Current state of science in machine learning methods for automatic infant pain evaluation using facial expression information: study protocol of a systematic review and meta-analysis

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ABSTRACT

Introduction Infants can experience pain similar to adults, and improperly controlled pain stimuli could have a long-term adverse impact on their cognitive and neurological function development. The biggest challenge of achieving good infant pain control is obtaining objective pain assessment when direct communication is lacking. For years, computer scientists have developed many different facial expression-centred machine learning (ML) methods for automatic infant pain assessment. Many of these ML algorithms showed rather satisfactory performance and have demonstrated good potential to be further enhanced for implementation in real-world clinical settings. To date, there is no prior research that has systematically summarised and compared the performance of these ML algorithms. Our proposed meta-analysis will provide the first comprehensive evidence on this topic to guide further ML algorithm development and clinical implementation.

Methods and analysis We will search four major public electronic medical and computer science databases including Web of Science, PubMed, Embase and IEEE Xplore Digital Library from January 2008 to present. All the articles will be imported into the Covidence platform for study eligibility screening and inclusion. Study-level extracted data will be stored in the Systematic Review Data Repository online platform. The primary outcome will be the prediction accuracy of the ML model. The secondary outcomes will be model utility measures including generalisability, interpretability and computational efficiency. All extracted outcome data will be imported into RevMan V5.2.1 software and R V3.3.2 for analysis. Risk of bias will be summarised using the latest Prediction Model Study Risk of Bias Assessment Tool.

Ethics and dissemination This systematic review and meta-analysis will only use study-level data from public databases, thus formal ethical approval is not required. The results will be disseminated in the form of an official publication in a peer-reviewed journal and/or presentation at relevant conferences.

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Strengths and limitations of this study

► This research will be the first systematic review and meta-analysis quantitatively comparing accuracy among current facial expression-based machine learning neonatal and infant pain prediction algorithms.
► This research will be the first study to comprehensively assess accuracy, generalisability, interpretability and computational efficiency of these machine learning algorithms by both model characteristics (eg, algorithm type, task type, data input format, etc) and patient/procedure characteristics (eg, age, disease type, procedure type, etc).
► The major limitation of this study will be the potential clustering effects due to the limited number of infant facial expression databases collected in real-world clinical environments or controlled trials available for modelling research.
► Many of these machine learning prediction studies will use the same database for modelling, and we will use mixed-effects meta-regression to address this clustering effect.

INTRODUCTION

Neonates and infants feel and experience pain much like or even more sensitively than adults, but their pain management is under-emphasised even for today.1 2 Historically, some clinicians and scientists believed that babies’ brains are not fully developed enough to experience pain as adults do. Combined with the fear of usage of pain medications in infants due to potential side effects, pain relief treatments are inadequately provided to infants and neonates receiving painful procedures despite the fact that these treatments are provided to elder children and adults every day.5–7 However, previous research has found that individuals’ pain experience during infancy can have both short-term...
and long-term adverse influences on their cognitive and neurological function development. Therefore, appropriate pain relief for infants is a necessity, and there is a need for development of a systematic guideline for infant and neonatal pain management.

The biggest challenge to developing an infant and neonatal pain management guideline is the accurate measurement of pain. Infant pain is known to be difficult to evaluate because infants cannot accurately assess and verbally communicate their pain experience. The current evaluation system heavily relies on observer-based measurements obtained by trained clinicians and nurses. These observer-based assessment tools commonly integrate both physiological variations (e.g., breathing pattern, heart rate, oxygen saturation, etc.) and behavioural changes (e.g., facial expression, crying, body activity, sleeping state, etc.), and a summarised score is calculated based on clinical observations and physiological monitoring results. In the last decades, several indicator-based pain scale systems have been developed and validated for infant and neonatal pain assessment. Nevertheless, these pain scale-based systems have two major limitations: subjectivity and human resource expense. Because pain measures are obtained by human observers, the pain assessment process is inevitably subjective and suffers from observer bias. Depending on the practitioner’s clinical experience, training level and even spontaneous or personalised factors, their assessment results can be vastly different and inaccurate, which could be either overly sensitive or fail to discriminate between different levels of pain or pain from normal physiological activities (e.g., discomfort, hunger, stress, etc). In addition, these tools are human-resource intensive and require a considerable amount of training to master. Under scenarios when continuous frequent pain monitoring is needed (e.g., postoperation, necrotising enterocolitis, abdominal colic, epidermolysis bullosa, etc), the traditional human observer-based assessment method is inefficient and resource-intensive.

