BMC Psychiatry

STUDY PROTOCOL

Open Access

Towards accurate screening and prevention for PTSD (2-ASAP): protocol of a longitudinal prospective cohort study

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Abstract

Background Effective preventive interventions for PTSD rely on early identification of individuals at risk for developing PTSD. To establish early post-trauma who are at risk, there is a need for accurate prognostic risk screening instruments for PTSD that can be widely implemented in recently trauma-exposed adults. Achieving such accuracy and generalizability requires external validation of machine learning classification models. The current 2-ASAP cohort study will perform external validation on both full and minimal feature sets of supervised machine learning classification models assessing individual risk to follow an adverse PTSD symptom trajectory over the course of 1 year. We will derive these models from the TraumaTIPS cohort, separately for men and women.

Method The 2-ASAP longitudinal cohort will include $N=863$ adults ($N=436$ females, $N=427$ males) who were recently exposed to acute civilian trauma. We will include civilian victims of accidents, crime and calamities at Victim Support Netherlands; and who were presented for medical evaluation of (suspected) traumatic injuries by emergency transportation to the emergency department. The baseline assessment within 2 months post-trauma will include self-report questionnaires on demographic, medical and traumatic event characteristics; potential risk and protective factors for PTSD; PTSD symptom severity and other adverse outcomes; and current best-practice PTSD screening instruments. Participants will be followed at 3, 6, 9, and 12 months post-trauma, assessing PTSD symptom severity and other adverse outcomes via self-report questionnaires.

Discussion The ultimate goal of our study is to improve accurate screening and prevention for PTSD in recently trauma-exposed civilians. To enable future large-scale implementation, we will use self-report data to inform the prognostic models; and we will derive a minimal feature set of the classification models. This can be transformed into a short online screening instrument that is user-friendly for recently trauma-exposed adults to fill in. The eventual short online screening instrument will classify early post-trauma which adults are at risk for developing PTSD. Those at risk can be targeted and may subsequently benefit from preventive interventions, aiming to reduce PTSD and relatedly improve psychological, functional and economic outcomes.

Keywords PTSD, Trauma, Longitudinal, Supervised machine learning, Sex, Gender

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Background

Exposure to potentially traumatic events (PTE) is common, with the overlarge majority of the global population being exposed to at least one PTE throughout their lives [1]. Similarly in the Dutch general civilian population, lifetime exposure is estimated at 80% [2]. Approximately 8% of Dutch civilians develop posttraumatic stress disorder (PTSD) at some point throughout their lives as a result of trauma exposure [2]. PTSD is a psychiatric disorder characterized by involuntary trauma re-experiencing, avoidance of trauma-related reminders; negative alterations in mood and cognitions; hyperreactivity; and hyperarousal [3]. PTSD is associated with a high risk for comorbid psychological symptoms and psychiatric disorders, including mood-, anxiety-, substance abuse- and sleep/wake disorders [4]. Furthermore, the presence of PTSD is associated with impaired well-being, daily functioning, and (health-related) quality of life, increased morbidity and mortality; and relatedly high societal costs due to for example health care use and productivity loss at work [5–12]. Although several evidence-based treatments are available, 40% of those who are affected are never treated; average time to treatment start is 4.5 years post-trauma; and approximately one third of treated patients does not respond adequately to treatment [13, 14]. Thus, once PTSD has developed it has a high likelihood for chronicity and negative consequences for affected individuals and larger society. As PTSD by definition has its onset after traumatic events, the first period post-trauma provides a unique opportunity for preventive interventions to reduce PTSD and related adverse psychological, functional and economic outcomes. Over the past decade there has been increasing evidence that such preventive interventions should not be administered in a universal manner to all trauma-exposed individuals. Instead, selective or targeted preventive intervention strategies are more promising (e.g., [15–17]). Herein one strategy could be to offer preventive interventions to those for whom can be established early following trauma that they are at high risk for developing PTSD. However, existing validated prognostic risk screening instruments for PTSD classify a high proportion of individuals who do not develop PTSD as at risk (e.g., low specificity ranging between 59–72% with sensitivity at 80% for available instrument for Dutch general civilian population; [18]). Thus, there is a need for more accurate prognostic risk screening instruments that can be used to determine an individuals' risk for PTSD early post-trauma.

