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Analysis

A systematic review of machine learning findings in PTSD and their relationships with theoretical models

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In recent years, the application of machine learning (ML) techniques in research on the prediction of post-traumatic stress disorder (PTSD) has increased. However, concerns regarding the clinical relevance and generalizability of ML findings hamper their implementation by clinicians and researchers. Here in this systematic review we examined (1) the extent to which pre-, peri- and post-traumatic risk factors identified using ML approaches coincide with the theoretical understanding of the disorder; (2) whether new insights were gained through ML techniques; and (3) whether ML findings, combined with previous research, enable an integrative model of PTSD risk encompassing both predictor categories and their theoretical relevance. We reviewed ML studies on PTSD risk factors in PubMed, Web of Science and Scopus. Studies were included if they specified when predictors and PTSD symptoms were collected in temporal relation to the traumatic event. A total of 30 studies with 12,908 participants (mean age 36.5 years) were included. After extracting the 15 most important predictors from all studies, we categorized them into pre-, peri- and post-trauma exposure predictors and examined their associations with established theoretical models of PTSD. Many studies exhibited a risk of bias, assessed using the prediction model risk of bias assessment tool (PROBAST). However, we found overlaps in identified predictors across studies, a concordance between data-driven results and theory-driven research, and underexplored predictors identified through ML. We propose an integrative model of PTSD risk that incorporates both data-driven and theory-driven findings and discuss future directions. We emphasize the importance of standards on how to apply and report ML approaches for mental health.

More than 70% of adults worldwide experience a traumatic event at some point in their lives[1]. PTSD is the most prevalent psychopathological consequence of such experiences[2], characterized by persistent feelings of imminent threat, strong avoidance of reminders of the triggering event, alteration of mood and cognition, disturbed sleep and hypervigilance[2]. Identifying risk factors that increase the likelihood of developing PTSD after trauma exposure is crucial for both early intervention[3] and advancing our understanding of the underlying mechanisms. However, PTSD risk is impacted by a complex interaction between psychological, social and biological factors[4–7] that challenges traditional statistical methods such as linear regression. ML methods have emerged as important tools to capture these intricate associations, informing crucial clinical purposes such as diagnosis, risk assessment and personalized treatment[7]. ML methods are broadly categorized into two types: classification (categorical outcome; for example, PTSD diagnosis) and regression (continuous outcomes;

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BOX 1

Clinical models of PTSD

Model	Hypothesis
Cognitive model of PTSD (Ehlers and Clark, 2000)[16]	Chronic PTSD develops when trauma survivors perceive the traumatic event as a current threat. This perception arises from negative appraisals and memory characteristics of the trauma. Pre-traumatic factors (social support and previous traumatic events), peri-traumatic (symptoms and sleep) and post-traumatic factors (strategies used to reduce the perceived threat) contribute to the development and maintenance of PTSD.
Dual representation theory (Brewin et al., 1996)[17]	Traumatic events are encoded in two distinct memory systems: situationally accessible memory (SAM) and verbally accessible memory (VAM). SAM consists of image-based trauma memories that are automatically activated by perceptually similar cues, while VAM comprises trauma memory representations that can be deliberately retrieved through conscious processing. Disruptions in the balance between sensory and contextual memory representations contribute to the manifestation of intrusive memories and other PTSD symptoms.
Emotional processing theory (Brewin and Holmes, 2003; Dalgleish, 2004; Foa et al., 2006)[18–20]	PTSD symptoms arise from the interaction of three key components: memory records (pre-trauma memories, the trauma memory itself and post-trauma memories), schema violations and post-traumatic appraisals. This theory draws on the fear network model by incorporating additional factors such as pre-trauma beliefs, trauma-related information and post-trauma reactions.
Social cognitive model (Sharp et al., 2012)[21]	Early experiences with attachment figures create attachment schemas that shape an individual's understanding of the self and others. In insecure attachments, the self is seen as unworthy and others as unreliable. This negatively impacts the development of social cognition, which in turn impairs one's ability to effectively process social information and reach out for needed social support when faced with a traumatic stressor, thereby increasing vulnerability to PTSD.
Emotion regulation model (Gross, 2015)[92]	To regulate their emotions, people can use five strategies that can be adaptive or maladaptive, depending on the context. Adaptive strategies contribute to emotional well-being, while maladaptive strategies may exacerbate emotional distress.
Acceptance and commitment therapy model (Hayes et al., 1999, 2006)[22,23]	Psychological flexibility is at the core of the ACT therapeutic model of behavior change and would be central to emotional health and well-being. The opposite is termed psychological inflexibility, characterized by a behavioral pattern of excessive control with a tendency to avoid unpleasant internal experiences and would be associated with negative mental health outcomes.
Metacognitive model (Wells, 2009; Wells and Sembi, 2004)[25,93]	The way in which one interacts with their thoughts, versus the thought content alone, influences the development and maintenance of PTSD. Specifically, maladaptive beliefs about thinking, termed metacognitive beliefs, are proposed to activate a host of maladaptive self-regulatory strategies, which constitute the cognitive attentional syndrome.

for example, severity of PTSD symptoms)[8]. These ML approaches can be used in both longitudinal and cross-sectional studies to identify relevant predictive features, such as demographic data, medical history or even patterns of brain activity, providing insights into the factors associated with PTSD.

Multiple reviews have assessed the statistical accuracy of these ML models[9–11], showing their effectiveness from a quantitative standpoint. However, there is a notable gap in the literature: none of these reviews has critically evaluated the clinical relevance of these models, an essential aspect to determine their real-world applicability and relevance in improving our understanding of PTSD. In addition, some studies adopted a bottom-up approach where, for example, all available data from electronic health records were included without a theory-based selection of predictors[12]. While this approach might enhance the feasibility of algorithm implementation in real-world settings, it raises concerns about the alignment of these predictors with the established theoretical understanding of PTSD and the mechanistic understanding of the disorder based on these identified predictors. As a consequence, despite that ML models have shown to improve the accuracy to diagnose patients[9,11], many clinicians and researchers remain skeptical about the findings derived from ML methods[13]. Part of this skepticism is due to their use of so-called black box algorithms that are difficult to interpret[13]. Uncertainty about the extent to which ML findings are consistent with the current mechanistic understanding of PTSD etiology may be a further barrier. Moreover, the natural course of PTSD adds a layer of complexity to integrating ML-derived findings with existing clinical and theoretical knowledge. The timing of predictors' assessment (pre-, peri- and post-trauma) must be considered: predictors assessed shortly after trauma exposure might express specific dimensions of acute responses and PTSD pathogenesis, whereas those identified later may reflect longer-term biological and psychological alterations and PTSD persistence and pathophysiology. To fit clinical and theoretical knowledge, therefore, the growing research using ML techniques[7] must consider data acquisition chronology toward establishing etiological and pathogenetic theories.

To address these concerns, we conducted a systematic literature review of ML-derived predictors of PTSD severity, PTSD diagnosis or longitudinal symptom trajectories. This Analysis aimed to answer three key questions. (1) Do pre-, peri- and post-traumatic predictors identified using data-driven methods align with those discussed in well-established theories of the etiology of PTSD? We evaluate ML findings in light of well-established theories of PTSD, chosen on the basis of two recent reviews of pertinent psychological theories of PTSD[14,15]. These theories include information processing models (the cognitive model of Ehlers and Clark[16] and the dual representation theory of Brewin et al.[17]), schema-based (the emotional processing theory described by Brewin and Holmes[18]; Dalgleish[19]; and Foa et al.[20]) and social (the social cognitive model of Sharp et al.[21]) theories of PTSD as well as general models of therapeutic intervention widely used in the treatment of PTSD (the acceptance and commitment therapy model of Hayes et al.[22,23], the emotion regulation model of Gross[24] and the metacognitive model of Wells[25]). These models comprehensively address maladaptive appraisals, memory disturbances, psychological flexibility, emotion regulation strategies and metacognitions. A more detailed description of these models can be found in Box 1. We also explore the contribution of ML to understanding the neurobiological pathways associated with PTSD etiology and pathophysiology (see Box 2 for details on biological pathways). (2) Can ML offer insights into

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BOX 2

Neurobiological pathways linked with PTSD

Hypothalamic–pituitary–adrenal (HPA) axis	The HPA axis has a crucial role in the adaptive response to stress via homeostatic mechanisms, allowing appropriate stress reactions. In the case of chronic stress, HPA axis mechanisms would be modified to avoid suffering from a constant high level of cortisol. In other words, the HPA axis would be hyperreactive due to the frequent alerts it has received, a situation it would counterbalance by maintaining a low level of cortisol through a decrease of cortisol production[94].
Frontolimbic alterations	PTSD has been linked with dysregulation of emotion and neural inhibition mediated by midline prefrontal inhibition of limbic regions[95]. While the prefrontal cortex should normally regulate the emotional intensity processed by the limbic system, in PTSD this regulatory mechanism has been shown to fail, leading to overwhelming emotional responses and impaired coping mechanisms[96,97]. These areas include the ventromedial prefrontal cortex, rostral anterior cingulate cortex, amygdala, hippocampus, insular cortex, orbitofrontal cortex and subcortical white matter networks[95].

PTSD, such as identifying risk factors not yet been discussed in established theories of PTSD? We investigate whether these findings could be integrated into theoretical models of PTSD. (3) Can ML findings be synthesized into an integrative model of PTSD? We aim to gather risk factors identified through ML studies and discuss potential associations with existing theoretical models of PTSD, thereby contributing to the ongoing efforts in understanding the complexity of PTSD and providing directions for future research directions.