In the emerging field of computer vision and emotion research, human facial expression, a promising behavioural indicator for emotion and pain recognition, has been studied and used for automated infant pain assessment for years. Modern data scientists can use state-of-the-art machine learning (ML) algorithms to extract, track and analyse human facial expressions from recorded images and video data to predict pain and emotions. Compared with traditional observer-based pain scale systems, the ML algorithm has a unique opportunity to provide objective and continuous pain detection and assessments for neonates and infants. The first published ML-based infant pain evaluation study, known as the Classification of Pain Expressions (COPE) project, collected facial image data in four routine clinical procedures and used three different face classifiers (principal component analysis, linear discriminant analysis and support vector machine) to recognise infant painful expressions. Since then, researchers have developed several different ML methods (e.g., Probabilistic Neural Network, Gaussian, Nearest Mean, Convolutional Neural Networks, Boosted Gabor Features, etc) to classify pain/no-pain images using COPE or similar databases, and many have shown satisfactory performance. In recent years, there have also been several modern projects directly analysing infant facial video sequences using deep learning methods to recognise and assess pain, which have also presented considerable high accuracy. ML-based automated pain assessment algorithms have the potential to control observer/recording bias from human observations, help reduce the training costs and relieve human resource burden when continuous or high-frequency clinical pain measurements are required. However, no research has quantitatively analysed and compared the performance of these pain prediction methods. In addition, these computational algorithms are rarely published in general or professional medical journals, therefore their clinical utility and interpretability are limited. In our proposed project, we will conduct a systematic review and meta-analysis to provide summarised and quantitative evidence on the performance of facial expression-based ML methods for infant pain assessment.

Objectives

The primary objective of our study is to assess the accuracy (outcome) of automatic facial expression ML algorithms (test measurement method) compared with various indicator-based pain assessments (gold-standard) in assessing pain intensity for infants experiencing pain (population). Additionally, we plan to perform subgroup analyses to compare model accuracy, generalisability, interpretability and computational efficiency by both model and study population characteristics.

Methods and analysis

Our study team prepared this study protocol following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols checklist. Our research question was developed based on the PICO/PECO research framework. Details are reported in table 1.

Eligibility criteria

Our proposed project will systematically search and include all eligible ML methodological and application studies that use facial information to automatically assess pain among infants. The population of our study will be infants experiencing pain. Infants will be defined as young children no more than 12 months, including newborn or neonate, full term, premature and postmature infants. Infant pain can be heel stick, arterial puncture, intravenous cannula, finger stick, nasal aspiration or postoperation pain. We intend to include computer science algorithms papers (methodology and performance evaluation), clinical research (application studies), systematic reviews and meta-analysis research for analysis. Regular...
reviews and qualitative studies will be excluded from the analysis, but their reference lists will be screened to identify potential eligible studies. Systematic review and meta-analysis will be used for the extraction of citations for reducing publication bias. The study exclusion criteria will include: (1) algorithm not for automatic infant pain assessment; (2) algorithm not using facial expression information; (3) not computer science algorithms paper (methodology and performance evaluation), clinical research (application studies) or systematic reviews and meta-analysis concerning ML methods; (4) no measurement of algorithm accuracy (primary outcome); (5) facial expression data not in image or video format; (6) children more than >12 months and adults; (7) research not written in English language.

