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Sudden Unexpected Death in Epilepsy: A Personalized Prediction Tool

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Abstract

Objective: To develop and validate a tool for individualised prediction of Sudden Unexpected Death in Epilepsy (SUDEP) risk, we re-analysed data from one cohort and three case-control studies undertaken 1980-2005.

Methods: We entered 1273 epilepsy cases (287 SUDEP, 986 controls) and 22 clinical predictor variables into a Bayesian logistic regression model.

Results: Cross-validated individualized model predictions were superior to baseline models developed from only average population risk or from generalised tonic-clonic seizure frequency (pairwise difference in leave-one-subject-out expected log posterior density = 35.9, SEM +/-12.5, and 22.9, SEM +/-11.0 respectively). The mean cross-validated (95% Credibility Interval) Area Under the Receiver Operating Curve was 0.71 (0.68 to 0.74) for our model versus 0.38 (0.33 to 0.42) and 0.63 (0.59 to 0.67) for the baseline average and generalised tonic-clonic seizure frequency models respectively.

Model performance was weaker when applied to non-represented populations.

Prognostic factors included generalized tonic-clonic and focal-onset seizure frequency, alcohol excess, younger age of epilepsy onset and family history of epilepsy. Anti-seizure medication adherence was associated with lower risk.

Conclusions: Even when generalised to unseen data, model predictions are more accurate than population-based estimates of SUDEP. Our tool can enable risk-based stratification for biomarker discovery and interventional trials. With further validation in unrepresented populations it may be suitable for routine individualized clinical decision-making. Clinicians should consider assessment of multiple risk factors, and not only focus on the frequency of convulsions.

Introduction

Sudden Unexpected Death in Epilepsy (SUDEP) is the commonest category of epilepsy-related death¹. Diagnosis requires exclusion of other potential causes of death since there are no pathognomonic autopsy findings². The incidence of 1.2 per 1000/patient/years in adults³ is an underestimate because insufficient history and ambiguous pathological findings lead to misclassification^{4,5}.

Why do some people suffer SUDEP after their second seizure whilst others survive thousands of convulsive seizures? Ongoing convulsions are a major prognostic factor^{6,7} but adjusted analyses are less consistent as to whether early age of epilepsy onset, long epilepsy duration, symptomatic aetiology, nocturnal convulsions, and a high

number or nonadherence of anti-seizure medications are independently predictive^{8,9}.

We cannot, however, accurately predict *individualized* SUDEP risk.

This is critical for two reasons. Firstly, prospective research into electroencephalographic (EEG), cardiovascular and imaging biomarkers requires a large cohorts followed for long periods unless high-risk subpopulations are targeted^{10,11}. A risk assessment tool based on heart-rate variability, the SUDEP-7 inventory¹¹, failed to generalize even at the population level¹². Predicting individualized risk would help identify SUDEP biomarkers.

Secondly, most people with epilepsy and families desire information on SUDEP risk even if the probability is low¹³. Guidelines suggest informing all individuals of the *average* risk but do not specify how to assess *personalized* risk, leaving individuals poorly informed about their risk. A personalized prediction tool could provide reassurance, motivation to change, or feedback following a clinical intervention.

We use a large SUDEP dataset⁸ to develop and validate a personalized predictive tool optimized for clinical use requiring only routine clinical data.

Methods

OBSERVATIONAL STUDY DESCRIPTION

We reanalysed one cohort (USA) and three case-controlled (England and Wales, Sweden, Scotland) studies⁸ (see Table 1). SUDEP diagnosis required (1) a history of epilepsy (>1 epileptic seizure within 5 years of study enrolment); and death that was (2) sudden, (3) unexpected, and (4) remained unexplained after investigative efforts, including autopsy. Definite SUDEP required all four criteria and probable required the first three criteria.

PREDICTOR INCLUSION STRATEGY

We harmonised the source data to obtain 29 common clinical predictor variables – data available from Dryad at <https://doi.org/10.5061/dryad.cfxpvnv4c> (Additional Methods). Of these, five had greater than 50% missing data (abnormal imaging, epileptiform features on electroencephalography, psychiatric comorbidity, dementia, brain tumour) and were excluded from further analysis. Levetiracetam was removed from the analysis because it was rarely used in this dataset. Length of epilepsy, is merely the difference between Age of epilepsy onset and Age at endpoint and so was not included to reduce co-linearity. Notably, we use Generalized Tonic-Clonic Seizures (GTCS) to refer to GTCS (previously known as primary GTCS) as well as focal to bilateral tonic clinic seizures (previously known as secondary GTCS), whilst focal seizures refers to the remaining focal onset seizures.

All binary variables were represented by single terms where 1=presence and 0=absence of the feature. Aetiology is an assignment into one of four categories and was modelled as four binary variables. Continuous predictor variables (age of epilepsy onset and age at endpoint) were standardized by removing the mean and dividing by the standard deviation to create a similar scale to the dummy-coded categorical data¹⁴ facilitating specification of priors. GTCS and focal seizure frequency were standardised by dividing the frequency by an arbitrary number (10), again to put them on a similar scale to other data whilst keeping a meaningful value for zero.

MODEL BUILDING STRATEGY

All analysis was done using Rstudio v1.1447 (RStudio Team (2016). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA <http://www.rstudio.com/>) and Matlab v2018a (The MathWorks, Inc., Natick, Massachusetts, United States). We used

Bayesian multiple logistic regression to develop a 'Full' model of SUDEP risk. SUDEP status (a binary variable) was entered as the dependent variable, whilst the remaining clinical variables were entered as predictors. A Bayesian model is specified by the likelihood and the priors.

$$(1) \quad p(y_i = 1, X_i, \alpha, \beta) \sim \frac{1}{1 + \exp(-(\alpha + X_i^T \beta))} \quad \text{for } i = 1, \dots, N$$

$$(2) \quad \beta_j \sim N(\mu_j = 0, \sigma_j = 1) \quad \text{for } j = 1, \dots, J$$

$$(3) \quad \alpha_k \sim N(\mu_k = 0, \sigma_k = 1) \quad \text{for } k = 1, \dots, K$$

The logistic regression likelihood is described in equation (1) above, where $y_i = 1$ is the SUDEP status for subject i of N and, X_i is a J -dimensional vector of predictors for each subject i . The intercept is modelled as α_k whilst β_j represents the regression coefficient for the j th predictor. We specified a separate intercept α_k for each centre (K centres) to account for their differing case:control ratios. As these are *a priori* known to be different, we did not introduce pooling of these estimates via a further hierarchical term. The prior distribution for regression coefficients (equation 2) and the intercept (equation 3) were chosen to be normally distributed with a mean of zero and standard deviation of one.

