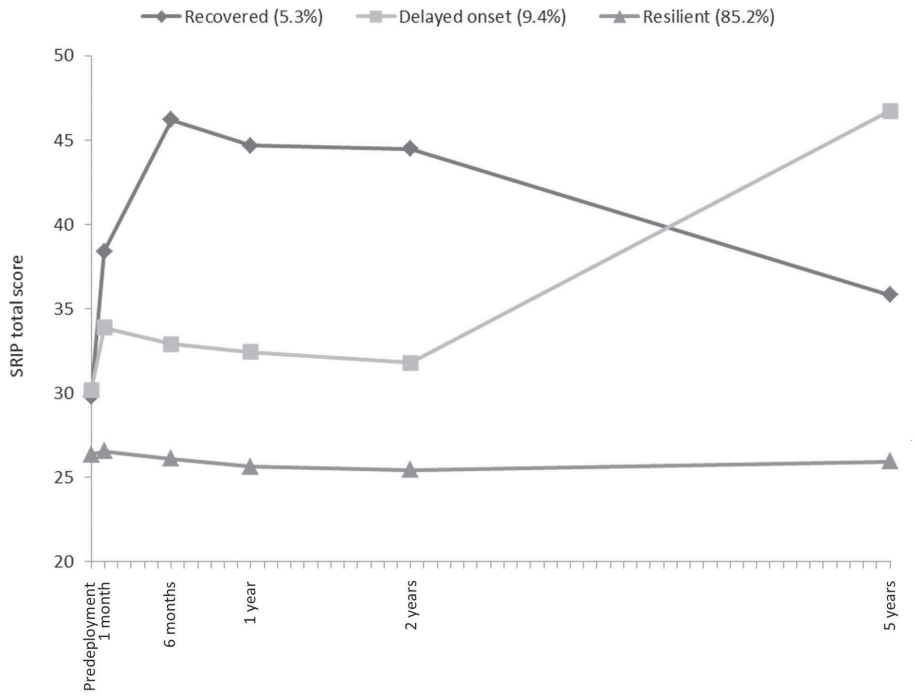

Figure 4. Latent developmental trajectories of post-traumatic stress symptoms in the Prospective Research in Stress-Related Military Operations cohort (n=960). SRIP, Self-Rating Inventory for Post-Traumatic Stress Disorder.

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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