



Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Climate change and epilepsy: Insights from clinical and basic science studies



Medine I. Gulcebi^a, Emanuele Bartolini^b, Omay Lee^c, Christos Panagiotis Lisgaras^{d,e}, Filiz Onat^{f,g}, Janet Mifsud^h, Pasquale Strianoⁱ, Annamaria Vezzani^j, Michael S. Hildebrand^k, Diego Jimenez-Jimenez^l, Larry Junck^m, David Lewis-Smithⁿ, Ingrid E. Scheffer^o, Roland D. Thijs^p, Sameer M. Zuberi^q, Stephen Blenkinsop^r, Hayley J. Fowler^s, Aideen Foley^t, Epilepsy Climate Change Consortium (Simona Balestrini^{aa}, Samuel Berkovic^{ab}, Gianpiero Cavalleri^{ac}, Daniel José Correa^{ad}, Helena Martins Custodio^{ae}, Marian Galovic^{af}, Renzo Guerrini^{ag}, David Henshall^{ah}, Olga Howard^{ai}, Kelvin Hughes^{aj}, Anna Katsarou^{ak}, Bobby P.C. Koeleman^{al}, Roland Krause^{am}, Daniel Lowenstein^{an}, Despoina Mandelenaki^{ao}, Carla Marini^{ap}, Terence J. O'Brien^{aq}, Adrian Pace^{ar}, Luca De Palma^{as}, Piero Perucca^{at}, Asla Pitkänen^{au}, Finola Quinn^{av}, Kaja Kristine Selmer^{aw}, Charles A. Steward^{ax}, Nicola Swanborough^{ay}, Roland Thijs^{az}, Phil Tittensor^{ba}, Marina Trivisano^{bb}, Sarah Weckhuysen^{bc}, Federico Zara^{bd}), Sanjay M. Sisodiya^{l,*}

^{aa} Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology, London, UK and Chalfont Centre for Epilepsy, Bucks, UK

^{ab} Epilepsy Research Centre, Department of Medicine, Austin Health, University of Melbourne, Melbourne, Victoria, Australia

^{ac} Department of Molecular and Cellular Therapeutics, The Royal College of Surgeons in Ireland, Dublin 2, Ireland; The FutureNeuro Research Centre, Dublin 2, Ireland

^{ad} Saul R. Korey Department of Neurology, Albert Einstein College of Medicine and Montefiore Medical Center, 1410 Pelham Parkway South, K-312, Bronx, NY 10461, USA

^{ae} Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology, London, UK; Chalfont Centre for Epilepsy, Bucks, UK

^{af} University Hospital Zurich, Switzerland

^{ag} Department of Child Neurology and Psychiatry, University of Pisa and IRCCS Fondazione Stella Maris, 56018 Calambrone, Pisa, Italy

^{ah} FutureNeuro SFI Research Centre, Royal College of Surgeons in Ireland, 123 St Stephen's Green, Dublin D02 YN77, Ireland

^{ai} UCB Pharma Ltd, Slough, UK

^{aj} Dravet Syndrome UK, UK

^{ak} Laboratory of Developmental Epilepsy, Saul R. Korey Department of Neurology, Albert Einstein College of Medicine, Bronx, New York, USA

^{al} University Medical Center, Utrecht, The Netherlands

^{am} Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Esch-sur-Alzette, Luxembourg

^{an} Department of Neurology, University of California, San Francisco, CA, USA

^{ao} Department of Pediatric Neurology, Queen Fabiola Children's University Hospital, Brussels, Brussels Capital Region, Belgium

^{ap} Neuroscience Department, Children's Hospital A. Meyer-University of Florence, Florence, Italy

^{aq} Melbourne Brain Centre, Departments of Medicine and Neurology, Royal Melbourne Hospital, University of Melbourne, VIC, Australia; Departments of Neuroscience and Neurology, Central Clinical School, Monash University, The Alfred Hospital, Melbourne, VIC, Australia

^{ar} Gozo General Hospital, Malta

^{as} Neurology Unit, Department of Neuroscience, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

^{at} Department of Neuroscience, Central Clinical School, Monash University, Melbourne, VIC, Australia; Departments of Medicine and Neurology, The Royal Melbourne Hospital, The University of Melbourne, Melbourne, VIC, Australia; Department of Neurology, Alfred Health, Melbourne, VIC, Australia

^{au} A.I. Virtanen Institute for Molecular Sciences, University of Eastern Finland, PO Box 1627, FIN-70211 Kuopio, Finland

^{av} ILAE-IBE Congress Secretariat, Dublin, Ireland

^{aw} National Centre for Rare Epilepsy-related Disorders, Oslo University Hospital, Oslo, Norway; Department of Medical Genetics, Oslo University Hospital, University of Oslo, Oslo, Norway

^{ax} Congenica Ltd, Wellcome Genome Campus, Hinxton, Cambridge, CB10 1DR, UK; Wellcome Sanger Institute Wellcome Genome Campus, Hinxton, Cambridge CB10 1SA, UK

^{ay} Epilepsy Society, Bucks, UK

^{az} Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, Netherlands; Department of Neurology, Leiden University Medical Centre, Leiden, Netherlands; NIHR University College London Hospitals Biomedical Research Centre, UCL Queen Square Institute of Neurology, London, UK

^{ba} Royal Wolverhampton NHS Trust, Wolverhampton, UK

^{bb} Rare and Complex Epilepsy Unit, Department of Neuroscience and Neurorehabilitation, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

^{bc} Neurogenetics Group, Center for Molecular Neurology, VIB, University of Antwerp, Antwerp 2610, Belgium

* Corresponding author at: Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology, London, UK.

E-mail addresses: emanuele.bartolini@uslcentro.toscana.it (E. Bartolini), Christos.Lisgaras@nyulangone.org (C.P. Lisgaras), Janet.mifsud@um.edu.mt (J. Mifsud), annamaria.vezzani@marionegri.it (A. Vezzani), michael.hildebrand@unimelb.edu.au (M.S. Hildebrand), diego.jimenez@ucl.ac.uk (D. Jimenez-Jimenez), ljunck@med.umich.edu (L. Junck), david.lewis-smith@newcastle.ac.uk (D. Lewis-Smith), is.scheffer@unimelb.edu.au (I.E. Scheffer), rthijs@sein.nl (R.D. Thijs), sameer.zuberi@nhs.net (S.M. Zuberi), stephen.blenkinsop@newcastle.ac.uk (S. Blenkinsop), hayley.fowler@newcastle.ac.uk (H.J. Fowler), a.foley@bbk.ac.uk (A. Foley), s.sisodiya@ucl.ac.uk (S.M. Sisodiya).

<https://doi.org/10.1016/j.yebeh.2021.107791>

1525-5050/© 2021 Elsevier Inc. All rights reserved.

