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

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CHAPTER 6

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

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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.

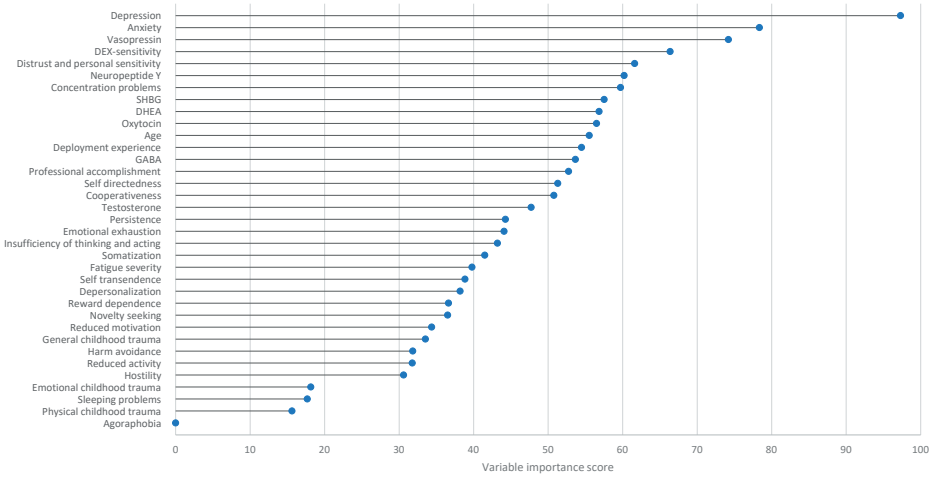

Figure 1. Average variable importance scores of all predictor variables for predicting PTSD symptom development. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled to range 0-100.

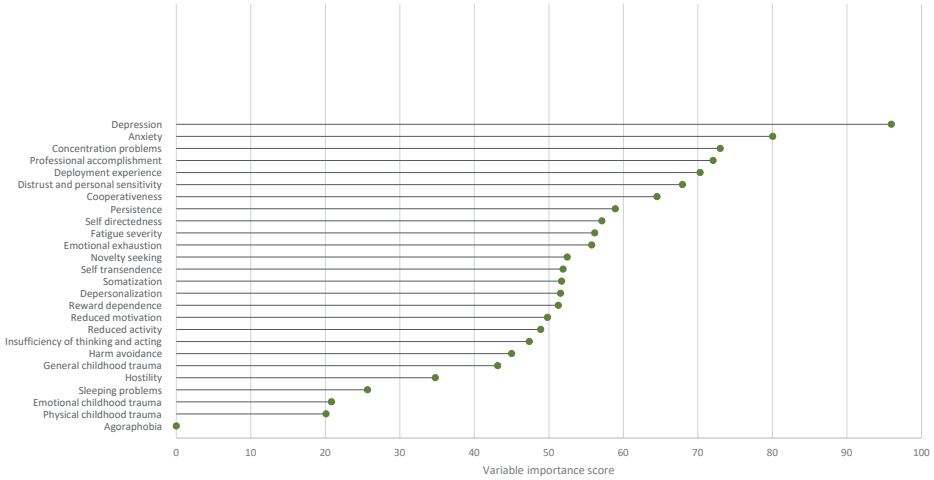

Figure 2. Average variable importance scores of all psychological predictor variables for predicting PTSD symptom development using datasets with only psychological predictors included. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents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

Acknowledgements
The authors thank the Dutch commanders and troops, and all members of the PRISMO team involved in data acquisition for their commitment to the study. This work was supported by the Dutch Ministry of Defence. The funder had no role in the design and reporting of the study.