Results

A total of 30 studies were included in this Analysis (Table 1): 12 cross-sectional studies[26–37] and 18 longitudinal studies[38–55]. Most of the studies focused on post-trauma variables only ($n = 26$)[26–36,38–51], whereas one study assessed both pre-trauma and post-trauma variables[53] and three studies focused on pre-trauma variables[52,54,55]. Twenty-one studies used a classification approach to predict probable PTSD diagnosis ($n = 12$)[27,28,30,31,34,36,37,44,47,50,51,55], PTSD trajectory membership from latent growth mixture models ($n = 6$)[39–42,46,53], both ($n = 2$)[45,52] or symptom profile from latent profile analysis ($n = 1$)[54]. Seven studies used a regression approach to predict the severity of PTSD symptomatology[29,32,33,35,38,43,48]. Two used both classification and regression approaches[26,49].

Only four studies used the gold standard and validated the generalizability of the results using an external sample[43,46,51,55], and eight studies validated their model in a holdout set[26,30,38,45,47,50–52]. In addition, 13 studies used resampling techniques[26,30,38–40,43,45–47,50–52,55] such as cross-validation (*k*-folds[30,43,46,51,55] and leave-one-out[26,38,45,50,52]) and bootstrapping[39,40,47] techniques, 3 used nested cross-validation[28,35,42] and 4 studies did not specify their validation method[29,33,34,53]. Two studies made comparisons between cross-validation methods: One study compared nested cross-validation with holdout cross-validation[35], and the other examined the differences between external validation and holdout cross-validation[48]. Finally, one study used a nested cross-validation approach to choose the optimal hyperparameters and then applied a tenfold stratified cross-validation assesses the model's overall performance and reliability[42].

PTSD was assessed using the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) diagnostic criteria in 19 studies: 4 used the Clinician Administrated PTSD Scale IV (CAPS-IV)[27,33,45,49], 6 used the Post-traumatic Checklist IV (PCL-IV)[30,35,37,51,53,55], 4 used the PTSD Symptom Scale (PSS)[29,39,41,42], 2 used the Impact of Event Scale[40,43], 1 used the Primary Care Posttraumatic Stress Disorder Screen[44], 1 used both PCL and CAPS[28] and 1 used both the CAPS and the Structured Clinical Interview for DSM Disorders (SCID)[34]. DSM-5-based diagnostic criteria were used in nine studies (five used the PCL-5[26,46–48,52], two used the CAPS-5[31,36], two used both PCL-5 and CAPS-5[38,54] and one used the Posttraumatic Diagnostic Scale[32]). Finally, one study assessed PTSD using both the CAPS-IV and CAPS-5[50], and one used the PCL-civilian version without specifying the specific version (DSM-IV or DSM-5)[55].

Model performance

A total of 76 models across 30 included studies were evaluated. Although most models demonstrated good predictive accuracy, authors also reported models that show suboptimal performance closer to chance. For example, eight classification models had an AUC below 0.7 (refs. 34,50,52). Among these, seven were benchmark models that relied on subset of predictors, such as only demographics[50], clinical scales to measure comorbidities[50], neurocognitive measures[52] or biomarkers[52]. When the full set of predictors was utilized, these models showed improved clinical accuracy. One model, which used whole-brain MRI data to differentiate PTSD from trauma-exposed healthy controls (TEHC)[34] achieved good predictive performance only when comparing individuals with PTSD with healthy controls but not with TEHC. Furthermore, one ML model was not able to distinguish individuals with PTSD from TEHC using structural functional magnetic resonance imaging (fMRI) features alone (accuracy below 0.5)[37]. Even after including clinical features, the model's performance improved only to an accuracy of 0.65. For regression models, one study reported an R^2 of 0.09, which improved to 0.21 after adjusting the cross-validation technique. All 76 models are presented in detail in 'Included studies' in Supplementary Data 1.

Typically, authors selected the best-performing model to extract the predictors that substantially contributed to the model's predictive performance. However, it should be noted that in two studies[37,47] the predictors selected did not belong to the best-performing model. Zhang et al.[37] presented results from a model using only structural brain features. The more complex model included also clinical predictors achieved a higher predictive accuracy. Wshah et al.[47] presented the predictors identified using random forest (accuracy 0.82) despite minimal higher predictive performance in the ensemble model (accuracy 0.86). Predictors were extracted from in total 35 models across 30 included studies.

The following predictive performance were found for classification models: mean area under the curve (AUC) of 0.84 (0.71–0.96), mean sensitivity of 0.80 (0.63–1.00), mean specificity of 0.79 (0.65–1.00), mean precision of 0.81 (0.68–0.97), mean recall of 0.82 (0.77–0.85) and mean accuracy of 0.78 (0.65–0.91). For regression models, the mean R^2 was 0.41, with a range from 0.21 to 0.60.

The majority of the classification studies aimed to distinguish between patients with PTSD and trauma-exposed individuals without PTSD symptoms, with only four studies[27,28,34,37] including healthy controls who were not exposed to any traumatic events.

Predictors

A detailed description of the predictors identified by ML algorithms can be found in Table 1 and Extended Data Tables 2–5. An overview of predictors for PTSD risk identified in ML models is shown in Fig. 1.

Table 1 | Description of the included ML studies

Author	Data	Aim	Design	Sample	ML model	Metrics	Result
Biological data							
Malan-Muller et al. (2022)[31]	Gut microbiome from stool	Classification outcome: PTSD diagnosis	Cross-sectional TA predictors + outcome: 7 years	79 PTSD 58 TEHC	RF	ACC 66.4	Four genera: *Mitsuokella*, *Odoribacter*, *Catenibacterium* and *Olsenella*.
Kuan et al. (2022)[30]	Metabolites from blood sample	Classification outcome: PTSD diagnosis	Cross-sectional TA predictors + outcome: 17–18 years	World Trade Center responders *N*=124 PTSD 56 TEHC 68	Elastic net	AUC 0.89 Sens 0.77 Spec 0.84	Five metabolites: 5-oxoproline, 6-oxopiperidine-2-carboxylate, β-hydroxyisovalerate, caproate (6:0) and glycocholate.
Schultebraucks et al. (2021)[45]	Biomedical collected within 48 h post-trauma	Classification outcome: (1) PTSD diagnosis (2) PTSD trajectory	Longitudinal TA predictors: in the ED; TA outcome: 1 year	Patients admitted to two level-1 trauma centers *N*=417	Extreme gradient boosting	Diagnosis: AUC 0.89 Sens 1.00, Spec 0.81, Prec 0.97 Trajectory: AUC 0.89 ACC 0.79 Prec 0.83	Diagnosis: thyroid-stimulating hormone (TSH) (mEl^{-1}), time admitted to ED, cortisol ($nmoll^{-1}$), perceived threat of own life (yes), dehydroepiandrosterone sulfate (DHEAS) ($nmoll^{-1}$), systolic blood pressure, total impact of prior traumatic events, free thyroxine (T4) ($pmoll^{-1}$), age, nonopiate anesthetics (doses), amnesia (self-reported, yes), nonopiate analgesics (doses), opiate analgesics (doses), prior traumatic events (number of types), pulse Trajectory: antibiotics use (doses), Glasgow Coma Scale, cortisol ($nmoll^{-1}$), age, DHEAS ($nmoll^{-1}$), pulse, free triiodothyronine (T3) ($pmoll^{-1}$), TSH (mEl^{-1}), free T4 ($pmoll^{-1}$), prior traumatic events (number), time admitted to ED, ICU admission (yes), head injury sustained (yes), systolic blood pressure, opiate analgesics (doses).
Hinrichs et al. (2019)[41]	Skin conductance; socio-demo; clinical	Classification outcome: PTSD trajectory	Longitudinal TA predictors: in the ED; TA outcome: 1 year	95 individuals from ED room	Lasso regression elastic net	With only skin conductance response: AUC 0.90	Skin conductance was the strongest predictor, followed by baseline PTSD.
Galatzer-Levy et al. (2017)[40]	Neuroendocrine + clinical + socio-demo + ED features	Classification outcome: PTSD trajectory	Longitudinal TA predictors: 10 days; TA outcome: 5 months	Trauma survivors from ED, *N*=152	SVM	AUC 0.82	Number of cigarettes per day, age, being a smoker, previous trauma, income, previous psychological treatment, appraisal in ER, plasma cortisol in ER, pulse, subjective reaction in ER, ER hourly urinary cortisol, arousal at week 1, depression at week 1, social support at week 1.
Brain imagery							
Zhang et al. (2023)[37]	White matter fibers	Classification outcome: PTSD diagnosis	Cross-sectional TA predictors and outcome: 4–6 months	Typhoon survivors 27 PTSD 33 TEHC 30 HC not exposed to typhoon	SVM	SVM using only white matter structure data: PTSD versus HC: ACC 0.65 Sens 0.63 Spec 0.66 Precision 0.68 PTSD versus TEHC: ACC 0.48 Sens 0.54 Spec 0.41 Precision 0.49	PTD versus HC: anterior thalamic radiation, right uncinate fasciculus, PTSD versus TEHC: left uncinate fasciculus and bilateral cingulum cingulate.
Fitzgerald et al. (2022)[38]	Resting state fMRI	Regression outcome: PTSD severity	Longitudinal TA predictors: within 1 month post-trauma; TA outcome: 6 months	ED patients from a level-1 trauma-center	Kernel ridge regression analysis (PRoNTo)	r=0.46, P=0.002; MSE 217.38, P=0.003; R^2=0.21, P=0.007	Acute hippocampal resting state functional connectivity across the whole brain predicted the outcome. Among the regions are the cerebellum, amygdala, hippocampus, cerebellar vermis midline, parahippocampal gyrus, dorsomedial prefrontal cortex and Heschl's gyrus.

