Report on a problem studied in the N-CODE Study Group April 2025

Group 3. Sudden Unexpected Death in Epilepsy (SUDEP): Predicting Risk of SUPEP Using Biomarkers and an AI Framework

Lance Watkins, Brenden Mclean , Al-Nuaimi, Zygimantas Puras Phil Tittensor, Suvadeep Maiti, Rongkai Li, Ruoxue Duan, Leandro Junges, Amir Aly Christopher James, Rohit Shankar.

The Problem:

Epilepsy is a chronic neurological disorder manifesting with seizures caused by abnormal electrical activity in the brain and affects over 70 million people globally [1]. Epilepsy is not a benign neurological condition. Sudden Unexpected Death in Epilepsy (SUDEP) is the leading cause of death for people with epilepsy (PWE) but remains poorly understood [2]. It may account for approximately 17–50% of epilepsy-related deaths in the US [3] and 42% in the UK. Between 1999–2017, US epilepsy-related mortality rose by 98.8%, while the UK saw a 69% increase from 2004-2014 [4]. Annually, SUDEP causes about 7,000 deaths in the US and Europe [5]. Total epilepsy costs to the NHS are approximately £2 billion annually [6]. The prevalence of SUDEP in people with epilepsy in general is approximately 1.4 per 1000 person years [7]. However, with cumulation of risk factors this increases, and the prevalence in treatment resistant epilepsy is significantly higher.

With no methods existing to effectively predict SUDEP risk [8], preventing SUDEP remains challenging, highlighting the need to understand aetiology, risk factors, and identify potential biomarkers [9]. There are established risk factors associated with SUDEP deaths. Some of these risk factors are static and some may be modifiable. Factors with the strongest association include active seizures, frequency of generalized tonic-clonic seizures (GTCS), and presence of Intellectual Disability [10]. Other important modifiable factors include medication compliance, sleep pattern, sleep position, Nocturnal GTC seizures, night-time monitoring, and other lifestyle choices [11]. Unfortunately, to date we are unable to accurately predict SUDEP risk on an individual basis. There is not enough evidence to demonstrate the weighting of any of these risk factors on the outcome.

SUDEP often occurs following a GTCS, more frequently at night/during sleep [7]. Continuous ECG monitoring for PWE with frequent GTCS can identify high-risk individuals [9]. GTCS are associated with specific EEG patterns reflecting aberrant brain activity during seizures [10]. Artificial Intelligence (AI) is increasingly utilised in healthcare, which can enhance diagnostic accuracy [12].

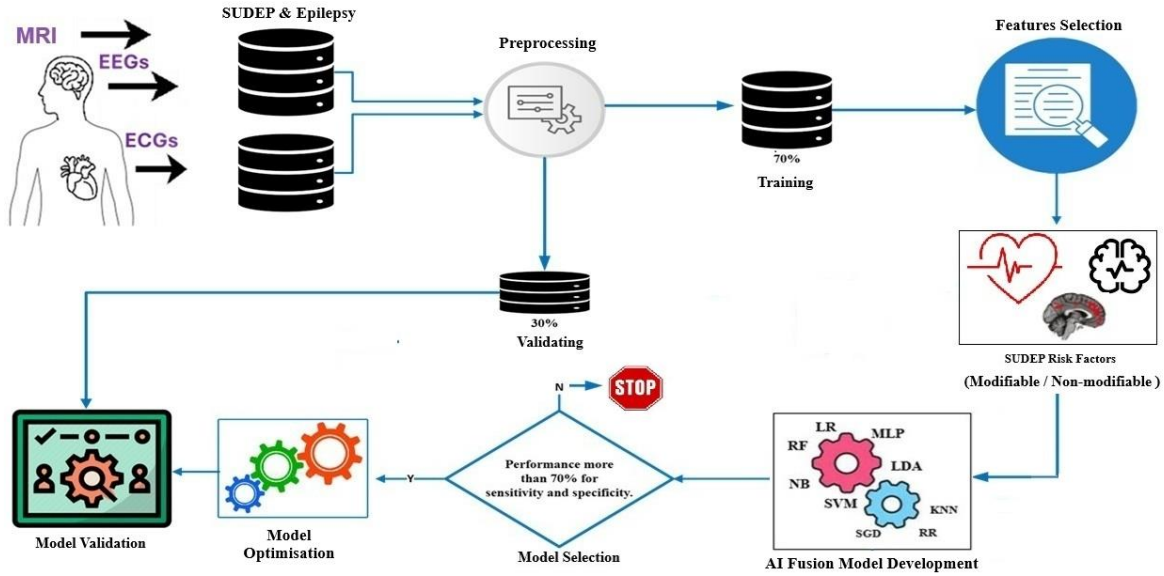
The aim of this investigation is to develop an Artificial Intelligence (AI) supported model to identify risk markers for SUDEP from pre-existing clinical data, including Electroencephalogram (EEG), Electrocardiogram (ECG), clinical characteristics (including known SUDEP risk factors). From this the group will look to develop a clinical tool that will be able to stratify clinical risk on an individual level based upon the interpretation of standard clinical information.

The Proposed Solutions:

Methodology

AI-driven methods can be employed to analyse large datasets and identify novel features beyond traditional clinical indicators. AI serves as a powerful tool for developing intelligent models capable of handling and evaluating a vast number of features using diverse analytical techniques. Our goal is to identify key features that show a strong association with SUDEP, which could aid in early diagnosis. This study specifically aims to declare asymptomatic features and assign the risk factors related to SUDEP.

Figure 1 illustrates the pipeline procedure for developing the AI fusion model to diagnose SUDEP



1. Dataset

Three types of datasets will be investigated to develop an AI model for detecting people at high risk of SUDEP. These datasets include EEG, ECG, and MRI.

These datasets will be incorporated with AI to develop a new feature based on combining the features of EEG, ECG, and MRI.

2. Preprocessing

3. Features Extraction

Three categories of features will be explored, each corresponding to a different dataset type. The following are examples of features that will be analysed.

a. EEG features
b. ECG features
c. MRI features

4. Features Selection

Selected features will be stratified into modifiable and non-modifiable risk factors based on clinical relevance. Modifiable factors such as medication adherence and smoking status will receive special emphasis during model interpretation to guide potential preventive interventions. Non-modifiable

factors (e.g., age, sex) will be treated as covariates to control for confounding influences. The stratification into modifiable and non-modifiable factors reflects clinical insights incorporated during feature selection.