Previous research reported a broad range of risk and protective factors for PTSD, including demographic; socio-economic; psychiatric; psychosocial; biological; trauma history; and environmental domains [19–22]. Recent studies with a computational approach strongly indicate that these risk and protective factors for PTSD interact in dynamic non-linear ways and seem to differ between PTSD symptom trajectories (e.g., [23, 24]). Increasing empirical evidence supports the existence four common distinct courses or trajectories of PTSD symptoms following trauma exposure [25]. Of these, resilient and recovery trajectories are considered adaptive as they are associated with minimal long-term symptoms. Chronic and delayed onset trajectories reflect adverse outcome as they are associated with long-term high symptoms and the presence of diagnostic PTSD. Thus, there is considerable heterogeneity in PTSD symptom courses following trauma, even when comparing those with similar long-term outcome.

A growing number of studies support the potential of machine learning in prognostic risk classification. These studies achieved good accuracy in classifying recently traumatized individuals into their subsequent PTSD diagnostic status and/or symptom trajectory (e.g., [23, 24, 26–30]). However, most of these existing prognostic risk classification models cannot be applied beyond acute medical care settings, as they mainly include acute biomedical and hospital patient record information. To promote large-scale applicability within a broader population, it would be preferable to develop prognostic screening instruments based on self-report data. This approach would enable recently trauma-exposed individuals to fill out the instrument without requiring involvement of a health care professional. Moreover, this could promote user empowerment, engagement and sense of self-control and thereby increase its uptake and acceptability [31]. However, the currently available studies using self-report data only prognostically classify PTSD outcomes in the first 3 months post-trauma, for example 1 month post-trauma in adults after emergency department (ED) admission and 3 months post-trauma in family members of intensive care unit (ICU [32, 33]). Thus, there is a lack of studies using self-report data to predict PTSD over a longer time period post-trauma. Moreover, prior to large-scale implementation of derived prognostic screening instruments, external validation in an independent sample to investigate generalizability of model performance is required [34]. To date there are few studies performing external validation of machine learning models: for example in ED patients assessing PTSD course at 6 months (Area Under the Receiver Operator Characteristic [ROC] curve [AUC] of external validation set ranging between 0.46 [low] and 76 [fair]; [35]), and at 12 months (AUC of external validation set ranging between 0.78 [fair] to 0.86 [good]; [24]). To date, no studies have performed external validation of

prognostic risk screening instruments within a broader civilian population.

There is a growing focus on examining sex (i.e., biology) and gender (i.e., social identity) in traumatic stress studies, with twice as many studies incorporating sex or gender in the last five years compared to earlier periods [36, 37]. This is considered especially relevant as women are commonly found to have a higher conditional risk of PTSD development than men following comparable trauma exposure [20, 38–40]. Moreover, we recently found differences between men and women in trajectories assignment and within-trajectory differences [41]. We observed that women were more often assigned to the recovery trajectory while men were more often assigned to the delayed trajectory, and women had higher symptom severity in the resilient trajectory than men [41]. This emphasizes the need for adequate methodological approaches such as stratification or disaggregation when establishing classification models (see also SAGER guidelines in [42]) to prevent considerable bias and incorrect trajectory assignment in the underrepresented group (in this case women). Yet, although gender and/or sex have been included as prognostic features, only few studies investigated differential prognostic value of risk and protective factors for later PTSD outcomes between men and women (e.g., [36, 43–45]). Furthermore, no studies have investigated whether deriving prognostic risk screening instruments separately for women and men is relevant for improving early PTSD risk detection.

In summary, there is a need for accurate prognostic risk screening instruments for PTSD, validated both internally and externally, that can be widely implemented in recently trauma-exposed civilians. We will derive full machine learning classification models for men and women separately. We will also derive classification models using a minimal feature set to eventually develop a prognostic risk screening instrument for men and women separately. These models will be derived using the existing TraumaTIPS prospective cohort of $N=852$ adults (65% men) with (suspected) acute serious injury [18]. This involves training and internally validating supervised machine learning classification models for women's and men's risk to follow an adverse PTSD symptom trajectory. This will be measured over the course of 1 year following acute civilian trauma. These models will be based on self-report information on known PTSD risk and protective factors collected early post-trauma. Subsequently, we will externally validate the classifications models in a broader population using the newly established 2-ASAP (Towards Accurate Screening and Prevention for PTSD) cohort consisting of recently trauma-exposed adults, of which the study protocol is described below.

