SUDEP UPDATES

Mahyar Noorbakhsh

Epileptologist

- SUDEP definition
- SUDEP epidemiology
- SUDEP risk factors
- SUDEP awareness
- Genetics of SUDEP
- SUDEP mechanisms
- SUDEP biomarkers

What is SUDEP?

Panel: Research classification for sudden unexpected death in epilepsy[6]

Definite sudden unexpected death in epilepsy (SUDEP)
Sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death that occurs in benign circumstances in an individual with epilepsy, with or without evidence for a seizure, and excludes documented status epilepticus, in which post-mortem examination does not reveal a cause of death.

Definite SUDEP plus
Death satisfying criteria for definite SUDEP, if a concomitant condition other than epilepsy is identified before or after death, if the death might have been due to the combined effect of both conditions, and if autopsy or direct observations or recording of the terminal event did not prove the concomitant condition to be the cause of death.

Probable SUDEP or probable SUDEP plus
Same definition as definite SUDEP or SUDEP plus, but without autopsy.

Possible SUDEP
A competing cause of death is present.

Near-SUDEP or near-SUDEP plus
A patient with epilepsy who survives resuscitation for more than an hour after cardiorespiratory arrest and has no structural cause identified after investigation.

Not SUDEP
A clear alternative cause of death is identified.

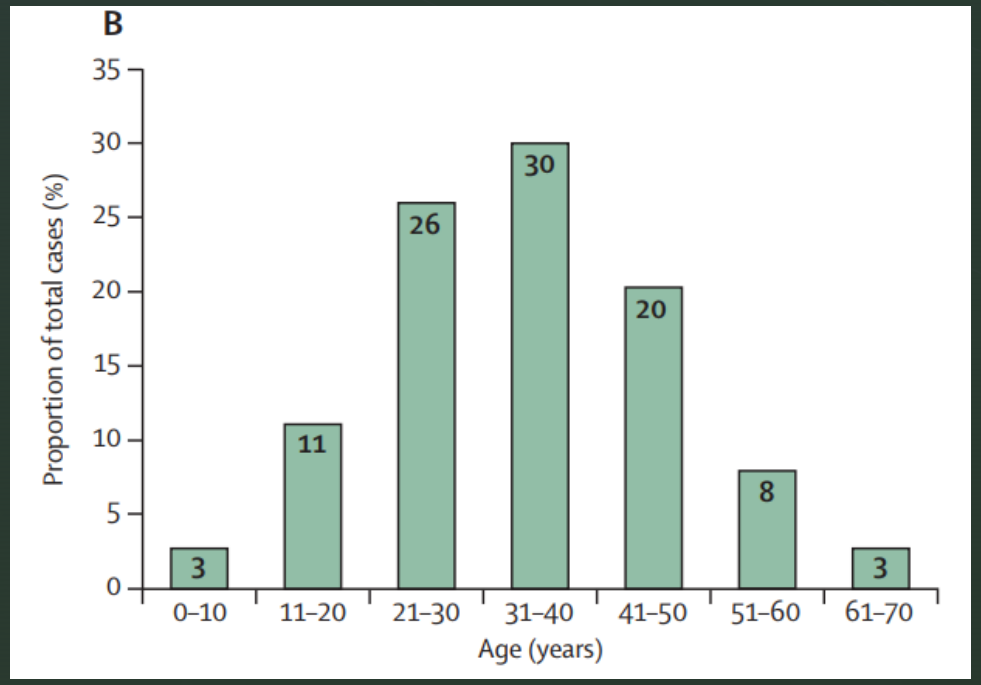
Unclassified
Incomplete information available; impossible to classify.

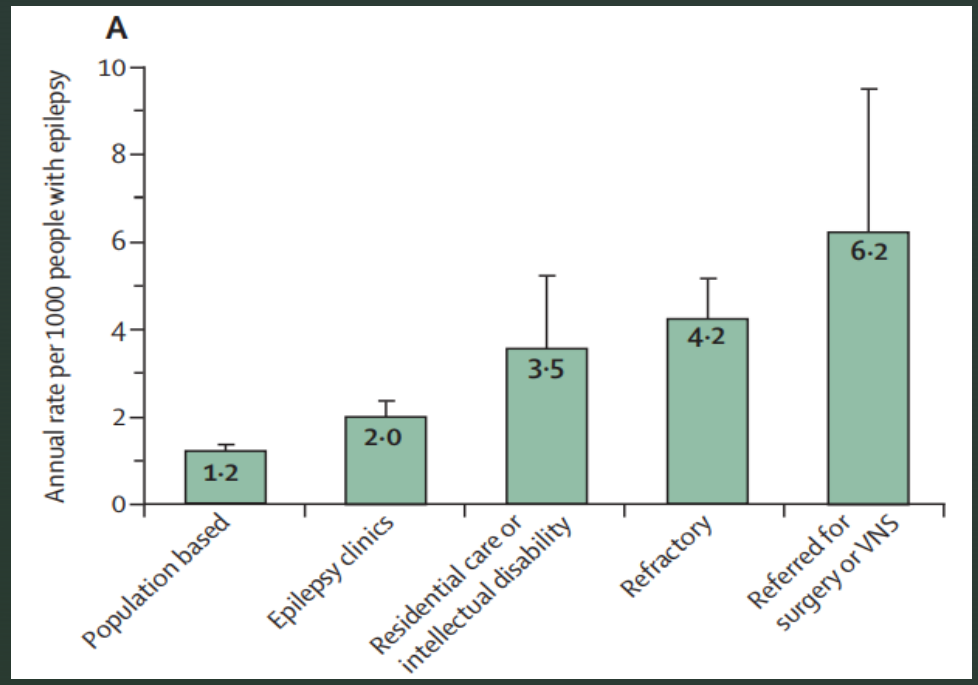
► Devinsky O, Hesdorffer DC, Thurman DJ, Lhatoo S, Richerson G. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. The Lancet Neurology. 2016 Sep 1;15(10):1075-88.