5. Model Development

Each extracted clinical feature (e.g., focal onset seizures, seizure duration, ictal tachycardia, insular cortex changes) and derived mathematical features (e.g., fractal dimension, power spectrum analysis, connectivity, coherence) from three datasets: EEG, ECG, and MRI will be integrated to develop AI-based fusion diagnostic models. This process will highlight key modifiable risk factors to support clinical interpretation and intervention planning. Each model will be evaluated for its effectiveness in diagnosing SUDEP by calculating performance metrics such as accuracy, sensitivity, specificity, precision, area under the curve (AUC), and receiver operating characteristic (ROC) curves. Inputs (EEG, ECG, and MRI features) that contribute to achieving sensitivity and specificity above 70% will be used in model optimisation. Features that contribute to meeting or exceeding this threshold will be prioritised, as they represent key risk factors for SUDEP. The final fusion model will provide feature importance scores, with a particular focus on modifiable factors, to enable personalised risk management strategies for SUDEP prevention.

6. Model Optimisation

AI model optimisation is the process of adjusting model parameters and hyperparameters to improve accuracy and performance. Techniques like gradient descent, learning rate tuning, and regularisation are used to minimise loss and prevent overfitting, ensuring the model generalises well to unseen data and performs efficiently in real-world tasks.

7. Model Validation

AI model validation is the process of assessing how well a trained model performs on unseen data to ensure it generalises beyond the training set. It helps detect overfitting and ensures the model is reliable, accurate, and robust before deployment in real-world applications. Common validation techniques include k-fold cross-validation, where the data is divided into k parts and the model is trained and validated k times, each time using a different fold as the validation set. This helps ensure that the evaluation is not biased by the choice of a particular subset. Robust validation is essential in healthcare, where misclassifications can have serious consequences.

AI techniques, such as machine learning and deep learning methods like Support Vector Machines (SVM), Random Forests (RF), k-Nearest Neighbours (k-NN), Logistic Regression (LR), Gradient Boosting, Convolutional Neural Networks (CNNs), and Recurrent Neural Networks (RNNs) / LSTM, will be investigated to analyse brain activity, cardiac signals, and structural anomalies to identify subtle, asymptomatic risk factors. AI techniques uncover complex patterns, enabling a comprehensive risk profile. This multimodal approach helps clinicians detect high-risk patients early, supporting timely intervention and personalised care, ultimately enhancing SUDEP prediction, prevention, and overall epilepsy management.

8.Feature Selection and Causal Analysis of Modifiable Risk Factors

Core Objective
To identify modifiable risk factors with clinically actionable significance for SUDEP prevention through data-driven feature selection and causal inference, providing interpretable predictions to guide personalized risk management.

Data Preparation and Preprocessing

*Purpose***:** SUDEP cases are rare, and missing values in certain features may impair model performance. The first step is to construct a high-quality and balanced dataset to ensure the reliability and generalizability of subsequent modelling.

Key Considerations:

1. Missing Value Handling:
    - *Low-Missing Features:* For features with low missing rates (e.g., <30%), several statistical methods are employed to fill in the missing values to maintain unbiased effect estimates and valid inferences.
    - *High-Missing Features:* Exclude features with high missing rates or non-random missingness (e.g., privacy-related variables) to ensure data quality.
2. Class Imbalance Correction:
    - *Synthetic Minority Oversampling Technique (SMOTE):* Generate synthetic samples with similar characteristics to real cases to balance class distribution while preserving data integrity, prioritised as the primary method.
    - Oversampling Alternative: Used in sensitivity analyses due to its simplicity but risk of overfitting.

LASSO-based Feature Selection

Purpose: Select 5 to 10 high-predictive features from 28 candidates in the safety checklist to avoid redundancy in subsequent causal analysis.

Key Considerations:

1. LASSO Regression:
    - *Feature Selection:* Automatically shrink coefficients of irrelevant features to zero via L1 regularization, ensuring a concise subset of features explaining major variations in SUDEP risk.
    - *Stability Validation:* Reduce random variability through statistical simulations to confirm feature significance.
2. Clinical Validation: Neurologists review selection results. Features excluded by LASSO but deemed clinically critical (e.g., seizure frequency) will be re-evaluated in sensitivity analyses.

Feature Stratification: Modifiable vs. Non-modifiable Factors

Purpose: Clarify clinical intervention targets by distinguishing modifiable factors from non-modifiable ones (e.g., age).

Key Considerations:

1. Clinically-Driven Classification:
    - *Non-modifiable Factors:* Variables such as age and sex, though associated with SUDEP, are included as confounders in causal models due to their non-modifiable nature.
    - *Modifiable Factors:* Defined through neurologist consensus (e.g., AED dose adjustment, smoking status).

Causal Inference for Modifiable Factors

Purpose: Quantify the Average Treatment Effect (ATE) of modifiable factors on SUDEP risk, controlling for confounding bias, and provide clinically credible and interpretable predictions.

Key Considerations:

1. Independent Effect Analysis*:* Establish causal models for each modifiable factor (e.g., AED dose, smoking status) defined in Section 2.3, estimating their individual ATE while controlling for confounders (including partially modifiable factors).
2. Robustness Validation:
    - *E-value:* Quantify the potential impact of unmeasured confounding to measure the robustness of the model.
    - *Bootstrap Method:* Estimate confidence intervals for effect sizes through resampling to assess model uncertainty.

Expected Outcomes

1. *Prioritized List of Key Factors:* Differentiating modifiable and non-modifiable factors.
2. *Quantified Causal Effects*: Clinically interpretable metrics for modifiable factors (e.g., dose adjustment, smoking cessation) on SUDEP risk.

9.From Prediction to Action Reducing the Risk of SUDEP

Existing SUDEP prediction efforts have largely used single-modality data or clinical registries. Clinical models have identified key factors but are limited in accuracy. For instance, Liu et al. [16] derived a logistic regression model from a rural Chinese cohort using five clinical variables (e.g., ≥1 GTCS in the last month, BMI, age at onset) and achieved an AUC of approximately 0.79–0.83. Such models emphasize convulsive seizures and patient demographics but ignore physiological signals. In contrast, Chen et al. [17] applied machine learning to interictal EEG and ECG features from long-term monitoring, finding that a simple logistic model using EEG band-power ratios and heart-rate variability yielded an AUC of approximately 0.77. This suggests that EEG/ECG biomarkers can add predictive power, but Chen's study was retrospective, modest in size (30 SUDEP cases), and did not include other data types (e.g., genetics, sleep). No prior work has combined comprehensive multimodal data in a unified SUDEP risk model.