These values were chosen because prior predictive modelling revealed that this resulted in the broad but sensible prior assumption that 95% of standardised adjusted posterior log odds ratios would lie between -1.94 and +1.98. A sensitivity analysis was performed – data available from Dryad (Additional Results). In order to quantify the improvement in predictive power over current practice we also developed two comparator models. A 'Baseline' model which had the intercepts (a separate intercept α_k for each centre) as predictors but with no other clinical information was used to represent current clinical guidance where only the average population risk is conveyed

to individuals with epilepsy. A 'Baseline GTCS' model which had the population intercepts and also GTC seizure frequency was also fitted to represent current research practice which relies on GTC seizure frequency as a surrogate for SUDEP risk. Due to the number of predictors involved and the complexity of the missing data analysis, we avoided modelling interactions within the linear term.

POSTERIOR ESTIMATION

Calculating the Bayesian posterior for such a model can be analytically intractable and therefore posterior parameter estimates were generated using a Markov Chain Monte Carlo (MCMC) procedure. We used RStan software (Stan Development Team (2018). RStan: the R interface to Stan. R package version 2.18.2. <http://mc-stan.org/>) which implements Hamiltonian Monte Carlo with No-U-Turn sampling^{14,15}. Using the default recommendations, we ran four chains from random starting values. After discarding 4000 warm-up samples (similar but not identical to 'burn-in' in other software), posterior estimates were derived from a further 4000 samples across all chains (no thinning) and were assessed for chain stability and convergence using visualisation of trace plots and standard Rhat metrics within the software¹⁴.

MISSING DATA ANALYSIS

Combining data across heterogeneous studies inevitably results in missing data. Restricting analysis to observations with fully available predictors (a complete-case approach) can cause bias in addition to reducing study power¹⁶. We used a multiple imputation approach. Assuming that missingness was random conditioned on observed predictors, each variable with missing data was modelled with its own likelihood function and predictors. The benefit of this step is that the resulting regression coefficient estimates are relatively unbiased and that the appropriate uncertainty is propagated to

the posterior. The drawbacks are that it is slow - it requires the simultaneous fitting of 12 different likelihood models at each step of the sampling procedure – and requires applied knowledge of the potential causal structure of the data. Continuous missing data were subsequently multiply imputed as part of the posterior sampling procedure, but Stan has the drawback of being unable to sample from discrete distributions¹⁷. Categorical missing data were, therefore, analytically marginalised over their likelihoods during model fitting instead. Further data available from Dryad (Additional Methods)

MODEL EVALUATION AND INTERNAL/EXTERNAL VALIDATION

Our strategy was to produce an optimally accurate and well-calibrated model with fully adjusted and unbiased parameter estimates. A variable selection step is often used to reduce the size of clinical prediction models, however, in settings where there are a large number of candidate predictors, this procedure is liable to overfit the data (i.e. some variables are selected or removed by chance)¹⁸. Given these concerns and the desire to reduce the overall number of cross-validated model comparisons, we did not pursue predictor selection beyond the remaining 22 variables.

The overall internal performance of the ‘Full’, ‘Baseline’ and the ‘Baseline GTCS’ models were assessed with their respective log loss rates¹⁹ - a proper scoring rule based on the residual error that takes into account the entire predictive distribution. Average internal discriminative performance was also assessed with an Area Under the Receiver Operating Curve (AUROC), whilst calibration of the ‘Baseline GTCS’ and ‘Full’ models were assessed with a calibration plot (the ‘Baseline’ model will inherently have poor calibration). Beyond internal validity, the question arises as to how well the model will generalise to external unseen data. Especially in scenarios where the model is developed using data from a single centre, one risk is that the model predictions will be

over-optimistic when applied to individuals from other centres ('over-fitting'). Model generalisability (external validation) is optimally assessed by estimating the model's accuracy on a completely external dataset from a different geographical population or time-period, but this was non-trivial in our case because different centres had different case numbers, matching ratios, clinical predictor definitions and degrees of missing data. Thus, we performed two types of external validation: approximate leave-one-subject-out cross-validation and leave-one-centre-out cross-validation each with their strengths and weaknesses. Leave-one-subject-out cross-validation estimates how well the model would perform on *new* individuals originating from the heterogeneous populations already represented (European and North American). In this scenario, external validation can be performed using hold out cross-validation where the data are repeatedly split into a training- and testing- datasets and model performance estimates are summarised on the held-out data over many runs¹⁷. This procedure is computationally prohibitive in the Bayesian MCMC setting (data available from Dryad (Additional Methods)) and information criterion are traditionally used as an alternative way to compare a predictive model's generalisability. Bayesian leave-one-out cross-validation is, however, now computationally tractable due to an approximate technique based on Pareto smoothed importance-sampling¹⁷. This approximation can be assumed to be reliable as long as the Pareto tail parameters (k) fall below 0.7. The resulting external validation metrics are the leave-one-out expected log posterior density (lower is better) and the leave-one-out information criterion (lower is better). The final comparison of how well the 'Full', the 'Baseline' and the 'Baseline GTCS' models generalised to new individuals was performed with the paired difference between their respective leave-one-out expected log posterior densities (the worse model has a negative value relative

to the preferred model which has a reference value of 0). We also assessed cross-validated discriminative power with approximate leave-one-subject-out AUROC.

To determine how well the 'FULL' predictive model generalised to individuals from *new source populations*, we performed leave-one-centre-out cross-validation. Here, each of the smallest three datasets (USA, Scotland, Sweden) was held out whilst the 'FULL' model was trained on the remaining data. The discriminative power of the model was then tested on data from the held-out centre with leave-one-out AUROC. The largest centre (England and Wales) included too many cases of SUDEP (~54% of the total) to hold out of the training procedure and so leave-one-centre-out cross-validation was only performed on the remaining three smaller datasets. We present our results in accordance to the TRIPOD criteria²⁰.

CLINICAL UTILITY

The model prediction can be interpreted as an estimate of the latent stochastic SUDEP risk for a given individual characterised by a given constellation of clinical features. In order to demonstrate the utility of this risk prediction in clinical practice, we applied the model to ten individuals with epilepsy known to one of the authors (BD) from her recent clinics, and selected by her to demonstrate different clinical scenarios where a risk prediction may have been useful. This required adding a term to the intercept of the logit model (based on the sampling frequencies of cases and controls) which converts expected observed case-control risk to expected population risk²¹ assuming a background incidence of 1.2/1000-person-years. This assumption is also necessary to translate the unitless model output (a prediction from log odds ratios) into a prediction with meaningful units (risk of SUDEP per 1000-person-years). Model evaluations took place initially blinded to the fact that two of the individuals had suffered SUDEP.