^{bd} Unit of Medical Genetics, IRCCS Istituto Giannina Gaslini, Genoa, Italy; Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOEMI), University of Genoa, Italy

^a Department of Medical Pharmacology, Marmara University, School of Medicine, Istanbul, Turkey

^b USL Centro Toscana, Neurology Unit, Nuovo Ospedale Santo Stefano, Via Suor Niccolina Infermiera 20, 59100 Prato, Italy

^c Department of Neurology and Clinical Neurophysiology, St. George's University Hospitals NHS Foundation Trust, London, UK

^d New York University Langone Health, 100 First Ave., New York, NY 10016, USA

^e The Nathan S. Kline Institute for Psychiatric Research, Center for Dementia Research, 140 Old Orangeburg Rd., Orangeburg, NY 10962, USA

^f Department of Medical Pharmacology, Marmara University School of Medicine, Istanbul, Turkey

^g Department of Medical Pharmacology, Acibadem University School of Medicine, Istanbul, Turkey

^h Department of Clinical Pharmacology and Therapeutics, University of Malta, Msida MSD2040, Malta

ⁱ Paediatric Neurology and Muscular Diseases Unit, DINOEMI-Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, IRCCS "Giannina Gaslini" Institute, Genoa, Italy

^j Laboratory of Experimental Neurology, Department of Neuroscience, IRCCS "Mario Negri" Institute for Pharmacological Research, Milan, Italy

^k Department of Medicine (Austin Health), University of Melbourne, and Murdoch Children's Research Institute, Melbourne, Victoria, Australia

^l Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology, London, WC1N 3BG, UK and Chalfont Centre for Epilepsy, Bucks, UK

^m Department of Neurology, University of Michigan, Ann Arbor, MI, USA

ⁿ Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK

^o University of Melbourne, Austin Health and Royal Children's Hospital, Florey Institute and Murdoch Children's Research Institute, Melbourne, Australia

^p Department of Neurology, Leiden University Medical Centre (LUMC), PO Box 9600, 2300 RC Leiden, the Netherlands

^q Paediatric Neurosciences Research Group, Royal Hospital for Children & Institute of Health & Wellbeing, University of Glasgow, Fraser of Allander Neurosciences Unit, Royal Hospital for Children, UK

^r School of Engineering, Newcastle University, Newcastle upon Tyne, UK

^s Centre for Earth Systems Engineering Research, School of Engineering, Newcastle University, UK

^t Department of Geography, Birkbeck College University of London, London, UK

ARTICLE INFO

Article history:

Received 6 November 2020

Revised 24 December 2020

Accepted 3 January 2021

Available online 10 February 2021

Keywords:

Global warming

Emergency

Seizure

Temperature

Extreme weather events

Public health

ABSTRACT

Climate change is with us. As professionals who place value on evidence-based practice, climate change is something we cannot ignore. The current pandemic of the novel coronavirus, SARS-CoV-2, has demonstrated how global crises can arise suddenly and have a significant impact on public health. Global warming, a chronic process punctuated by acute episodes of extreme weather events, is an insidious global health crisis needing at least as much attention. Many neurological diseases are complex chronic conditions influenced at many levels by changes in the environment. This review aimed to collate and evaluate reports from clinical and basic science about the relationship between climate change and epilepsy. The keywords climate change, seasonal variation, temperature, humidity, thermoregulation, biorhythm, gene, circadian rhythm, heat, and weather were used to search the published evidence. A number of climatic variables are associated with increased seizure frequency in people with epilepsy. Climate change-induced increase in seizure precipitants such as fevers, stress, and sleep deprivation (e.g. as a result of more frequent extreme weather events) or vector-borne infections may trigger or exacerbate seizures, lead to deterioration of seizure control, and affect neurological, cerebrovascular, or cardiovascular comorbidities and risk of sudden unexpected death in epilepsy. Risks are likely to be modified by many factors, ranging from individual genetic variation and temperature-dependent channel function, to housing quality and global supply chains. According to the results of the limited number of experimental studies with animal models of seizures or epilepsy, different seizure types appear to have distinct susceptibility to seasonal influences. Increased body temperature, whether in the context of fever or not, has a critical role in seizure threshold and seizure-related brain damage. Links between climate change and epilepsy are likely to be multifactorial, complex, and often indirect, which makes predictions difficult. We need more data on possible climate-driven altered risks for seizures, epilepsy, and epileptogenesis, to identify underlying mechanisms at systems, cellular, and molecular levels for better understanding of the impact of climate change on epilepsy. Further focussed data would help us to develop evidence for mitigation methods to do more to protect people with epilepsy from the effects of climate change.

© 2021 Elsevier Inc. All rights reserved.

1. Introduction

Climate change will affect many aspects of life for everyone on Earth. The SARS-CoV-2 pandemic has illustrated how vulnerable human health is to unprecedented global challenges. The SARS-CoV-2 pandemic has been acute, and the global response has had to be dramatic and swift, showing that deep changes at societal level are possible – and incidentally have been associated with minor reductions in carbon emissions [1,2]. Like the SARS-CoV-2 pandemic, climate change is global in its reach and likely consequences; in contrast, climate change is more chronic and insidious. Climate change causes multiple health impacts through many routes, leading to calls for action on climate change and public health by the World Health Organization (WHO) [3]. Low- and

middle-income countries will be most affected, as noted by the International Monetary Fund [4,5], including in the health domain, as recognized by the UN Secretary General [6]. Health services are inevitably embedded within a global system built around fossil fuels and unsurprisingly themselves contribute significantly to climate change. For example in the UK, the National Health Service is one of the most significant contributors to climate change from the public sector. It was the first national health system in the world to develop and publish its carbon reduction strategy and commitment [7], with reductions made since 2007 equivalent to the annual emissions of a small country such as Cyprus [8]. Notably, many organizations are taking action to reduce their environmental footprints [8–10]. The interplay between climate change and health is therefore bidirectional and significant in magnitude.

The term “global warming” refers to the average long-term change in global surface temperatures since the pre-industrial period, forced by increasing anthropogenic greenhouse gas emissions into the atmosphere. ‘Forcing’ refers to physical processes affecting the climate through a number of forcing factors which drive the climate to change. Warming during the period 1986–2005 has been estimated to have ranged between 0.55° and 0.80 °C [11]. The increases are unequally distributed across the world, with different regions experiencing different trends [12], some regions experiencing more extreme winter events [13]. Importantly, in tropical regions with relatively small historical climate variability, a perceptible local warming signal may already be emerging [14]. The term “climate change” refers to the wider range of local, regional, and global changes in average weather patterns, primarily driven, over the last 100 years, by anthropogenic activities [15]. Overall, the change in mean temperature modulates temperature extremes, leading to a weakening of cold extremes but a strengthening of hot extremes [16].