SUDEP epidemiology

SUDEP, Some facts:

- PWE have 3x increased mortality.
- PWE are 24x more likely to die of sudden death.
- SUDEP is the commonest cause of death in epilepsy.





Population	SUDEP/1,000 patient-years (CI)	Confidence level
Overall	0.58 (0.31–1.08)	Low
Childhood	0.22 (0.16–0.31)	Moderate
Adulthood	1.2 (0.64–2.32)	Low

Incidence of sudden unexpected death in epilepsy in children is similar to adults

Anne E. Keller, MPH, Robyn Whitney, MD, Shelly-Anne Li, MSc, Michael S. Pollanen, MD, PhD, and Elizabeth J. Donner, MD, MSc

Neurology® 2018;0:1-5. doi:10.1212/WNL.0000000000005762

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The incidence of SUDEP

A nationwide population-based cohort study

Method	Included classifications of SUDEP	No. of SUDEP cases	Epilepsy prevalence, %	Incidence (95% CI) per 1,000 patient-years
Crude analysis	All	17	0.27	1.17 (0.68–1.88)
	Definite, definite plus, probable	16	0.27	1.11 (0.63–1.79)
Sensitivity analysis	Definite, definite plus, probable	16	0.21	1.42 (0.81–2.31)
	Definite, definite plus, probable	16	0.34	0.88 (0.50–1.42)
Capture-recapture analysis	Definite, definite plus, probable	21	0.27	1.45 (0.90–2.22)

From the literature

Source	Included classifications of SUDEP	Population	Incidence (95% CI) per 1,000 patient-years
AAN guidelines[1]	Definite, definite plus,[a] probable	"Childhood"	0.22 (0.16–0.31)
	Definite, definite plus,[a] probable	"Adult"	1.22 (0.64–2.32)
Sveinsson et al.[2]	Definite, definite plus, probable	<16 y	1.11 (0.45–2.29)
	Definite, definite plus, probable	16–50 y	1.13 (0.76–1.62)
	Definite, definite plus, probable	>50 y	1.29 (0.88–1.82)

Risk Factors for SUDEP

Factor	Odds ratio (CI)	Confidence level
Presence of GTCS vs lack of GTCS	10 (7–14)	Moderate
Frequency of GTCS	OR 5.07 (2.94–8.76) for 1–2 GTCS per y, and OR 15.46 (9.92–24.10) for >3 GTCS per y	High
Not being seizure free for 1–5 y	4.7 (1.4–16)	Moderate
Not adding an AED when patients are medically refractory	6 (2–20)	Moderate
Nocturnal supervision (risk reduction)	0.4 (0.2–0.8)	Moderate
Use of nocturnal listening device (risk reduction)	0.1 (0.0–0.3)	Moderate

The evidence is **low** that the following factors are associated with altering SUDEP risk::

- Nocturnal seizures (associated with increased risk)
- Any specific AED (none associated specifically with increased risk)
- LTG use in women (associated with increased risk)
- Never having been treated with an AED (associated with increased risk)
- Number of AEDs used overall (associated with increased risk)
- Heart rate variability (not associated with increased risk)
- Extratemporal epilepsy (associated with increased risk)
- Intellectual disability (associated with increased risk)
- Male gender (associated with increased risk)
- Anxiolytic drug use (associated with increased risk)

The evidence is **very low** or **conflicting** that the following factors are associated with altering SUDEP risk:

- Overall seizure frequency when evaluated by using all seizure types
- Medically refractory epilepsy vs not having well-controlled seizures defined as no seizures for the past year
- Monotherapy vs polytherapy
- CBZ, PHT, or VPA levels that are above, below, or within the reference range
- Psychotropic drug use
- Mental health disorders, lung disorders, or alcohol use
- LTG use in people with highly refractory epilepsy
- Frequent changes in AEDs
- Therapeutic drug monitoring

TABLE 2 | The SUDEP Risk Inventory (SUDEP-7, version 2.0) with each risk factor, weighting, and scoring convention.

SUDEP Risk Inventory (version 2.0)	Odds ratio	Weighting $\log_e \times$ odds ratio	Number of subjects with each risk factor
1. More than three tonic–clonic seizures in last year	8.1	0 or 2	6
2. One or more tonic–clonic seizures in last year (if factor 1 present, score as 0)	2.4	0 or 1	9
3. One or more seizures of any type over the last 12 months (if factor 4 present, score as 0)	2.2, 3.8, 4.6	0 or 1	24
4. >50 seizures of any type per month over the last 12 months	11.5	0 or 2	3
5. Duration of epilepsy >30 years	13.9	0 or 3	7
6. Use of three or more AEDs	4.0	0 or 1	9
7. Developmental disability, I.Q. <70 or too impaired to test	5.0	0 or 2	3

►Novak JL, Miller PR, Markovic D, Meymandi SK, DeGiorgio CM. Risk assessment for sudden death in epilepsy: the SUDEP-7 inventory. Frontiers in neurology. 2015 Dec 9;6:252.

FULL-LENGTH ORIGINAL RESEARCH

Improving prediction of sudden unexpected death in epilepsy: From SUDEP-7 to SUDEP-3

Roozbeh Tarighati Rasekhi, Kathryn N. Devlin, Joely A. Mass, Mustafa Donmez, Burcu Asma, Michael R. Sperling, Maromi Nei

First published: 04 June 2021 | https://doi.org/10.1111/epi.16928

A novel SUDEP-3 inventory comprising GTC seizure frequency, seizure frequency, and intellectual disability ($p < 0.001$) outperformed the SUDEP-7 inventory ($p = 0.010$) in predicting SUDEP.

SUDEP awareness

- Family and Community Involvement: Need for Education

- Reducing Seizures and Monitoring Can Save Lives

  - Control seizures as best we can
  - Stay with patient during recovery period
  - Ensure nothing obstructing their breathing
  - Position – Lie in recovery position , sleep on back
  - Stimulate patient after a seizure
  - Administer oxygen if necessary
  - Consider nocturnal alarm , monitoring device , supervision

SUDEP genetics

- Preliminary studies suggest that SUDEP victims have higher rates of pathogenic or potentially pathogenic variants in genes that affect neuroexcitability and cardiac rhythmicity.