Goals of the current study

Primary study objectives

The primary objective is to perform external validation of both full and minimal feature set supervised machine learning-based classification models assessing individual risk to follow an adverse PTSD symptom trajectory over the course of 1 year following acute civilian trauma. The classification models will be derived from the TraumaTIPS cohort in men and women separately.

Secondary study objectives

First, to investigate the predictive value of new potential risk and protective factors based on self-report information for PTSD risk in men and women separately. Second, to derive an updated prognostic classification model assessing individual risk to follow an adverse PTSD symptom trajectory by adding information on potential risk and protective factors to the supervised machine learning classification models in men and women separately. Third, we will assess differences in common co-morbid psychological symptoms to PTSD and functional and economic outcomes between recently trauma-exposed individuals classified as low versus high risk based on the derived and validated prognostic screening instrument. Last, we will compare the accuracy of the prognostic screening instrument with current best-practice screening instruments for PTSD.

Methods

Participants and study design

The 2-ASAP cohort will include $N=863$ adults (stratified by sex irrespective of self-identified gender for consistency with the existing TraumaTIPS cohort data [50% women, 50% men], taking previously established PTSD trajectory prevalence and dropout rates in the TraumaTIPS cohort into account [18], $N=436$ females, $N=427$ males) who were recently exposed to a (traffic) accident with injuries or violence (i.e., assault, threat, robbery or theft by force). We will include civilian victims of accidents, crime and calamities who have been reached out by Victim Support Netherlands (Slachtofferhulp Nederland), the largest institute in the Netherlands to provide emotional and practical support upon (mostly police) referral; or who were presented for medical evaluation of (suspected) traumatic injuries by emergency transportation to the ED of an Urban Level-1 Trauma Center in Amsterdam (Amsterdam University Medical Center [UMC]). Inclusion criteria of the 2-ASAP cohort are: age 18 years or older; experience of a traumatic event according to Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) PTSD A criterion (i.e., exposure to actual or threatened death, serious injury or sexual violence [3]) maximally 2 months post-trauma at

baseline; the traumatic events need to be directly experienced by the participant themselves, have an acute onset and external cause of a civilian nature; and have the potential to lead to serious physical injury (i.e., not a preceding medical condition). Exclusion criteria are: evidence of homocidality; suicidality, injuries due to intentional self-inflicted injury; evidence of ongoing or repeated trauma exposure, such as ongoing domestic violence; evidence of an inability to understand study procedures, risks or being otherwise unable to give informed consent; evidence of being unable to follow protocol (due to any reason, including visual or cognitive or physical impairment precluding completion of protocol); impairment in ability to use or no regular access to e-mail and mobile phone required for completion of online informed consent and internet-connected smartphone, tablet or computer for completion of online assessments; insufficient understanding of Dutch language to follow protocol. The 2-ASAP cohort was approved by the institutional review board of Amsterdam UMC (2022.0030).

Procedures

Participants will be recruited in collaboration with Victim Support Netherlands and ED of Amsterdam UMC. Potential participants will be identified via electronic client or patients records within 18–24 days post-trauma and invited for study participation by the recruitment sites. Potential participants who have contacted us for study participation will receive a participant's information letter, and will be called for an eligibility screening (T0). Upon meeting all inclusion criteria and none of the exclusion criteria, we will obtain informed consent online or through postal services. After inclusion, a baseline (T1) and 4 follow-up assessments (T2-T5) will be performed via online self-report questionnaires at 3, 6, 9 and 12 months post-trauma (see Fig. 1). The baseline assessment needs to be completed within 2 months after their traumatic event and includes self-report questionnaires on demographic, medical and traumatic event characteristics; potential risk and protective factors for PTSD; PTSD symptom severity and other adverse outcomes; and current best-practice PTSD screening instruments (see Table 2; measures section). The follow-up assessments include PTSD symptom severity and other adverse outcomes (see Table 2; measures section).