REFERENCES

1. Wisco, B. E., Marx, B. P., Wolf, E. J., Miller, M. W., Southwick, S. M., & Pietrzak, R. H. (2014). Posttraumatic stress disorder in the US veteran population: results from the National Health and Resilience in Veterans Study. *The Journal of Clinical Psychiatry, 75*(12), 1338–1346.
2. van der Wal, S. J., Vermetten, E., & Elbert, G. (2020). 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. *European Psychiatry, 64*(1), e10.
3. Fulton, J. J., Calhoun, P. S., Wagner, H. R., Schry, A. R., Hair, L. P., Feeling, N., Elbogen, E., & Beckham, J. C. (2015). The prevalence of posttraumatic stress disorder in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans: a meta-analysis. *Journal of Anxiety Disorders, 31*, 98–107.
4. Stevelink, S., Jones, M., Hull, L., Pernet, D., MacCrimmon, S., Goodwin, L., MacManus, D., Murphy, D., Jones, N., Greenberg, N., Rona, R. J., Fear, N. T., & Wessely, S. (2018). Mental health outcomes at the end of the British involvement in the Iraq and Afghanistan conflicts: a cohort study. *The British Journal of Psychiatry, 213*(6), 690–697.
5. Schein, J., Houle, C., Urganus, A., Cloutier, M., Patterson-Lomba, O., Wang, Y., King, S., Levinson, W., Guérin, A., Lefebvre, P., & Davis, L. L. (2021). Prevalence of post-traumatic stress disorder in the United States: a systematic literature review. *Current Medical Research and Opinion, 37*(12), 2151–2161.
6. Doody, C. B., Robertson, L., Cox, K. M., Bogue, J., Egan, J., & Sarma, K. M. (2021). Pre-deployment programmes for building resilience in military and frontline emergency service personnel. *The Cochrane Database of Systematic Reviews, 12*(12), CD013242.
7. Schultebraucks, K., & Galatzer-Levy, I. R. (2019). Machine Learning for Prediction of Posttraumatic Stress and Resilience Following Trauma: An Overview of Basic Concepts and Recent Advances. *Journal of Traumatic Stress, 32*(2), 215–225.
8. Nissen, L. R., Tsamardinos, I., Eskelund, K., Gradus, J. L., Andersen, S. B., & Karstoft, K. I. (2021). Forecasting military mental health in a complete sample of Danish military personnel deployed between 1992-2013. *Journal of Affective Disorders, 288*, 167–174.
9. Karstoft, K. I., Tsamardinos, I., Eskelund, K., Andersen, S. B., & Nissen, L. R. (2020). Applicability of an Automated Model and Parameter Selection in the Prediction of Screening-Level PTSD in Danish Soldiers Following Deployment: Development Study of Transferable Predictive Models Using Automated Machine Learning. *JMIR Medical Informatics, 8*(7), e17119.
10. Johnson, K. W., Torres Soto, J., Glicksberg, B. S., Shameer, K., Miotto, R., Ali, M., Ashley, E., & Dudley, J. T. (2018). Artificial Intelligence in Cardiology. *Journal of the American College of Cardiology, 71*(23), 2668–2679.
11. Cuocolo, R., Caruso, M., Perillo, T., Ugga, L., & Petretta, M. (2020). Machine Learning in oncology: A clinical appraisal. *Cancer Letters, 481*, 55–62.
12. Rutledge, R. B., Chekroud, A. M., & Huys, Q. J. (2019). Machine learning and big data in psychiatry: toward clinical applications. *Current Opinion in Neurobiology, 55*, 152–159.

13. Siegel, C. E., Laska, E. M., Lin, Z., Xu, M., Abu-Amara, D., Jeffers, M. K., Qian, M., Milton, N., Flory, J. D., Hammamieh, R., Daigle, B. J., Jr, Gautam, A., Dean, K. R., Reus, V. I., Wolkowitz, O. M., Mellon, S. H., Ressler, K. J., Yehuda, R., Wang, K., Hood, L., … Marmar, C. R. (2021). Utilization of machine learning for identifying symptom severity military-related PTSD subtypes and their biological correlates. *Translational Psychiatry, 11*(1), 227.

14. Kessler, R. C., Bauer, M. S., Bishop, T. M., Demler, O. V., Dobscha, S. K., Gildea, S. M., Goulet, J. L., Karras, E., Kreyenbuhl, J., Landes, S. J., Liu, H., Luedtke, A. R., Mair, P., McAuliffe, W., Nock, M., Petukhova, M., Pigeon, W. R., Sampson, N. A., Smoller, J. W., Weinstock, L. M., … Bossarte, R. M. (2020). Using Administrative Data to Predict Suicide After Psychiatric Hospitalization in the Veterans Health Administration System. *Frontiers in Psychiatry, 11*, 390.

15. Leightley, D., Williamson, V., Darby, J., & Fear, N. T. (2019). Identifying probable post-traumatic stress disorder: applying supervised machine learning to data from a UK military cohort. *Journal of Mental Health, 28*(1), 34–41.

16. Karstoft, K. I., Statnikov, A., Andersen, S. B., Madsen, T., & Galatzer-Levy, I. R. (2015). Early identification of posttraumatic stress following military deployment: Application of machine learning methods to a prospective study of Danish soldiers. *Journal of Affective Disorders, 184*, 170–175.

17. Dean, K. R., Hammamieh, R., Mellon, S. H., Abu-Amara, D., Flory, J. D., Guffanti, G., Wang, K., Daigle, B. J., Jr, Gautam, A., Lee, I., Yang, R., Almli, L. M., Bersani, F. S., Chakraborty, N., Donohue, D., Kerley, K., Kim, T. K., Laska, E., Young Lee, M., Lindqvist, D., … Marmar, C. (2020). Multi-omic biomarker identification and validation for diagnosing warzone-related post-traumatic stress disorder. *Molecular Psychiatry, 25*(12), 3337–3349.

18. Schultebraucks, K., Qian, M., Abu-Amara, D., Dean, K., Laska, E., Siegel, C., Gautam, A., Guffanti, G., Hammamieh, R., Misganaw, B., Mellon, S. H., Wolkowitz, O. M., Blessing, E. M., Etkin, A., Ressler, K. J., Doyle, F. J., 3rd, Jett, M., & Marmar, C. R. (2021). Pre-deployment risk factors for PTSD in active-duty personnel deployed to Afghanistan: a machine-learning approach for analyzing multivariate predictors. *Molecular Psychiatry, 26*(9), 5011–5022.

19. Rosellini, A. J., Stein, M. B., Benedek, D. M., Bliese, P. D., Chiu, W. T., Hwang, I., Monahan, J., Nock, M. K., Sampson, N. A., Street, A. E., Zaslavsky, A. M., Ursano, R. J., & Kessler, R. C. (2018). Predeployment predictors of psychiatric disorder-symptoms and interpersonal violence during combat deployment. *Depression and Anxiety, 35*(11), 1073–1080.