- It is unclear whether any of the epilepsies associated with genetic disorders (eg, mutations in SCN1A and DEPDC5) confer an increased SUDEP risk independent of seizure severity and frequency.

	Clinical disorders	Gene product or function	Expression sites (RNAseq)	Potential SUDEP mechanisms
Primary epilepsy or brain gene				
SCN1A[8]	Dravet syndrome or epileptic encephalopathy, generalised epilepsy with febrile seizures plus	Sodium channel $Na_v1.1$	Brain, heart, lung	Postictal parasympathetic hyperactivity; increased epilepsy severity
SCN2A	Epileptic encephalopathy	Sodium channel $Na_v1.2$	Brain, heart, lung	Increased epilepsy severity[36]
SCN8A[41]	Epileptic encephalopathy	Sodium channel $Na_v1.6$	Brain, heart, lung	Increased epilepsy severity[42]
PRRT2[43]	Benign familial infantile seizures	Proline-rich transmembrane protein 2	Brain	Potentially via interaction with SNAP-25, involved in presynaptic neurotransmitter release
DEPDC5[44,45]	Focal epilepsy (broad spectrum of phenotypes)	G-protein signalling pathway; component of the GATOR1 complex, which inhibits the mTORC1 pathway	Brain, heart, lung	Uncertain; potentially increased epilepsy severity
CSTB	Unverricht-Lundborg disease	A stefin that inhibits intracellular thiol protease; might prevent protease leakage from lysosomes	Brain, heart, lung	Increased epilepsy severity neurological impairment due to progressive myoclonic epilepsy
TSC2, *TSC1*	Tuberous sclerosis complex	Hamartin (TSC1), tuberin (TSC2); downregulate the mTORC1 pathway	Brain, heart, lung	Potentially increased epilepsy severity
HCN2[43]	Generalised epilepsy	Hyperpolarisation activated cyclic nucleotide gated potassium channel 2; contributes to spontaneous rhythmic activity in heart (sinoatrial node) and brain	Brain, heart, lung	Unknown; potential impairment of brainstem or cardiac pacemaker cells
Primary cardiac genes				
KCNQ1[42]	Long QT syndrome	Potassium channel $K_vLQT1/K_v7.1$; ventricular repolarisation	Brain, heart, lung	No definite SUDEP cases; potential arrhythmogenic effect
KCNH2[42,43]	Long QT syndrome	Potassium channel hERG1/$K_v11.1$; repolarisation of cardiac action potential	Brain, heart, lung	Unknown[42]
SCN5A[42,43]	Long QT syndrome	Sodium channel, $Na_v1.5$; rapid depolarising sodium current underlying cardiac action potential upstroke	Brain, heart, lung	Identified in SUDEP cases; potentially combined epilepsy and arrhythmia
NOS1AP[42]	Long QT syndrome	Cytosolic protein that binds to neuronal nitric oxide synthase	Brain, heart, lung	Identified in SUDEP case; potentially combined epilepsy and arrhythmia[42]
RYR2[42,43]	Sudden cardiac death	Cardiac ryanodine receptor 2, acts as intracellular calcium release channel, coupling excitation–contraction	Brain, heart, lung	Identified in SUDEP case; potentially combined epilepsy and arrhythmia[43]
HCN4[42,43]	Bradycardia; sick sinus syndrome	Hyperpolarisation activated cyclic nucleotide gated potassium channel 4; slow kinetics of activation and inactivation, cardiac pacemaker role	Brain, heart, lung	Variant identified in SUDEP case
Genetic disorders*				
Dup15q11[8]	Epileptic encephalopathy; variable epilepsy phenotype	Supernumerary isodicentric chromosome 15; extra copies of *UBE3A* (Angelman syndrome) and *GABRB3* (GABA receptor)	*UBE3A* and *GABRB3*: brain, heart, and lung	Increased epilepsy severity; neurological impairment
5q14.3 deletion[46]	Variable severity of epilepsy and neurodevelopmental disability	Haploinsufficiency of *MEF2C* (role in myogenesis) and *EFNA5*, receptor protein-tyrosine kinases involved in neurodevelopment	*MEF2C* and *EFNA5*: brain, heart, and lung	Increased epilepsy severity; neurological impairment

SUDEP=sudden unexpected death in epilepsy. *No animal models exist for these genetic disorders; with most genes, it is uncertain whether the risk of SUDEP is solely accounted for by the severity of epilepsy and developmental delays.

***Table 2*: Genetic influences on SUDEP risk by probable gene**

SUDEP mechanisms

	Species	Cause of fatal seizures	Cause of death	Insights on mechanisms and prevention
5-HT_{2c} knockout[54]	Mouse	Audiogenic and spontaneous	Respiratory arrest	First evidence that serotonin defects can increase risk of SUDEP
DBA/1 and DBA/2[53]	Mouse	Audiogenic	Respiratory arrest	Animals have abnormalities in serotonin receptors and death is prevented by selective serotonin reuptake inhibitors
Kcna1 Knockout[43,62]	Mouse	4-aminopyridine-induced	Respiratory arrest and brainstem spreading depression	Seizures can lead to massive and irreversible dysfunction of the brainstem
Scn1a mutations[62,52]	Mouse	Heat-induced, 4-aminopyridine-induced, and spontaneous	Bradycardia and brainstem spreading depression	Bradycardia and death are prevented by atropine
Genetic deletion of serotonergic neurons[55]	Mouse	Maximal electroshock	Respiratory arrest	5-hydroxytryptamine has independent effects on seizure susceptibility and risk of death from seizures
Wistar audiogenic rats[63,64]	Rat	Audiogenic	Dysautonomia and cardiac dysfunction	β blocker reduced cardiac and sympathetic defects that might contribute to death from seizures
Anaesthetised rats[65]	Rat	Hippocampal stimulation	Respiratory depression (animals do not die)	Serotonergic neurons are inhibited by seizures
Epileptic baboons[66]	Baboon	Spontaneous	Unknown	Sudden unexpected death in adolescence and young adults; pathological changes similar to human SUDEP
Status epilepticus model[67]	Sheep	Systemic bicuculline	Respiratory arrest	Mechanisms of death from status epilepticus can have some overlap with those in SUDEP

SUDEP=sudden unexpected death in epilepsy.