The need for integrated data is increasingly recognized. The NIH-funded Centre for SUDEP Research developed the Multimodal SUDEP Data Resource (MSDR), aggregating data from over 2,700 patients with EEG, ECG, MRI, and clinical information [18]. Similarly, Threeanaew et al. [19] discussed methods to collect and preprocess EEG and other physiological signals for SUDEP biomarker discovery. These efforts underscore the value of pooling heterogeneous data, but to date, no published model has fully exploited such datasets for risk stratification.

In general, machine learning and deep learning are transforming epilepsy research (e.g., seizure detection, outcome prediction), but clinical uptake requires trust and interpretability. Physicians tend to prefer models whose logic can be explained, and studies show that providing model-agnostic explanations (e.g., SHAP values) increases clinician trust [20]. We will incorporate state-of-the-art explainable AI techniques so that the SUDEP risk model highlights the contributing factors for each patient (e.g., seizure burden, EEG/ECG biomarkers). We also will leverage large language models (LLMs) to generate narrative summaries: recent reviews note that LLMs (e.g., GPT variants) can effectively draft medical reports and educational content [21], potentially improving communication of complex risk information to clinicians.

10.Methods

Multimodal SUDEP Risk Model Development

We will construct a predictive model using the full patient dataset, which includes:

- **EEG**: Data from inpatient monitoring or wearable devices.
- **ECG**: Continuous cardiac monitoring.
- **Sleep Profiles:** Data from polysomnography or EEG-based sleep stage classification.
- **Seizure Annotations**: Timing, type, duration, especially generalized tonic-clonic
- seizures (GTCS) and nocturnal events.
- **Medication Records:** Including drug types, dosages, and adherence patterns.
- **Genetic Data:** Known epilepsy/SUDEP-associated genes and polygenic risk scores, if available.

Each modality will undergo preprocessing to extract salient features: time-domain and spectral biomarkers from EEG (e.g., power in specific frequency bands, postictal suppression metrics), heart rate variability (HRV) features from ECG, sleep pattern statistics (e.g., sleep stage distribution, arousals), medication exposure encodings, and indicators of selected genetic variants.

The team will explore machine learning architectures capable of handling heterogeneous data, such as gradient-boosted trees (e.g., XGBoost) for tabular features and convolutional or recurrent neural networks for time-series inputs. Strategies for feature-level fusion or ensemble methods will be considered to integrate multimodal data effectively. Model training will employ cross-validation techniques and a held-out test set, including known SUDEP cases, to assess discrimination (e.g., area under the receiver operating characteristic (ROC) curve) and calibration metrics. Where data availability permits, deep learning approaches will be applied to raw EEG and ECG epochs to identify novel predictive features.

To facilitate clinician use, we will develop an LLM-based reporting component. The model will generate a natural-language summary of each patient's risk profile, highlighting key drivers (e.g. "The patient's frequent nocturnal GTCS and abnormal EEG low-gamma power contribute most to the elevated risk"). This draws on recent evidence that LLMs can assist in crafting medical documents and summarizing complex data [22]. We will fine-tune or prompt a state-of-the-art LLM (e.g. GPT-4) to convert model outputs and features into clear clinical narratives. Expert neurologists will review these reports for accuracy and usefulness.

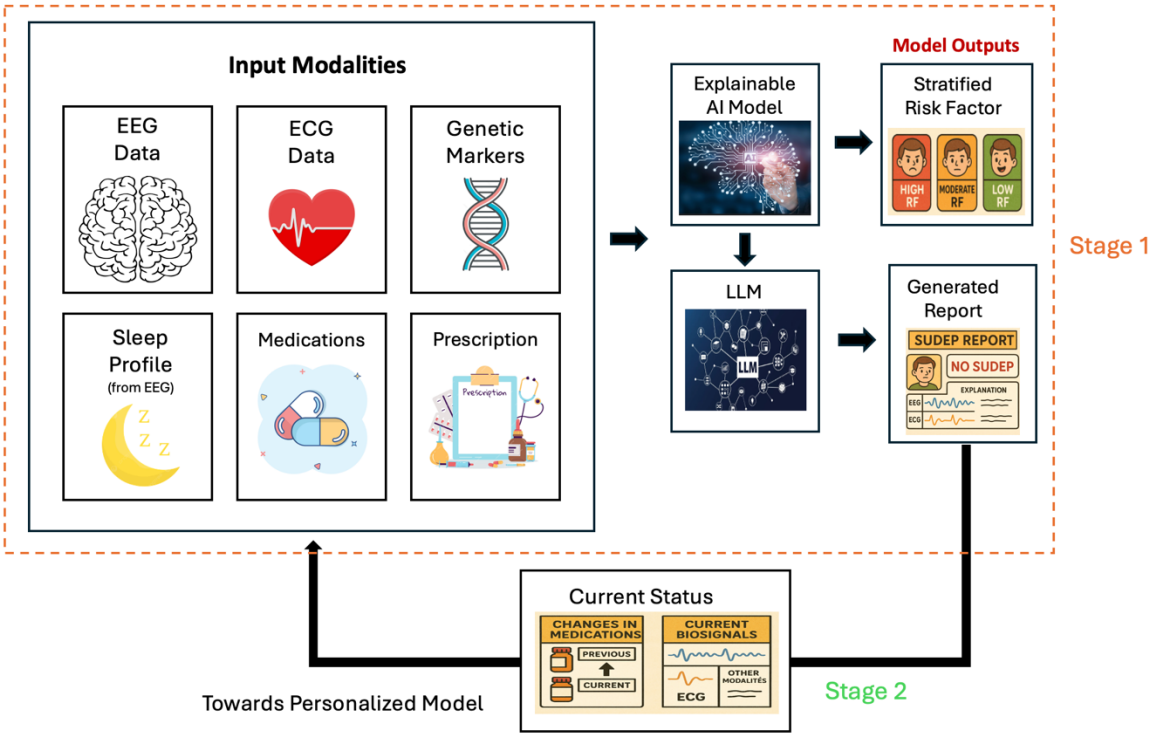


Figure 2: Proposed architecture of the dynamic SUDEP risk prediction system.