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Table 1 (continued) | Description of the included ML studies

Author	Data	Aim	Design	Sample	ML model	Metrics	Result
Zhu et al. (2021)[36]	Resting state fMRI	Classification outcome: PTSD diagnosis	Cross-sectional TA predictors and outcome: 10–15 months	Earthquake survivor 91 PTSD 126 TEHC	Deep learning	ACC 80 Sens 80.9 Spec 79.2	The top 10 features were identified within the default mode, central executive network (CEN) and salience network (SN). Specifically, these regions were inferior frontal gyrus, triangular part, left (L) (CEN) lenticular nucleus, putamen, right (R) (SN), angular gyrus, R (DMN), superior temporal gyrus, R (DMN), rolandic operculum, L, calcarine fissure and surrounding cortex, R, fusiform gyrus, L, lenticular nucleus, pallidum, R (SN) middle frontal gyrus, R (CEN).
Suo et al. (2020)[33]	Resting state functional connectivity	Classification outcome: PTSD diagnosis	Cross-sectional TA predictors and outcome: 10–15 months	Earthquake survivors	Connectome-based predictive modeling	Significant correspondence between predicted and actual values (r=0.30, P=0.001).	Connections between occipital lobe and cerebellum and connections of the limbic lobe with cerebellum and occipital lobe were primary predictors.
Zhang et al., (2016)[34]	Multimodal MRI	Classification outcome: PTSD diagnosis	Cross-sectional TA predictors and outcome: 10–15 months	Earthquake survivors 17 PTSD 20 TEHC 20 HC	SVM	ACC PTSD versus HC 89.2 TEHC versus HC 90 PTSD versus TEHC 67.6	The most discriminative power between groups was identified in both brain hemisphere and all the four lobes. The regions displaying most difference in gray matter volume appeared in the bilateral middle occipital gyrus, right inferior parietal lobule, left superior frontal gyrus, right cerebellum and the bilateral middle frontal gyrus; amplitude of low-frequency fluctuations difference mainly exhibited in the right precuneus, left temporal pole (superior temporal gyrus), left calcarine fissure, right caudate nucleus and the left superior frontal gyrus (medial); regional homogeneity difference appeared in the right temporal pole (middle temporal gyrus).
Gong et al. (2014a)[28]	Structural MRI	Classification outcome: PTSD diagnosis	Cross-sectional TA predictors and outcome: 10–15 months	Survivors of the Sichuan earthquake of 2008 50 PTSD 40 TEHC	SVM	ACC 91.25 Sens 95 Spec 87.5	The use of an arbitrary threshold corresponding to the top 30% of the maximum absolute weight vector score revealed that discrimination between the two groups was driven by gray matter and white matter differences in a widely distributed network of prefrontal, temporal, parietal and occipital regions.
Gong et al. (2014b)[35]	Resting-state fMRI	Regression outcome: PTSD severity	Cross-sectional TA predictors and outcome: 10–15 months	Survivors of the Sichuan earthquake of 2008	Relevance vector regression	MSE 176.88	Accurate prediction was based on functional activation in several prefrontal, parietal and occipital regions.
Demographics and clinical scales							
Papini et al. (2023)[55]	Clinical scales	Classification outcome: PTSD diagnosis	Longitudinal TA predictors: 2 months to 1 month before deployment; TA outcome: 3 to 9 months after deployment	4,771 military personnel	Stacked ensemble, penalized logistic regression (elastic net), gradient-boosting machine	Gradient-boosting machine (GBM) AUC 0.74 (0.71–0.77)	Feeling restless, fidgety, keyed up (frequency, past month), sleep problems (frequency, past month), feeling jumpy or easily startled (severity, past month), emotionally numb after stressful experience (severity, worst month), expected pain (severity, future 5 years), first use of 5 or more alcoholic drinks (age), age at first alcohol or drug problem, difficulty concentrating after stressful experience (severity, past month), feeling jumpy or easily startled (severity, worst month), stopped counseling and talked to friends/family instead, unit leaders embarrass soldiers (frequency), unit leaders show concern for safety (frequency), age when first had nicotine dependence, likely to seek help from mental health counselor if needed, feeling discriminated against because of age, gender, race, or ethnicity, explosive anger (frequency).
Kim et al. (2022)[43]	Socio-demo; clinical; cognitive	Classification outcome: PTSD diagnosis	Longitudinal TA predictors: in the ED; TA outcome: 6 months	1,546 American survivors of motor vehicle collisions	KNN, Lasso, RF, SVM, NN, SuperLearn	Lasso AUC 0.79	Top predictors included acute pain severity, recovery expectations, socioeconomic status, psychological symptoms (feeling dizzy during the event), self-reported race.

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Table 1 (continued) | Description of the included ML studies

Author	Data	Aim	Design	Sample	ML model	Metrics	Result
Karstoft et al. (2020)[51]	Deployment experience + clinical + socio-demo	Classification outcome: PTSD diagnosis	Longitudinal TA predictors: 7 months; TA outcome: 2.5 and 6 years	TEHC and PTSD from 3 cohorts deployed to Afghanistan *N*=845–871	RF	2.5 years: AUC 0.77 Sens 0.71 Spec 0.70 6 years: AUC 0.78 Sens 0.73 Spec 0.70	Hypervigilance, total level of PTSD symptoms at 6 months and military rank were three of the most important predictors for PTSD at 2.5 years Total level of PTSD symptoms at 6 months, startle response, and military rank were three of the most important predictors for PTSD at 6.5 years Three features showed high cumulative importance in both cohorts: military rank, diminished interest in being with friends and family, and total level of PTSD symptoms 6 months after returning home.
Rousseau et al. (2022)[54]	Self-reported scales	Classification outcome: LPA profile of post-traumatic stress	Longitudinal TA predictors: last trimester of pregnancy; TA outcome: 4 months postpartum	Symptom profile after childbirth *N*=182	Chi-square automatic interaction detector	ACC 80.6	Fear of birth, number of children (including the child from the current pregnancy), childbirth plans, childbirth self-efficacy, expectancy regarding length of the labor, trust in staff that will provide support during the labor.
Schultebraucks et al. (2020)[46]	Electronic medical records	Classification outcome: PTSD trajectory	Longitudinal TA predictors: in the ED; TA outcome: 1 year	Patients who were admitted to the ED of a level 1 trauma center after experiencing a trauma *N*=598	Deep super learner	Nonremitting versus resilient: AUC 0.83 Prec 0.86 Recall 0.85 f1 0.85 Nonremitting versus all other PTS trajectories: AUC 0.78 Prec 0.83 Recall 0.75 f1 0.78	Immediate stress reaction checklist (ISRC) total score, ISRC item 26 (*I get upset when something reminds me of what happened*), biomarkers (neutrophils, lymphocytes, blood glucose, creatinine, mean corpuscular hemoglobin, mean corpuscular volume, plasma osmolality, sodium), age, ISRC item 27 (*I feel "hyper" or like I can't stay still*), ISRC item 6 (*I felt like I was not there – like I was not part of what was going on*), blood urea nitrogen, ISRC item 7 (*I felt confused*), Peritraumatic Dissociative Experiences Questionnaire (PDEQ), chloride, hematocrit, anion gap, systolic blood pressure, diastolic blood pressure, PDEQ item 3 (*Sense of time changed… slow motion*), PDEQ item 4 (*Seemed unreal… dream or movie*), monocytes, ISRC item 15 (*I felt sick because what was happening seemed so horrible*).
Wshah et al. (2019)[47]	Self-reported scales via smartphone	Classification outcome: PTSD diagnosis	Longitudinal TA predictors: mean through 30 days; TA outcome: 1 month	90 patients with TE	RF (model selected for the feature importance graph)	AUC 0.78 ACC 0.82	A subset of 7 standard early symptoms used to predict PTSD by care providers is adequate to predict elevated PTSD 1 month after a trauma. Days since trauma: days since trauma occurred. Reexp2: emotional reactivity to trauma cues; NACM1: negative beliefs about self and the world; NACM2: loss of interest in activities; sleep: sleep difficulty; pain: self-reported pain.
Papini et al. (2018)[44]	Variables routinely collected at the hospital + Clinical	Classification outcome: PTSD diagnosis	Longitudinal TA predictors: in the ED; TA outcome: 3 months	Patients at a level 1 trauma center *N*=271	XGBoost	AUC 0.85	Nine features with an information gain >0.05, five were from the psychological battery (current depression, social support, current nightmares, history of anxiety disorder, current PTSD symptomatology) and four were from routine collection (age (being younger), pulse, injury severity, orthopedic injury).
Su et al. (2018)[32]	Self-reported scales related to the event (burn) and cognitive functioning	Regression outcome: PTSD severity	Cross-sectional TA predictors and outcome: 2 years	Survivors of explosion 116 TE	RF	R^2 = 0.53	Maladaptive cognitive coping and negative appraisal of symptoms were the two most important predictors, followed by perceived social support and burn-related disabilities.
Karstoft et al. (2015a)[42]	ED features + features assessed 10 days after trauma	Classification outcome: PTSD trajectory	Longitudinal TA predictors: in the ED; TA outcome: 15 months	Patients admitted to ED	Step I: identification of risk indicators sets using Markov boundary Step II: SVM	AUC 0.75	Predictive features include age, time in the ED, head injury, perceived ED pain, patient and clinician's clinical global impression, total PSS and K6 scores, reporting nightmares, concentration problems, feeling worthless, wanting help, and quality of social support.