***Table 3*: Animal models of SUDEP**

- SUDEP pathological changes:
  - focal myocardial fibrosis
  - moderate to severe pulmonary congestion and edema

- SUDEP is a heterogeneous event, typically occurring in a critically obtunded **postictal phase** of a generalized tonic-clonic seizure.
- possible combinations includes:
  - respiratory dysfunction
  - arousal failure
  - non-tachyarrhythmic cardiac dysfunction
  - postictal generalized EEG suppression
  - autonomic dysfunction
  - Brainstem neurotransmitters and neuromodulators

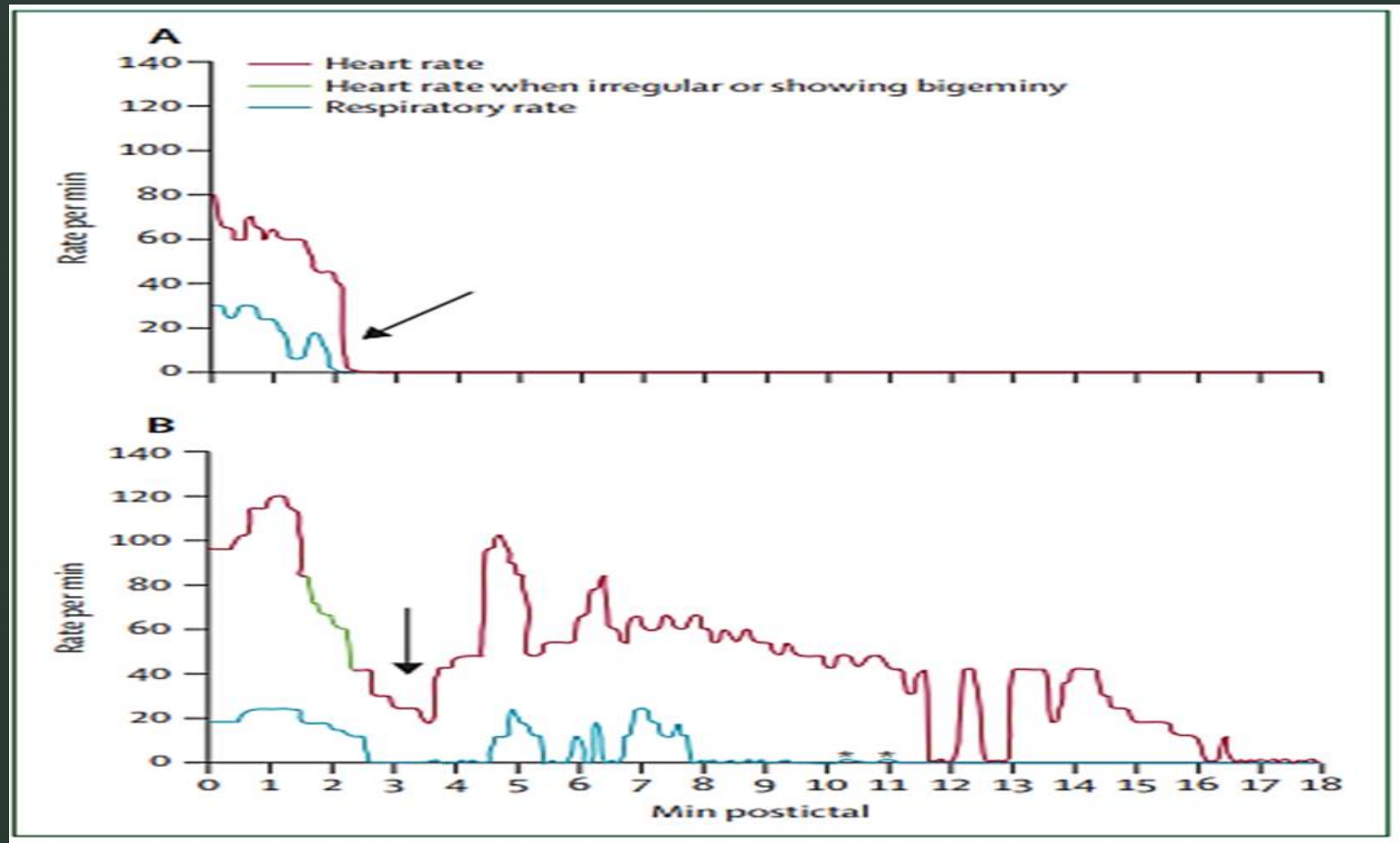


***Figure 4*: Variations of sequential changes in heart rate and breathing in two cases of sudden unexpected death in epilepsy**

Physiological recordings made in an epilepsy monitoring unit during sudden unexpected death in epilepsy. (A) The patient rapidly developed postictal terminal apnoea and terminal asystole. (B) The patient developed apnoea and bradycardia early, followed by intermittent resumption of breathing efforts; heart rate continued much longer than breathing. Arrows indicate early postictal parallel collapse of respiratory and cardiac rates. Modified from Ryvlin P and colleagues,[71] by permission of Elsevier.