### Search strategy

An experienced medical librarian (LLP) with systematic review expertise will conduct searches in four major public electronic medical and computer science databases including Web of Science, PubMed, Embase and IEEE Xplore Digital Library from January 2008 to present. We will search from 2008 onwards because to the best of our knowledge, major advances in ML techniques, especially for deep learning methods (eg, Convolutional Neural Network), started to rapidly evolve and be widely applied within the most recent 5-6 years due to the unprecedented functional improvement of hardware (eg, GPU for computing) and parallel-computing capacity (eg, Hadoop).\(^3\)\(^3\) Thus, algorithms developed 10 or 20 years ago may not be applicable or clinically meaningful because new modern algorithms would easily outperform them. In our study, we intend to include a balanced collection of both classic and modern algorithms, so we have decided to search for studies starting from January 2008 to assure an extended 10-year long search period for good coverage of ML studies. To account for publication bias, we will include qualitative review articles and systematic review and meta-analysis articles to identify missing unpublished literature through their reference lists. We will perform forward and backward citation screening through citations and reference lists of systematic reviews to find more relevant papers. We will also search related professional meeting abstracts and preprints (eg, IEEE conferences, Conference on Computer Vision and Pattern Recognition, Conference on Neural Information Processing Systems, Topics and Advances in Pediatrics, Florida Academy of Pain Medicine, 2018 and 2019 Annual Scientific Meeting, arXiv.org). We will use keywords and subject headings related to three concepts: infants, pain and ML. Multiple synonyms for each concept will be incorporated into the search. Details of search strategies are provided in Table 2.

### Study selection

Two authors (DL and DC) will independently review and screen searched article records to identify eligible studies according to our inclusion and exclusion criteria using the Covidence digital platform. A third investigator (HD or WZ) will resolve the disagreements between these two evaluators. In this step, two authors will screen titles and abstracts of searched articles for primary exclusion on the Covidence platform. We will pilot the process by screening the first 10 studies under the principal investigator (PI)’s supervision. Since our study topic is uniquely focused on ML algorithms on infant pain prediction, it will require expertise in two fields including computer science and medicine. We believe that it will be preferable and time-efficient to have both the computer scientist and the physician work together to review the full-text to avoid selection bias (ie, only read the sections they are familiar with) in the full-text screening process. It would be ideal to have two independent groups of specialists (two computer scientist-physician pairs as review teams), but our research team has only one data scientist (DL). Therefore, in our study, two authors DL (computer scientist) and DC (physician) will screen the full-text together to decide the eligibility of included studies after the title and abstract screening round. The PI (HD) will resolve the conflicts or answer questions when needed. Moreover, because many health-related computer science studies are reported with limited details,\(^3\) it is difficult for a single field specialist (either a computer scientist or a physician) to understand and extract the necessary information alone. We will further discuss this issue in the ‘Discussion’ section. Once eligible studies are identified, we will extract study information for data synthesis. The measures in the identified studies contain both quantitative and qualitative data, thus we will perform quantitative data synthesis or qualitative summary as appropriate. Excluded studies will be listed in the PRISMA flow chart with specific reasons for exclusion in figure 1.

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**Table 1** PICO/PECO research question development

| Name          | Description                                                                                                                                 |
|---------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Population    | Infants experiencing pain.                                                                                                                   |
| Intervention/ | The intervention/exposure will be pain assessment using automatic facial recognition ML algorithms.                                           |
| Exposure      |                                                                                                                                              |
| Control       | The study control will be indicator-based pain assessment gold-standard (eg, pain scale, pain score and category).                           |
| Outcome       | Primary outcome: Model accuracy by predicted assessment measures type: 1. Numeric score: mean SE or equivalence; 2. Categorical pain degree (yes/no; no/moderate/severe); Concordance statistic (AUC ROC) or equivalence. Secondary outcomes: 1. Generalisability; 2. Interpretability; 3. Computational efficiency and related costs. |

Definition of infants: infants will be defined as young children no more than 12 months, including newborn or neonate, full term, premature and postmature infants.