Measures

PTSD symptom severity

PTSD symptom severity over the past month will be measured at all assessments using the Dutch validated version of the PTSD checklist for DSM-5 (PCL-5; [46, 47]. This self-report questionnaire consists of 20 items corresponding to the DSM-5 diagnostic symptoms of PTSD, measuring how much participants have been bothered by each symptom, ranging from not at all (0) to extremely (4) on a 5-point Likert scale. Domain scores will be calculated based on summing the corresponding DSM-5 symptom clusters: intrusions (5 items), avoidance (2 items), negative alterations in cognitions and mood (7 items), and hyperarousal (6 items). The total score will be calculated by summing all items, resulting in a total score ranging from 0 to 80, with higher scores indicated higher PTSD symptom severity.

Risk and protective factors

Both known and potential new risk and protective factors for following an adverse trajectory of PTSD symptoms will be measured at baseline. The following known risk and protective factors will be included for the primary objective: demographic and health characteristics; medical and psychiatric history; current trauma characteristics; peri-traumatic distress; psychological and physical symptoms; alcohol use; social support; post-traumatic cognitions; prior trauma [21, 23, 48, 49].

For the secondary objective we will assess potential new risk and protective factors for following an adverse trajectory of PTSD symptoms. These factors are known to be associated with PTSD, but are not yet investigated prospectively in relation to PTSD symptom course or without adequate sized samples. These include pre-trauma and immediate post-trauma chronotype; sleep characteristics; perceived psychological resilience to cope with adversity; and female hormonal status; acute pre-trauma and acute post-trauma general health and related impairments; and acute pre-trauma psychological

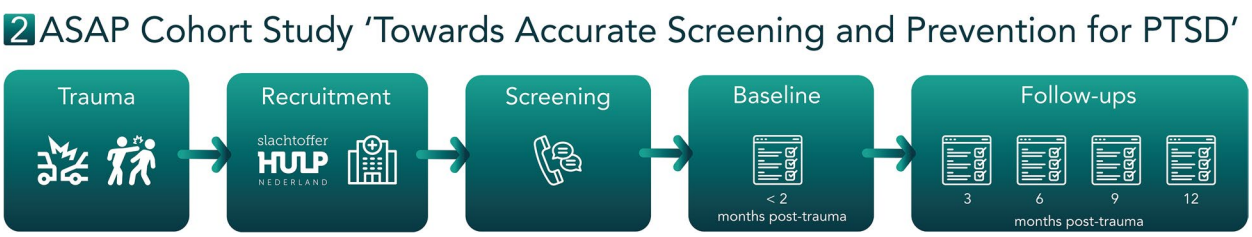

Fig. 1 Study design of the 2-ASAP cohort study

symptoms [50–54]. See Table 1 for an overview of all measures.

Secondary outcomes

Secondary outcomes include co-morbid psychological, functional and economic outcomes; and the current best-practice PTSD screening instruments. See Table 1 for an overview of all measures and assessment timing.

Covariates

Throughout the assessments, we will assess various factors with known potential confounding effects on PTSD symptom severity and other adverse psychological outcomes, including new traumatic events; received psychological treatment and medication use; pre-existing and new medical conditions; pain and health impairments; and Body Mass Index (BMI), nicotine use and caffeine

Table 1 Measurements Conducted at Baseline Assessment (T1) and Follow-up Assessments (T2, T3, T4, T5)