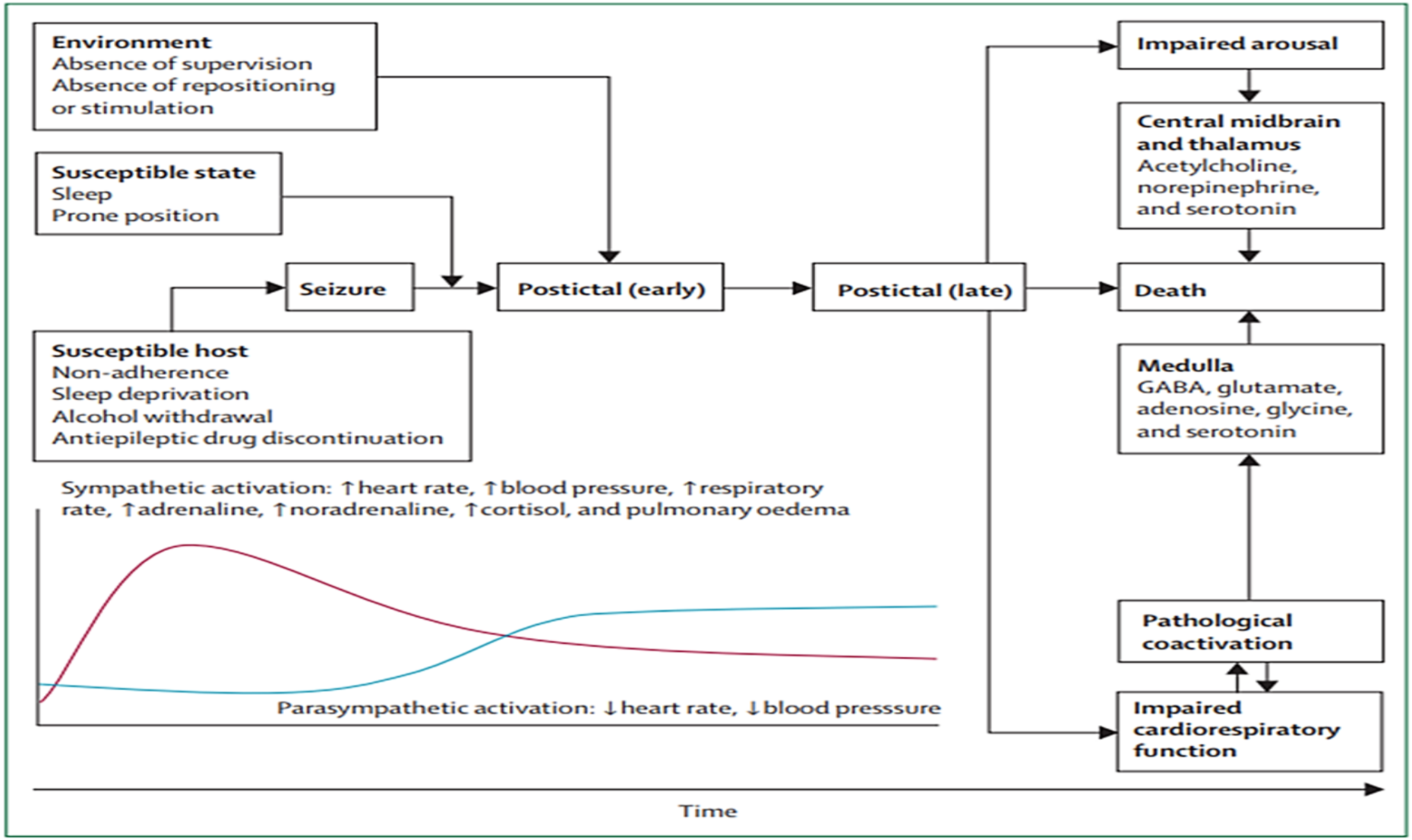


Figure 2: **Model of sudden unexpected death in epilepsy pathophysiology**
Suppression of brainstem function, arousal, and respiration seem to be crucial mechanisms, along with many other factors that can contribute to risk of sudden unexpected death in epilepsy.

SUDEP biomarkers

- **PGES**

1. Not all generalized tonic-clonic seizures produce PGES, even in the same patient.
2. Not all SUDEP studies.
3. More common in convulsive seizures with bilateral, symmetrical tonic arm extension.
4. Duration can vary widely.

- **Neuroimaging ????**

Neuroimaging of Sudden Unexpected Death in Epilepsy (SUDEP): Insights From Structural and Resting-State Functional MRI Studies

Luke A. Allen [1,2,3], Ronald M. Harper [3,4,5], Samden Lhatoo [3,6], Louis Lemieux [1,2] and Beate Diehl [1,2,3]*