Dynamic Learning and Clinical Portal

In Stage 2, a clinician-accessible portal will be developed to allow real-time updates of patient data (e.g., seizures, EEG/ECG, medications). The underlying SUDEP risk model will be dynamically updated using incremental learning or Bayesian methods, enabling a continuously adapting predictor without full retraining [20]. For instance, new nocturnal GTCS events would increase a patient's predicted risk.

The portal will be piloted with retrospective data to simulate longitudinal updates. Clinicians will test usability and interpretability, supported by explainable AI outputs and LLM- generated summaries [21]. The system will comply with data security and interoperability standards and be ready for prospective validation.

11.Diary and Future work

Day 1: Initial discussion and scene setting
Day 2: Planning, data sets and features, prototype creation
Day 3: Presentation and next steps

Day 1: Initial discussion and scene setting
Points discussed
- Can we map the brain networks associated to, e.g., cardiac arrest?
- most SUDEP happens during sleep. Sleep staged data markers?
- Risk quantification and presentation of SUDEP
- Quantify the difference in management due to improved risk assessment.

- Feature analysis to inform management (feature target).

Day 2: Planning, datasets, objectives, features & methods, prototype creation
Points discussed
Datasets:

- Mortemus (16 deaths + 9 near-deaths)
  - EEG, Video, ECG,… (all clinic, pre surgical)
  - Not sure if there are past EEG for these people. To check
- EEG from SUDEP and not-SUDEP
  - Minimal data: 20 min EEG + ECG
  - Dataset in Cornwall (10 SUDEP+other deaths (e.g. status epileticus, which is more common)+ not deaths): very certain SUDEP
  - Additional
  - EEG recordings with scale of certainty of SUDEP
- Epilepsy deaths registry UK? (potential validation)
- SUDEP Action dataset.
- Control for age and treatment

Objectives:
- Evaluate SUDEP risk (long term)
- Evaluate eminent risk of SUDEP (relevant to monitoring units).

<u>Data features</u>

Sure

- Background EEG
- Background ECG
- Medication at time of EEG
- Basic Metadata (Age, gender)
- Metadata (onset of seizure)

Maybe extra
- EEG+ECG with stimulation (e.g., hyperventilation, photic-stimulation)
- Sleep EEG
- Imaging (MRI to persistent epilepsy)
- medication history
  - medication at time of death
  - Changes in medication in the last 12 months
  - cardiac/non cardiac
- Alcohol consumption
- Written text (LLM)
  Probably best test report.

<u>Methods</u>

Feature selection

1. validated features in literature
2. best correlates to SUDEP otherwise
3. narrowing down clinical value
4. Using Lasso to find 1 or 2 extra

- Lit review for validated features.

- Can we compare pre- with at-SUDEP data? Is it relevant?
- Respiratory/cardiac feature from EEG?

Day 3: Presentation and Next steps

Next steps discussed
- Literature review and meta-analysis
  - What is missing (i.e., what is not know from literature and is relevant)
  - Risk factors
  - Data and features
- Discussion about data sharing? (especially the "living controls").
- Demo of the prototype (interface)
- Demo of the report

Group 1: Lit review
- Use Refman to identify trends in literature.
- Google Notebook LM to obtain references associated to others.
- Potential opinion papers about the challenge

Group 2: Classifier and mathematical model
- Causality methods to support feature identification?
- Uncertainty quantification/communication.
  - Methods for data imbalance (e.g. focal-loss function?)
  - Best classification methods for this context.

Group 3: Interface and visualisation

12.Population

Five confirmed SUDEP cases identified through Cornwall Partnership NHS Foundation Trust. Retrospective review of historical medical records. Data review will include investigations and clinical characteristics including specific consideration of known SUDEP risk factors.

Intervention and Comparison

The investigation will be dived into two Work Packages (WPs). WP1 will include data collection and assimilation. WP 2 will include proposed models for data analysis.

<u>Work Package 1: Data collection and assimilation, with Focused Literature review</u>

Medical data will be collected retrospectively. Each record will be reviewed as far back as available. Data will be collected on **five** confirmed SUDEP cases. Literature review will consider parameters SUDEP/Risk Factors/Biomarkers/AI to ensure all potential factors are considered.

Data for Collection (N=5)
(from existing medical records)**:**
Demographics
EEG-full recording
ECG
Brain imaging (MRI/CT)
Genetic profile
Sleep profile

Seizure records
Medication records

Work Package 2: Proposed models for data analysis

1. WP2.A. Feature Selection and Causal Analysis of Modifiable Risk Factors
2. WP2.B. Multimodal SUDEP Risk Model Development

Outcomes

WP2.A

Prioritize List of Key Factors: Differentiating modifiable and non-modifiable factors.
Quantified Causal Effects: Clinically interpretable metrics for modifiable factors (e.g., dose adjustment) on SUDEP risk.

WP2.B a clinician-accessible portal will be developed to allow real-time updates of patient data (e.g., seizures, EEG/ECG, medications). The underlying SUDEP risk model will be dynamically updated using incremental learning or Bayesian methods, enabling a continuously adapting predictor without full retraining. The portal will be piloted with retrospective data to simulate longitudinal updates. Clinicians will test usability and interpretability, supported by explainable AI outputs and LLM-generated summaries. The system will comply with data security and interoperability standards and be ready for prospective validation.