Measures	Instrument	T1	T2	T3	T4	T5
PTSD symptom severity	PCL-5	X	X	X	X	X
PTSD symptom severity	IES-R	X				
Best-practice PTSD screener	PC-PTSD5	X				
Best-practice PTSD screener	GPS	X				
Best-practice PTSD screener	MIRROR	X				
Traumatic events	LEC5	X	X	X	X	X
Demographic characteristics		X				
Health characteristics		X	X	X	X	X
Medical conditions	CBS checklist	X		X		X
Psychiatric history		X				
Psychological treatment		X	X	X	X	X
Current Trauma characteristics		X				
Peri-traumatic distress	PDEQ	X				
Peri-traumatic Distress	PDI	X				
Social Support	SSL-D short version	X				
Physical symptoms	VVV	X				
Post-traumatic cognitions	PTCI short version	X				
Female hormonal status		X				
Depression, anxiety and stress symptom severity	DASS-21	X	X	X	X	X
Depression and anxiety symptom severity	HADS	X				
Alcohol use disorder	AUDIT	X				X
Subjective stress		X	X	X	X	X
Quality of Life	WHOQOL-BREF	X	X	X	X	X
Daily functioning and health-related quality of life	EQ-5D-5L	X	X	X	X	X
Wellbeing	WHO5		X	X	X	X
Medical consumption costs	iMCQ			X		X
Productivity costs	iPCQ			X		X
Resilience	RES	X				
Nocturnal thoughts and dreams	Nocturnal mentation					
Sleep quality	PSQI short version	X	X	X	X	X
Insomnia severity	ISI	X	X	X	X	X
Chronotype/circadian rhythm	MCTQ	X				X

PCL-5 PTSD Checklist for DSM-5 [47], *IES-R* Impact of Event Scale-Revised [55], *PC-PTSD5* Primary Care PTSD Screen for DSM-5 [56], *GPS* Global Psychotrauma Screen [57], *MIRROR* Mobile insight in risk, Resilience, and Online Referral [58], *LEC5* Life Events Checklist for DSM-5 [59], *CBS checklist* Centraal Bureau voor de Statistiek [60], *PDEQ* Peritraumatic Dissociative Experiences Questionnaire [61], *PDI* Peritraumatic Distress Inventory [62], *SSL-D short version* Sociale Steun Lijst-Discrepanties [63], *VVV* Verkorte Vermoeidheidsvragenlijst [64, 65], *PTCI short version* Short version of Posttraumatic Cognitions Inventory [66], *DASS-21* Depression, Anxiety, and Stress Scale [67], *HADS* Hospital Anxiety and Depression Scale [68], *AUDIT* Alcohol Use Disorders Identification Test [69], *WHOQOL-BREF* World Health Organization Quality of Life-BREF [70], *EQ-5D-5L* EuroQol (Quality of Life) 5-Dimension 5-Level [71], *WHO5* World Health Organization Well-Being Index [72], *iMCQ* iMTA (Institute for Medical Technology Assessment) Medical Cost Questionnaire [73], *iPCQ* iMTA Productivity Costs Questionnaire [74], *RES* Resilience Evaluation Scale [75], Nocturnal mentation = Assessment of Nocturnal Dream Mentation [76], PSQI short version = Pittsburgh Sleep Quality Index short version [77], ISI = Insomnia Severity Index [78], MCTQ = Munich Chronotype Questionnaire [79]

intake. See Table 1 for an overview of all measures and assessment timing.

Sex and gender

We will measure both sex and gender at baseline. Sex will be based on their reported assignment at birth, categorizing individuals into male, female or other. We will ask participants their gender, i.e., whether they self-identify as men, women or otherwise.

Statistical analyses

PTSD Symptom Trajectories

First, PTSD symptom trajectories will be determined using an unsupervised machine learning technique, specifically latent growth mixture modeling (LGMM) on the repeatedly assessed PCL-5 total scores across the 1 year follow-up period. Hereby we empirically derive the optimal latent (unobserved) trajectories based on similarities in initial symptom severity and change over time across participant subgroups. In order to increase model accuracy in the context of the expected imbalance in the prevalence of the expected trajectories (i.e., with the adverse outcome trajectories being relatively small compared to the adaptive trajectories), we will apply informative priors for the model parameters to be estimated (i.e., the expected number and proportions of latent trajectories, and the expected symptom severity immediately after trauma [intercept] and change over time [slope] for a given trajectory; [80]). This approach has already been established and applied to the existing TraumaTIPS cohort [41], resulting in an optimal model containing 4 latent PTSD symptom trajectories. The prior parameters of the current analyses are derived from similarly observed parameters (i.e., CAPS-IV) of the 4 trajectories in the TraumaTIPS cohort [41]. Subsequently, we will determine participants' probability of belonging to each observed PTSD symptom trajectories and assign participants to one of these trajectories based on the highest probability. Missing data will be estimated using maximum likelihood estimation (MLE).