AUC ROC, area under the curve for receiver operating characteristic curve.
Table 2  Search strategy

| PubMed | | Embase | | IEEE | | Web of Science |
| --- | --- | --- | --- | --- | --- |
| #1 | ‘Infant’(Mesh) | | | | |
| #2 | (infant*(Title/Abstract)OR neonat*(Title/Abstract)OR baby(Title/Abstract)OR babies(Title/Abstract)OR newborn*(Title/Abstract)) | | | | |
| #3 | #1 OR #2 | | | | |
| #4 | ‘Pain’(Mesh) OR ‘Pain Measurement’(Mesh) | | | | |
| #5 | (pain*(Title/Abstract)OR hurt*(Title/Abstract)OR agonising*(Title/Abstract)OR agonising*(Title/Abstract)OR suffering*(Title/Abstract)OR distress*(Title/Abstract)) | | | | |
| #6 | #4 OR #5 | | | | |
| #7 | (‘Machine Learning’(Mesh) OR ‘Algorithms’(Mesh:NoExp)OR ‘Expert Systems’(Mesh) OR ‘Limit of Detection’(Mesh) OR ‘Artificial Intelligence’(Mesh:NoExp)OR ‘Neural Networks’ (Computer)”(Mesh) OR ‘Facial Recognition’(Mesh) OR ‘Biometric Identification’(Mesh:NoExp)OR ‘Facial Expression’(Mesh:NoExp)OR ‘pattern recognition, automated’(Mesh)) | | | | |
| #8 | (‘facial recognition’(title/abstract)OR ‘pain recognition’(title/abstract)OR ‘pain detection’(Title/Abstract)OR ‘detecting pain’(title/abstract) OR automated(Title/Abstract)OR automatic(Title/Abstract)OR ‘recognising pain’(title/abstract)OR ‘machine learning’(Title/Abstract)OR ‘deep learning’(Title/Abstract)OR algorithm*(Title/Abstract)OR ‘neural network’(Title/Abstract)OR ‘neural networks’(Title/Abstract)OR SVM(Title/Abstract)OR ‘support vector machine’(Title/Abstract)OR ‘support vector machines’(Title/Abstract)OR ‘artificial intelligence’(Title/Abstract)OR RVM(Title/Abstract)OR ‘relevance vector machine’(Title/Abstract)OR ‘relevance vector machines’(Title/Abstract)OR AAM(Title/Abstract)OR ‘active appearance model’(Title/Abstract)OR ‘active appearance models’(Title/Abstract)OR ‘k NN’(Title/Abstract)OR ‘k nearest neighbour’(Title/Abstract)OR ‘random forest trees’(Title/Abstract)OR ‘random forest tree’(Title/Abstract)OR PNN(Title/Abstract)OR ‘gaussian classifier’(Title/Abstract)OR ‘gaussian classifiers’(Title/Abstract)OR ‘nearest mean classifier’(Title/Abstract)OR ‘nearest mean classifiers’(Title/Abstract)) | | | | |
| #9 | #7 OR #8 | | | | |
| #10 | #3 AND #6 AND #9 AND (“2008/01/01”(PDAT) : ‘3000/12/31’(PDAT)) | | | | |
| #1 | ‘infant’/exp | | | | |
| #2 | infant*:ab,ti OR neonat*:ab,ti OR baby:ab,ti OR babies:ab,ti OR newborn*:ab,ti | | | | |
| #3 | #1 OR #2 | | | | |
| #4 | ‘pain’/exp OR ‘pain measurement’/de | | | | |
| #5 | pain*:ab,ti OR hurt*:ab,ti OR agony:ab,ti OR agonising:ab,ti OR suffering:ab,ti OR distress*:ab,ti | | | | |
| #6 | #4 OR #5 | | | | |
| #7 | ‘algorithm’/de OR ‘machine learning’/exp OR ‘expert system’/de OR ‘limit of detection’/exp OR ‘artificial intelligence’/exp OR ‘pattern recognition’/exp | | | | |
| #8 | (‘facial recognition’:ab,ti OR ‘pain recognition’:ab,ti OR ‘pain detection’:ab,ti OR ‘detecting pain’:ab,ti OR automated:ab,ti OR automatic:ab,ti OR ‘recognising pain’:ab,ti OR ‘machine learning’:ab,ti OR ‘deep learning’:ab,ti OR algorithm*:ab,ti OR ‘neural network’:ab,ti OR ‘neural networks’:ab,ti OR SVM:ab,ti OR ‘support vector machine’:ab,ti OR ‘support vector machines’:ab,ti OR ‘computer vision’:ab,ti OR ‘artificial intelligence’:ab,ti OR ‘relevance vector machine’:ab,ti OR ‘relevance vector machines’:ab,ti OR AAM:ab,ti OR ‘active appearance model’:ab,ti OR ‘active appearance models’:ab,ti OR ‘k NN’:ab,ti OR ‘k nearest neighbour’:ab,ti OR ‘random forest trees’:ab,ti OR ‘random forest tree’:ab,ti OR PNN:ab,ti OR ‘gaussian classifier’:ab,ti OR ‘gaussian classifiers’:ab,ti OR ‘nearest mean classifier’:ab,ti OR ‘nearest mean classifiers’:ab,ti | | | | |
| #9 | #7 OR #8 | | | | |
| #10 | #3 AND #6 AND #9 AND(2008–2019)/py | | | | |
| | | | | | |
AAM, active appearance model; PNN, probabilistic neural network; RVM, relevance vector machine; SVM, support vector machine.
Data management
We will import all eligible study records information including author, title and abstract into the Covidence platform. This online tool will facilitate the literature review process by integrating all reviewing activities on one platform with logged records. We will design a digital data extraction form to store study information using the Systematic Review Data Repository (SRDR) online repository website. Moreover, we will upload related data for each step and will update our protocols and analytic plans on the Open Science Framework website for transparency and version control purposes (https://osf.io/f9t4v/).