Projections of future global climate are derived from physically based climate models, principally general circulation models (GCMs) which are driven by different scenarios of future emissions of greenhouse gases. Climate projections are therefore sensitive to the selection of scenarios and uncertainties arise from the model structure (e.g. resolution), and parameterization within individual models and model simulations. Consequently, there are significant uncertainties associated with regional and local climate responses to greenhouse gas forcing. Nonetheless, climate modeling indicates the potential for more heatwave days in a warmer world, with substantial tracts of Africa, Central and South America, and South East Asia projected to experience more than 30 extra seasonal heatwave days per °C of global warming [17]. Climate change also has consequences for the hydrological cycle, with the intensification of heavy rainfall [18] and drought [19] in Europe. These physical changes in climate clearly have potential to directly affect health (e.g. [20]), but they also have a range of context-specific effects on regional and local environmental and social systems which could indirectly impact health, through effects on food security (e.g. [21]), water security (e.g. [22]), and livelihood systems (e.g. [23,24]).

We previously raised general concerns that climate change might also affect epilepsy [25]. Here, we review published evidence around potential consequences of climate change for people with epilepsy. The potential direct consequences, such as deterioration of seizure control by enhancement of seizure precipitants or disruption of drug delivery, and the potential indirect consequences, such as aggravation of comorbidities or increase in risk of Sudden Unexpected Death in Epilepsy (SUDEP), related to climate change were evaluated through the current literature, which we acknowledge is of widely variable quality. Epilepsy can have profound and pervasive effects on people with epilepsy and their caregivers such as psychologic comorbidities, behavioral, cognitive, and social problems, all diminishing quality of life for patients, families, and caregivers. The associated economic consequences are huge [26,27], amounting to 0.5% of the overall global burden of disease [27,28], disproportionately greater among the ~30% of people with treatment-resistant epilepsy [26,29–32]. Since there are associated direct financial burdens, it is reasonable to infer that those with fewer financial resources may experience greater adverse outcomes related to disease burden. The reported quality of life is much lower among those with poor seizure control and socioeconomic disadvantage [33]. Personal resilience to a variety of situational changes in terms of quality of life is multifactorial [34,35], but seizures [36] and economic disadvantage [37], for example through less-well thermoregulating housing, can have negative influences. Most studies addressing these issues have been undertaken in countries with healthcare systems, or those

with higher levels of healthcare funding [31,34–37], whereas burdens are often unquantified in low- and middle-income countries, but seem likely to be at least of the same, if not greater, magnitude [27]. Here, we seek to collate information available in the field.

2. Climate change and epilepsy: insights from population and clinical studies

Interactions of intrinsic factors, such as the cause of epilepsy or individual physiology, and extrinsic factors such as ambient temperature, humidity, or sunlight exposure can play important roles in seizure occurrence [38–44]. Temperatures considered unusually low for the study region (e.g. below 17 °C in Taiwan), or low atmospheric pressure or high humidity, may trigger seizures [38–40]. The effects on epilepsy of changing outdoor and indoor temperatures and humidity, and their diurnal variation, as a result of new patterns of climate extremes, are likely to prove more complex, and additionally, the occurrence of many seizure precipitants is expected to increase with climate change. Precipitants may act directly, affecting human physiology, or indirectly, such as socioeconomic disruption acting through stress, fatigue, and sleep deprivation [41], which are common seizure triggers [43]. In addition to risks for aggravation of pre-existing epilepsy, climate change may increase the incidence of acquired epilepsy due to spread of vector-borne diseases, other infections and central nervous system (CNS) trauma.

2.1. Climate change and seizure or epilepsy precipitants

2.1.1. Stress and sleep deprivation

Although specific studies on the correlation between climate change, stress, and epilepsy are still needed, climate-related stress will very likely pose a serious challenge to seizure control. Emotional stress triggers seizures in over 80% of people with epilepsy [41,43]. People prone to stress-induced seizures experience a distinct brain response to stress hormones, in which cortisol levels are positively correlated with interictal discharges and negatively correlated with global functional connectivity on EEG [44]. Fatigue and sleep deprivation are also very common seizure precipitants [43] and all these factors can be affected by weather variations, compounding their consequences. The climate change-related rise in average and extreme temperatures, and their distribution across day and night [45] will affect sleep patterns. A large-scale US survey indicated that a +1 °C deviation in night-time temperature was associated with an increase of three nights of self-reported insufficient sleep per 100 people per month [46]. The urban heat island effect has a bigger effect on night-time temperatures than daytime ones and the elevation of night-time temperature may have a negative compounding effect, as poor sleepers exposed to high air temperature suffer even more fatigue compared to those sleeping at a lower temperature [47]. Extreme weather events, change in precipitation, floods, droughts, and wildfires may all disrupt sleep because of augmented stress levels, food insecurity, displacement from home, rising water-borne infections, and increased sleep-related breathing disorders [48]. Studies performed after hurricanes in the United States [49–51], after floods in Australia [52] and China [53], and after wildfires in Greece [54] have highlighted a high prevalence of sleep disturbances, often comorbid with mood and post-traumatic stress disorders. Therefore, climate change may synergistically induce stress, fatigue, and sleep deprivation, potentially putting many people with epilepsy at risk of deterioration of seizure control, as well as possible consequences on associated comorbidities and non-seizure aspects of the epilepsies. The combined action of these triggers may also overlap with potentially epileptogenic traumatic brain injuries after rapid-

onset natural hazards or as a consequence of climate-related conflicts. The kinetic energy released by hurricanes, typhoons, tornadoes, and landslides provokes traumatic brain injuries through compression fractures as well as penetrating and crushing wounds [55], which can result in acute symptomatic seizures or chronic post-traumatic epilepsy. Climate change is also a potential cause of increased armed confrontations, including 'water wars', leading to such injuries, as people are displaced and deprived of basic necessities. Extremes of rainfall and higher temperatures significantly increase risk of military conflicts due to a mixture of causes, especially in low- and middle-income countries whose economies rely heavily on agriculture [56–58]. Global warming up to 2 °C beyond pre-industrial levels (i.e. the stated limit of the Paris Climate Agreement) is predicted to increase globally by 13% the risk of conflict within countries. This figure has been estimated for current societies, assuming current levels of socioeconomic development, population, and government capacity [59].

2.1.2. Tropical causes of epilepsy and microbiology aspects

A number of vector-borne infections are associated with a higher incidence of acquired epilepsy in low-income countries [60,61]. Previous studies have suggested complexities in the exact relationship between climate change and infectious disease, and the sequelae of epilepsy secondary to infection. These effects need to be urgently characterized.

2.1.2.1. Malaria. Malaria is already a major public health problem, with an estimated 228 million cases in 2018 [62]. WHO estimates that if global temperatures rise by 2–3 °C, the population at risk of malaria will increase by 3–5% [63], due to an increase in the range and intensity of transmission, and may include previously naïve populations. The malaria parasite is thought to be highly sensitive to changing environmental conditions [64–67]. While malaria is affected by seasonal differences, including humidity [68], increased temperature can reduce the typical seasonality of malaria epidemics regardless of rainfall patterns [69]. Cerebral malaria is the leading cause of acute encephalopathy with febrile and acute seizures in endemic regions [70] and is associated with the occurrence of epilepsy particularly in regions of sub-Saharan Africa [71–73]. Hence, increased temperature and humidity as a consequence of climate change are very likely to have implications for the incidence and prevalence of cerebral malaria-related epilepsy.