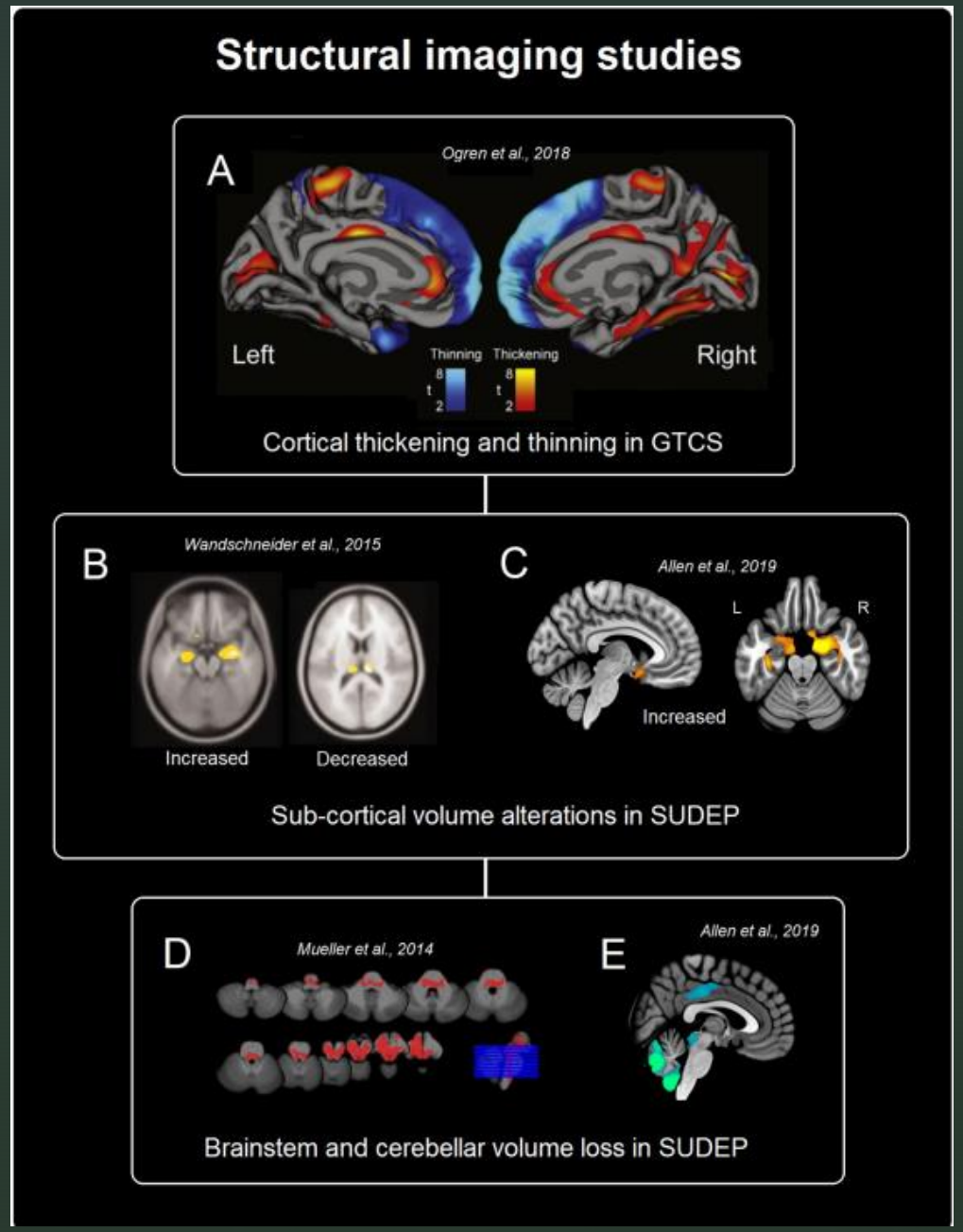
- ortex), and midbrain/cerebellar/brainstem sitesortex), and midbrain/cerebellar/brainstem sites

Structural Imaging Findings:

Evidence from morphometry and cortical thickness studies in SUDEP and at-risk groups (i.e., patients with GTCS) demonstrates:

- Reduced volume and cortical thinning in thalamic (primarily within posterior portions), frontal (medial and orbital cortex) and midbrain/cerebellar/ brainstem sites.

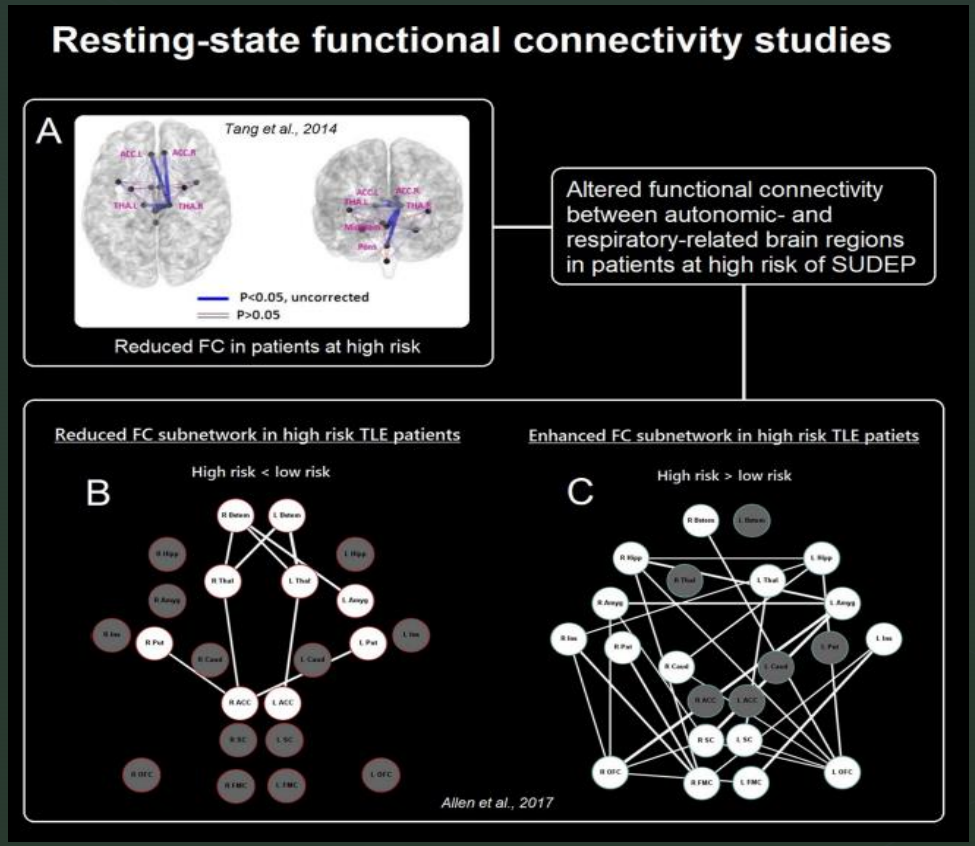
- Increased volume and regional cortical thickness appear in limbic regions, primarily anterior mesial temporal, especially the amygdala, and cingulate structures, the insula, and sensory areas.



- Causal link between volume changes and autonomic and respiratory dysfunction is yet to be established in the SUDEP.

Functional Imaging Findings

- Studies investigated patients at high and low risk for SUDEP,but no resting-state fMRI studies to date have included cases of actual SUDEP.
- Overall, RS-fMRI has provided insights into connectivity changes in patients at high risk of SUDEP which indicate altered communication among key brain regions contributing to autonomic and breathing regulatory processes.