13.Work package 1 Development:

Search Strategy

SUDEP biomarker overview search terms

1. "SUDEP" OR "Sudden unexpected death in epilepsy" AND "biomarker"
    a. What is known about SUDEP biomarkers in current literature generally
2. "SUDEP" OR "Sudden unexpected death in epilepsy" AND "biomarker" AND ("EEG" OR "electroencephalography" OR "electroencephalogram")
    a. What is known about SUDEP biomarkers re EEG in current literature
3. "SUDEP" OR "Sudden unexpected death in epilepsy" AND "biomarker" AND ("ECG" OR "EKG" OR "electrocardiography" OR "electrocardiogram")
    a. What is known about SUDEP biomarkers re ECG in current literature
4. "SUDEP" OR "Sudden unexpected death in epilepsy" AND "biomarker" AND ("neuroimaging" OR "imaging" OR "scan" OR "MRI" OR "magnetic resonance" OR "magnetic resonance imaging" OR "CT" OR "computed tomography" OR "tomography")
    a. What is known about SUDEP biomarkers re neuroimaging in current literature
5. "SUDEP" OR "Sudden unexpected death in epilepsy" AND "biomarker" AND ("genetic" OR "genetics" OR "genomic" OR "genome" OR "gene")
    a. What is known about SUDEP biomarkers re genetics in current literature

AI applications search terms

1. "SUDEP" OR "Sudden unexpected death in epilepsy" AND ("Artificial intelligence" OR "AI" OR "machine learning" OR "deep learning" OR "modelling" OR "model")
    a. Current scope of AI applications to SUDEP research
2. "SUDEP" OR "Sudden unexpected death in epilepsy" AND "biomarker" AND ("Artificial intelligence" OR "AI" OR "machine learning" OR "deep learning" OR "modelling" OR "model")
    a. Current scope of AI applications to SUDEP biomarker research
3. "SUDEP" OR "Sudden unexpected death in epilepsy" AND "biomarker" AND ("Artificial intelligence" OR "AI" OR "machine learning" OR "deep learning" OR "modelling" OR "model") AND ("EEG" OR "electroencephalography" or "electroencephalogram")
    a. Current scope of AI applications to SUDEP biomarker research with respect to EEG only
4. "SUDEP" OR "Sudden unexpected death in epilepsy" AND "biomarker" AND ("Artificial intelligence" OR "AI" OR "machine learning" OR "deep learning" OR "modelling" OR "model") AND ("ECG" OR "EKG" OR "electrocardiography" OR "electrocardiogram")
    a. Current scope of AI applications to SUDEP biomarker research with respect to ECG only
5. "SUDEP" OR "Sudden unexpected death in epilepsy" AND "biomarker" AND ("Artificial intelligence" OR "AI" OR "machine learning" OR "deep learning" OR "modelling" OR "model") AND ("neuroimaging" OR "imaging" OR "scan" OR "MRI" OR "magnetic resonance" OR "magnetic resonance imaging" OR "CT" OR "computed tomography" OR "tomography")
    a. Current scope of AI applications to SUDEP biomarker research with respect to neuroimaging only
6. "SUDEP" OR "Sudden unexpected death in epilepsy" AND "biomarker" AND ("Artificial intelligence" OR "AI" OR "machine learning" OR "deep learning" OR "modelling" OR "model") AND ("genetic" OR "genetics" OR "genomic" OR "genome" OR "gene")
    a. Current scope of AI applications to SUDEP biomarker research with respect to genetics only

14.AI generated search (Notebook LM)

SUDEP Briefing Document

Date: October 26, 2024

Subject: Comprehensive Review of Sudden Unexpected Death in Epilepsy (SUDEP): Risk Factors, Biomarkers, and Prevention

This briefing document synthesizes key information from the provided sources regarding Sudden Unexpected Death in Epilepsy (SUDEP). It outlines the definition, incidence, significant risk factors, emerging biomarkers, and potential avenues for prediction and prevention.

1. Definition and Incidence

SUDEP is defined as the sudden, unexpected, non-traumatic, and non-drowning death in individuals with epilepsy, with or without evidence of a seizure, where post-mortem examination does not reveal a toxicological or anatomical cause of death (Nashef, 1997; Tomson et al., 2008; Monté et al., 2007). Cases are categorized as "definite SUDEP" if SUDEP is the primary cause of death, or "possible SUDEP" if the cause is reported as "epilepsy," "complications of epilepsy," "consistent with epilepsy," "sudden death in association with seizure disorder," or "undetermined" (Tu et al., 2010).

The incidence of SUDEP varies depending on the study population:

General Epilepsy Population: Incidence rates range from 0.22 to 6.9 per 1000 person-years (DeGiorgio et al., 2018; Monté et al., 2007; Tomson et al., 2005).

One study found an incidence of 5.9 per 1000 person-years in adults and children with chronic epilepsy (Nashef et al. cited in DeGiorgio et al., 2018).
Another reported an incidence of 2.46 per 1000 person-years in chronic epilepsy, double the rate in newly diagnosed cases (Mohanraj et al. cited in DeGiorgio et al., 2018).
Children: While previously thought to be lower, recent studies indicate SUDEP rates in children are similar to or even higher than sudden infant death syndrome (SIDS) rates, and similar to adult rates (Keller et al. cited in DeGiorgio et al., 2018; Berge et al. cited in DeGiorgio et al., 2018). For example, Keller et al. found a rate of 1.11 per 1000 in children, comparable to 1.2 per 1000 in adults (DeGiorgio et al., 2018).
Specific Populations: Higher incidences are observed in populations such as those with refractory epilepsy or undergoing epilepsy surgery. For example, epilepsy surgery programs have reported incidences up to 6.7 per 1000 person-years (Sperling et al., 1996 cited in Tomson et al., 2005).
Age-related Incidence: One study found SUDEP incidence to be 0 in age groups 0-19 and over 60, with the highest rates in the 20-29 (1.73 per 1000) and 50-59 (2.43 per 1000) age ranges (Hauser et al., 2001). However, other sources indicate young age is a general risk factor (Monté et al., 2007).
2. Established Risk Factors
Multiple studies consistently identify several key risk factors for SUDEP:
Generalized Tonic-Clonic Seizures (GTCS): This is the single most important and consistently identified risk factor.
High frequency of GTCS is a strong predictor, with risks increasing significantly with >3 GTCS in the last year (Odds Ratio = 8), or >50 seizures per month (Odds Ratio = 11.5) (Walczak et al., 2001 cited in DeGiorgio et al., 2018; Hesdorffer et al., 2011).
The risk of SUDEP increases dramatically with increasing GTCS frequency and polytherapy (Hesdorffer et al., 2011). For instance, >3 GTCS and polytherapy was associated with an OR of 25.20 (Hesdorffer et al., 2011).
Nocturnal GTCS is also a significant risk factor, with a history of nocturnal TCS being associated with increased SUDEP incidence rates, especially when combined with high seizure frequency (Tomson et al., 2025).
Seizure Frequency (Overall): Higher overall seizure frequency is a major risk factor (Monté et al., 2007).
Chronic Epilepsy / Duration of Epilepsy: A longer duration of epilepsy increases SUDEP risk.
Epilepsy duration >30 years is a strong risk factor (Odds Ratio = 13.9) (Walczak et al., 2001 cited in DeGiorgio et al., 2018).
For patients with onset age <16 years, duration of epilepsy >15 years was associated with a 3.2-fold increased risk (Hesdorffer et al., 2011).
Anti-Epileptic Drug (AED) Non-adherence / Polytherapy:Poor compliance with AEDs is a noted risk factor (Monté et al., 2007; Tu et al., 2010).
The use of >2 antiseizure medications is a risk factor (Monté et al., 2024).
While polytherapy in general is associated with increased risk, for patients with older age at onset, AED monotherapy was associated with a protective effect, whereas polytherapy increased risk (Hesdorffer et al., 2011).
Frequent changes in AEDs (e.g., 3-5 changes per year) also increase risk (Nilsson et al. cited in DeGiorgio et al., 2018).
Developmental Disability/Mental Retardation: IQ <70 is a strong risk factor (Odds Ratio = 5) (Walczak et al., 2001 cited in DeGiorgio et al., 2018; Monté et al., 2024).
Male Sex: Male gender is associated with a 1.4-fold increased risk for SUDEP (Hesdorffer et al., 2011; Monté et al., 2007).
Early Onset Epilepsy: Onset of epilepsy younger than 16 years had a statistically significant 1.72-fold increased risk for SUDEP compared to onset between 16 and 60 years (Hesdorffer et al., 2011).
Structural Brain Lesion/Symptomatic Epilepsy: These are listed as risk factors (Monté et al., 2007).
Posttraumatic Epilepsy: Mentioned as a risk factor (Monté et al., 2007).
Psychiatric Illness / Psychotropic Drug Prescription: Psychiatric illness and the use of antidepressants, anxiolytics, or antipsychotics are considered risk factors (Monté et al., 2007). One study found depression to be significantly more prevalent in epilepsy controls than SUDEP patients (fneur-13-