Data extraction
We will extract the study-level data from all eligible studies using a prepared data extraction form created by the SRDR online tool. We will divide items within the data collection form into four blocks: (1) study information including publication year, author information, funding or sponsorship information, type of study, journal name and PICO elements; (2) database information including name, subject size, image or video size; (3) patient demographic information including gender, age, race, disease diagnosis and types of pain; (4) ML methodological information including ML model name, type, format of input feature, optimisation algorithm, objective function, feature extraction methods, type of extraction feature and computational efficiency and cost, etc. An example of the data extraction form is presented in table 3.

Machine learning methods
The most commonly used ML methods for this particular question could include multiple general categories of models such as support vector machine, relevance vector machine, active appearance model and k-nearest neighbour, random forest trees, probabilistic neural
network (PNN), Gaussian and nearest mean classifier, etc. In order to summarise and analyse these ML methods systematically, each ML algorithm will be presented and partitioned into a set of technical properties including: (1) feature: which features the algorithm uses (eg, pixel feature, action units, landmarks or transformed feature); (2) model: the underlying mathematical model (eg, artificial neural networks, random forests); (3) optimisation: the computational algorithm to find the optimum solution (eg, stochastic gradient descent, Bayesian variational inference); (4) performance: the measures for assessing the performance of the model (eg, our primary outcome accuracy, computational efficiency, etc). In this study, we will first collect the qualitative and descriptive information of these properties and then explore whether we can manually categorise them into fixed and organised classes. If enough data points can be obtained for each class, we will further perform an intraclass correlation analysis for subgroup analysis.