Accuracy of classification models

In order to externally validate the derived classification models from the TraumaTIPS cohort, we will perform the same supervised machine learning classification techniques as within development and internal validation of the model. To select the optimal machine learning technique for model building, we compared the accuracy of several classification techniques in a meta-modelled simulation study using data from population characteristics of the TraumaTIPS cohort. Overall, ensemble techniques performed better than multinominal techniques regarding the sample size. For model building we start with eXtreme Gradient Boosting (XGBoost), in case of insufficient accuracy we will continue with a Naïve Bayes classifier, followed by Support Vector Machine classifiers [81–83]. To guard against hyperparameter overfitting we will use repeated cross-validation. In addition, we will use random oversampling of the PTSD symptom trajectory with the smallest sample size to ensure a balanced set for model training. As the number of available cases for the delayed trajectory in the existing TraumaTIPS data is too small to perform reliable machine learning analyses, we will oversample the chronic trajectory. This way the model will not only focus on correctly classifying participants of adaptive PTSD symptom trajectories, but those with an adverse trajectory as well [84]. These analyses will be performed in men and women separately, to prevent similar bias for the underrepresented sex as observed for the unsupervised machine learning analyses. Moreover, to eventually derive a novel prognostic screening instrument, we will extract the minimal feature (item) set necessary for good accuracy from the training set. The primary metric for assessing optimal model selection based on training performance will be the AUC. The AUC reflects the accuracy in correctly classifying participants into their assigned PTSD symptom trajectories. Individuals are considered at risk if the model classifies them into an adverse trajectory versus adaptive (i.e., resilient or recovering) trajectory. Identical pre-processing steps will be repeated in the test set, which is subsequently used for internal validation to test whether the prognostic accuracy for the selected best model holds. We will assess the following accuracy parameters: AUC (primary parameter); cumulative gain AUC (penalizing incorrect classification of smallest class); f1 score; precision and recall [82, 85].

We will perform external validation in the 2-ASAP cohort in men and women separately by testing the accuracy of the full derived models in a first external test set and the minimal feature sets in a second external test set. The classification models are generalizable, reliable and robust when we achieve good accuracy, that is, AUC of preferably ≥ 0.8 (good) and acceptable if ≥ 0.7 (fair; [86, 87]). Moreover, we will descriptively compare the derived models in men and women by applying explainable machine learning to investigate the relative contributions of the most important features and to interpret the decision rules incorporated in the classification models. We will use SHAP (SHapley Additive exPlanation) values for decision tree-based non-linear models [88]. State-of-the-art guidelines will be followed in reporting results of prognostic models [89].

New potential risk and protective factors

We will first examine the predictive value of the new potential PTSD risk and protective factors per above mentioned domains, separately for men and women, and adjusting for relevant covariates. The predictive value will be examined using multinominal logistic regression modelling following a recommended 3 step approach to add predictors to latent class models such as the applied LGMM [90]. To account for the number of regression analyses performed with interrelated data, we will correct the false discovery rate for multiple comparisons. Subsequently we will update the full feature classification models in men and women separately by adding new potential risk and protective factors. The same machine learning classification techniques as in the TraumaTIPS cohort will be used for training and internal validation of the updated model.

Secondary outcomes

We will compare differences in co-morbid psychological, functional and economic outcomes between the obtained risk classifications of PTSD trajectory memberships, using either ANCOVA's or linear mixed model (LMM) depending on the number of assessments for the specific outcome. Separate analyses will be performed for men and women, and for each investigated outcome. To examine at which time point potential differences of adverse outcomes between PTSD trajectories occur, we will perform false discovery rate-corrected post-hoc pairwise comparisons of estimated means by the LMM. Furthermore, we will examine the accuracy for correctly classifying participants in their assigned PTSD symptom trajectory based on total scores of the 3 current best-practice PTSD screening instruments (i.e., GPS, PC-PTSD-5, MIRROR). The same accuracy parameters as within our previous analyses will be used. Subsequently, we will statistically test differences in the AUC of each existing screening instrument with the derived PTSD risk classification models, using a z-test approximation accounting for paired data, with alpha = 0.05 (2 sided).