STANDARD PROTOCOL APPROVALS, REGISTRATIONS, AND CONSENTS

Ethical approval was previously obtained by the original source studies. No additional ethical approval was sought for this re-analysis of data that was de-identified prior to statistical analysis⁸.

DATA AVAILABILITY

Requests for data should be directed to the authors of the four source studies^{7,22–24}. We suggest that this model be restricted to clinical researchers pending external validation in different source populations. We aim to use the model as a basis for a freely available online risk calculation tool for use by clinical researchers only. In the interim, those interested should contact the first author who will provide analytic support.

Results

DEMOGRAPHICS

We included 1273 cases (287 SUDEP, 986 controls). Baseline demographic data and sampling frequency of all considered 29 predictor variables are available from Dryad (Table e1). There were significant missing data (data available from Dryad (Table e1)), and so only 22 predictors with <50% missing data were taken forward for analysis. The main sources of dataset heterogeneity reflected variation in aetiology (an excess of Symptomatic cases in Sweden (77.6%) and an excess of Cryptogenic cases in Scotland (75.4%) possibly representing overlapping classification criteria across these two categories) focal seizure frequency (higher in the USA (4/month) than England and Wales (0.2/month) and Sweden (1.2/month), missing in Scotland) and epilepsy surgery (more frequent in the USA (23.7%) compared with other datasets(1.4% in England and

Wales, 0.4% in Sweden), reflecting the variable availability of this treatment across the world).

PREDICTIVE PERFORMANCE

Internal validation

All MCMC chains converged adequately with $R_{hat}=1$ for all relevant model parameters and no reported divergences¹⁴. Internal validation model performance metrics are provided in tables 2 and e4 and figure 1. The 'Full' model had better predictive performance than either the 'Baseline GTCS' or the 'Baseline' model having the lowest log loss rate. Overall performance metrics combine evaluation of model calibration and discriminative power, but these aspects were also separately evaluated.

Model calibration evaluates the degree to which model predictions fit the observed data across different stratifications. Cases were split into deciles ranked by their posterior model risk estimates. The observed SUDEP rate for each decile is plotted against the model prediction in Figure 1a and confirms excellent calibration for the 'Full' model, compared to poor calibration for the 'Baseline GTCS' model -data available from Dryad (Figure e1). Calibration for the 'Baseline' model is inherently poor as every decile receives the same prediction regardless of the observed rate of SUDEP. Discrimination is the ability of the model to separate observed SUDEP from Control cases based on their predicted risk. The risk distributions for both case types are shown in Figure 1b, whilst the sensitivity and specificity of the model is shown across all thresholds as a Receiver Operating Curve in Figure 1c. The mean internal (95% Credibility Interval) AUROC for the 'Full' model (0.72 (0.71 to 0.74)) was better than the 'Baseline GTCS' (0.69 (0.68 to 0.71)) and 'Baseline' model (0.57 (0.57 to 0.57))(see tables 2 and e4).

External Validation

The approximate leave-one-subject-out cross-validation technique was reliable with only one out of 1273 observations being associated with a Pareto $K > 0.7$ (0.1%). This showed that the 'Full' model generalised to new individuals better than either the 'Baseline GTCS' or 'Baseline' models. (paired difference in leave-one-out expected log posterior density Full v Baseline GTCS = -22.9, SEM +/-11.0; Full v Baseline = 35.9, SEM +/-12.5). Further model comparison measures supported this conclusion (see tables 2 and e5). Reweighting model predictions by their Pareto smoothed importance sampling weights also allowed us to approximate the leave-one-subject-out AUROC, as a measure of how well the discriminative power of the model generalises. The 'Full' model generalises better than the 'Baseline GTCS' model or the 'Baseline' model to new subjects in terms of AUROC also(see tables 2 and e5).

We performed leave-one-centre-out cross-validation of the 'Full' model for the smaller three datasets (see table e6). When trained on a significantly reduced amount of data and generalised to a sample from an unseen source population, model performance in terms of the AUROC (95% bootstrap CI), was more uncertain but remained on average reasonable for Scotland (0.66 (0.57 to 0.74)) and Sweden (0.61 (0.52 to 0.69)). Cross-validated model AUROC (95% bootstrap CI) for the USA, was highly uncertain and poor on average (0.55 (0.41 to 0.69)), but the interpretation of this is difficult as it was also the smallest centre (including only 20 cases of SUDEP) with the highest degree of data imbalance (see Discussion).

INFERENCE

The adjusted posterior log odds ratios of the fitted logistic regression model are presented in Figure 2. Example relations have been transposed onto their natural scales in Figure 3, to simplify clinical interpretation. Bayesian models have no arbitrary

significance threshold, so we assessed the strength of associations based on the mean effect-size (odds ratio) and surrounding uncertainty. Several variables were strongly independently associated with SUDEP, however, the observational nature of observational studies limit *causal* interpretations (see Discussion).

INDIVIDUALISED PREDICTION

Over and above the power of the model to discriminate SUDEP cases from controls within an observation period, we can also view the model output as an estimate of *latent* stochastic SUDEP risk. Variation in this risk across individuals may be clinically useful, even if does not cross a discriminatory threshold. We illustrated the model's potential clinical and research utility by personally forecasting absolute SUDEP risk for ten individuals with epilepsy (see Figure 4). The resulting figures show a quantification of risk with uncertainty that may be of benefit in clinical studies aiming to stratify individuals based on risk and potentially in clinical discussions between individuals with epilepsy and their medical team.