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Table 1 (continued) | Description of the included ML studies

Author	Data	Aim	Design	Sample	ML model	Metrics	Result
Karstoft et al. (2015b)[53]	Pre- and early post-deployment variables + clinical	Classification outcome: PTSD diagnosis	Longitudinal TA predictors: 1.5 months pre-trauma and 1–3 weeks post-trauma; TA outcome: 2.5 years	Danish soldiers deployed to Afghanistan in 2009 *N*=561	SVM Model 1: pre-deployment only Model 2: pre- and post-deployment variables	Model 1: AUC 0.84 Model 2: AUC 0.88	Six predeployment features were identified as predictors in <75% of cross-validation runs: feeling detached or estranged before, feeling of foreshortened future before, total PTSD symptom-level before, number of previous traumas, avoiding thoughts of trauma before deployment, and having received psychological treatment before deployment. Nine postdeployment features were selected in < 75% of cross-validation runs. Several were assessed before deployment: feeling detached or estranged, feeling of foreshortened future, total PTSD symptom-level, number of previous trauma, having received psychological treatment before deployment, and avoiding thoughts of trauma before deployment. After deployment features included: total PTSD-symptom level, level of thought suppression, and negative emotions.
Köbach et al. (2015)[29]	Traumatic experiences both underwent and perpetuated	Regression outcome: PTSD severity	Cross-sectional TA predictors and outcome: 66 months	Male Burundian ex-combatants *N*=367	Conditional inference random forests	*R*=24%	The total number of experienced traumatic event types was the most important predictor for post-traumatic stress.
Galatzer-Levy et al. (2014)[39]	ED features; clinical; Socio-demo within 10 days after trauma	Classification outcome: PTSD trajectory	Longitudinal TA predictors: in the ED; TA outcome: 15 months	Trauma survivors from ED, *N*=957	SVM	AUC 0.82	Sixteen features appeared in ≥95% of cross-validation runs. These features included feeling worthless, nightmares, PTSD symptom severity, K6 scores, clinician-reported CGI, wanting help, time in the ED, age, trauma being a terrorist attack, head injury, pain level, derealization, avoid thinking about the trauma, difficulty concentrating, social support.
Behavioral data							
Morris et al. (2022)[49]	Baseline info; saliva + heart rate before and after a stress task; cognitive functioning (D-KEFS + WCST)	Classification and regression outcome: PTSD diagnosis and severity	Longitudinal TA predictors: 45 days; TA outcome: 6 months	58 women, ages victims of physical and/or sexual assault	Two GBMs	For diagnosis: AUC 0.96 For severity: R^2=0.27	For diagnosis: 27 relevant variables were identified, including age of onset of first major depressive disorder (MDD) episode, household income, pre-stress cortisol, primary control coping (RSQ), α-amylase reactivity, baseline PTSD symptom severity, pain interference, overall pain severity, number of prior depressive episodes, childhood trauma exposure, age, depressive symptoms, cognitive functioning (DF attempted designs in D-KEFS and failure to maintain set in WCST), days since index trauma, resting heart rate pre-stress), functional impairment (social, family, work/ school) For severity: 18 relevant variables were identified, not detailed in the paper or supplement. It is to be noted that the authors mention that baseline CAPS-IV severity scores alone explained 27% of variability in CAPS-IV severity scores at 6-month follow-up. Predictors identified by both GBM models included age of onset of first MDD episode, baseline PTSD symptom severity, pain interference, overall pain severity, functional impairment (social, family, work/ school), number of prior depressive episodes, childhood trauma exposure, GAD severity, and days since index trauma.
Schultebraucks et al. (2022)[50]	Socio-demo + clinical + neurocognitive	Classification outcome: PTSD diagnosis	Longitudinal TA predictors: 1 month; TA outcome: 14 months	Trauma survivors from ED *N*=138	Extreme gradient boosting	AUC 0.88	The largest contribution emanating from PCL total score, poorer cognitive flexibility, processing speed, motor coordination, controlled and sustained attention, emotional bias, and higher response inhibition, recall memory, years of education and depression symptoms.

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Table 1 (continued) | Description of the included ML studies

Author	Data	Aim	Design	Sample	ML model	Metrics	Result
Schultebraucks et al. (2021)[52]	Biological + clinical + routine lab + cognitive testing	Classification outcome: (1) PTSD diagnosis, (2) trajectory	Longitudinal TA predictors: 2 weeks pre-deployment; TA outcome: 3–6 months post-deployment	Active-duty army personnel *N*=473	SVM RF	For diagnosis: SVM AUC 0.88 Sens 0.89 Spec 0.79 For trajectory: RF SVM AUC 0.87 Sens 0.80 Spec 0.85	Among both models, pre-deployment sleep quality, anxiety, depression, sustained attention, and cognitive flexibility. Blood-based biomarkers including metabolites (lactate, citrate, eicosanoids, and glutamine), epigenomic (DNA methylation at the cg17137457 CpG site, associated with the *CPT1B* gene, which has a role in mitochondrial fatty acid oxidation), immune and inflammatory (monocytes, basophil and C-reactive protein) and metabolic function markers (lipid panel, including low-density lipoprotein (LDL) cholesterol) complemented the most important predictors.
Augsburger et al. (2020)[48]	Cognitive and emotional functioning	Regression outcome: PTSD severity	Longitudinal TA predictors: 1 month; TA outcome: 3 months	Patients admitted to ED room *N*=94	SVM RF Boosted models Neural net Decision tree Bagged tree	RF: PTSD symptom severity (R^2=0.28)	Accuracy during incongruent trials in the face recognition task (emotion recognition) was the most important predictor. This was followed by errors in the verbal interference task (inhibition), reaction time in the go/no-go task (inhibition), errors of commission in the continuous performance (sustained attention) and time of completion of the digit span. In other terms, sustained attention and emotion recognition bias during incongruent stimuli demonstrated the greatest predictive impact across symptom clusters.
Breen et al. (2018)[27]	Sleep (objective, subjective); memory metabolites	Classification outcome: PTSD diagnosis	Cross-sectional TA predictors and outcome: 12.2 months	60 women 20 PTSD 20 TEHC 20 HC	SVM Two models: (1) HC versus trauma—both TEHC and PTSD); (2) PTSD versus TEHC	PTSD versus HC: AUC 0.70 Sens 0.80 Spec 0.61 PTSD versus TEHC AUC 0.7 Sens 0.8 Spec 0.61	Five features (three related to subjective measures of sleep quality and two related to polysomnography measures) distinguished PTSD and TEHC: better subjective laboratory sleep quality, poorer subjective home sleep, and earlier bedtime were associated with a PTSD diagnosis, along with increased spontaneous arousals and awakenings during laboratory sleep were also associated with a PTSD diagnosis, rather than with trauma exposure alone.
Video/audio/text data							
Schultebraucks et al. (2020)[26]	Audio + video recordings from a brief qualitative interview	Classification and regression outcome: (1) PTSD diagnosis, (2) severity	Cross-sectional TA predictors and outcome: 1 month	Trauma-exposed patients from ED *N*=81	Deep learning	PTSD diagnosis: AUC 0.9 Precision 0.83 Recall 0.84 f1 0.8 PTSD severity: R^2 = 0.60 RMSE 10.31 MAE 6.38	PTSD diagnosis: NLP features, but also features of voice prosody such as audio intensity, pitch and facial features of emotion. Specifically, higher fear expressivity and anger expressivity, increased use of first-person singular pronouns, lowered audio intensity and reduced pitches per frame provided probabilistic information in classifying PTSD. Finally, the most important predictors were the use of the word 'self-assured' followed by 'compare'. PTSD severity: The most important predictors were age and gender, followed by audio intensity and NLP interrogative forms.

ACC, accuracy; CGI, clinical global impression; D-KEFS, Delis–Kaplan executive function system; DMN, default mode network; ED, emergency department; HC, healthy controls; ICU, intensive care unit; KNN, Knearest neighbor; LPA, latent profile analysis; MAE, mean absolute error; MSE, mean square error; NLP, natural language processing; NN, neural networks; Pre, precision; PTS, post traumatic symptoms; RF, random forest; RMSE, root mean square rreor; RSQ, responses to stress questionnaire; Sens, sensitivity; Socio-demo, socio-demographic; Spec, specificity; SVM, support vector machine; TA, timing of assessment; WCST, Wisconsin card sorting test.