2.1.2.2. Neurocysticercosis. Neurocysticercosis is the result of *Taenia solium* infection of the CNS [74] due to unintentional ingestion of *Taenia solium* eggs, mainly from food contaminated by people with taeniasis. It is a major risk factor for acquired epilepsy in African, Asian, and Latin American countries, and is the main cause of epilepsy in about 1% of the population in endemic countries [74], but may cause up to 30–50% of epilepsy cases, depending on geographic region [75,76]. Although there have been no direct studies on the effects of increased temperature and humidity on incidence of cysticercosis, warmer environments, as well as worsening socioeconomic conditions leading to inadequate sanitation, may facilitate the spread of the disease [77].

2.1.2.3. Arboviruses and other Tick-borne infections. Climate change is likely to facilitate territorial expansion of arboviruses and their diseases, such as West Nile virus, dengue fever, and tick-borne encephalitis [78]. Although not directly associated with the development of epilepsy per se, all of these infections may increase the risk of fever-induced seizures, posing a serious risk for people with pre-existing epilepsy [76]. African countries may experience a worsening of tuberculosis epidemics as a consequence of climate change, although further evidence is required [79], and CNS tuberculosis is strongly associated with epilepsy and seizures [76].

2.1.3. Human genetic variants that influence temperature sensitivity

Climate change, and, in particular, global warming and an increased occurrence of sustained high temperatures and temperature peaks [80], could affect some people with epilepsy through their individual genetics, for example mediated through genetic variants that modulate physiological responses to temperature. Human thermoregulatory capacity is not insuperable; heat stress and heat stroke are recognized clinical disorders [81], exacerbated by elevated humidity [82,83], and can be aggravated especially in the very old and very young, and by particular built environments. Exertional heat stress is another cause of hyperthermia, the increase in body core temperature following an imbalance between body heat gain and heat loss [82]. In adults, only limited retrospective data exist on the incidence of seizure after heat stroke, with presentations including acute status epilepticus, altered mental status, and post-cooling convulsions [84]. The fact that 3% of children have febrile seizures, and that seizures in some genetic epilepsy syndromes clearly show fever-sensitivity, demonstrates that body temperature can influence the likelihood of the occurrence of seizures. We note that body temperature alone may not be the only cause of fever-related seizures; for example, associated systemic inflammation is also likely to contribute in the context of infection-related fever. On the other hand, temperature alone may also have an effect, independent of fever or infection. In most children, the peak of body temperature plays a more important role in the pathogenesis of a febrile seizure than the rapidity of the temperature rise [85]. There is a polygenic, common variant-determined, genetic susceptibility for febrile seizures including variants in a gene knockout of which in rats influences the proportion of heat-sensitive neurons in the thermoregulating anterior hypothalamic nucleus and hippocampal neuronal excitability [86]. Low atmospheric pressure, a small amount of precipitation, and low relative air humidity may increase the risk of febrile seizures [87], but these findings need replication and may be influenced by both local clinical practice and population genetics. There is a heritability of the epilepsies due to common genetic variation (single nucleotide polymorphisms in particular), such that we should not ignore potentially widespread vulnerability due to genetic constitution: this cannot be altered, but its understanding may also help us understand better risks for people for whom additional care may be needed given their inherent, unmodifiable vulnerability. Moreover, an increasing number of genetic causes of large effect are being identified in the epilepsies. Though individually rare, collectively they account for an important part of the burden of the epilepsies. For example, most cases with Dravet syndrome, in which frequent, often prolonged, febrile seizures occur at the onset of epilepsy, are associated with pathogenic variants in the gene *SCN1A*, which encodes a temperature-sensitive ion channel ($Na_v1.1$) [88], with seizures that can be precipitated by even mild increases in body temperature via fever, ambient warmth, cold-warm shifts, warm baths, or physical exercise [89] – extreme climate events may be additionally important in this context. There are other genes involved in epilepsies with an increased risk of seizures triggered by fever, including *SCN1B*, *GABRG2*, *GABRD*, *CHD2*, *STX1B*, *PCDH10*, *HCN2*, and *ZNT3* [90–94]. Variants in genes causing the mainly rare, severe, fever-sensitive epilepsies can also be found in the more common epilepsies [95,96].

The major human temperature sensors consist of a family of ion channels, the temperature-sensitive transient receptor potential (TRP) cation channels, which are activated in response to changes within specific temperature ranges [97]. The cold-sensitive channels TRPM8 and TRPA1 and the heat-sensitive channel TRPV1 are activated at 15 °C, 17 °C and 40 °C, respectively [98]. High encoding-gene variability among the TRP vanilloid subgroup (TRPV family) members has been reported [99]. Whether such variation

can link global warming and altered seizure frequency in people carrying such variants is yet to be determined, but the existence of temperature-sensitive epilepsies, in general, attests to the possibility. Human genetic variation, which has evolved over a long period of relative temperature stability and particular temperature ranges and variation, may therefore affect physiological response to temperatures, while being less capable of rapidly adapting to brisk but sustained global warming. The greater incidence of extremes of variation within a changing climate therefore poses real risks in epilepsy, whether these are rare genetic epilepsies with known temperature sensitivity, or more common epilepsies, if thermoregulation becomes compromised.

2.2. Climate change, epilepsy comorbidities, and mortality

People with epilepsy have a six-fold increase in the prevalence of both neurocognitive and cerebrovascular disorders [100]. The frail equilibrium of people with neurocognitive disorders may be easily unsettled by extreme weather events such as heat waves as well as by wide temperature fluctuations day-to-day, even more so when seizures are comorbid. The morbidity of cerebrovascular disorders may similarly be affected by climate change, as persistent colder temperatures, heatwaves, and large day-to-day temperature variations are associated with stroke incidence [101,102]. Abrupt weather changes may increase blood viscosity, blood pressure, and platelet reactivity [103,104]. Stroke is the major cause of acquired epilepsy in older adults, accounting for up to 50% of newly diagnosed epilepsy in those over 60 years of age [105]. The majority of weather-related excess mortality is attributable to cardiovascular and respiratory disorders [106], which are common epilepsy comorbidities (respectively 2.5 and 2.9-fold increased risk for people with epilepsy) [107,108]. Climate change could also heighten the risk of SUDEP. Although a study from the United Kingdom found no correlation between SUDEP and outdoor temperature variation over the year, and a slight excess of SUDEP occurred on days with a mean temperature lower than the 10th percentile [109], rising temperatures could increase seizure frequency, and therefore SUDEP risk, especially in some fever-sensitive epilepsies, such as Dravet syndrome [110], conditions already associated with a particularly high risk of SUDEP under current temperature conditions [111,112]. The displacement of people due to climate change will be associated with reduced healthcare provision as epilepsy is among the most common neurological conditions in refugee camps [113]. Displacement and supply chain disruption can interrupt medication provision since non-adherence (here enforced) increases seizure risk [114], and thus increases SUDEP risk [115].