Power calculation

We calculated the required sample size for sufficiently powered accuracy for developing and updating the prognostic screening instruments. The required number of participants in the test sets are calculated for sufficiently powered discriminatory accuracy (primary parameter = AUC). Power calculations were performed in EasyROC (version 1.3.1; [91]) for men and women separately, using the approach of Obuchowski for single test regarding AUC of 2 machine learning classifiers [92], using a type-1 error of 0.05, and the allocation ratio based on previously determined prevalence of PTSD symptom trajectories for men in the TraumaTIPS cohort (see Table 2, [41]). For the purpose of external validation of the derived machine learning classification models we will require 2 independent test sets: a full feature and minimal feature test set. We used an AUC of 0.7 (fair) as the minimally acceptable accuracy of our classification models instead of 0.8 (good), considering that external validation samples contain less homogenous population characteristics than training and internal validation samples and will thus likely result in lower accuracy. We require $n = 13$ cases; $n = 150$ non-cases for men; total $n = 163$ per test set, resulting in a total sample size of $N = 338$ (163*2 + $n = 12$ for 3.5% expected to delayed trajectory) for men. We require $n = 13$ cases; $n = 159$ non-cases for women; total $n = 172$) per test set, resulting in a total sample size of $N = 344$ (172*2) for women.

Table 2 Previously Determined Sample Size and Prevalence for the 4 PTSD Symptom Trajectories in the TraumaTIPS cohort in van Zuiden et al. [41]

	Men ($n = 346$)	Women ($n = 208$)
Resilient trajectory	269 (77.7%)	160 (76.9%)
Recovering trajectory	36 (10.4%)	31 (14.9%)
Chronic trajectory	29 (8.4%)	17 (8.2%)
Delayed onset trajectory	12 (3.5%)	0 (0%)

Furthermore, we calculated the required sample size for sufficiently powered accuracy for updating the prognostic screening instruments. For this purpose, we used an AUC of 0.8; and require an 80:20 split of the participants into a training and a test set. The test sets require a sample size of $n = 75$ ($n = 6$ cases; $n = 69$ non-cases) for men, and $n = 82$ ($n = 6$ cases; $n = 74$ non-cases) for women. In order to meet the proposed rule of thumb of at least 25 cases available in the training set, this requires to include a minimum of 31 cases in both samples [24]. Expecting minimally the same allocation ratio of the chronic trajectory relative to the resilient and recovery trajectory as in the TraumaTIPS cohort, this translates into a total sample size of n = (74.964*5) * 1.035 (to account for delayed trajectory) = 388 men, and n = (79.17*5) = 396 women. This sample size was increased by 10% to account for anticipated drop-out resulting in a required sample of $n = 427$ (388*1.10) men and $n = 436$ (396*1.10) women. This leads to a total sample size of $N = 863$ participants.

Discussion

We presented the protocol for the 2-ASAP longitudinal prospective cohort study of recently trauma-exposed adults in the Netherlands. The primary goal of this study is to externally validate machine learning classification models (i.e., full and minimal feature sets) predicting

early post-trauma the individual risk to follow an adverse PTSD symptom trajectory over the course of 1 year following trauma, that we will derive from the TraumaTIPS cohort [18]. The secondary goals are to update the classification model by examining new potential risk and protective factors; and compare the classification models with current best-practice screening methods for PTSD. We will also assess differences in adverse psychological, functional and economic outcomes between adults classified as low versus high risk.

This is the first study to perform external validation of machine learning prognostic models (full and minimal feature sets) based on self-report data in a broad recently trauma-exposed adults, for men and women separately. External validation of prognostic classification models is necessary for generalizability to new and different individuals beyond those in which the model was developed [93]. Hence, the 2-ASAP cohort will include trauma exposed adults at the ED of Amsterdam UMC similar to those in the acute injury population of the TraumaTIPS cohort in which the model was developed [18], as well as adults from a broader trauma population with a higher proportion of interpersonal traumatic events at Victim Support Netherlands. Moreover, it is also recommended to have separate models for men and women to prevent bias and incorrect trajectory assignment for the underrepresented group (in this case women). To enable future large-scale implementation, self-report data to inform the prognostic models will be used; and a minimal feature set of the classification models will be derived. These sets will be transformed into a short online screening instrument assessing the risk of developing PTSD that is user-friendly for recently trauma-exposed adults to fill in.