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Table 2 | Results derived from cross-sectional designs

Post-traumatic factors	
Demographics	Age[26]
	Gender[26]
Trauma characteristics	Total number of experienced traumatic events encountered during war deployment[29]
Residual impact of trauma	Functional impairment: social, family, work/school[32]
Biomarkers	Indicators of inflammatory and immune functioning: gut microbiomes[31] (*Mitsuokella*, *Odoribacter*, *Catenibacterium* and *Olsenella* genera), metabolites[30] (5-oxoproline, 6-oxopiperidine-2-carboxylate, β-hydroxyisovalerate, caproate (6:0) and glycocholate)
Brain imagery	Structural differences in white matter fibers within the right anterior thalamic radiation and right uncinate fasciculus was found to distinguish PTSD from HC[37]. To distinguish PTSD from TEHC, white matter fibers within the left uncinate fasciculus and bilateral cingulum cingulate were examined[37]. Neuroanatomical differences in both gray and white matter in a widespread network of prefrontal, temporal, parietal and occipital regions as well as subcortical structures[28] were also identified. Structural differences in gray matter volume in a widely distributed network of prefrontal, temporal, parietal and occipital regions were replicated[34]. Specifically, differences were found in the bilateral middle occipital gyrus, right inferior parietal lobule, left superior frontal gyrus, right cerebellum and bilateral middle frontal gyrus.
	Resting-state fMRI: functional alterations across the whole brain, including in particular, prefrontal, parietal and occipital areas bilaterally in addition to cingulate, cerebellar and subcortical regions[35]. In addition, features within the default mode[36], central executive[36] and salience networks[36] were identified. These regions were the inferior frontal gyrus, triangular part, left (L) (CEN) lenticular nucleus, putamen, right (R) (SN), Angular gyrus, R (DMN), Superior temporal gyrus, R (DMN), rolandic operculum, L, calcarine fissure and surrounding cortex, R, fusiform gyrus, L, lenticular nucleus, pallidum, R (SN) middle frontal gyrus, R (CEN)[36]. Finally, connections between the occipital lobe and cerebellum as well as connections of limbic regions (including hippocampus) with the occipital lobe and cerebellum[33] were identified.
	Amplitude of low-frequency fluctuations[34] in the right precuneus, left temporal pole (superior temporal gyrus), left calcarine fissure, right caudate nucleus and left superior frontal gyrus (medial)
	Regional homogeneity differences[34] in the right temporal pole (middle temporal gyrus)
Coping strategies	Maladaptive cognitive coping[32]: trauma-related rumination and thought suppression
	Negative appraisal of trauma intrusion[32]
	Perceived social support[32]
Sleep	Subjective sleep[27] (in the laboratory and at home), bedtime[27] (assessed with the Pittsburgh Sleep Quality Index)
	Laboratory measures of arousals[27] and awakenings[27]
Digital phenotyping	Digital biomarkers from video and audio recordings based on participants' free discussion of their trauma experience[26]: higher fear expressivity and anger expressivity, lowered audio intensity and reduced pitches per frame
	Natural language processing[26]: increased use of first-person singular pronouns, use of negative words: 'self-assured', 'compare'; use of interrogative forms

Cross-sectional studies. Twelve cross-sectional studies were included in this Analysis, each assessing post-traumatic factors at varying intervals: 1 month post-trauma ($n = 1$)[26], 4–6 months ($n = 1$)[37], 10–15 months ($n = 5$)[27,28,33,35,36], 2 years ($n = 2$)[32,34] and more than 5 years post-trauma ($n = 3$)[29–31]. Nine of these studies utilized solely biological measures, including gut microbiomes[31], metabolites[30] and brain imagery data (both structural[28,34,37] and functional MRI[33,35,36]). Table 2 presents the predictors identified by all cross-sectional studies.

The following predictive performance were found for classification models: mean AUC of 0.86 (0.8–0.9), mean sensitivity of 0.80 (0.63–0.95), mean specificity of 0.80 (0.65–1.00), mean precision of 0.75 (0.68–0.83), mean recall of 0.84 (0.84–0.84) and mean accuracy of 0.75 (0.65–0.91). For regression models, the mean R^2 was 0.46, with a range from 0.24 to 0.60.

Longitudinal studies. Eighteen longitudinal studies were included, among which three focused on pre-trauma factors[52,54,55], one assessed both pre- and post-trauma factors[53], nine assessed peri-traumatic factors[39–47] and five examined post-traumatic risk factors[38,48–51] (Table 3). PTSD status and/or severity was predicted 1 month to 6.5 years after the traumatic event. All four included studies that were using an external validation set to examine the generalizability of their findings were longitudinal studies (Extended Data Table 5). In comparison with cross-sectional studies, longitudinal studies included the assessment of cognitive functions pre- and post-trauma, as well as acute care setting environment, which was not done cross-sectionally.

The following predictive performance was found for classification models: mean AUC of 0.84 (0.71–0.96), mean sensitivity of 0.82 (0.7–1.0), mean specificity of 0.81 (0.79–0.85), mean precision of 0.83 (0.83–0.97), mean recall of 0.82 (0.77–0.85) and mean accuracy of 0.79 (0.77–0.88). For regression models, the mean R^2 was 0.39, with a range from 0.21 to 0.53.

Risk of bias

A notable challenge during the selection of studies to be included in this Analysis was the lack of detailed information on the timing of the trauma event and evaluation of PTSD symptomatology, which led to the exclusion of numerous studies. This rigorous selection criterion was indispensable to uphold the validity and consistency of this Analysis, as manifested by the uniformly low risk of bias in the predictor, participant and outcome sections. However, this also limited the breadth of this Analysis. For example, we were forced to exclude a multitude of studies concentrating on genetic risk factors (for example, ref. 56), resulting in only one paper that included such information[52].

Important bias was identified in the predictor section, based on the fact that only two studies reached the suggested minimum recommended number of predictors per participant[30,55].

Substantial bias was also identified concerning the analyses performed, as most studies reported only one predictive performance metric, such as AUC, and usually only the mean model performance. Providing information about calibration (that is, the degree to which the predicted probabilities of an outcome align with the actual observed outcomes) or predicted risk distribution (that is, a distinction between

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Table 3 | Results derived from longitudinal designs

Pre-traumatic factors	
Demographics	Number of children[54]
	Smoking habits: age when first had nicotine dependence[55]
	Alcohol/drugs: age of first use of five or more alcoholic drinks[55], age at first alcohol or drug problem[55]
	Military rank[51]
Anticipation	Anticipated fear of the trauma[54]
	Anticipated trust in support to be received post-trauma[54]
	Expected pain (severity, future 5 years)[55]
	Anticipated plans to deal with trauma[54] (childbirth plans, self-efficacy, length of labor)
Psychological history	Prior psychological treatment[39,53]
	Previous trauma[53]
	Depression symptomatology[52]
	Prior anxiety diagnosis[44], anxiety symptomatology[52]
	PTSD symptoms: total score[53] and specific PTSD symptoms[53] (feeling detached or estranged[53], feeling of foreshortened future[53], avoiding thoughts of trauma[53], feeling emotionally numb after stressful experience (severity, worst month)[55]
	Symptoms related to anxiety or hyperarousal: feeling restless, fidgety, keyed up (frequency, past month), feeling jumpy or easily startled (severity, past month)[55], difficulty concentrating after stressful experience (severity, past month)[55], feeling jumpy or easily startled (severity, worst month)[55], explosive anger[55]
Biomarkers	Peripheral inflammatory and immune markers in the blood[52]: monocytes, basophil and C-reactive protein
	Mitochondrial metabolites: lactate, citrate, eicosanoids and glutamine[52]
	Epigenetic mechanism: mitochondria-related DNA methylation—cg17137457—of the *CPT1B* gene[52]
	Metabolic dysregulation: lipid panel, including LDL cholesterol l[52]
Cognitive functioning	Computerized neurocognitive measures: cognitive flexibility[52], sustained attention[52]
Social network	Stopped counseling and talked to friends/family instead[55]
	Unit leaders embarrass soldiers (frequency)[55]
	Unit leaders show concern for safety (frequency)[55]
	Likely to seek help from mental health counselor if needed[55]
	Feeling discriminated against because of age, gender, race or ethnicity[55]
Sleep	Self-reported sleep quality[52]
	Sleep problems (frequency, past month)[55]
Peri-traumatic factors	
Demographics	Age[39,40,42,44–46], socioeconomic status[43], race[43], income[40]
	Smoking habits: being a smoker[40] and number of cigarettes per day[40]
	Previous psychological treatment[40]
	History of anxiety disorders[44]
Trauma characteristics	Trauma severity: event-related features (type of event: terrorist attack[39], number of days since the event[47]), injury characteristics (head injury[39,42,45], pain level[39,42,43,47], injury severity[44], orthopedic injury[44], Glasgow Coma Scale[45]), perceived trauma severity[40]
Residual impact of trauma	Total impact of prior traumatic events[45], number of prior traumatic events[40,45], childhood trauma[40]
Immediate biological stress reaction	Endocrine measures of the hypothalamic–pituitary–thyroid axis: thyroid markers TSH, free T4 and free T3[45]
	Cortisol levels[40,45] (both plasma[40,45], urinary[40])
	Proxies of immune and inflammatory response[46]: neutrophils, lymphocytes, blood glucose, monocytes, mean corpuscular hemoglobin, mean corpuscular volume, plasma osmolality, sodium
	Indicators of kidney functions[46]: creatinine, blood urea nitrogen and anion gap
	General markers of body functioning: chloride[46], hematocrit[46], systolic blood pressure[45,46], diastolic blood pressure[46], pulse[40,44,45], heart rate[40], dehydroepiandrosterone sulfate[45], skin conductance[41]

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Table 3 (continued) | Results derived from longitudinal designs