2.3. Climate change and antiseizure medications

Few studies have been published on whether antiseizure medications (ASMs) may work differently in distinct climatic conditions or whether their stability is affected by temperature and/or humidity or whether their pharmacokinetics could change with circadian rhythms. Some studies have suggested a seasonal variation in ASM effectiveness. One possible reason is that an increase in ambient temperature, with the resulting increase in body sweat, may have an impact on serum levels of some ASMs. Parnas et al. [116] found that, in a small sample of eight people with epilepsy receiving chronic ASM treatment, phenytoin sweat concentration was independent of sweat flow, while phenobarbitone sweat concentration increased with increasing sweat flow. Data are also available from a sample of 10 people on diphenylhydantoin [117], with a decrease in serum levels at the end of summer due to an increase in perspiration. A study from Russia among 107 people with epilepsy, who received either valproic acid or carba-

mazepine, found that the serum levels of carbamazepine and valproate were significantly lower in spring compared to autumn [118]. No reason was given for this result.

Sunlight has been suggested as possible palliative treatment in epilepsy. In a UK study over 363 days looking at 1715 seizures in an inpatient facility for people with epilepsy, epileptic seizures, especially focal impaired awareness seizures, were less likely to occur on bright sunny days than on dull days [119]. Endogenous circadian rhythms may contribute to seizure patterns, with ASM chronotherapy suggested as a method to optimize seizure control in selected people with epilepsy [120]. Circadian patterns of epileptiform activity vary by seizure-onset zone, with a peak during sleep, that itself may be affected by climate change as discussed above [121]. These rhythms were best described by a dual oscillator (circadian and ultradian (i.e. short term)) model, which could be subject-specific. Some authors have suggested that while longer term circadian rhythms are adaptations to predictable changes in the environment, episodic ultradian events could contribute to adaptation by preparing organisms and biological functions for unpredictability [122]; genetic variation may contribute to both types of adaptability. Ultradian rhythms are more likely to be affected by climate change than infradian rhythms. As climate change will likely affect many physiological variables, many endogenous rhythms may be disrupted, with consequences for seizure control. On the other hand, these findings could provide mitigation through insights and pharmacological targets to address seizure worsening due to environmental stressors aggravated by climate change.

Storage conditions for ASMs may determine product shelf-life. This may be particularly important in formulations which are sensitive to humidity, temperature, and sunlight, such as certain blister pack preparations, injections, and syrups. Storing carbamazepine and phenytoin formulations in hot, humid conditions impaired the stability of pharmaceutical forms and reduced bioavailability by up to 50% [123]. Valproate is particularly hygroscopic; its stability may change when enteric-coated tablets are removed from their original packaging and repackaged into dosette boxes (or dose administration aids). In hot, humid environments, valproate in a dosette should be stored in a refrigerator [124]. While the summary of product characteristics of phenobarbital states that it should be stored below 25 °C and in a dry place [125], no such recommendations are found for other ASMs. The SARS-CoV-2 pandemic has highlighted the vulnerability of current supply chains [126,127]. Disruption of ASM supply chains due to weather events as a result of climate change, including floods and fires, may compromise seizure control in people with epilepsy. We can infer this from recent non-climatic natural hazards, such as the 2011 Great East Japan earthquake and subsequent devastating tsunami [128].

3. Climate change and epilepsy: insights from basic science studies

Brain (cortex) and core body temperatures closely follow each other [129]. Typically, an elevated body temperature is caused by fever due to infection. During fever induced in adult rodents by intraperitoneal injection of IL-1beta, or hyperthermia induced by handling stress, the thermal curves measured in the peritoneum (core) and in the cortex were similar, independent of the thermal state [129]. Core (skin) and brain temperatures measured in normothermic immature rats were on average 2.8 °C higher in the brain than the core [130]. Thermoregulatory disturbances have been reported in various clinical epilepsy syndromes and seizures may affect neuronal circuitries involved in thermoregulation. The effect of temperature on neuronal function and excitability is well

established, and an increase in core and brain temperature can precipitate seizures in susceptible people with epilepsy and in animal models [131]. Dysregulation of body temperature has been reported in Dravet syndrome [132]; the human reflex epilepsy “hot-water epilepsy” is characterized by seizures triggered by bathing with hot water, or pouring hot water on the head during bathing, as typically occurs in certain cultures [133]. Reproducing this phenomenon in adult rats, raising the core temperature to 40 ± 2 °C for 3–5 minutes, resulted in an increase in blood pressure and blood–brain barrier breakdown [134]. Hyperthermia may occur as the result of exposure to extremely hot and humid environmental conditions, or exertional heatstroke, pharmacological interventions, or other pathological conditions. In adult rodents, hyperthermia aggravates both seizures and hippocampal damage provoked by either neurotoxic or non-neurotoxic doses of kainic acid following the elevation of core body temperature to 42 °C [135]. Similarly, brain damage, expressed as neuronal necrosis in neocortex, globus pallidus, hippocampus, or substantia nigra pars reticulata, was worsened in hyperthermic adult rats (41 °C) exposed to fluorothyl-induced seizures for 10 min compared to animals with lower (39 °C, 40 °C) core body temperatures following a 20-min period of fluorothyl-induced status epilepticus [136]. Thirty minutes of hyperthermia (39 °C core and brain temperature) in postnatal day 10 rats increased the epileptogenicity of status epilepticus and its neuropathological sequelae compared to body temperature at 35 °C [137]. These results demonstrate that increased body temperature may play an important “second hit” role in the control of epileptic seizures and seizure-related brain damage. Experimental models have identified factors by which fever or hyperthermia can cause seizures and may result in epilepsy and cognitive dysfunction. These factors include (Table 1): genetic susceptibility (see above); increased brain temperature affecting permeability and function of native ion channels, such as TRPV channels [138] or L-type Ca^{2+} channels [139] influencing both excitatory and inhibitory neurons; activation of the innate immune system during both fever and hyperthermia, contributing to seizure precipitation if pro-inflammatory cytokines, such as IL-1 β and TNF, overshoot their homeostatic threshold [140]; and hyperventilation-induced alkalosis, which, when occurring during hyperthermia, may promote neuronal excitability and seizures [141,142].

The maximal electroshock seizure (MES) model recapitulates aspects of generalized tonic-clonic seizures and has been widely used as a model for drug therapy screening [143]. Changes in ambient temperature alter seizure threshold in the MES model. Changes in body temperature (20–45 °C) affect seizure threshold, duration, and post-seizure recovery in the MES model in the rat [144]. In particular, higher body temperature has been correlated to a higher seizure threshold and lower seizure duration as compared to lower

body temperatures. The time of recovery following an MES was longer when the body temperature was maintained at 30 °C and shorter for higher body temperatures (40–42 °C) [144]. Even in very well-controlled environmental conditions, seasonal changes in seizure threshold have been observed, which might be related, but not limited to, fluctuations in temperature and/or humidity throughout the year. Notably, myoclonic and clonic seizures in the pentylenetetrazole (PTZ) model show seasonality, but tonic seizures in the MES do not [145]. This observation suggests that different seizure types, invoking different networks, show differing susceptibility to seasonal influences. As climate change alters weather patterns, there may be unpredictable effects on seizure susceptibility, both in experimental and human settings.