858333.pdf). However, another study found comorbid mental health disorder was not significantly associated with SUDEP risk (Hesdorffer et al., 2011).
Alcohol Abuse: Regular and marked alcohol consumption has been inconsistently linked to SUDEP. One study found a significant association in males, while another failed to identify it as a significant risk factor after adjustment (Tomson et al., 2005; Hesdorffer et al., 2011).
3. Potential Mechanisms and Emerging Biomarkers
SUDEP is likely multifactorial, involving interactions between brain, cardiac, and respiratory systems.
3.1. Cardiac Dysfunction
Ion Channelopathies: Mutations in genes encoding cardiac ion channels (e.g., KCNQ1, KCNH2, SCN5A) can cause cardiac arrhythmias (Long QT Syndrome - LQTS) and sudden death (Tu et al., 2010; Surges et al., 2012). These channels are also functionally expressed in the brain, suggesting a common underlying susceptibility (Surges et al., 2012).
Specific DNA variants in LQTS genes like KCNH2 (rs36210422, Arg176Trp) and SCN5A (rs45533640, His118His; rs45522138, Leu561Leu; rs36210423, Ala572Asp; rs1805125, Pro1090Leu) have been identified in SUDEP cases (Tu et al., 2010).
Induced pluripotent stem cells (iPSCs) from Dravet syndrome patients show increased sodium currents and spontaneous contraction rates in cardiac myocytes, which were clinically confirmed, suggesting iPSCs as a tool for risk assessment (Scurrying to Understand Sudden Expected Death in Epilepsy, 2022).
Autonomic Dysfunction (Heart Rate Variability - HRV):Seizures can disrupt autonomic nervous system regulation, leading to cardiac sympathetic denervation (Surges et al., 2012).
Reduced heart rate variability (HRV), particularly RMSSD (Root Mean Square of Successive Differences), a measure of vagus-mediated HRV, is associated with SUDEP risk factors (DeGiorgio et al., 2010; Heart rate variability in epilepsy, 2019).
Biochemical Markers: Post-mortem analysis of bodily fluids in SUDEP cases showed significant changes compared to non-epileptic deaths:
Increased sodium, CK-MB, and CK-NAC levels in serum, CSF, vitreous humor, and pericardial fluid.
Decreased potassium levels in serum, CSF, vitreous humor, and pericardial fluid (Biochemical findings in sudden unexpected death in epilepsy, 2019).
3.2. Brain Abnormalities
EEG Suppression: Post-ictal generalized EEG suppression (PGES) is a strong biomarker of SUDEP risk, consistent with respiratory and cardiac arrest mechanisms (Mier et al., 2020; Risks and predictive biomarkers of SUDEP, 2019).
Studies on EEG low gamma sleep/wake power ratios show significant differences between SUDEP patients and controls, potentially indicating altered brain network activity (fneur-13-858333.pdf).
Structural Brain Changes (MRI):SUDEP and high-risk patients show increased volume in the right anterior mesial temporal region and decreased volume in the pulvinar (Risks and predictive biomarkers of SUDEP, 2019).
Greater atrophy of the dorsal mesencephalon and volume loss in the raphe/medulla oblongata at the obex level have been observed in SUDEP patients (Risks and predictive biomarkers of SUDEP, 2019).
Reduced cortical thickness in the right paracentral lobule, inferior parietal lobule, supramarginal gyrus, and middle temporal lobe was found in patients with GTCS and PGES (Risks and predictive biomarkers of SUDEP, 2019).
3.3. Respiratory Dysfunction
Seizure-related respiratory compromise (e.g., central apnea, obstructive apnea, hypoventilation) is a hypothesized mechanism contributing to SUDEP. The role of PGES in post-ictal respiratory failure is a significant area of research.
4. Prediction and Prevention Strategies
4.1. Risk Assessment Tools
SUDEP-7 Inventory: This tool helps assess SUDEP risk based on key factors like GTCS frequency, duration of epilepsy, IQ, and number of AEDs (DeGiorgio et al., 2010; Odom & Bateman, 2018).
Modified SUDEP-7 Inventory (Monté et al., 2024): A revised scoring system (0-10 total score) incorporates:
Age at onset of epilepsy (0 or 1 for onset <15 years)
Chronic epilepsy (>10 years) (0 or 1)