20. Breiman, L. (2001). Random Forests. *Machine Learning, 45*, 5–32.

21. van der Wal, S. J., Gorter, R., Reijnen, A., Geuze, E., & Vermetten, E. (2019). Cohort profile: the Prospective Research In Stress-Related Military Operations (PRISMO) study in the Dutch Armed Forces. *BMJ Open, 9*(3), e026670.

22. Hovens, J. E., van der Ploeg, H. M., Bramsen, I., Klaarenbeek, M. T., Schreuder, J. N., & Rivero, V. V. (1994). The development of the Self-Rating Inventory for Posttraumatic Stress Disorder. *Acta Psychiatrica Scandinavica, 90*(3), 172–183.

23. Hovens, J. E., Bramsen, I., & van der Ploeg, H. M. (2002). Self-rating inventory for posttraumatic stress disorder: review of the psychometric properties of a new brief Dutch screening instrument. *Perceptual and Motor Skills, 94*, 996–1008.

24. Derogatis, L. R. (1994). *SCL-90-R. Administration, scoring and procedures manual* (3rd ed.). National Computer Systems.

25. Vercoulen, J. H., Swanink, C. M., Fennis, J. F., Galama, J. M., van der Meer, J. W., & Bleijenberg, G. (1994). Dimensional assessment of chronic fatigue syndrome. *Journal of Psychosomatic Research, 38*(5), 383–392.

26. Schaufeli, W. B., & van Dierendonk, D. (2000). *Utrechtse Burnout Schaal (UBOS): Voorlopige handleiding [Utrecht Burnout Scale (UBOS): Preliminary manual]*. Swets & Zeitlinger.

27. Duijsens, I. D., Spinhoven, P., Verschuur, M., Eurelings-Bontekoe, E. H. M. (1999). De Nederlandse Verkorte Temperament en Karakterschaal (VTCI) [The Dutch Temperament and Character Inventory-short form (TCI-SF)]. *Nederlands Tijdschrift voor Psychologie, 54*, 276–283.

28. Bremner, J. D., Bolus, R., & Mayer, E. A. (2007). Psychometric properties of the Early Trauma Inventory-Self Report. *The Journal of Nervous and Mental Disease, 195*(3), 211–218.

29. Reijnen, A., Rademaker, A. R., Vermetten, E., & Geuze, E. (2015). Prevalence of mental health symptoms in Dutch military personnel returning from deployment to Afghanistan: a 2-year longitudinal analysis. *European Psychiatry, 30*(2), 341–346.

30. Reijnen, A., Geuze, E., Eekhout, I., Maihofer, A. X., Nievergelt, C. M., Baker, D. G., & Vermetten, E. (2018). Biological profiling of plasma neuropeptide Y in relation to posttraumatic stress symptoms in two combat cohorts. *Biological Psychology, 134*, 72–79.

31. Reijnen, A., Geuze, E., & Vermetten, E. (2017). Individual variation in plasma oxytocin and vasopressin levels in relation to the development of combat-related PTSD in a large military cohort. *Journal of Psychiatric Research, 94*, 88–95.

32. Reijnen, A., Geuze, E., & Vermetten, E. (2015). The effect of deployment to a combat zone on testosterone levels and the association with the development of posttraumatic stress symptoms: A longitudinal prospective Dutch military cohort study. *Psychoneuroendocrinology, 51*, 525–533.

33. Schür, R. R., Boks, M. P., Geuze, E., Prinsen, H. C., Verhoeven-Duif, N. M., Joëls, M., Kahn, R. S., Vermetten, E., & Vinkers, C. H. (2016). Development of psychopathology in deployed armed forces in relation to plasma GABA levels. *Psychoneuroendocrinology, 73*, 263–270.

34. van Zuiden, M., Heijnen, C. J., Maas, M., Amarouchi, K., Vermetten, E., Geuze, E., & Kavelaars, A. (2012). Glucocorticoid sensitivity of leukocytes predicts PTSD, depressive and fatigue symptoms after military deployment: A prospective study. *Psychoneuroendocrinology, 37*(11), 1822–1836.

35. van Buuren, S., & Groothuis-Oudshoorn, K. (2011). Mice: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software*, *45*, 1–67.

36. Kuhn, M. (2021). Caret: Classification and Regression Training (R package v. 6.0-88). https://cran.r-project.org/package=caret.

37. John, C. R. (2020). MLeval: Machine learning evaluation (R package v. 0.3). https://cran.r-project.org/package=MLeval.

38. van der Wal, S. J., Maihofer, A. X., Vinkers, C. H., Smith, A. K., Nievergelt, C. M., Cobb, D. O., Uddin, M., Baker, D. G., Zuithoff, N., Rutten, B., Vermetten, E., Geuze, E., & Boks, M. P. (2020). Associations between the development of PTSD symptoms and longitudinal changes in the DNA methylome of deployed military servicemen: A comparison with polygenic risk scores. *Comprehensive Psychoneuroendocrinology, 4*, 100018.