Kindling is an animal model for focal epilepsy induced by repeated application of subthreshold electrical stimuli to the limbic system, or administration of chemical stimuli such as PTZ, and is a model of chronically decreased seizure threshold [146,147]. Seizure threshold in electrically induced kindling, the most widely used model for focal epilepsy, did not change between different calendar months [148]. Neither the threshold of kindling nor the response to the antiseizure effect of phenytoin correlated with the seasons or atmospheric pressure in the amygdala kindling of rats [149]. In electrical- or PTZ-induced kindling model, seizure stages were aggravated in both of the kindling models with application of an agonist to the temperature-sensitive TRPV1 channel [150]. In mouse models of generalized seizures, phenobarbital, carbamazepine, and valproate had their lowest efficacy and potency in March and April, i.e. in early spring in Europe [151]. Changes in the metabolism of phenobarbital and carbamazepine led to reduced brain levels in March and April, while for valproate this was due to changes in pharmacodynamic activity [151]. Further influences of temperature, humidity, and sunlight on these models have been little studied.

Experimental animal models of non-convulsive generalized absence seizures defined by EEG, behavioral or pharmacological characteristics are classified as either pharmacological/chemical or genetic [152], and include the genetic rat model, genetic absence epilepsy rats from Strasbourg (GAERS), a well-validated rodent model of childhood absence epilepsy, with spontaneous absence seizures and spike-and-wave discharges on cortical electroencephalography accompanied by behavioral arrest [153]. Despite derivation from one original colony in Strasbourg and the same genetic mutation in the *Cacna1h* gene in all rats, there are variations in the spike-and-wave discharges, seizure phenotypes and behavioral characteristics among the main GAERS colonies present in institutes in Melbourne, Strasbourg, Istanbul, and Grenoble [154]. The seizure frequency in the rat colony of Grenoble was four times higher than the GAERS colony in Melbourne. These findings are currently unexplained, but they may reflect the impact of environmental conditions on the severity of absence seizures.

3.1. Other models and in vitro studies

The zebrafish model is efficient for high-throughput drug therapy screening, especially for genetic epilepsies [155]. Temperature can regulate susceptibility in zebrafish to a PTZ-induced seizure [156]. More specifically, when the water temperature was increased from the standard (26 °C) to 30 °C, the latency to a PTZ-induced seizure decreased and, conversely, when it was lowered to 22 °C, significantly increased. A mechanistic explanation might be attributed to glutamatergic neurotransmission since the application of the NMDA channel blocker MK-801 mitigated the hyperthermia-induced seizure susceptibility. In larval zebrafish, hyperthermia-induced seizures were dependent on thermosensitive channels such as those coupled to the TRPV4 channel and

Table 1

Mechanistic insights determined for the relationship between raised body temperature and seizures.

Raised body temperature and seizures: possible mechanisms (different combinations may be relevant depending on the cause of the raised body temperature)	
Genetic susceptibility (channelopathies)	Voltage-gated Na^+ channels (<i>SCN1B</i> , <i>SCN1A</i>) GABA-A ligand-gated/receptor-coupled ion channel subunits Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels
Change in permeability of native ion channels	Temperature-sensitive TRPV channels L-type Ca^{2+} channels (Cav1.2 subunit)
Activation of the innate immune system	Pro-inflammatory cytokines (IL-1 β , TNF)
Induction of hyperventilation	Alkalosis

pharmacological blockade of these channels resulted in seizure reduction, while GABA re-uptake inhibitors, or TRPV1 antagonists, failed to modulate electrographic seizures [138]. Overall, experimental evidence from a commonly used vertebrate model organism suggests that changes in temperature are sufficient to trigger electrographic and behavioral seizures, providing additional experimental evidence that temperature can affect seizure susceptibility in both the mature and developing brain. Electrophysiological recordings from mutated flies that model GEFS+ suggest decreased GABAergic inhibition as a potential mechanism for the temperature-sensitive seizure phenotype [157]. Another temperature-sensitive seizure mutant in *Drosophila melanogaster* implicated the phosphoglycerate kinase enzyme, which is involved in ATP generation, linking changes in ATP levels with abnormal seizure activity and structural synaptic defects [158]. Epileptiform activity induced by hyperthermia has been shown using *in vitro* and *in vivo* studies in different brain regions such as the cortex and the hippocampus [159–161].

These data from model systems show temperature changes evidently have complex effects in seizure models, especially when thermoregulation is compromised. It is not always clear what the implications from such studies might be for human epilepsies, but as more extreme heat events occur through a changing climate, it seems unlikely that such phenomena will be irrelevant to human epilepsies, especially those well reproduced in model systems.

4. Discussion

The effects of climate change on epilepsy have not yet been directly studied systematically, but published data suggest it is unlikely that there will be no impact of climate change on epilepsy. On the contrary, the risks are multiple, may act synergistically, and may affect most those least resilient to the challenges ahead. The data suggest there is an urgent need to understand the possible effects of climate change on epilepsy.

There are key areas which need to be addressed in order to accurately understand and predict such effects. The impact of climate change on seizure precipitants needs evaluation. Elevated body temperature is a key seizure precipitant (but may not be the only contributor) in well recognized febrile seizure-related epilepsy syndromes, and other known seizure precipitants, such as stress, fatigue, and sleep disturbance, associated with many common epilepsies, are all likely to be more prevalent with climate change. Climate change can be expected to increase seizure severity and frequency in many epilepsies, potentially putting many people with epilepsy at higher risk of seizures and their adverse outcomes, such as SUDEP, as well as exacerbating associated neurological and systemic comorbidities of the epilepsies.

Although significant uncertainties remain in projections of regional and local responses of climate to increased greenhouse gas forcing, the Intergovernmental Panel on Climate Change report highlighted the serious risk that climate change poses for the spread of vector-borne infections [162]. Tackling the health threat of vector-borne infections will require a collective approach including population screening, further experimental models to study mechanisms of epileptogenesis after brain infections, and changes to policies which might encompass further development and distribution of vaccines, vector control, and the development of therapeutics for at-risk populations. The SARS-CoV-2 pandemic has demonstrated that such work raises challenges in many domains of relevance to epilepsy, from molecular genetics to global political levels.