Discussion

Our model predicted individual risk more accurately than either a model based on GTCS frequency alone or one based on the population-level average even when generalised to *unseen subjects*. Its ability to discriminate SUDEP from controls was reasonable (leave-one-subject-out AUROC=0.71 (0.68 to 0.74)). When a version of the model with access to limited training data was generalised to a sample from an *unseen source population*, the model's discriminative capability was reasonable for Scotland and Sweden, and less certain for the USA possibly because of its small size, inclusion of children or distinct data definition and collection procedures (see table e6). Use of the model in non-represented populations should, therefore, be cautious. The AUROC

and prediction risk distributions (see Figure 1b and 1c) show that predictions are uncertain. This suggests that risk is a stochastic latent process and categorising it in binary terms – high-risk versus low-risk – may be misleading; risk should be conveyed as a probability distribution. Our model can stratify *individuals* based on their risk (see figure 4), which may be useful for research studies and has the potential to enhance clinical decision-making and communication. . Our model also identified a novel association of focal-onset seizure frequency with SUDEP risk and confirmed previously reported associations with increased GTCS frequency, younger age of epilepsy onset and male sex. We also found evidence that lamotrigine, benzodiazepines and carbamazepine are associated with increased SUDEP risk, although the potential causal role of these medications remains undetermined by our current analysis. Combining heterogeneous datasets with different case ascertainment procedures, origin and risk periods inevitably requires careful harmonisation of clinical variables where it is possible and accounting for missing data where it is not (data available from Dryad(Additional Methods)). Some clinical predictors were more consistently defined across individual datasets than others⁸. Anti-seizure medications and seizure types were the most consistently defined. Family history was obtained from primary care records in England and Wales as opposed to secondary care records in Scotland. Alcohol use, respiratory and cardiac comorbidities and learning difficulties had strongly overlapping but distinct definitions in each individual dataset. Adherence was defined according to serum levels of anti-seizure medications in the USA sample, and primary care evaluation of clinical records in the England and Wales sample. These discrepancies may increase the uncertainty of their respective odds-ratios and subsequently impair generalisability between datasets. In spite of this, adherence, family history and co-morbidities all remain *individually* influential in our model. The

combined effect of these inconsistencies between datasets was also tested by the leave-one-centre-out analysis. The most uncertain performance was seen when predicting the out-of-sample USA outcomes. A finding that may be partly explained by the different definitions used in the USA dataset as compared to the others.

Missing data were multiply imputed to reduce bias and appropriately reduce the confidence of subsequent predictions as compared to single imputation or a complete case approach¹⁶. Potential bias due to heterogeneity in case-control matching ratios and population sampling distributions of each centre²¹ was accounted for by explicitly including an intercept for each centre. Lastly, any Bayesian approach may be criticized because of the need for prior distributions for the model parameters. We used weakly informative priors consistent with expert knowledge²⁵, and altering the prior did not alter the model performance substantially.

We developed and evaluated the model to optimise its predictive capabilities but the potential inferential findings require further discussion particularly as they may be interpreted as challenging previous reports^{8,9}. We highlight two broad principles. Firstly, due to the impracticability of interventional trials, risk factors are generally derived from observational data and are therefore prognostic rather than causal factors derived from clinical trial data^{1,3,8,26,27}. Secondly, odds ratios are difficult to meaningfully compare when adjusted by different variable sets – we adjust for an extended set of variables as compared to previous studies. Given such caveats, we confirmed that those with a younger age of epilepsy onset had a higher risk, and that risk increases slowly with age. Men had a slightly higher risk of SUDEP as previously suggested⁸, but learning disability did not independently increase risk. This finding is important, as unlike earlier studies⁷, we adjusted for the effect of multiple factors including aetiology, medication

adherence and seizure frequency. Thus, those with those with learning disabilities have similar risk to other individuals all other things being equal and may equally benefit from risk factor modification. A history of epilepsy in 1st degree relatives increased SUDEP risk and was present in ~4% of our dataset. This may be partially explained by mutations that cause epileptic encephalopathies and treatment resistant epilepsies such as *SCN1A* and *SCN8A* but other more highly prevalent (e.g., *DEPDC5*) and possibly non-mendelian mechanisms may also contribute¹.

We found that an increased frequency of *both* convulsions (including GTCS and focal to bilateral tonic-clonic seizures) and non-generalising focal-onset seizures conferred a higher risk of SUDEP. This is a departure from previous reports that estimate a higher average relative risk from GTCS frequency^{8,9}, and have found no significant association between focal-onset seizures and SUDEP^{7,9}. These differences could be explained by variation in the data themselves or the strategies used for analysis. No significant relation was found between focal-onset seizures and SUDEP from analyses not only of the most recent and homogeneously ascertained data⁹ but also of one of our source studies⁷. In fact stratified relative risk from convulsions was higher in a previous analysis of the same combined source data as ours⁸, suggesting that differences in data can only partially explain the conflicting results. An alternative reason is that, uniquely, our analysis aimed to provide individualised predictions, whereas others aimed to infer average effects over a population^{8,9}. Subsequently, we include as many data features as possible in the same *single* model (22 clinical factors), rather than seeking to interpret the output of *multiple* smaller models^{8,9}. We also removed arbitrary seizure frequency cut-offs (e.g. <3 per year) to improve individualization and inter-study comparability but assumed a monotonic relation between seizure frequency and outcome. We sought to identify prognostic rather than causal risk factors and within

these constraints convulsion frequency was not the only metric of SUDEP risk¹⁰, and indeed performs poorly if used as the sole predictive factor (see Table 2). The novel finding that non-generalising focal-onset seizure frequency is prognostic conflicts with other major analyses⁹, and requires further investigation as it has potentially wide-ranging implications for clinical practice. Whether non-generalised focal seizures can directly cause SUDEP or may be proxies for breakthrough tonic-clonic seizure risk in individuals who were previously free of convulsions also remains uncertain. Lastly, some predictors were variably clinically defined and so our interpretations must be cautious. Even so, medication adherence was associated with reduced risk, whilst alcohol/drug abuse was associated with increased risk. This highlights two modifiable behaviours that, if causal, could reduce risk if addressed.

The independent associations between various treatments and SUDEP risk also require further explanation. Whilst our results support prior studies that have found a protective role for epilepsy surgery²⁸, almost all anti-seizure medications are independently associated with slightly increased SUDEP risk. This needs to be interpreted cautiously since adjusted odds ratios represent the effect of adding anti-seizure medications without any benefit on seizure control – a situation which may either represent increased risk due to the medication, or increased risk due to selection of those with treatment-resistance. Excluding vigabatrin which is rarely used and probably falls into the second category, lamotrigine, benzodiazepines and carbamazepine were associated with increased SUDEP risk compared to other medications, but interventional trials would be needed to determine whether this association is causal or not. Similarly, although cardiac and respiratory comorbidity is associated with reduced risk, this observation may be confounded by a competing risk (these individuals are more likely to die from a non-epilepsy related cause) or by increased prevalence of co-

existent pathological findings associated with SUDEP misclassification (e.g., 40% left anterior descending coronary artery occlusion)⁵.