39. Pyne, J. M., Constans, J. I., Wiederhold, M. D., Gibson, D. P., Kimbrell, T., Kramer, T. L., Pitcock, J. A., Han, X., Williams, D. K., Chartrand, D., Gevirtz, R. N., Spira, J., Wiederhold, B. K., McCraty, R., & McCune, T. R. (2016). Heart rate variability: Pre-deployment predictor of post-deployment PTSD symptoms. *Biological Psychology, 121*, 91–98.

40. Samuelson, K. W., Newman, J., Abu Amara, D., Qian, M., Li, M., Schultebraucks, K., Purchia, E., Genfi, A., Laska, E., Siegel, C., Hammamieh, R., Gautam, A., Jett, M., & Marmar, C. R. (2020). Predeployment neurocognitive functioning predicts postdeployment posttraumatic stress in Army personnel. *Neuropsychology, 34*(3), 276–287.

41. Gautam, A., Donohue, D., Abu-Amara, D., Hoke, A., Genfi, A., Blessing, E., Hammamieh, R., Marmar, C., & Jett, M. (2018). Metabolomic profiling associated with deployment-related stressors in Army personnel. *FASEB Journal, 32*, 658.8.

42. 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.

43. Xue, C., Ge, Y., Tang, B., Liu, Y., Kang, P., Wang, M., & Zhang, L. (2015). A meta-analysis of risk factors for combat-related PTSD among military personnel and veterans. *PloS One, 10*(3), e0120270.

44. LeardMann, C. A., Smith, T. C., Smith, B., Wells, T. S., Ryan, M. A., & Millennium Cohort Study Team (2009). Baseline self reported functional health and vulnerability to post-traumatic stress disorder after combat deployment: prospective US military cohort study. *BMJ, 338*, b1273.

45. Searle, A. K., Van Hooff, M., Lawrence-Wood, E. R., Grace, B. S., Saccone, E. J., Davy, C. P., Lorimer, M., & McFarlane, A. C. (2017). The impact of antecedent trauma exposure and mental health symptoms on the post-deployment mental health of Afghanistan-deployed Australian troops. *Journal of Affective Disorders, 220*, 62–71.

46. Shen, Y. C., Arkes, J., & Lester, P. B. (2017). Association between baseline psychological attributes and mental health outcomes after soldiers returned from deployment. *BMC Psychology, 5*(1), 32.

47. Nickerson, A., Priebe, S., Bryant, R. A., & Morina, N. (2014). Mechanisms of psychological distress following war in the former Yugoslavia: the role of interpersonal sensitivity. *PloS One, 9*(3), e90503.

48. Amone-P'Olak, K., & Elklit, A. (2018). Interpersonal Sensitivity as Mediator of the Relations Between War Experiences and Mental Illness in War-Affected Youth in Northern Uganda: Findings From the WAYS Study. *Traumatology, 24*(3), 200–208.

49. Moldofsky, H., Rothman, L., Kleinman, R., Rhind, S. G., & Richardson, J. D. (2016). Disturbed EEG sleep, paranoid cognition and somatic symptoms identify veterans with post-traumatic stress disorder. *BJPsych Open, 2*(6), 359–365.

50. Freeman, D., Thompson, C., Vorontsova, N., Dunn, G., Carter, L. A., Garety, P., Kuipers, E., Slater, M., Antley, A., Glucksman, E., & Ehlers, A. (2013). Paranoia and post-traumatic stress disorder in the months after a physical assault: a longitudinal study examining shared and differential predictors. *Psychological Medicine, 43*(12), 2673–2684.

51. Ponce de León, B., Andersen, S., Karstoft, K. I., & Elklit, A. (2018). Pre-deployment dissociation and personality as risk factors for post-deployment post-traumatic stress disorder in Danish soldiers deployed to Afghanistan. *European Journal of Psychotraumatology, 9*(1), 1443672.

52. Polusny, M. A., Erbes, C. R., Kramer, M. D., Thuras, P., DeGarmo, D., Koffel, E., Litz, B., & Arbisi, P. A. (2017). Resilience and Posttraumatic Stress Disorder Symptoms in National Guard Soldiers Deployed to Iraq: A Prospective Study of Latent Class Trajectories and Their Predictors. *Journal of Traumatic Stress, 30*(4), 351–361.

53. Syed Sheriff, R., Van Hooff, M., Malhi, G., Grace, B., & McFarlane, A. (2019). Associations Among Childhood Trauma, Childhood Mental Disorders, and Past-Year Posttraumatic Stress Disorder in Military and Civilian Men. *Journal of Traumatic Stress, 32*(5), 712–723.

54. Brewin, C. R., Andrews, B., & Valentine, J. D. (2000). Meta-analysis of risk factors for post-traumatic stress disorder in trauma-exposed adults. *Journal of Consulting and Clinical Psychology, 68*(5), 748–766.

55. Neumann, I. D., & Landgraf, R. (2012). Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behaviors. *Trends in Neurosciences, 35*(11), 649–659.

56. Sipos, E., Török, B., Barna, I., Engelmann, M., & Zelena, D. (2020). Vasopressin and post-traumatic stress disorder. *Stress, 23*(6), 732–745.

57. de Kloet, C. S., Vermetten, E., Geuze, E., Wiegant, V. M., & Westenberg, H. G. (2008). Elevated plasma arginine vasopressin levels in veterans with posttraumatic stress disorder. *Journal of Psychiatric Research, 42*(3), 192–198.