Pre-traumatic factors	
Immediate psychological stress reaction	Feeling of perceived threat[45]
	Severity of early PTSD symptoms[40–42,44,49,50,53]
	Isolated symptoms within the four PTSD clusters: reexperiencing (nightmares[39,42,44]), hyperarousal (difficulty concentrating[39,42], arousal[40], emotional reactivity to trauma cues[47], sleep difficulty[47], items from the Immediate Stress Response Checklist[46], see Table 1 for details), avoidance (avoid thinking about the event[39]), and negative mood and cognition (amnesia – lower levels[45], negative beliefs about self and the world[47], loss of interest in activities[47])
	Other symptomatology such as depression[40,44], negative emotions[53], psychological distress (K6 scale)[39,42], feeling worthless[39,42], self-appraisal (wanting help[39,40,42], patient's global impression, CGI scale[39,42])
	General functioning[40]
	ED[40] reported distress
Acute care setting	Time spent in the ED[39,42]
	Time of admittance in the ED[45]
	ICU admission[45]
	Medication prescribed by the physician in the ED: opiate[45] and nonopiate[45] analgesics, antibiotics[45]
	Clinical impression from the physician[39,40,42] and patient[42]
	Patient's recovery expectations[43]
	Social support[39,40,42,44]
Cognitive processing	Peri-traumatic dissociation symptoms[43,46] from the Michigan Critical Events Perception Scale (MCEPS)[43] or the Peritraumatic Dissociative Experiences Questionnaire[46], see Table 1 for details
	Negative appraisals[40]: negative perception of one own responses
	Coping mechanism: thoughts suppression[53]
Post-traumatic factors	
Demographics	Age[49]
	Household income[49]
	Years of education[50]
	Childhood trauma exposure[49]
	Age of onset of onset of prior depression diagnosis[49] number of prior major depressive disorder diagnosis[49]
	Military rank[51]
Residual impact of trauma	Pain: inference[49], severity[49]
	Functional impairment: social, family, work/school[49]
	Days since trauma[49]
Symptomatology	PTSD symptom severity[49–51]
	Hyperarousal symptoms: hypervigilance[51] and startle response[51]
	Comorbidities: depression[49,50], anxiety[50]
	Patient's perception of their symptom severity[50]
	Avoidance symptomatology[40]
	Diminished interest in being with friends and family[51]
Biomarkers	Biological stress reactions: baseline cortisol levels[49], α-amylase reactivity after a social stress task[49], resting heart rate[49]
Brain imagery	Acute hippocampal resting state functional connectivity with different regions across the whole brain[38], with notable contributions of parietal and occipital regions[38]. Specifically, features such as negative connectivity between the hippocampus and cerebellum (left and right), cerebellar vermis midline, left parahippocampal gyrus, right hippocampus (representing a decreased intrahippocampal connectivity) and left Heschl's gyrus were predictive of PTSD[38]. Features composed of positive connectivity between the hippocampus and the right amygdala, right parahippocampal gyrus and right dorsomedial prefrontal cortex right Heschl's gyrus were identified as predictors[38].
Coping strategies	Primary control coping[49]
Cognitive processing	Sustained attention[48,50]
	Executive functioning: general executive functions[48,49], working memory[48], inhibition[48,50], flexibility[50], processing speed[48,50], motor coordination[50]
	Recall memory[50]
	Emotion-related processes: emotion recognition[48], emotional bias[50] (as assessed through WebNeuro)

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Fig. 1 | PTSD risk factors identified in ML models. Predictors for PTSD risk identified in ML models categorized into pre-, peri- and post-traumatic feature sets. Created with BioRender.com.

different risk levels) enables examinination of the clinical utility of a ML model. This gap underscores the need for more comprehensive evaluation of ML models.

Furthermore, only four studies[43,44,46,51] externally validated their models, raising questions about the generalizability. Finally, the issue of transparent reporting also contributed to the overall high risk of bias of the studies examined. For instance, two studies used the same sample[39,42], which may create a perception of replication but potentially curtail generalizability. Moreover, some studies using brain-imagery data did not clearly disclose the total number of features included in

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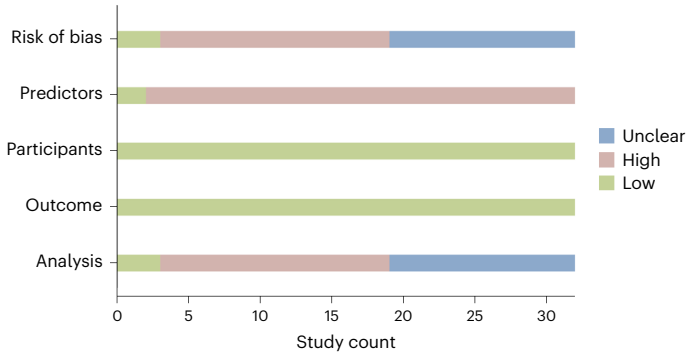

Fig. 2 | Risk-of-bias assessment. Risk of bias according to the PROBAST guidelines.

their algorithm after preprocessing of raw signal, thereby impeding our comprehension of their analytical process[28,33–35,38].

Despite these constraints, the consistency of the predictors across multiple studies and algorithms provides preliminary evidence of the robustness of these results and, thus, underscores the need for more rigorous external validation in future studies.

Details of the risk of bias of each study can be found in Extended Data Table 6 (as well as an overview in Fig. 2).

Discussion

This systematic review identified 30 studies in which both the timing of the traumatic event (that is, the assessment of PTSD outcomes) and predictors were defined. The results showed that ML techniques can predict PTSD risk from 1 month to over 2 years after a traumatic event with a high predictive accuracy, ranging from 0.71 to 0.96 AUC for classifications and 0.21 to 0.6 R^2 for regressions.

PTSD is a complex mental disorder, not only in terms of etiological factors[2] but also in terms of how the disorder manifests itself[57] and develops over time[58]. Therefore, the use of ML approaches appears particularly promising. As expected, we found that a variety of predictors are associated with PTSD. In addition to the complexity of the disorder, the variability of the identified predictors is also influenced by the factors assessed and the time point at which these factors were evaluated.

The goal of this Analysis was to systematically list all the predictors identified by the algorithms (Extended Data Tables 2–5). We then evaluated the relationship of these predictors with the clinical understanding of the pathology to assess their relevance and coherence with well-established theories of PTSD. This methodological framework allowed us to critically assess whether the identified predictors were consistent with the mechanistic understanding of the disorder, thus providing a structured interpretation of ML results.

Does the application of data-driven methods replicate the theory-driven understanding of PTSD?

The ML-derived predictors of PTSD risk are in line with the cognitive model of Ehlers and Clark[16,59], encompassing pre-, peri- and post-trauma factors such as previous trauma exposure, peri-traumatic dissociation, coping mechanisms and psychiatric comorbidities. Other important aspects of this model, as well as key concepts of the dual representation theory[17], the emotional processing theory[18–20] or the social cognitive model[21], have not yet been considered in the ML algorithms included. Among these are processes such as memory fragmentation, associative learning, social cognition, attachment styles, and self and world schemas. In addition, while social support has been found to be relevant several studies[32,39,40,42,44], the underlying mechanisms of social cognition described in the social cognitive model[21] have yet to be considered in ML studies.

Several included studies also emphasized the importance of cognitive functioning in PTSD[48–50,52], such as flexibility or sustained attention. This is in line with evidence showing that individual differences in inhibition and flexibility before the trauma are associated with the development of PTSD symptoms[60]. The theory of emotion regulation of Gross, the metacognitive model of Wells and the acceptance and commitment therapy (ACT) model of Hayes all suggest a connection between cognitive processing and symptomatology, emphasizing the importance of attentional control and cognitive flexibility in altering emotional experience and maintaining psychological wellbeing[24]. However, the nature of this relationship—whether as a preexisting vulnerability or as a consequence of PTSD symptomatology—warrants further investigation through longitudinal research.

In addition, the included studies have identified several biomarkers as relevant predictors, such as genetic, epigenetic, endocrine, autonomic nervous system, inflammatory and immune markers[40,41,44,45,49,50]. Those ML-derived predictors are in line with a large body of research aiming to deepen the biological understanding of PTSD[61,62]. As already shown in previous studies, a distinction should be made here as to whether these markers are assessed before or after the trauma, as they can either be vulnerability factors that increase susceptibility before exposure (for example, ref. 63), demonstrate alterations cause by the trauma (for example, ref. 64) or both (for example, ref. 65). The included studies also confirmed the importance of frontolimbic system in PTSD, among others, by determining the functional connectivity of the hippocampus or the amygdala[38].

Individuals exposed to trauma who display PTSD symptoms but do not meet the diagnostic criteria have shown similar neurobiological patterns to those diagnosed with PTSD[66,67]. Consistent with this, studies found that ML models using neurobiological data alone[28,34,37] were not able to distinguish between individuals with a PTSD diagnosis and trauma-exposed individuals without PTSD diagnosis. This underscores the importance of investigating the mechanisms underlying the heterogeneous responses to trauma[68].

Does ML expand the current knowledge of PTSD?

ML algorithms have substantially advanced PTSD research by integrating objective risk factors (such as the time spent in the emergency department and biomarkers) with subjective risk factors (including the clinical impressions of physicians[39,42,45] or self-reported questionnaires).

This holistic approach, which is in line with the biopsychosocial model[69–71], allows the heterogeneity of the development and manifestation of PTSD to be taken into account[72]. The results of the included studies also show that accurate risk stratification and diagnosis is possible even with different sets of predictors. This emphasizes that PTSD is complex and can be accurately described by different sets of predictors. The variability of predictors across studies, influenced by the specific data available in each context, underscores the ability of ML to create comprehensive multidimensional models of PTSD risk. This variability highlights the adaptability of these assessments in different settings, demonstrating that robust risk stratification and diagnosis can be conducted effectively with different sets of predictors, depending on the information accessible in a particular context. Importantly, the alignment of the findings with theoretical models emphasizes that, despite differences in predictors across studies, the underlying theoretical coherence is sound.