Dead in the Night: Sleep-Wake and Time-Of-Day Influences on Sudden Unexpected Death in Epilepsy

*Benton S. Purnell[1,2,3], Roland D. Thijs[4,5,6] and Gordon F. Buchanan[1,2,3]**

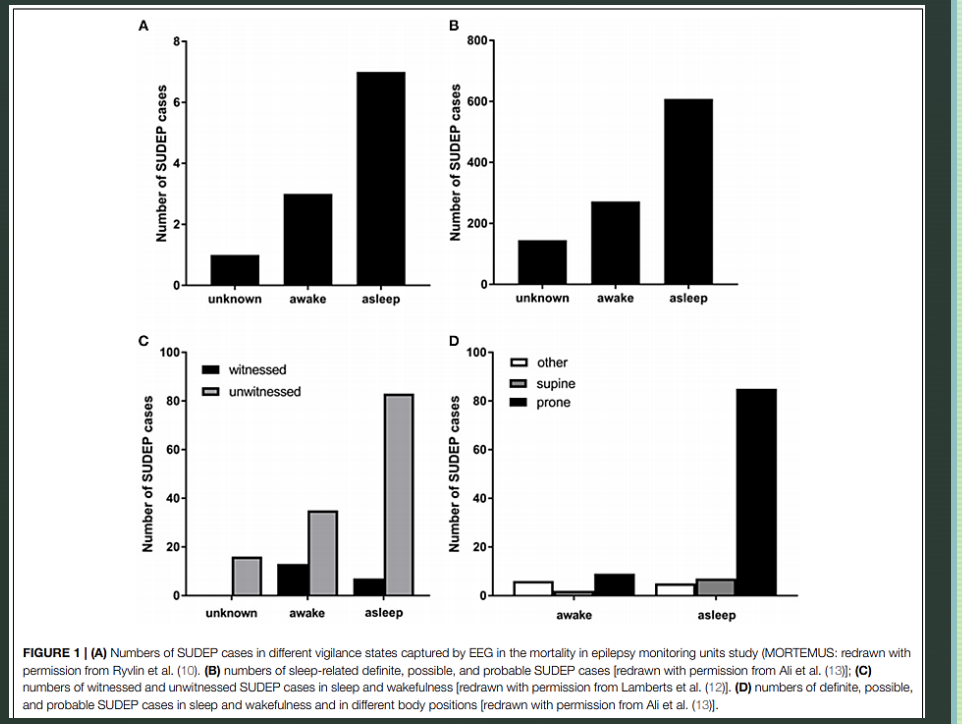


FIGURE 1 | (A) Numbers of SUDEP cases in different vigilance states captured by EEG in the mortality in epilepsy monitoring units study (MORTEMUS: redrawn with permission from Ryvlin et al. (10). **(B)** numbers of sleep-related definite, possible, and probable SUDEP cases [redrawn with permission from Ali et al. (13)]; **(C)** numbers of witnessed and unwitnessed SUDEP cases in sleep and wakefulness [redrawn with permission from Lamberts et al. (12)]. **(D)** numbers of definite, possible, and probable SUDEP cases in sleep and wakefulness and in different body positions [redrawn with permission from Ali et al. (13)].

- The reason that SUDEP happens more during the night is likely multifactorial involving both situational factors, such as being unattended, and physiological changes due to the influence of sleep and circadian rhythms.
- When the factors associated with being without a witness and prone are added to the mix along with the potential effects of sleep and circadian phase SUDEP might be more likely.