Regardless of the inferential findings and uncertainties, our model's predictive power remains valid. Its potential ability to either reassure or to motivate *individuals* by forecasting their current risk (see Figure 4) will focus discussions on prevention, rather than dwelling on an abstract population estimate of death. Improving anti-seizure medication adherence and sleep hygiene, eliminating excess alcohol, employing strategies to reduce seizures in specific settings (e.g. malabsorption of medications due to vomiting or diarrhoea), and avoiding seizure-provoking factors in those susceptible (e.g., decongestants, environmental stimuli such as flashing lights) may be emphasised in those at moderate risk. Whilst, those with highest risk may consider the use of monitoring (e.g., intermittent observation, seizure detection devices to alarm caretakers), especially with nocturnal convulsions. Lifestyle modifications and monitoring strategies are commonly recommended but remain unproven in reducing SUDEP risk partly due to the logistical challenges of large interventional studies. Our tool could help identify high-risk groups, thereby reducing the number of enrolled individuals to establish a treatment effect.

Conclusion

We developed and validated an individualised SUDEP prediction model, which relies on information available during a clinical consultation. This will be developed into an online risk prediction calculator for clinical research use. This prediction remains uncertain, but has potential utility in clinical and research settings. Future prospectively acquired large longitudinal studies are required to improve the model, and to establish its accuracy in non-represented populations. Beyond this, a granular understanding of the

pathophysiological factors contributing to SUDEP may contribute towards a mechanistic model which may have even higher accuracy.

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Appendix 1. Authors

Name	Location	Contribution
Ashwani Jha, PhD	NIHR University College London Hospitals Biomedical Research Centre, UCL Queen Square Institute of Neurology, London, WC1N 3BG, UK	Designed and conceptualized study; data analysis; drafted and revised the manuscript.
Cheongeun Oh, PhD	Division of Biostatistics, Department of Population Health, New York University Langone Health, New York, NY, USA	Data analysis; revised the manuscript.
Dale Hesdorffer, PhD	Department of Epidemiology, Columbia University Medical Center, New York, NY, USA	Original data collection and design, revised the manuscript.
Beate Diehl, PhD	NIHR University College London	Designed and conceptualized study;

	Hospitals Biomedical Research Centre, UCL Queen Square Institute of Neurology, London, WC1N 3BG, UK	data collection, revised the manuscript.
Sasha Devore, PhD	Comprehensive Epilepsy Center, New York University Langone Medical Center, New York, NY, USA	Revised the manuscript.
Martin Brodie MD	Epilepsy Unit, University of Glasgow, Glasgow, Scotland	Original data collection and design, revised the manuscript.
Torbjörn Tomson PhD	Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden	Original data collection and design, revised the manuscript.
Josemir W. Sander, FRCP	NIHR University College London Hospitals Biomedical Research Centre, UCL Queen Square Institute of Neurology, London,	Original data collection and design, drafted and revised the manuscript.

	WC1N 3BG, UK	
Thaddeus S. Walczak MD	MINCEP University of Minnesota Medical School Epilepsy Care, Minneapolis, MN, USA	Original data collection and design, revised the manuscript.
Orrin Devinsky, MD	Comprehensive Epilepsy Center, New York University Langone Medical Center, New York, NY, USA	Designed and conceptualized study, drafted and revised the manuscript.

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Figure Legends

Figure 1: Internal evaluation of SUDEP model performance. Panel a is a calibration plot, where the observed cases are sorted into deciles based on the predicted risk from the model. For each subsequent decile, the observed rate of SUDEP in the dataset is plotted against the model prediction (black circle = average, red line = 80% Credibility Interval, black line 95% Credibility Interval). The model shows excellent calibration – perfect calibration would be aligned along the dotted line where both values are equal. **Panel b** shows the predicted risk probability distribution functions for SUDEP cases (red) and controls (black). Perfect discrimination would be illustrated by complete separation of the two distributions along the x axis, chance discrimination would be illustrated by complete alignment. Discrimination is reasonable but there is still a degree of overlap suggesting a remaining degree of uncertainty at risk estimates around 0.2-0.4. This is consistent with the ROC curve underneath (**Panel c**) which shows the specificity and sensitivity of predicting SUDEP in this dataset based on model output (red line = mean, red patch = 80% Credibility Interval, grey patch = 95% Credibility Interval) The internal AUROC is 0.72 (95% Credibility Interval 0.71 to 0.74) which is reasonable.

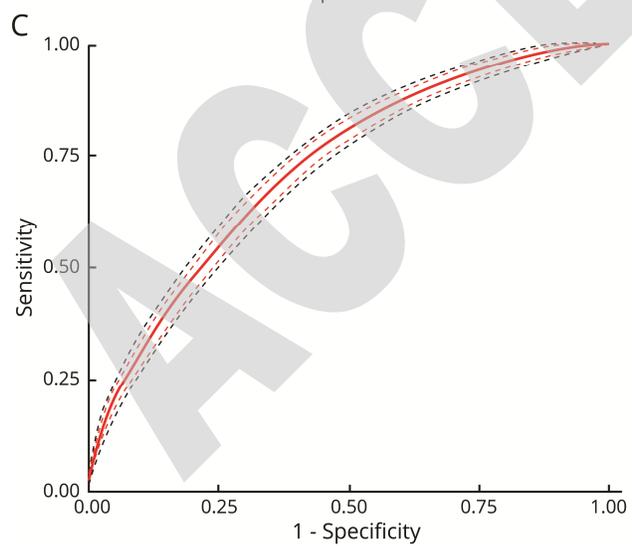
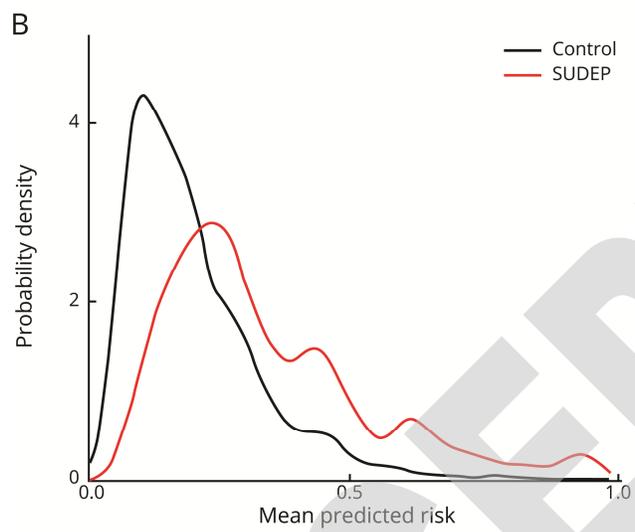
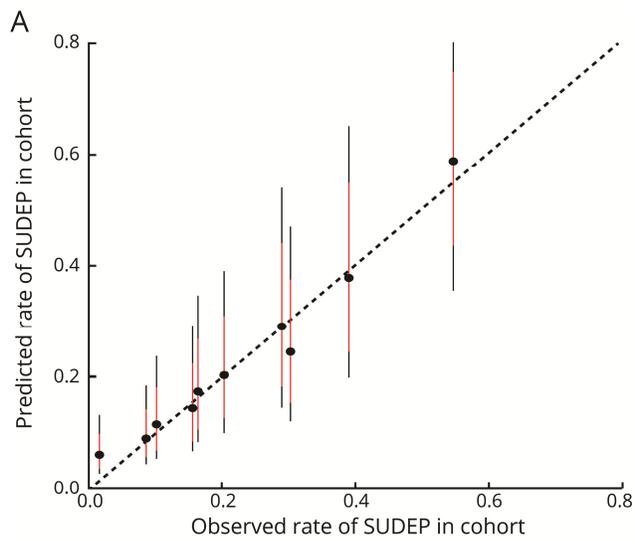