In addition, ML approaches have been shown to identify different risk profiles and, thus, have the potential to improve risk stratification. For example, in one study included in this Analysis, different predictors were identified for traumatized individuals and for individuals experiencing profound PTSD symptoms 1 month after trauma[50]. This distinction is crucial as it demonstrates the potential of ML to identify different sets of predictors in specific groups of individuals who are at different risk. This may also indicate the presence of different mechanisms in the development of pathology and may also be of great interest for future research. In other words, this shows the potential of ML to reveal different mechanisms of PTSD development within specific

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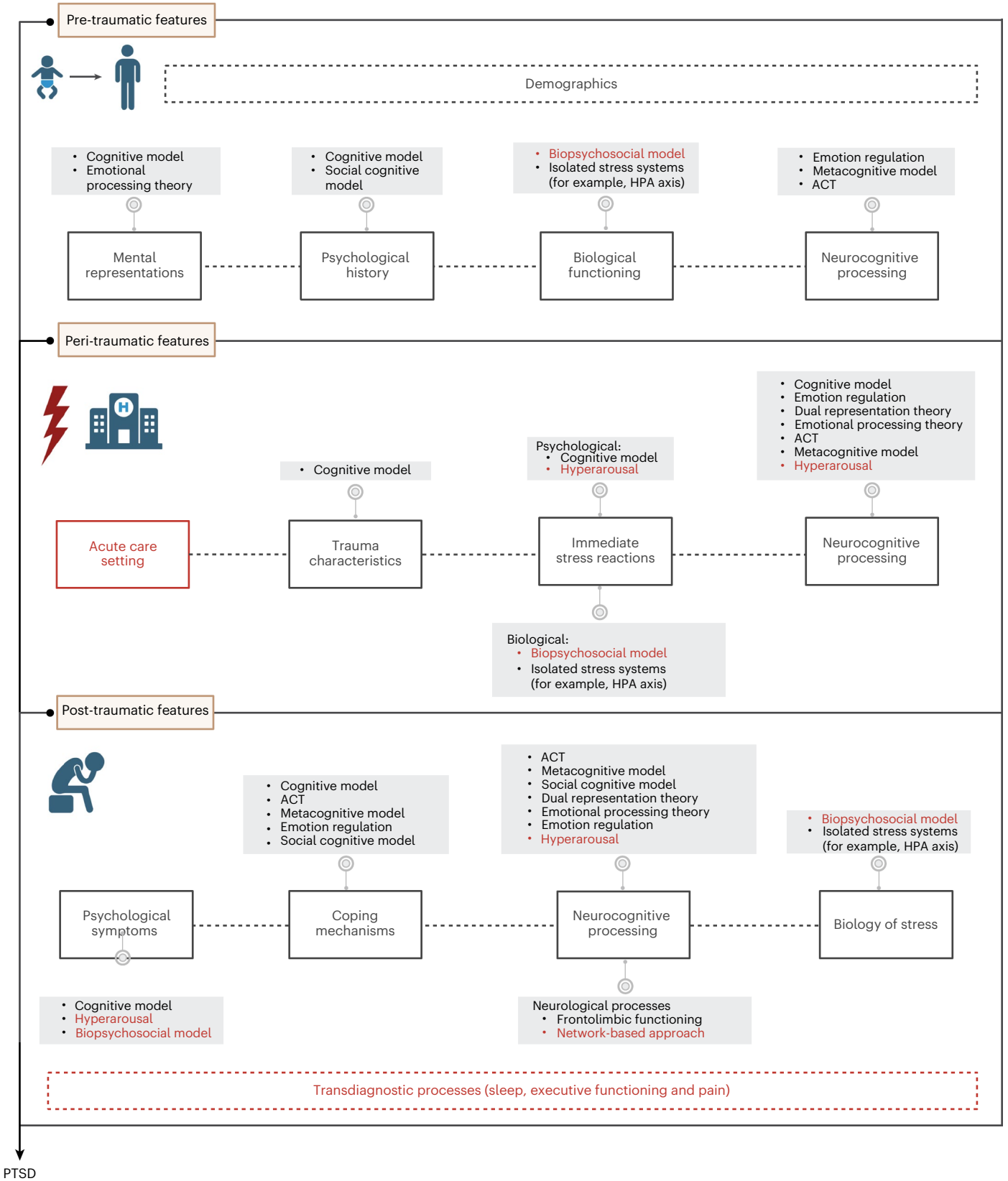

Fig. 3 | Integrative model of risk factors for PTSD development and/or severity. An integrative model is categorized into broader domains from current PTSD models. Risk factors insufficiently addressed by these models are marked in red. The structure reflects predictive values from ML models. The dashed lines represent potential links not evaluated in this review. Created with BioRender.com.

risk groups. Such findings may direct research toward a more detailed, mechanistic investigation of these predictors and, thus, improve our understanding and treatment of PTSD.

ML enables expansion of PTSD research also by identifying underrepresented group of predictors. Imaging studies revealed relevant regions beyond the frontolimbic pathway, such as the parietal and occipital areas, suggesting the necessity of a broader neural network perspective in PTSD[28,33–38]. These insights extend our understanding beyond the traditional focus on the hippocampus or amygdala, indicating a more complex neurobiological framework. Moreover, ML findings have highlighted risk factors from early medical and psychological care in acute settings[39,42,45]. Factors such as time of admission, medications prescribed and physicians' clinical impressions have emerged as highly predictive of PTSD development. These findings emphasize the influence of immediate medical care following trauma, highlighting an area that has been underresearched in PTSD models. Lastly, although theories have discussed the role of mental representations and preexisting knowledge about the traumatic events[16,18–20], only one study in this Analysis empirically assessed these aspects[54]. This study provided evidence of the impact of trauma anticipation on the likelihood to develop PTSD. This should be further investigated in future studies.

Can these findings be synthesized in an integrative model of PTSD?

The proposed integrative model does not aim to oversimplify the multifaceted nature of PTSD by forcing a universal synthesis of all predictors across disparate studies. Instead, it serves as an analytical tool to demonstrate the potential relationships between various predictors and established PTSD theories, respecting the timing of assessment (pre-, peri- and post-trauma) and their theoretical relevance. Its aim is to emphasize the complex interaction of these different areas, which traditional statistical and PTSD etiology models often overlook. ML approaches provide the opportunity to discuss this complexity. ML models have unique strengths in dealing with arrays of congruent and incongruent arguments without having to decide which predictor is 'true' or 'false' in the traditional sense. ML models do not create rigid hierarchies between features; instead, they allow the examination of multiple interacting predictors and their relationships to PTSD symptoms. This ability is particularly valuable given the heterogeneous nature of PTSD and the various factors that contribute to its development. The model shown in Fig. 3 organizes predictors into broad categories aligned with these temporal stages, which allows us to map how different predictors, even from diverse datasets such as gut microbiome, neuroimaging and demographic factors, relate to specific theoretical constructs of PTSD.

The included studies reviewed demonstrate that PTSD risk factors identified through ML approaches align with different theoretical models, even though these theoretical models often exist as separate entities and are not integrated.

For example, the ACT model emphasizes the relevance of cognitive flexibility for the development of PTSD, whereas Ehlers and Clark's cognitive model does not. These different model emphases, as well as the different time points for assessing the predictors, make it difficult for researchers and clinicians to interpret the ML results.

To address this, an integrative model has been developed that incorporates all these components and aims to highlight consensus and gaps in the current literature of ML-driven PTSD risk (Fig. 3). It encompasses pre-, peri- and post-traumatic factors linked to PTSD risk, categorizing them into broader themes consistent with existing theoretical models. The primary theoretical models considering these predictors in PTSD are noted, and underrepresented risk factors are highlighted in red for potential integration, which are further explained below.

Here, the example of the core symptom group hyperarousal[73] is used to illustrate how the various theoretical models and the results of the predictors derived with ML approaches can be connected and interpreted. Across studies, several predictors of PTSD were identified that, while playing an important role in research and clinical practice, are not yet adequately accounted for in the current mechanistic understanding of the disorder. For instance, several studies identified predictors presumably pertaining to hyperarousal such as sustained attention pattern[48,50,52], hyperreactivity[46,49], self-reported symptoms[39,40,42,46,47,51,55] or biological markers (such as heart rate[40,44,45], cortisol[40,49] and endocrine measures of hypothalamic–pituitary–thyroid (HPT) axis[45]). The clinical significance of hyperarousal symptoms in PTSD is well established: they contribute substantially to the disorder's overall symptomatology[74,75], exhibit resistance to therapeutic interventions[73,76] and may serve as a transdiagnostic link between PTSD and major depressive disorder[77,78]. Current research suggests these symptoms may arise from independent mechanisms[79], related to executive functions, attentional processes or emotion recognition[80], all of which were also found as independent predictors in included several studies[39,40,42,44–52,55]. Furthermore, this Analysis highlights the transdiagnostic nature of certain factors, particularly sleep disturbances. Sleep disturbances, identified through various measures[27,45,47,52,55], play a crucial role in PTSD, potentially extending beyond the avoidance strategy of nightmares as suggested by Ehlers and Clark's cognitive model[16]. For instance, rapid eye movement (REM) sleep deprivation impairs fear extinction memory consolidation[81,82], a core concept in PTSD models[16]. This demonstrates the need for a deeper understanding of these predictors as well as an understanding of the mechanisms and their transdiagnostic role in the development and maintenance of PTSD.