58. Hirsch, D., & Zukowska, Z. (2012). NPY and stress 30 years later: the peripheral view. *Cellular and Molecular Neurobiology, 32*(5), 645–659.

59. Rasmusson, A. M., Hauger, R. L., Morgan, C. A., Bremner, J. D., Charney, D. S., & Southwick, S. M. (2000). Low baseline and yohimbine-stimulated plasma neuropeptide Y (NPY) levels in combat-related PTSD. *Biological Psychiatry, 47*(6), 526–539.

60. Sah, R., Ekhator, N. N., Strawn, J. R., Sallee, F. R., Baker, D. G., Horn, P. S., & Geracioti, T. D., Jr (2009). Low cerebrospinal fluid neuropeptide Y concentrations in posttraumatic stress disorder. *Biological Psychiatry, 66*(7), 705–707.

61. Yehuda R. (2009). Status of glucocorticoid alterations in post-traumatic stress disorder. *Annals of the New York Academy of Sciences, 1179*, 56–69.

62. Dunlop, B. W., & Wong, A. (2019). The hypothalamic-pituitary-adrenal axis in PTSD: Pathophysiology and treatment interventions. *Progress in Neuro-psychopharmacology & Biological Psychiatry, 89*, 361–379.

63. Rohleder, N., Joksimovic, L., Wolf, J. M., & Kirschbaum, C. (2004). Hypocortisolism and increased glucocorticoid sensitivity of pro-Inflammatory cytokine production in Bosnian war refugees with posttraumatic stress disorder. *Biological Psychiatry, 55*(7), 745–751.

64. Yehuda, R., Golier, J. A., Yang, R. K., & Tischler, L. (2004). Enhanced sensitivity to glucocorticoids in peripheral mononuclear leukocytes in posttraumatic stress disorder. *Biological Psychiatry, 55*(11), 1110–1116.

65. de Kloet, C. S., Vermetten, E., Bikker, A., Meulman, E., Geuze, E., Kavelaars, A., Westenberg, H. G., & Heijnen, C. J. (2007). Leukocyte glucocorticoid receptor expression and immunoregulation in veterans with and without post-traumatic stress disorder. *Molecular Psychiatry, 12*(5), 443–453.

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*

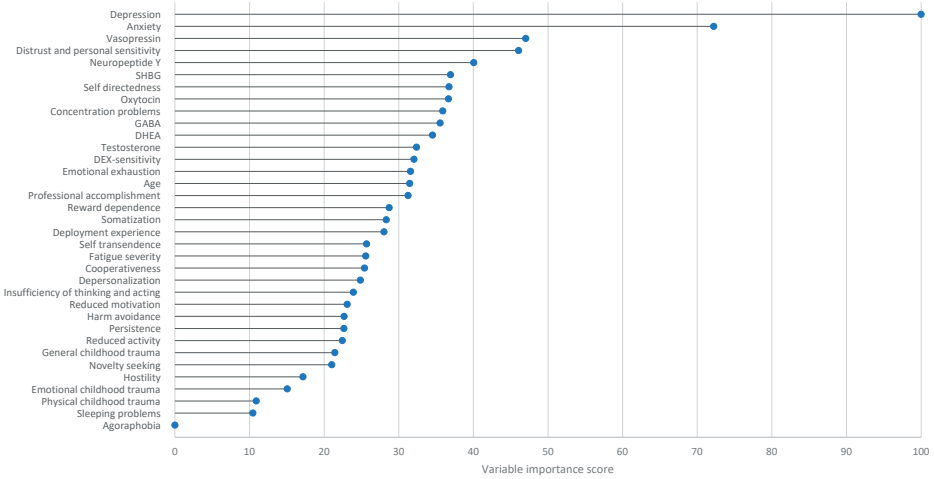

Figure S1. Variable importance scores of all predictor variables for predicting PTSD symptom development in dataset 1. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled to range 0-100.

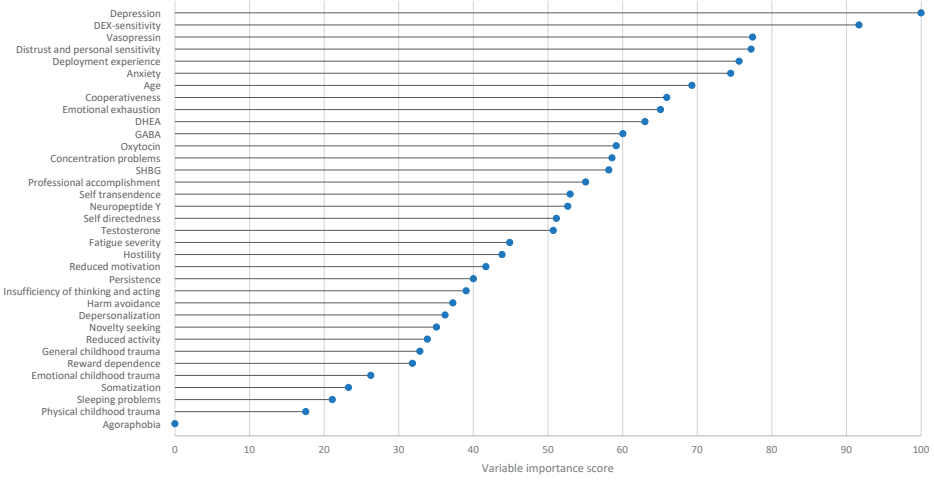

Figure S2. Variable importance scores of all predictor variables for predicting PTSD symptom development in dataset 2. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled to range 0-100.