Figure 2: Adjusted Log odds ratios from Bayesian Logistic regression model. The adjusted log odds ratios are shown. Values less than 0 are associated with a reduced risk of SUDEP, whilst values greater than 0 are associated with an increased risk of SUDEP, relative to the average population sample (black circle = average, red line = 80% Credibility Interval, black line 95% Credibility Interval). See main text for interpretation noting that the associations shown are not causal.

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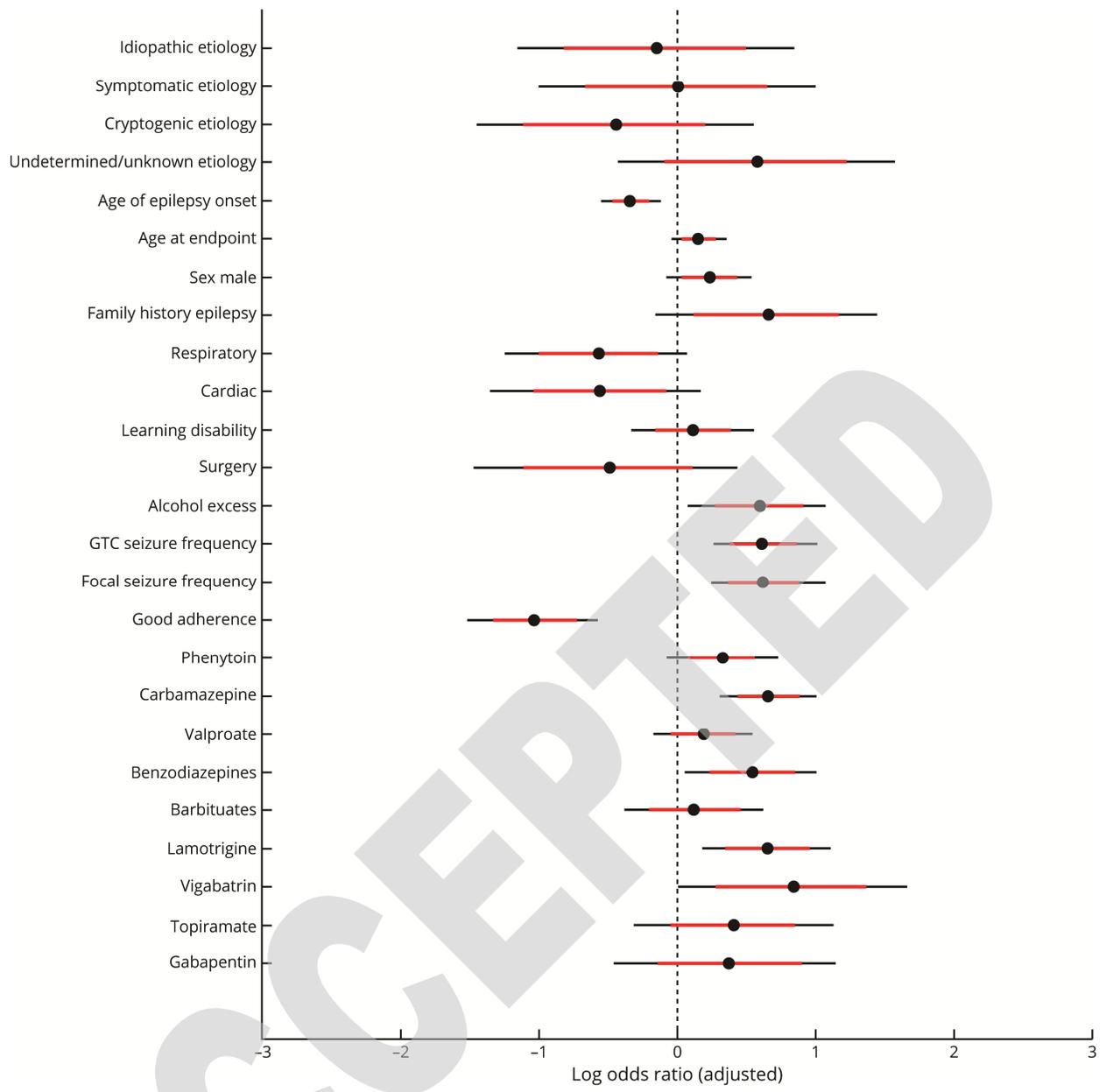


Figure 3: Marginal adjusted risk. Panel a: the marginal (average) predicted non-causal effect of GTCS frequency (top left), Focal seizure frequency (top right), Age of Epilepsy onset (bottom left) and Current Age (bottom right) on the odds of SUDEP ratio on their natural scales is shown. These values are relative to a seizure frequency of 0, and to the sample average Age of Epilepsy Onset and Current Age (red line = mean, red patch = 80% Credibility Interval, grey patch = 95% Credibility Interval). Note that the y axis is a log scale. **Panel b:** the combined non-causal effect of Age of Epilepsy Onset and Current Age on SUDEP risk is shown as a grid of values represented by a colour scale. Warmer colours represent increased risk and imply that those with a younger Age of Epilepsy Onset have the highest risk and that this risk increases as Current Age increases.