The eventual new screening instrument will classify early post-trauma which individuals are at risk for developing PTSD. Subsequently, these recently trauma-exposed adults at risk for developing PTSD can benefit from preventive interventions, aiming to reduce PTSD prevalence and relatedly improve psychological, functional and economic outcomes [16, 17]. This will contribute to our ultimate goal to improve accurate screening and prevention for PTSD in recently trauma-exposed civilians.

Study status

Currently recruiting participants since July 2022.

Abbreviations

2-ASAP	Towards Accurate Screening and Prevention for PTSD
APA	American Psychological Association
AUC	Area Under the ROC Curve
BMI	Body Mass Index
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th edition
ED	Emergency Department
LGMM	Latent Growth Mixture Modelling
LMM	Linear Mixed Model
MLE	Maximum Likelihood Estimation
PTE	Potentially traumatic event
PTSD	Posttraumatic stress disorder
ROC	Receiver Operator Characteristic
SHAP	Shapley Additive explanation
UMC	University Medical Center
XGBoost	EXtreme Gradient Boosting

Acknowledgements

We sincerely thank all participants in this study, as well as the preceding panel of experts-by-experience that provided their input to the study design for their valuable time and effort. Furthermore, we thank the 2-ASAP consortium partners and advisors for their collaboration and input. In addition, we would like to thank our recruitment sites Victim Support Netherlands (Slachtofferhulp Nederland) and the Emergency Department of Amsterdam University Medical Center (UMC), as well as the 2-ASAP research assistants for their efforts in participant recruitment.

Protocol version

Version 1: original, issue date 11–03-2022; Version 2: amendment adding the possibility for e-consent in coherence with new regulations by the Dutch Central Committee on Research Involving Human Subjects (CCMO), issue date 04–04-2023; Version 3: amendment adding Amsterdam UMC ED as recruitment site, issue date 02–01-2024.

Authors' contributions

M.v.Z. is the principal investigator and project leader of the 2-ASAP consortium and initiated the 2-ASAP cohort study as part of this consortium. M.v.Z. developed the study design together with R.v.d.S., M.O., J.A.H., and the related initial study protocol and amendments together with J.F.K, G.P. and C.H.. J.F.K. and G.P. are responsible for coordinating the study, supervised by M.v.Z. and C.H.. J.F.K. is responsible for writing the main manuscript text and figures with input from all co-authors. All authors reviewed the draft manuscript and approved submission of the final manuscript.

Funding

The 2-ASAP cohort study is part of the 2-ASAP consortium project funded by the Netherlands Organization for Health Research and Development (ZonMw; #636340004).

Data availability

To promote open science, statistical data analyses plans (SAP) related to the study's objectives will be pre-registered to Open Science Framework (OSF); manuscripts containing the results will be published in peer-reviewed Open Access journals; data of the study and the code to produce the results will be made publicly available upon study completion at OSF. Earlier requests for access to the data should be directed to the 2-ASAP principal investigator dr. M. van Zuiden. The study will be registered in the FAIR Traumatic Stress Data Sets library of the Global Collaboration on Traumatic Stress (GCTS).

Declarations

Ethics approval and consent to participate

The 2-ASAP cohort study was approved by the Institutional Review Board of the Amsterdam University Medical Centers on April 25, 2022 (NL80296.018.22; 2022.0030). The study is conducted according to the principles of the Declaration of Helsinki (1964, last updated 2013) and the Medical Research Involving Human Subjects Act (WMO). All researchers are trained in good clinical practice. Participants are extensively informed about the study both through information letters and orally and provide written informed consent prior to inclusion into the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 13 June 2024 Accepted: 23 September 2024
Published online: 15 October 2024

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