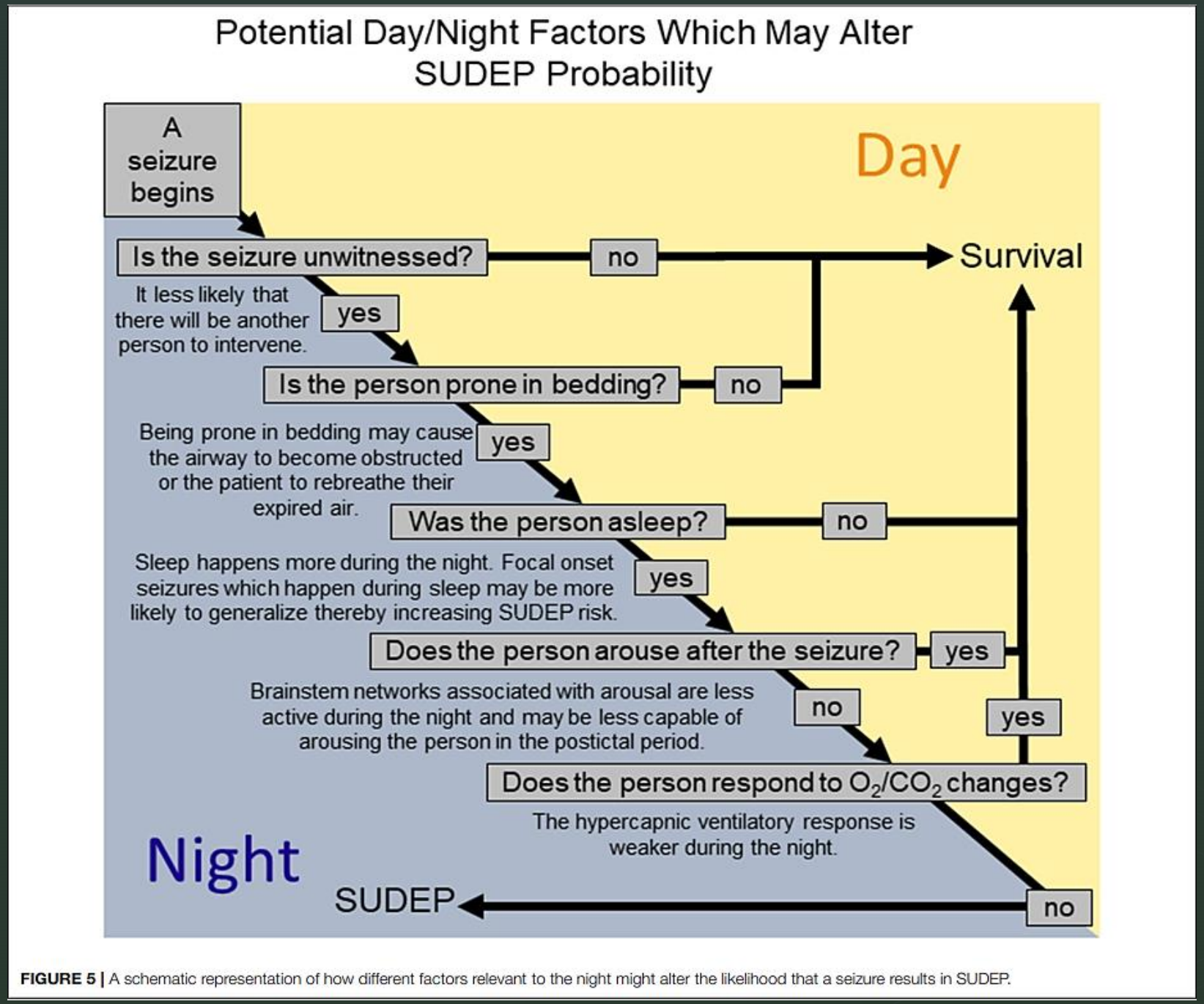


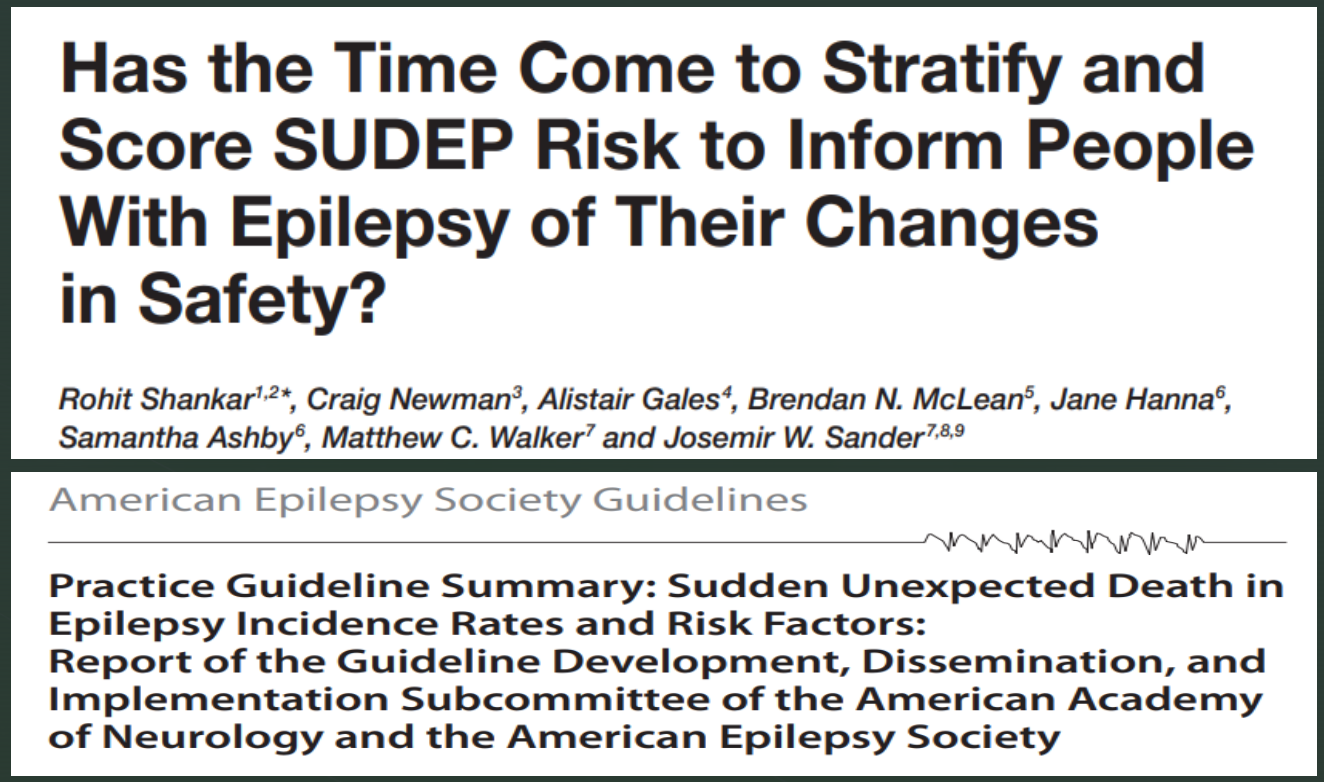
FIGURE 5 | A schematic representation of how different factors relevant to the night might alter the likelihood that a seizure results in SUDEP.

Time of Day and a Ketogenic Diet Influence Susceptibility to SUDEP in *Scn1a*$^{R1407X/+}$ Mice

Frida A. Teran[1,2,3†], YuJaung Kim[1,4†], Megan S. Crotts[1], Eduardo Bravo[1,3], Katlynn J. Emaus[1] and George B. Richerson[1,3,5,6]*

- This study shows that protection conferred by the KD on mortality in our DS mice is not due to an antiseizure effect.

- One possibility is that the KD prevents the propagation of seizures from the forebrain to brainstem nuclei that are critical for cardiorespiratory control.



Has the Time Come to Stratify and Score SUDEP Risk to Inform People With Epilepsy of Their Changes in Safety?

Rohit Shankar[1,2], Craig Newman[3], Alistair Gales[4], Brendan N. McLean[5], Jane Hanna[6], Samantha Ashby[6], Matthew C. Walker[7] and Josemir W. Sander[7,8,9]*

American Epilepsy Society Guidelines

Practice Guideline Summary: Sudden Unexpected Death in Epilepsy Incidence Rates and Risk Factors: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society

- People with epilepsy should have an **annual** seizure safety risk assessment at primary care.
- An earlier interim assessment needs to be triggered if any person with epilepsy presents with: **decline in seizure control**, **alteration to AEDs or relevant medications**, **change in comorbidities** in particular use of alcohol or other substances or with psychiatric issues.

- https://sudep.org/checklist
- https://sudep.org/epilepsy-self-monitor

Thank You for Your Consideration