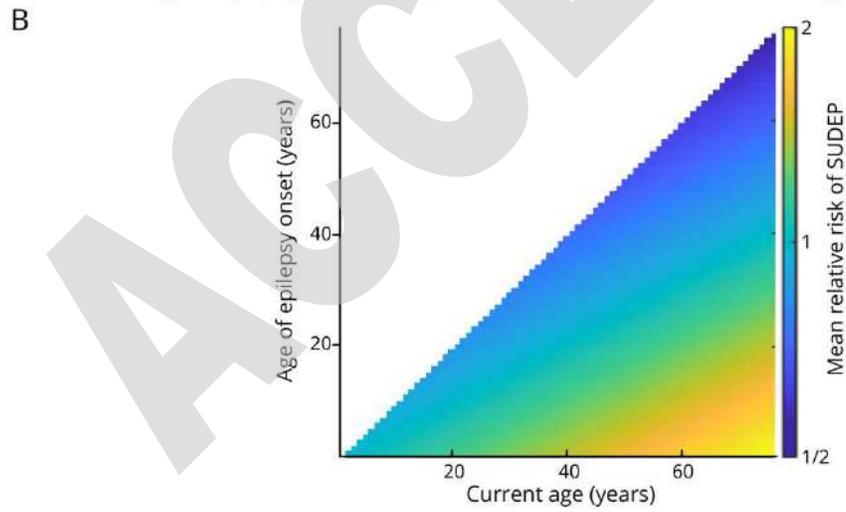
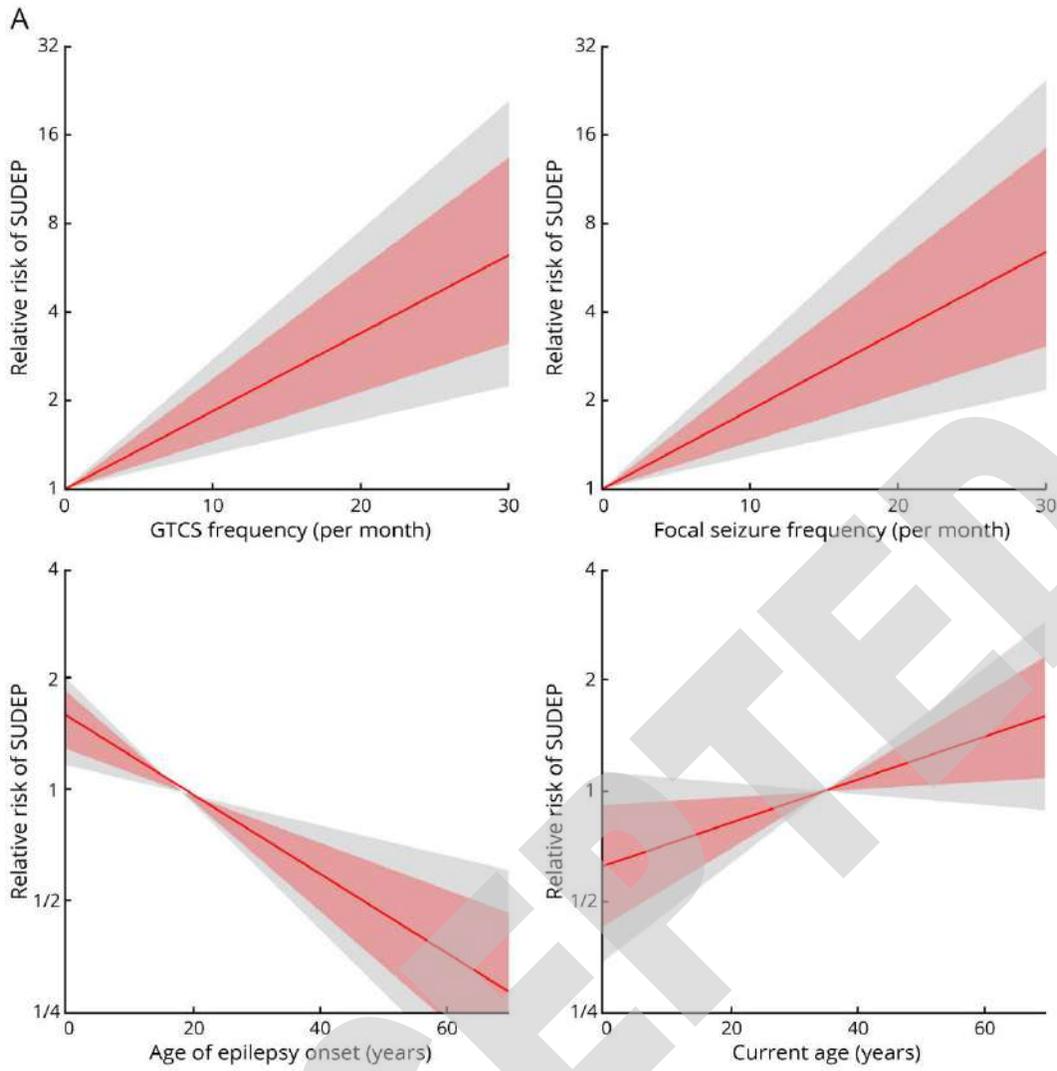
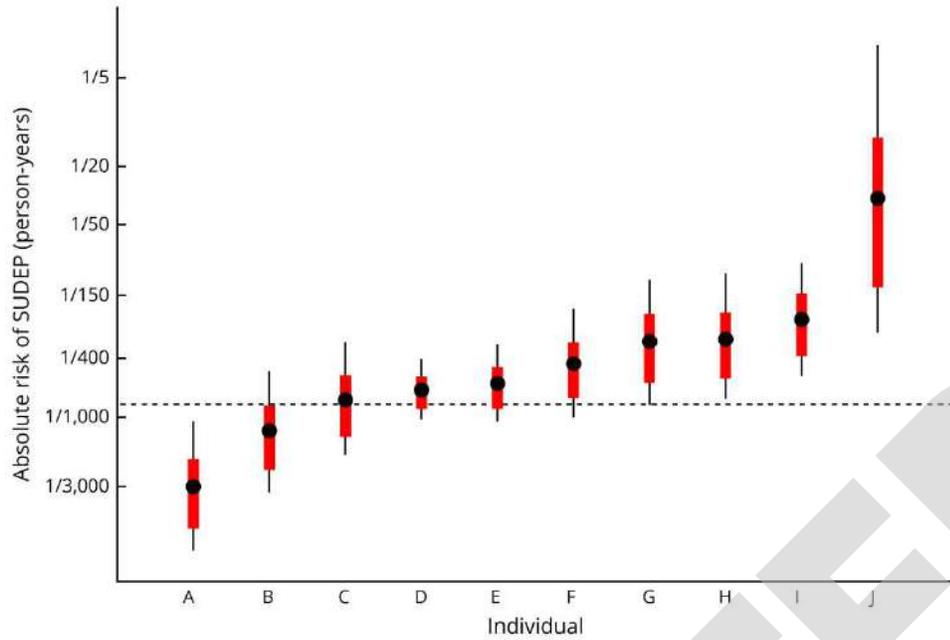