GTCS in the last year (0 or 1 for >0 seizures; 0 or 2 for >50 seizures)
Duration of epilepsy >30 years (0 or 3)
Use of >2 antiseizure medications (0 or 1)
Developmental disability, IQ <70 (0 or 2)
This tool demonstrated good sensitivity (82.3%) and specificity (82.7%) at a threshold of 3 (Monté et al., 2024).
Personalized Prediction Tools: Bayesian hierarchical models are being developed to estimate individual SUDEP risk using nationwide registry data, aiming for more precise counseling (Jha et al., 2021).
4.2. Seizure Detection Devices
Devices to detect seizures, particularly GTCS, are crucial for intervention and potentially reducing SUDEP risk.
EEG-based detection:Ear-EEG based on EMG analysis can detect GTCS (Zibrandtsen et al., 2018).
Advanced feature extraction and machine learning (e.g., convolutional neural networks like EEGNet) are being explored for categorizing EEG suppression and assessing SUDEP risk (Mier et al., 2020; Lawhern et al. cited in Mier et al., 2020).
Methods like Independent Component Analysis (ICA) are used to extract seizure onset from surface EEG (Extracting seizure onset from surface EEG, 2020).
Accelerometer-based devices: Patient-worn accelerometers are used for long-term home monitoring of hypermotor seizures (Van de Vel et al., 2013).
Other methods: Eigenvector methods (Pisarenko, MUSIC, Minimum-Norm) can analyze EEG signals to estimate frequency and power (Epileptic Seizure Detection and Experimental Treatment, 2020). Wavelet Transforms (WT), including Continuous Wavelet Transform (CWT) and Discrete Wavelet Transform (DWT), are also used for feature extraction from EEG signals (Epileptic Seizure Detection and Experimental Treatment, 2020).
4.3. Therapeutic Interventions
AED Optimization: Ensuring optimal AED therapy and compliance is paramount.
Nocturnal Supervision: The lack of nocturnal supervision is a recognized risk factor (Risks and predictive biomarkers of SUDEP, 2019). Sharing a bedroom can reduce SUDEP incidence, especially for those with no nocturnal GTCS and good adherence to medication (Tomson et al., 2025).
Vagal Nerve Stimulation (VNS): While VNS cohorts have shown varying SUDEP incidences (Annegers et al., 2000 cited in Tomson et al., 2005), its direct impact on SUDEP risk reduction needs further investigation.
Neuromodulation:Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS) are being investigated as experimental treatments, aiming to suppress seizure activity and potentially reduce SUDEP risk (Epileptic Seizure Detection and Experimental Treatment, 2020). Low-frequency rTMS has shown some reduction in interictal epileptiform abnormalities (Cantello et al., 2007).
Focused ultrasound is also being explored for its ability to modulate neuronal activity, with lower energy US increasing action potential and higher energy US reducing it (Epileptic Seizure Detection and Experimental Treatment, 2020).
Conclusion
SUDEP remains a significant concern for individuals with epilepsy. While the primary role of uncontrolled generalized tonic-clonic seizures is well-established, ongoing research continues to uncover complex genetic, cardiac, and neurological factors contributing to its occurrence. Advancements in risk assessment tools, seizure detection technologies, and a deeper understanding of underlying physiological mechanisms are crucial for developing more effective personalized prevention strategies and improving patient outcomes.

15.Potential mechanisms and emerging markers

Genetics:

- Ion Channelopathies
    - KCNQ1
    - KCNH2 (in particular variants rs36210422, Arg176Trp)

- SCN5A (in particular variants rs45533640, His118His; rs45522138, Leu561Leu; rs36210423, Ala572Asp; rs1805125, Pro1090Leu)

ECG-based markers

- Reduced Heart Rate Variability (HRV)
- Reduced Root Mean Square of Successive Differences (RMSSD)

Biochemical markers:

- Increased sodium, CK-MB, CK-NAC in serum, CSF, vitreous humour, pericardial fluid on post-mortem analysis

EEG-based markers

- Post-ictal generalised EEG suppression (PGES)
- Low gamma sleep/wake power ratios

MRI-based markers/structural brain changes

- Increased volume in right anterior mesial temporal lobe region
- Decreased volume in pulvinar region
- Greater atrophy of dorsal mesencephalon
- Volume loss in raphe/medulla oblongata at obex level
- Reduced cortical thickness in right paracentral lobule, inferior parietal lobule, supramarginal gyrus, middle temporal lobe

Respiratory

- Seizure-related apnoeas (central, obstructive)
- Seizure-related hypoventilation
- Post-ictal respiratory failure
-

Established risk factors

Seizure profile

- Generalised Tonic-Clonic Seizures (GTCS)
- High GTCS frequency
- Nocturnal GTCS

Epilepsy profile

- Duration more than 30 years
- Onset before 16 years of age

Treatment-related factors

- Poor adherence to ASM therapy
- Subtherapeutic ASM level
- Treatment resistance, polytherapy
- Frequent change in ASM prescription

Other non-modifiable risk factors

- Male sex
- Younger age
- Comorbid intellectual disability
- Comorbid psychiatric illness/psychotropic medication

16.Future Direction

Through this project we will develop a capable community of multiprofessional researchers with the required range of skill sets to effectively investigate the complex and rare problem of SUDEP.

1. We will produce a focussed literature review updating the current knowledge and understanding of SUDEP risk factors, potential biomarkers, and the role of AI and machine learning in approaching risk analysis.
2. The proposed models of analysis of SUDEP risk factors will be tested in a small cohort of known SUDEP cases (n=5) with access to full medical records and investigations.
3. Throughout the investigation we will build on the construct proposed and develop AI modelling based upon feedback from data analysis.
4. The AI model will be used to develop a clinical assessment tool that can be utilised by clinicians to stratify risk and move towards personalising risk based upon the presence or absence of SUDEP risk factors. At present there is no clinical assessment tool that is capable of providing a risk score or prediction.

This investigation is the first step in the development of a clinical application with the potential to change clinical approaches to SUDEP discussion and management. The development of a risk assessment tool using AI modelling and machine learning will start to provide clinicians with an understanding of those most at risk, and where modifiable risks need to be targeted. It will also help inform people with epilepsy on their risk status and move discussion towards a shared responsibility for monitoring and modifying risk through behavioural changes.