Work on human genetics and fever-sensitive epilepsies show that there are genetic polymorphisms which could potentially be associated with seizure susceptibility. Climate change has been

considered to have an impact on changes in tolerance to higher temperature [163], which could potentially affect those with fever-sensitive, or stress-sensitive, epilepsies. There are no systematic studies investigating the links between global warming and the polymorphic gene families or their functional roles in particular fever-sensitive epilepsies. More work integrating weather observations with clinical data for better understanding the relationship between weather or climate and epilepsy is needed and will be facilitated by the existence of large datasets of population-specific human genetic variation, not all of which will have been subject to negative selection pressure.

Basic science studies show the importance of increased body temperature for the control of epileptic seizures and seizure-related brain damage. Although seasonal variations have a number of effects on the physiology and biochemistry of laboratory animals despite constant environmental conditions [164–166], they have been neglected in most experimental studies, including those of epilepsy [151]. Experimental models of epilepsy could be of value in investigating the effects of climate change and/or changes in indoor and outdoor temperature and humidity on seizures and response to ASMs. Recent efforts, spearheaded by the ILAE/AES Translational Task Force [167], that aim to harmonize data collection practices in the preclinical setting, might be useful, especially to allow comparison of studies from different laboratories or institutions in different countries [168].

The evidence that we are facing a climate emergency, with its multiple attendant consequences, is among the strongest for any scientific observation ever [169]. Detailed projections and evaluations also clearly demonstrate the impending sizeable impacts on health and healthcare [170]. The impact of climate change on epilepsy is likely to be complex, and not just directly through temperature changes; indirect consequences also need consideration, such as effects on increasing stress, reducing healthcare availability and medicine supplies. The SARS-CoV-2 pandemic may not yet have had a discernible direct effect on epilepsy, beyond access to care and clinical management [171], but its global reach and impact show that global challenges happen, need to be anticipated for preparedness, analyzed when they happen, and responded to effectively. We already know much more about climate change than we did about SARS-CoV-2. We need to act now on the warnings around us all everyday, and so robustly shown by global scientific efforts, for healthcare in general, and for epilepsy.

There are significant challenges ahead from climate change that cannot be ignored. Climate change will not affect populations equally. Both the physical changes in climate and the capacity to cope with them will be distributed differently across nations, amplifying existing health resource disparities within and between countries since these multiple disparities will have consequences for people with epilepsy. We urgently need multi-level stakeholder collaborative efforts including international epilepsy and public health experts for more studies of the effects of climate change. Additional basic research data will help support innovative interventions to mitigate public health impacts. We need both increased engagement with people with epilepsy, who may already be experiencing the effects of climate change, and with national and regional legislators, public policy makers, engineers, and environmental specialists. This would allow better adaptation of our practices and lifestyles, and work to mitigate the effects of climate change for people with epilepsy through better adaptations.

Funding

We are grateful to the Epilepsy Society for their support of this work, and funding to SMS. This work was partly carried out at NIHR University College London Hospitals Biomedical Research

Centre, which receives a proportion of funding from the UK Department of Health's NIHR Biomedical Research Centres funding scheme.

Acknowledgements

PS developed his work within the framework of the DINOGMI Department of Excellence of MIUR 2018-2022 (legge 232 del 2016).

Conflicts of interest/financial disclosures

PS has received speaker fees and participated at advisory boards for Biomarin, Zogenyx, GW Pharmaceuticals, and has received research funding by ENECTA BV, GW Pharmaceuticals, Kolfarma srl., Eisai. SMZ has received research funding from Epilepsy Research UK, Glasgow Children's Hospital Charity, Dravet Syndrome UK and received honoraria for advisory boards/consultancy work/speaking at educational symposia from GW Pharma, Zogenix Ltd., Biocodex, UCB Pharma, Nutricia and Encoded Genomics. IES may accrue future revenue on pending patent WO61/010176 (filed: 2008): Therapeutic Compound; has a patent for SCN1A testing held by Bionomics Inc and licensed to various diagnostic companies; has a patent molecular diagnostic/theranostic target for benign familial infantile epilepsy (BFIE) [PRRT2] 2011904493 & 2012900190 and PCT/AU2012/001321 (TECH ID:2012-009) with royalties paid. She has served on scientific advisory boards for UCB, Eisai, GlaxoSmithKline, BioMarin, Nutricia, Rogcon and Xenon Pharmaceuticals; has received speaker honoraria from GlaxoSmithKline, UCB, BioMarin, Biocodex and Eisai; has received funding for travel from UCB, Biocodex, GlaxoSmithKline, Biomarin and Eisai; has served as an investigator for Zogenix, Zynerba, Ultra-genyx, GW Pharma, UCB, Eisai, Anavex Life Sciences, Ovid Therapeutics, Epigenyx, Encoded Therapeutics and Marinus; and has consulted for Zynerba Pharmaceuticals, Atheneum Partners, Ovid Therapeutics, Epilepsy Consortium and UCB.

RDT receives research support from Medtronic and De Christelijke Vereniging voor de Verpleging van Lijders aan Epilepsie, received consultancy fees from Theravance Biopharma and fees for lectures from Medtronic, UCB and Novartis.