Figure 4: Individualised model predictions of SUDEP. To demonstrate the potential research and clinical utility of this tool the individualised risk predictions of ten individuals with epilepsy are shown. These individuals are not known to the model, were drawn from recent practice and were selected as their SUDEP risk was of clinical interest. The risk is presented on the y axis as a summary measure of a probability distribution (black circle = mean, red line = 80% Credibility Interval, black line 95% Credibility Interval) for individuals A-J specified on the x axis and ordered by mean risk. Note the y axis is a log scale with risk quantified as a ratio for ease of interpretation. The dotted horizontal line represents the average population risk of 1.2/1000-patient-years. The predictions are probabilistic, intuitive and help focus discussions in a time-limited setting such as a clinical consultation. Important prognostic factors vary between the individuals and so multiple factors need to be considered together. For example in those five with the highest risk, focal seizure frequency is particularly important in F, H and J; GTCS frequency in G, and poor adherence in I. Two of the individuals with highest risk (marked with a red circle next to their names) have died of SUDEP. Abbreviations: ASM: anti-seizure medications, GTCS: Generalised Tonic-Clonic Seizures. *The influence of Levetiracetam was not modelled.

A



B

A	45M (seizure onset aged 21 years) Symptomatic etiology 24 GTCS, 0 focal seizures last year ASM: Levetiracetam* Previously undergone epilepsy surgery	F	41F (seizure onset aged 11 years) Idiopathic etiology 0 GTCS, 150 focal seizures last year ASM: Valproate, lamotrigine, levetiracetam*
B	30M (seizure onset aged 11 years) Unknown/indeterminate etiology 24 GTCS, 0 focal seizures last year Paroxysmal atrial fibrillation ASM: Valproate, levetiracetam*	G ●	33M (seizure onset aged 13 years) Indeterminate/unknown etiology 36 GTCS, 4 focal seizures last year ASM: Benzodiazepines, topiramate, levetiracetam*
C	26F (seizure onset aged 10 years) Symptomatic etiology 6 GTCS, 125 focal seizures last year ASM: Topiramate, levetiracetam*	H ●	20M (seizure onset aged 15 years) Symptomatic etiology 0 GTCS, 200 focal seizures last year ASM: Benzodiazepines, lamotrigine, levetiracetam*
D	26M (seizure onset aged 1 year) Symptomatic etiology 0 GTCS, 24 focal seizures last year ASM: Carbamazepine	I	24M (seizure onset aged 16 years) Idiopathic etiology 2 GTCS, 0 focal seizures last year Poor compliance, anxiety ASM: Valproate, benzodiazepines, lamotrigine, levetiracetam*
E	35M (seizure onset aged 24 years) Symptomatic etiology 24 GTCS, 0 focal seizures last year ASM: Carbamazepine, benzodiazepines, levetiracetam*	J	26F (seizure onset aged 10 years) Symptomatic etiology 3 GTCS, 600 focal seizures last year ASM: Carbamazepine, benzodiazepines, topiramate Previously undergone epilepsy surgery

Tables

Population	Age range (years)	Risk period	No. cases	No. controls	Case ascertainment criteria	Control sampling population	Matching ratio (Case: Control)	Matching criteria	Significant risk factors
England and Wales	16-50	1989-1998 (9 years)	154**	616	Retrospective from coroners, neurologists and bereaved families/charity.	General practice database, 1 seizure in last 5 years, or taking AED and in remission	1:4	Age and geographic location	frequent convulsions, polytherapy
USA	0-80+	June 1 1991 – Dec 31/1996 (5.5 years)	20	80	Prospective from 3 hospital-based upper Midwestern epilepsy centres	Same as cases	1:4	Calendar matching (same month), and geographic centre	Convulsion frequency, epilepsy duration, mental retardation, polytherapy
Scotland	18-85	1982-2005 (23 years)	64	119	Retrospective from hospital centre registry	Same as cases	1:2	Year of birth, sex, and aetiology	Epilepsy duration, recent convulsions (1 year)
Sweden	15-70	1980-1989/91* (11 years)	57	171	Hospital discharges with a diagnosis of epilepsy	Hospital discharges receiving one year of valproate, phenytoin or carbamazepine	1:3	Year of birth, sex, assessment period	>50 convulsions per year, polytherapy, early onset, frequent changes to medications

Table 1: Observational study descriptions. Four observational studies were analysed with a combined risk period extending from 1980-2005. All studies were case-control designs apart from the USA study which was a cohort study. The England and Wales data²¹ were sampled from a community population, whilst the Swedish²², Scottish²³ and American⁷ data were sampled from secondary care. All samples were open (dynamic) and therefore provide incident rate ratios given the steady state assumption. We included all available records regardless of matching and so total numbers may differ from those in the original studies slightly. *Cases were recruited from discharges from 1980-1989, but SUDEP Case status was determined 1991. **8 Cases without anti-seizure medication data were excluded (see missing data analysis).

	Baseline Model	Baseline + GTCS Model	Full model
	<i>Internal validation</i>		
Area Under the Receiver Operating Curve (95% CI)	0.57 (0.57 to 0.57)	0.69 (0.68 to 0.71)	0.72 (0.71 to 0.74)*
	<i>Approximate external cross-validation</i>		
Leave-one-subject-out area Under the Receiver Operating Curve (95% bootstrap CI)	0.38 (0.33 to 0.42)	0.63 (0.59 to 0.67)	0.71 (0.68 to 0.74)*
Pairwise difference in leave-one-subject-out expected log posterior density (+/- SEM)	-35.9 (12.5)	-22.9 (11.0)	0.0 (0.0)*

Table 2: Model Performance. The overall performance of the ‘Full’ model (with all clinical predictors) is compared to the ‘Baseline GTCS’ model (with only centre mean and GTCS frequency as predictors) and the Baseline model (with centre mean predictors only) with a number of metrics. Internal performance of the ‘Full’ model is better than either of the other two models with a higher Area Under the Receiver Operating Curve. External validation performed with approximate leave-one-subject-out cross-validation also confirmed that the ‘Full’ model is better than either of the other two models when predicting SUDEP in new patients within the same population. Formal

model comparison, based on the pairwise difference in leave-one-subject-out expected log posterior density preferred the 'Full' model (higher is better), and comparisons of the leave-one-subject-out Area Under the Receiver Operating Curve also highlighted the improved generalisability of the 'Full' model. CI = Credibility Interval. SEM = standard error of the mean. *Better model performance.

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