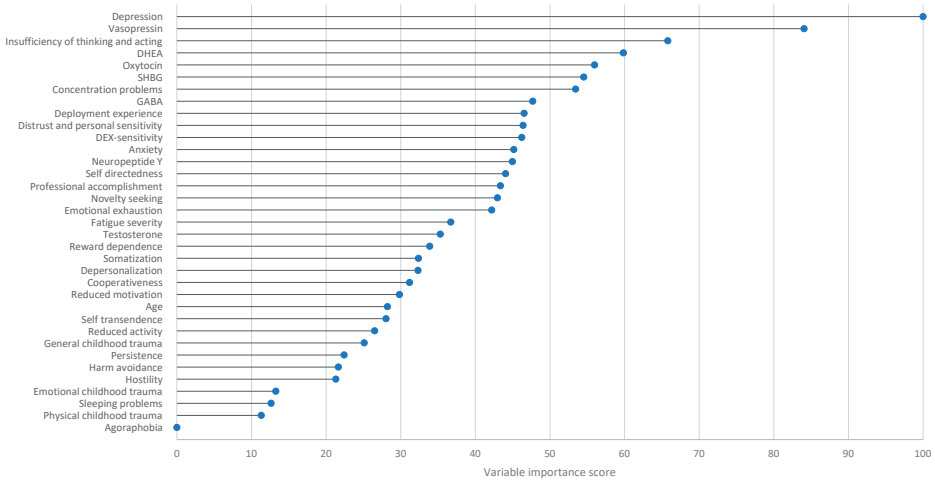

Figure S3. Variable importance scores of all predictor variables for predicting PTSD symptom development in dataset 3. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled to range 0-100.

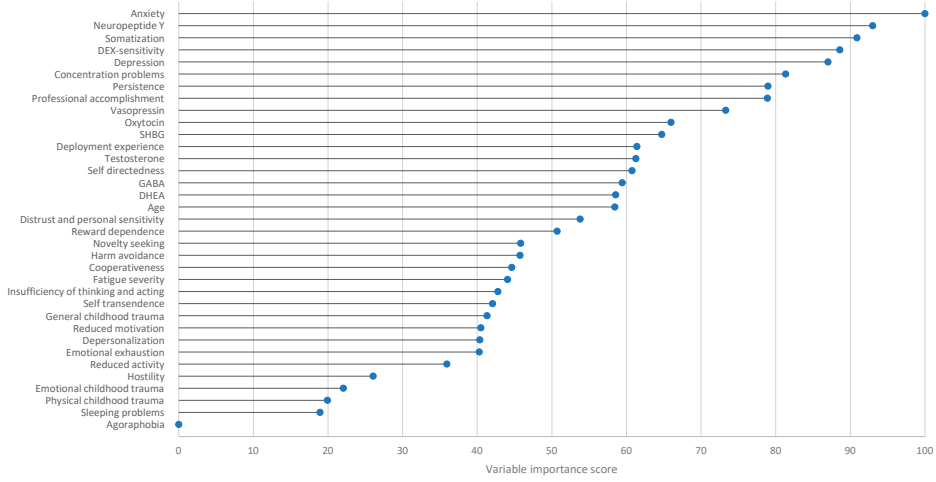

Figure S4. Variable importance scores of all predictor variables for predicting PTSD symptom development in dataset 4. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled to range 0-100.

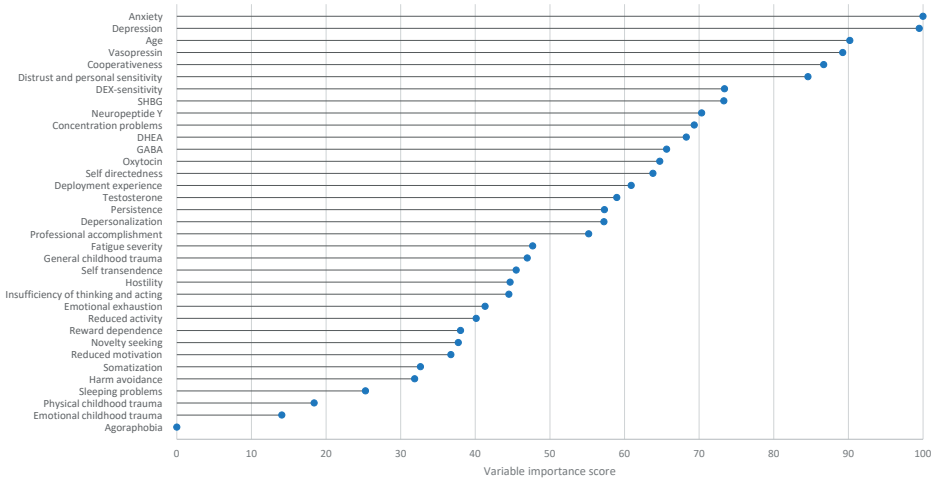

Figure S5. Variable importance scores of all predictor variables for predicting PTSD symptom development in dataset 5. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled to range 0-100.