Limitations

As with most other reviews, this Analysis is limited by the heterogeneity of its underlying primary research. To limit this heterogeneity, only studies with a clear timing of assessment of PTSD and predictors were included. In addition, we focused on pre-, peri- and post-traumatic symptoms for PTSD, although PTSD symptoms could theoretically be assessed shortly after the trauma or years later. Although this distinction is not usually made in clinical models of PTSD development, it may reduce the complexity of the reality of the disorder.

Furthermore, in Table 1, we present studies that have used regression models and those that used classification models. Both categories yielded similar findings, and therefore we present their results together in Fig. 1.

In addition, a potential limitation is that many studies do not transparently provide a comprehensive list of all predictors examined, which may limit the ability to measure the frequency and significance of individual predictors across studies. This problem is critical as it may affect the interpretability and generalizability of the results. It underscores the need for standardized reporting practices in future research to improve the reliability and clarity of conclusions from ML studies on PTSD.

Recommendations and future directions

Increased transparency. This Analysis, particularly through the assessment of risk of bias, highlights the urgent need for improved reporting transparency. First, there is a critical need for more detailed descriptions of the clinical populations studied, for example, demographic information, trauma characteristics, timing of assessment of predictors and symptoms, and clinical phenomenology. Furthermore, it is of great importance that studies with nonsignificant or negative results are published and that the studies not only present the best-performing models but also transparently present all models that were tested. Even in published papers, results where ML models do not achieve high predictive performance may not be clearly disclosed, and the reasons for this are usually not discussed. This lack of transparency can bias interpretation and may limit a full understanding of the challenges and limitations associated with applying these models to PTSD research.

Assessing the generalizability of ML predictors. This is a crucial step to ensure that the results are robust and reliable in different situations. While external validation using independent datasets is the gold standard for assessing model performance, it requires a considerable amount of time and resources and is not always feasible due to geographical and logistical limitations. Indeed, only four studies in this Analysis used external validation sets, limiting our ability to comprehensively assess the generalizability of the identified predictors. However, alternative methods such as train–test splits and nested cross-validation can still provide valuable insights into the generalizability of the model's performance and are a state-of-the-art approach to guard against overfitting. These techniques, particularly with larger sample sizes, have been shown to efficiently learn data patterns and evaluate generalizable model performance[83,84]. Moreover, incorporating robust features and model perturbations during training has been proved to reduce the performance gap between training and testing environments, improving the generalizability of the findings without the need for external datasets[85]. Furthermore, a comparative analysis of studies that used external validation and train–test splits (or nested cross-validation) reveals that results across these methodologies are comparable and consistently align with established theories of PTSD. While only four studies used such external validation set, the results across all included studies are encouraging since the identified factors align with theoretical understanding of PTSD, such as prior trauma, hyperarousal symptoms, peri-traumatic dissociations and trauma severity (Extended Data Table 5). This consistency suggests that, despite the acknowledged superiority of external validation in assessing generalizability, the results of studies that did not use external datasets are nevertheless reliable. Such comparability underscores the potential utility of these other well-established validation methods, particularly in contexts where external validation is impractical. Nevertheless, we recommend that state-of-the-art techniques be used to evaluate generalizability and reduce the risk of overfitting and encourage scientists to collaborate to enable external validation of their findings.

Toward theory-driven ML. This Analysis underscores a strong correspondence between existing PTSD theories and data-driven research findings, suggesting the importance of incorporating theoretical knowledge in developing future PTSD predictive algorithms[86]. Applying theory-based insights is crucial for enhancing the accuracy and clinical relevance of these models. Theory-driven predictors can better guide the selection of relevant features, thereby increasing the accuracy of ML models in predicting PTSD risk. This Analysis showed that important features identified in theoretical models (such as attentional processes, memory impairments, fear learning mechanisms, social cognition, and self and world schemas) have not yet been considered in the reviewed studies. Furthermore, using a theory-informed approach could address an important risk of bias identified in the studies, where the number of participants was too low relative to the number of predictors[87]. This imbalance, noted in the prediction model risk of bias assessment tool (PROBAST) risk-of-bias assessment, suggests a need for more patients per variable. Only two studies achieved the minimum recommended rule of thumb of ten events per variable[30,55]. Focusing on theory-driven hypotheses could help overcome this limitation by narrowing down the number of predictors.

Taking advantage of ML innovations. This Analysis highlights the potential of the innovative digital approaches for risk stratification and diagnosis. For example, digital biomarkers may be an efficient approach for predicting PTSD, addressing the time and cost constraints of traditional assessments. Digital biomarkers, collected through digital devices such as smartphones or wearable sensors, can offer objective measures of physiological and behavioral processes. Early research, for example, has used audio and video data from trauma narratives to predict PTSD risk[26]. Natural language processing from written narrative of the trauma experience has also shown preliminary evidence of predictive value for PTSD diagnosis[88]. Furthermore, a study included in this Analysis suggested that nighttime arrival in the ED, a predictor identified by their ML algorithm, could be an easily collectible proxy for early indication of sleep disruption[45]. More studies are needed to further validate digital biomarkers and its underlying mechanisms.

Shifting from static predictors to predictors reflecting dynamic changes. ML and digital approaches facilitate not only the collection of dynamic predictors but also their analysis and interpretation. For instance, understanding how information processing (such as attentional, memory or fear processes) evolves after experiencing trauma has been key in PTSD studies for many years[80]. Applying ML to objectively measure these changes over time could offer more precise insights into the mechanisms driving the disorder.

Explainable artificial intelligence. Explainable artificial intelligence refers to the ability to obtain understandable and interpretable explanations for the predictions and classifications provided by black box models. Only a small subset of the studies included in the present review used such techniques[26,38,44–46,50], limiting the understanding of predictor interactions and directionality of associations (Extended Data Table 7). It is important not only to develop highly accurate ML algorithms but also to be able to interpret their results, for example, to make the ML results understandable to scientists, clinicians and patients. This is especially, but not only, important for shared clinical decision-making[89].

Conclusion

Using ML algorithms, several potential predictors have been identified, most of which are consistent with existing knowledge of PTSD, while others extend existing knowledge. The use of ML to predict PTSD offers a promising avenue for identifying and stratifying individuals at risk in multiple settings. When applied in the medical field, ML approaches have the potential to provide insights that could determine new intervention targets and the right timing of intervention. Furthermore, it is crucial for progress in this area to recognize the current limitations of ML studies so that future research can address these knowledge gaps.

Methods

Literature search strategy

We conducted a web-based systematic literature search in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[90]. We selected the databases after defining the search string keywords pertaining to PTSD and ML (Extended Data Table 1). This study reviewed three databases on 13 November 2023: PubMed, Web of Science and Scopus. Inclusion criteria were as follows: (1) cross-sectional and longitudinal studies written in English and published in peer-reviewed journals; (2) use of supervised ML approaches to identify predictors for PTSD risk; (3) clear definition of the timeline for assessing both PTSD symptoms/diagnosis and predictors; (4) PTSD symptomatology based on DSM-III, DSM-IV, DSM-5, ICD-9 or ICD-10 criteria; and (5) inclusion of participants 18 years of age and older. This Analysis was not registered; therefore, the protocol was not prepared.

Exclusion criteria were as follows: (1) identification of risk factors with linear or logistic regressions or multilevel modeling and structural equation modeling; (2) meta-analyses or systematic reviews, (3) assessment of PTSD during an ongoing traumatic situation (such as domestic violence); and (4) use of another pathology as a comparison group for the algorithm (for example, traumatic brain injury).

Study selection

After removing duplicates, two assessors (first and last authors) independently identified studies eligible for inclusion through a two-step procedure. First, a selection based on title and abstract was made

using the above-mentioned criteria. Disagreements were discussed, and papers that raised doubts were considered in the next step. Subsequently, the full texts of this selection were critically examined to determine whether the papers met the inclusion criteria (Extended Data Fig. 1). Disagreements were resolved through discussion.

Data extraction and synthesis

We extracted the following information from all included studies: first author, year of publication, sample and demographic characteristics (sample size, age range, mean age, gender distribution, recruitment site and type of trauma), source of data, predicted outcome (classification or regression), characteristics of the ML approaches (including resample techniques, characteristics of model development and validation, type of ML approaches and predictive performance), top 15 predictors identified in the ML approach as contributing the most to the model's accuracy or predictive power depicted in the variable importance ranking, timeline of assessment of both PTSD outcome and predictors and type of PTSD assessment (self-reported or semi-structured interview) along with the classification system used for PTSD diagnosis.

The quality of the studies was evaluated through a risk-of-bias assessment using PROBAST[91]. PROBAST evaluates several key aspects of prediction model studies through 20 signaling questions grouped into four domains: participant selection, predictors, outcome and analysis[91]. These domains help in identifying methodological flaws and provide guidance on assessing the applicability of the model[91]. The tool aims to assess the risk of bias and any concerns regarding the applicability of studies developing, validating or extending prediction models[91]. This study involved a systematic review of literature across three databases: PubMed, Web of Science and Scopus, conducted on 13 November 2023. The systematic literature review was conducted following the PRISMA guidelines. All search terms and information about the reviewed articles are available in 'Keywords for literature searches' in Supplementary Information, data extracted from included studies (Supplementary Data 1).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

All of the data supporting the findings of this study are available in the Analysis and its Supplementary Information.

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Competing interests

The authors declare no competing interests.

Additional information

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