The purpose of this initial feasibility investigation is to build on the construct of the proposed models and utilise them on actual SUDEP cases with access to full medical and investigation data. This explorative study will demonstrate the effectiveness of the AI modelling based upon statistical analysis of the data, in actual SUDEP cases.

The next step in the AI model development will be to further explore in larger scale populations with a comparison group. Based upon the data this will require 80-100 SUDEP cases and matched controls.

If successful in this application, we propose application for a larger scale grant in order to proceed with the next stage of this investigation. This may include application to funding opportunities such as the Engineering and Physical Sciences Research Council (EPSRC).

17.References:

1. Fisher, R.S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J.H., Elger, C.E., Engel Jr, J., Forsgren, L., French, J.A., Glynn, M. and Hesdorffer, D.C., 2014. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*, *55*(4), pp.475-482.
2. Shlobin, N.A., Thijs, R.D., Benditt, D.G., Zeppenfeld, K. and Sander, J.W., 2024. Sudden death in epilepsy: the overlap between cardiac and neurological factors. *Brain Communications*, *6*(5), p.fcae309.

3. Shankar, R., Donner, E.J., McLean, B., Nashef, L. and Tomson, T., 2017. Sudden unexpected death in epilepsy (SUDEP): what every neurologist should know. *Epileptic Disorders*, *19*(1), pp.1-9.
4. Watkins, L., Henning, O., Bassett, P., Ashby, S., Tromans, S. and Shankar, R., 2024. Epilepsy professionals' views on sudden unexpected death in epilepsy counselling: A tale of two countries. *European journal of neurology*, *31*(9), p.e16375.
5. Ross, J., Tyrlikova, I., Giermek, A., Ochoa-Urrea, M., Lhatoo, S. and Klein, P., 2024. Sudden unexpected death in epilepsy during ambulatory Video-EEG monitoring at home. *Neurology*, *102*(2), p.e208041.
6. https://www.epilepsy.org.uk/news/neurology-crisis-costing-uk-96bn-economist-report
7. Mesraoua, B., Tomson, T., Brodie, M. and Asadi-Pooya, A.A., 2022. Sudden unexpected death in epilepsy (SUDEP): Definition, epidemiology, and significance of education. *Epilepsy & Behavior*, *132*, p.108742.
8. Giussani, G., Falcicchio, G., La Neve, A., Costagliola, G., Striano, P., Scarabello, A., Mostacci, B., Beghi, E., LICE SUDEP study group, Mecarelli, O. and Tinuper, P., 2023. Sudden unexpected death in epilepsy: A critical view of the literature. *Epilepsia Open*, *8*(3), pp.728-757.
9. Milne-Ives, M., Duun-Henriksen, J., Blaabjerg, L., Mclean, B., Shankar, R. and Meinert, E., 2023. At home EEG monitoring technologies for people with epilepsy and intellectual disabilities: a scoping review. *Seizure: European Journal of Epilepsy*, *110*, pp.11-20.
10. Monté, C.P.J.A., Arends, J.B.A.M., Lazeron, R.H.C., Tan, I.Y. and Boon, P.A.J.M., 2024. Update review on SUDEP: Risk assessment, background & seizure detection devices. *Epilepsy & Behavior*, *160*, p.109966.
11. Watkins, L., Shankar, R. and Sander, J.W., 2018. Identifying and mitigating Sudden Unexpected Death in Epilepsy (SUDEP) risk factors. *Expert review of neurotherapeutics*, *18*(4), pp.265-274.
12. Li, X., Tao, S., Lhatoo, S.D., Cui, L., Huang, Y., Hampson, J.P. and Zhang, G.Q., 2022. A multimodal clinical data resource for personalized risk assessment of sudden unexpected death in epilepsy. *Frontiers in big Data*, *5*, p.965715.
13. Zhu T, Lin Y, Liu Y. Synthetic minority oversampling technique for multiclass imbalance problems[J]. Pattern recognition, 2017, 72: 327-340.
14. Tibshirani R. Regression shrinkage and selection via the lasso[J]. Journal of the Royal Statistical Society Series B: Statistical Methodology, 1996, 58(1): 267-288.
15. Angrist J, Imbens G. Identification and estimation of local average treatment effects[J]. 1995.
16. Liu, Q., Tan, B., Zhang, J., Jin, Y., Lei, P., Wang, X., Li, M., Qin, Y. and Zhang, Q., 2023. Derivation and validation of a new prediction model for sudden unexpected death in epilepsy based on a longitudinal prospective population-based cohort. *Epilepsy & Behavior*, *147*, p.109446.
17. Chen, Z.S., Hsieh, A., Sun, G., Bergey, G.K., Berkovic, S.F., Perucca, P., D'Souza, W., Elder, C.J., Farooque, P., Johnson, E.L. and Barnard, S., 2022. Interictal EEG and ECG for SUDEP risk assessment: a retrospective multicenter cohort study. *Frontiers in Neurology*, *13*, p.858333.
18. Li, X., Tao, S., Lhatoo, S.D., Cui, L., Huang, Y., Hampson, J.P. and Zhang, G.Q., 2022. A multimodal clinical data resource for personalized risk assessment of sudden unexpected death in epilepsy. *Frontiers in big Data*, *5*, p.965715.

19. Threeanaew, W., MacDonald, J., Sinha, A., Kaffashi, F., Lhatoo, S.D. and Loparo, K.A., 2018. Collection and analysis of multimodal data for SUDEP biomarker discovery. *IEEE sensors letters*, *3*(1), pp.1-4.
20. Jenkins, D.A., Martin, G.P., Sperrin, M., Riley, R.D., Debray, T.P., Collins, G.S. and Peek, N., 2021. Continual updating and monitoring of clinical prediction models: time for dynamic prediction systems?. *Diagnostic and Prognostic Research*, *5*, pp.1-7.
21. Diprose, W.K., Buist, N., Hua, N., Thurier, Q., Shand, G. and Robinson, R., 2020. Physician understanding, explainability, and trust in a hypothetical machine learning risk calculator. *Journal of the American Medical Informatics Association*, *27*(4), pp.592-600.
22. Xiangbin Meng et al. "The application of large language models in medicine: A scoping review". In: Iscience 27.5 (2024).