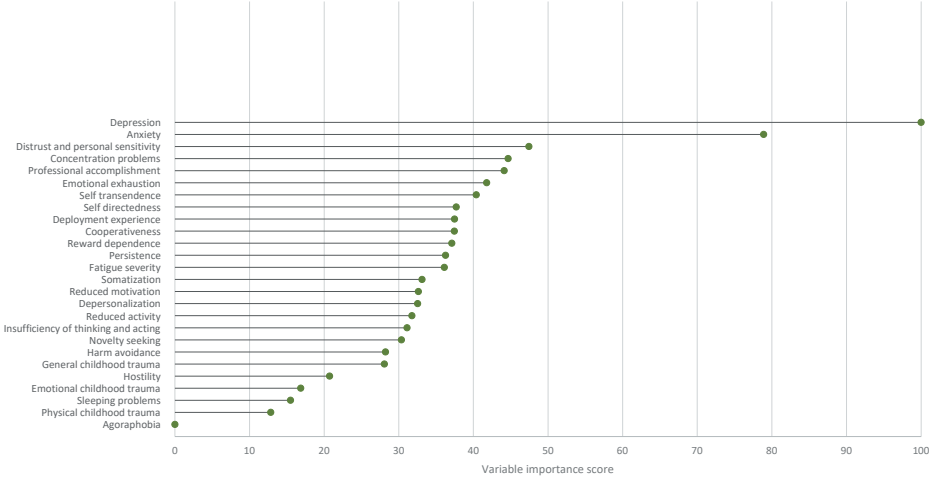

Figure S6. Variable importance scores of predictor variables for predicting PTSD symptom development in dataset 1 with only psychological variables included. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled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

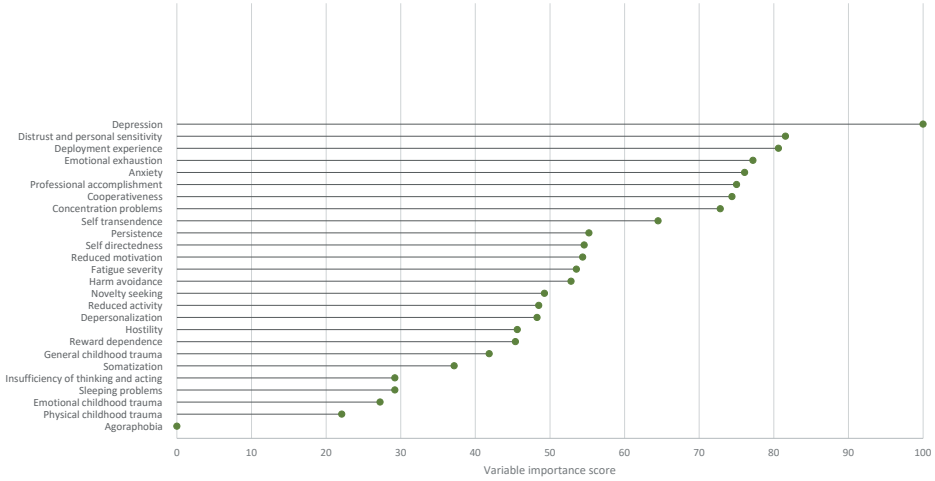

Figure S7. Variable importance scores of predictor variables for predicting PTSD symptom development in dataset 2 with only psychological variables included. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled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

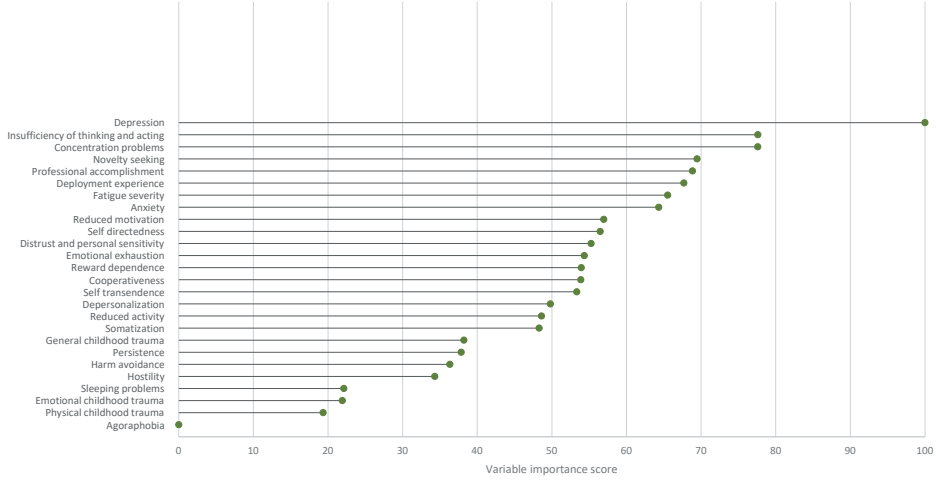

Figure S8. Variable importance scores of predictor variables for predicting PTSD symptom development in dataset 3 with only psychological variables included. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled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