### Study outcomes

Our primary outcome will be the measurement of model prediction accuracy (eg, area under the curve for receiver operating characteristic curve (AUC ROC), F1 score and proper score function such as Brier score if available). The secondary outcomes will be model utility measures including generalisability, interpretability, computational efficiency and cost.

#### Primary outcome: standardised measurement of model prediction accuracy

Based on our previous experience,25 36 it is likely that the experimental setting, patient population, methods and results reporting styles in these eligible studies could be heterogeneous in presentation but clustered by used infant pain databases. To describe the model prediction accuracy, we will extract both qualitative descriptions and quantitative measures from original texts in these studies. The accuracy of the model prediction usually comprises two pieces of information: calibration and accuracy. Considering computer science studies usually use a different system for model reporting (eg, SEs and correlation coefficients) compared with statistical learning (eg, discrimination, calibration, Brier score, etc), our study will mainly focus on the discrimination domain of the model. After collecting the qualitative description of these accuracy measures, we will perform standardisation procedures on them for further quantitative meta-analysis. For regression algorithms, error measurements (eg, mean absolute error) will be standardised and converted to mean square error (MSE) for parallel comparisons. All correlation measurements (eg, Pearson’s correlation) will be converted to ranked correlation (eg, Spearman’s correlation). For classification algorithms, all accuracy measures will be converted to AUC ROC and F1 score for comparisons. The measures that cannot be standardised will be qualitatively reported as original values and excluded from the analysis. If diagnostic test accuracy measures such as sensitivity and specificity are reported, this information will also be collected.

#### Secondary outcomes: generalisability, interpretability and computational efficiency

We will conduct qualitative assessment of model generalisability and interpretability as study secondary outcomes.
These qualitative assessments will be performed by our study staff (DL or DC) in the form of judgement ranks. The levels of judgement rank for secondary outcomes will include high, moderate, low and very low. Computational efficiency and cost data of models will be analysed if data are available for quantitative analysis. Otherwise, they will be assessed qualitatively in judgement ranks.

Incomplete information and missing data
We will try to collect missing study information by contacting the authors if we cannot find the information through public channels. If we cannot obtain sufficient data, then these missing data will be omitted from the data synthesis and analyses.

Risk of bias assessment
The risk of bias assessment will be performed by two authors (DC and DL) using the Prediction model study Risk of Bias Assessment Tool (online supplementary appendix 1). It includes 20 signalling questions across four domains (participants, predictors, outcome and analysis). Based on the ratings of signalling questions, risk of bias for each domain will be ranked as low risk, high risk or too unclear for judgement.

Assessment of reporting quality
Liu et al found that the reporting of studies evaluating ML models was often incomplete and non-standardised, which increasingly became a barrier to robust evaluation of artificial intelligence-based models. Collins et al highlighted that complete and transparent reporting of the key aspects of ML prediction model studies is vital to ensure the quality and interpretability of the studies in medical and technical fields. In order to assess the reporting quality of eligible studies, we will use Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (online supplementary appendix 2) checklist. Each item will be ranked as no report, inadequate report and adequate report, scored as 0, 1 and 2, respectively. To account for specific methodological aspects of ML algorithms studies, we developed a customised ML-specific reporting checklist for this study as the supplementary ML-method reporting assessment tool (online supplementary appendix 3). This assessment checklist includes description of database, research team, data preprocessing, method and approach, objective function, optimisation technique and computational efficiency. Each item will be ranked as no report, inadequate report and adequate report, scored as 0, 1 and 2, respectively.

Statistical analysis and data synthesis
Extracted outcome data stored in the SRDR website will be imported into RevMan V.5.2.1 software and R V.3.3.2 for analysis. Because reported model outputs may be different across individual studies, we will use standardised measures to synthesise model accuracy and calibration. In order to assess accuracy, we will use the C-statistic (AUC ROC) for classification models and MSE for regression models along with their 95% CIs. To assess calibration, we will use the Hosmer-Lemeshow $\chi^2$ test and ranked correlation, if applicable. To measure heterogeneity, we plan to use a Galbraith plot and Higgins and Thompson’s $I^2$. A fixed-effects model will be used only if there is no evidence of statistical heterogeneity. We will pool the summary measures across the studies using a random effects model optimised using DerSimonian and Laird’s method, if considerable heterogeneity is indicated ($I^2>50\%$). Furthermore, we will also explore the possible sources of heterogeneity from both clinical and methodological perspectives to provide an explanation or conduct subgroup analysis. Meta-regression will be conducted if applicable.

Subgroup analysis
We intend to conduct subgroup analyses by ML model types (eg, regression vs classification, neural networks vs traditional ML), facial data input format (eg, images vs landmarks) and medical procedure type (eg, acute procedural pain vs postoperative pain). More post hoc exploratory subgroup analyses will be decided during the process of data extraction and analysis.

Publication bias
We will search related professional meeting abstracts, technical preprints, reference lists of qualitative review articles, systematic reviews and meta-analysis articles to identify missing unpublished literature (details in ‘Search strategy’ section). We will use contour-enhanced funnel plots to assess publication bias.

Confidence in cumulative evidence
Confidence in cumulative evidence will be conducted in accordance with the Grading of Recommendations, Assessment, Development and Evaluations guideline. Inconsistency will be assessed using the $I^2$ test and Galbraith plot as described in previous sections. Indirectness will be assessed by examining the collected PICO elements of eligible studies and comparing generalisability (one of our secondary outcomes). Imprecision will be assessed by examining the study sample sizes and CIs of outcomes of interest.

DISCUSSION
Neonatal care has developed rapidly within the last decade and has greatly improved survival outcomes of premature and sick neonates. However, when large numbers of painful and stressful treatment procedures were performed on infant patients, only very few were accompanied by adequate analgesia. Several researchers found that neonatal intensive care unit (NICU) admission rates increased steadily yearly and large numbers of neonates could be exposed to acute pain from invasive procedures or prolonged pain from surgery or inflammation. Traditional observer-based infant pain assessment is difficult to train, time-consuming, labour-intensive,
subjective and a source of conflict in NICU care. Developing an automatic pain assessment instrument will be resource-saving and improve the quality of care through fast and accurate pain assessment.

Infants’ responses to pain and stress are non-specific and can be easily misinterpreted. The Newborn Individualised Developmental Care and Assessment Programme (NIDCAP) is widely used for infant stress assessment. Holsti et al also developed multidimensional assessments, including the full NIDCAP to distinguish pain and stress. However, these human-based instruments are by definition labour-intensive and expensive to implement, and understanding how pain and stress can affect infant development and properly evaluating them is a highly specialised practice area requiring substantial training. Mansor et al developed a PNN classifier to distinguish pain from other non-pain tasks (rest/cry, air puff, friction) in the COPE database, and results were remarkable with the classification accuracy >90%. This indicates that ML methods have the potential to distinguish pain and stress when combined with other clinical indicators.

The age of artificial intelligence has come. Computer scientists are now equipped with tools and algorithms to train machines to identify behavioural and physiological indicators associated with pain. Facial expression-based ML algorithms have the potential to overcome observational bias, reduce training costs and provide possibilities for continuous infant pain monitoring without clinician involvement. It is promising that these ML algorithms will provide fast, accurate and continuous pain assessment in both routine practice and NICU with better training data and more advanced ML methods. Our proposed systematic review and meta-analysis will provide the first systematic and quantitative report of model accuracy, generalisability and interpretation capability of different available ML algorithms for neonatal and infant pain assessment. Also, it is not common for computer scientists to clearly disclose costs related to their algorithms. We hope computer scientists can disclose both training and implementation.

cases of disagreement and ensure the absence of errors. All authors approved the publication of the protocol.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** This systematic review and meta-analysis will only use study-level data from public databases, thus formal ethical approval is not required.

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