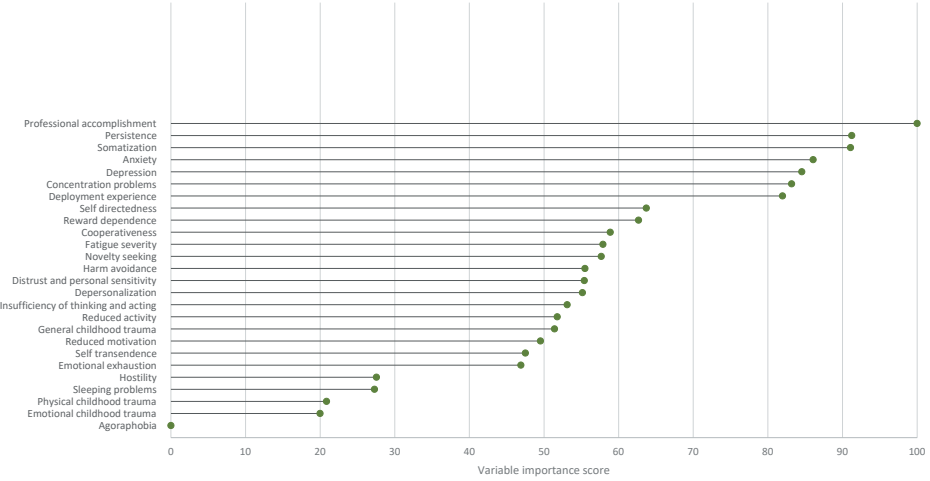

Figure S9. Variable importance scores of predictor variables for predicting PTSD symptom development in dataset 4 with only psychological variables included. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled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

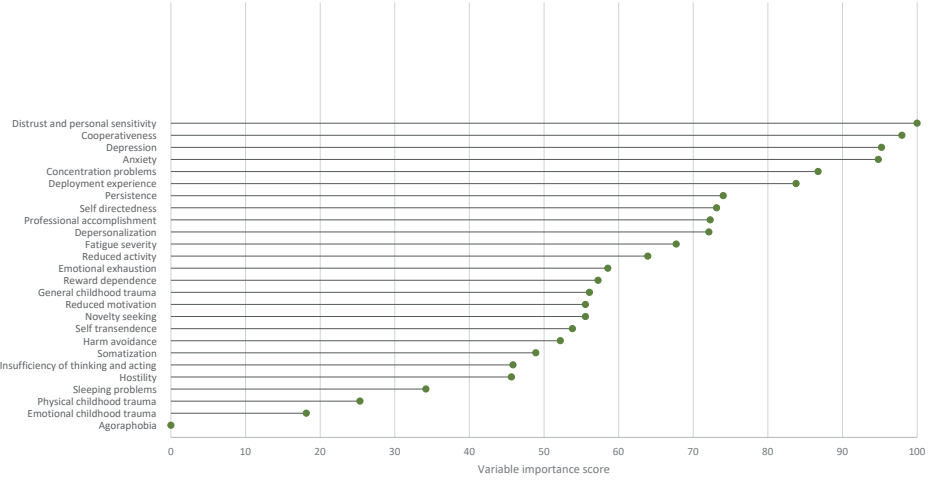

Figure S10 Variable importance scores of predictor variables for predicting PTSD symptom development in dataset 5 with only psychological variables included. The y-axis presents the importance ranking, with the top variables being the most important ones. The x-axis presents the importance score scaled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

REFERENCES

1. Hovens, J. E., van der Ploeg, H. M., Bramsen, I., Klaarenbeek, M. T., Schreuder, J. N., & Rivero, V. V. (1994). The development of the Self-Rating Inventory for Posttraumatic Stress Disorder. *Acta Psychiatrica Scandinavica, 90*(3), 172–183.
2. Derogatis, L. R. (1994). *SCL-90-R. Administration, scoring and procedures manual* (3rd ed). National Computer Systems.
3. Vercoulen, J. H., Swanink, C. M., Fennis, J. F., Galama, J. M., van der Meer, J. W., & Bleijenberg, G. (1994). Dimensional assessment of chronic fatigue syndrome. *Journal of Psychosomatic Research, 38*(5), 383–392.
4. Schaufeli, W. B., & van Dierendonk, D. (2000). *Utrechtse Burnout Schaal (UBOS): Voorlopige handleiding [Utrecht Burnout Scale (UBOS): Preliminary manual]*. Swets & Zeitlinger.
5. Duijsens, I. D., Spinhoven, P., Verschuur, M., & Eurelings-Bontekoe, E. H. M. (1999). De Nederlandse Verkorte Temperament en Karakterschaal (VTCI) [The Dutch Temperament and Character Inventory-short form (TCI-SF)]. *Nederlands Tijdschrift voor Psychologie, 54,* 276–283.
6. Bremner, J. D., Bolus, R., & Mayer, E. A. (2007). Psychometric properties of the Early Trauma Inventory-Self Report. *The Journal of Nervous and Mental Disease, 195*(3), 211–218.
7. Reijnen, A., Rademaker, A. R., Vermetten, E., & Geuze, E. (2015). Prevalence of mental health symptoms in Dutch military personnel returning from deployment to Afghanistan: a 2-year longitudinal analysis. *European Psychiatry, 30*(2), 341–346.