References

- <https://www.nature.com/articles/d41586-020-014970>.
- Kanniah KD, Kamarul Zaman NAF, Kaskaoutis DG, Latif MT. COVID-19's impact on the atmospheric environment in the Southeast Asia region. *Sci Total Environ* 2020;736:139658. <https://doi.org/10.1016/j.scitotenv.2020.139658>.
- <https://www.who.int/globalchange/commit/commit-to-ambitious-climate-action/en/index1.html>
- <https://www.imf.org/en/Publications/WEO/Issues/2017/09/19/world-economic-outlook-october-2017>
- <https://blogs.imf.org/2017/09/27/the-unequal-burden-of-rising-temperatures-how-can-low-income-countries-cope/>
- https://www.who.int/globalchange/commit/EN-health_commitment1_National_and_local_governments.pdf?ua=1
- <https://www.kingsfund.org.uk/blog/2019/04/nhs-climate-change>
- <https://www.sduhealth.org.uk/policy-strategy/reporting/natural-resource-footprint-2018.aspx>
- <https://digital.nhs.uk/data-and-information/national-indicator-library/carbon-dioxide-equivalent-emissions-for-nhs-trusts>
- <https://about.kaiserpermanente.org/community-health/improving-community-conditions/environmental-stewardship/climate-action>
- Hawkins E, Ortega P, Suckling E, Schurer A, Hegerl G, Jones P, et al. Estimating changes in global temperature since the preindustrial period. *Bull Am Meteorol Soc* 2017;98(9):1841-56.
- Løvsletten O, Rypdal M. Statistics of regional surface temperatures after 1900: long-range versus short-range dependence and significance of warming trends. *J Clim* 2016;29(11):4057-68.
- Cohen J, Pfeiffer K, Francis JA. Warm Arctic episodes linked with increased frequency of extreme winter weather in the United States. *Nat Commun* 2018;9(1):869.
- Mahlstein I, Knutti R, Solomon S, Portmann RW. Early onset of significant local warming in low latitude countries. *Environ Res Lett* 2011;6(3):034009.
- Bindoff NL, Stott PA, Achuta Rao KM, Allen MR, Gillett N, Gutzler D, et al. (2013). Chapter 10 - Detection and attribution of climate change: From global to regional. In: *Climate Change 2013: The Physical Science Basis*. IPCC Working Group I Contribution to AR5. Cambridge: Cambridge University Press.
- Kim YH, Min SK, Zhang X, Zwiers F, Alexander LV, Donat MG, et al. Attribution of extreme temperature changes during 1951-2010. *Clim Dyn* 2016;46(5-6):1769-82.
- Perkins-Kirkpatrick SE, Gibson PB. Changes in regional heatwave characteristics as a function of increasing global temperature. *Sci Rep* 2017;7(1):1-12.
- Fischer EM, Knutti R. Observed heavy precipitation increase confirms theory and early models. *Nat Clim Change* 2016;6(11):986-91.
- Hegerl GC, Black E, Allan RP, Ingram WJ, Polson D, Trenberth KE, et al. Challenges in quantifying changes in the global water cycle. *Bull Amer Meteor Soc* 2015;96(7):1097-115.
- Veenema TG, Thornton CP, Lavin RP, Bender AK, Seal S, Corley A. Climate change-related water disasters' impact on population health. *J Nurs Scholarsh* 2017;49(6):625-34.
- Bocchiola D, Brunetti L, Soncini A, Polinelli F, Gianinetto M. Impact of climate change on agricultural productivity and food security in the Himalayas: A case study in Nepal. *Agric Syst* 2019;171:113-25.
- Eekhout JP, Hunink JE, Terink W, de Vente J. Why increased extreme precipitation under climate change negatively affects water security. *Hydro Earth Syst Sci* 2018;22(11):5935-46.
- Kangalawe RY, Mung'ong'o CG, Mwakaje AG, Kalumanga E, Yanda PZ. Climate change and variability impacts on agricultural production and livelihood systems in Western Tanzania. *Clim Dev* 2017;9(3):202-16.
- Keshavarz M, Maleksaeidi H, Karami E. Livelihood vulnerability to drought: A case of rural Iran. *Int J Disaster Risk Reduct* 2017;21:223-30.
- Sisodiya SM, Fowler HJ, Lake I, Nanji RO, Gawel K, Esguerra CV, Newton C, Foley A. Climate change and epilepsy: Time to take action. *Epilepsia Open* 2019;4(4):524-36. Review.
- Hussain SA, Ortendahl JD, Bentley TGK, Harmon AL, Gupta S, Begley CE, et al. The economic burden of caregiving in epilepsy: An estimate based on a survey of US caregivers. *Epilepsia* 2020;61(2):319-29.
- GBD 2016 Epilepsy Collaborators. Global, regional, and national burden of epilepsy, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019;18(4):357-75.
- Wibecan L, Fink G, Tshering L, Bruno V, Patenaude B, Niroula DK, et al. Bhutan Epilepsy Project. The economic burden of epilepsy in Bhutan. *Trop Med Int Health* 2018;23(4):342-58.
- Lai ST, Tan WY, Wo MC, Lim KS, Ahmad SB, Tan CT. Burden in caregivers of adults with epilepsy in Asian families. *Seizure* 2019;71:132-9.
- Jensen MP, Liljenquist KS, Bocell F, Gammaitoni AR, Aron CR, Galer BS, et al. Life impact of caregiving for severe childhood epilepsy: Results of expert panels and caregiver focus groups. *Epilepsy Behav* 2017;74:135-43.
- Villanueva V, Girón JM, Martín J, Hernández-Pastor LJ, Lahuerta J, Doz M, et al. Quality of life and economic impact of refractory epilepsy in Spain: the ESPERA study. *Neurologia* 2013;28(4):195-204.
- O'Dell C, Wheless JW, Cloyd J. The personal and financial impact of repetitive or prolonged seizures on the patient and family. *J Child Neurol* 2007;22(5):615-70S. Review.
- Taylor J, Jacoby A, Baker GA, Marson AG, Ring A, Whitehead M. Factors predictive of resilience and vulnerability in new-onset epilepsy. *Epilepsia* 2011;52(3):610-8.
- Ring A, Jacoby A, Baker GA, Marson A, Whitehead MM. Does the concept of resilience contribute to understanding good quality of life in the context of epilepsy? *Epilepsy Behav* 2016;56:153-64.
- Jacoby A, Snape D, Baker GA. Determinants of quality of life in people with epilepsy. *Neurol Clin* 2009;27(4):843-63. Review.
- Tedrus GMAS, Limongi JM Junior, Zuntini JVR. Resilience, quality of life, and clinical aspects of patients with epilepsy. *Epilepsy Behav* 2020;103(PtA):106398.
- Walker C, Peterson CL. A sociological approach to resilience in health and illness. *J Eval Clin Pract* 2018;24(6):1285-90.
- Chang KC, Wu TH, Fann JC, Chen SL, Yen AM, Chiu SY, et al. Low ambient temperature as the only meteorological risk factor of seizure occurrence: A multivariate study. *Epilepsy Behav* 2019;100(Pt A):106283.
- Motta E, Gołba A, Bal A, Kazibutowska Z, Strzała-Orzeł M. Seizure frequency and bioelectric brain activity in epileptic patients in stable and unstable atmospheric pressure and temperature in different seasons of the year—a preliminary report. *Neurol Neurochir Pol* 2011;45(6):561-6.
- Rakers F, Walther M, Schiffner R, Rupprecht S, Rasche M, Kockler M, et al. Weather as a risk factor for epileptic seizures: A case-crossover study. *Epilepsia* 2017;58(7):1287-95.
- Bartolini E, Sander JW. Dealing with the storm: An overview of seizure precipitants and spontaneous seizure worsening in drug-resistant epilepsy. *Epilepsy Behav* 2019;97:212-8.
- Braithwaite I, Zhang S, Kirkbride JB, Osborn DPJ, Hayes JF. Air pollution (particulate matter) exposure and associations with depression, anxiety, bipolar, psychosis and suicide risk: A systematic review and meta-analysis. *Environ Health Perspect* 2019;127(12):126002.

- [43] Ferlisi M, Shorvon S. Seizure precipitants (triggering factors) in patients with epilepsy. *Epilepsy Behav* 2014;33:101–5.
- [44] den Heijer JM, Otte WM, van Diessen E, van Campen JS, Lorraine Hompe E, Jansen FE, et al. The relation between cortisol and functional connectivity in people with and without stress-sensitive epilepsy. *Epilepsia* 2018;59(1):179–89.
- [45] Donat MG, Alexander LV. The shifting probability distribution of global daytime and night-time temperatures. *Geophys Res Lett* 2012;39(14).
- [46] Obradovich N, Migliorini R, Mednick SC, Fowler JH. Nighttime temperature and human sleep loss in a changing climate. *Sci Adv* 2017;3(5):e1601555.
- [47] Fujii H, Fukuda S, Narumi D, Ihara T, Watanabe Y. Fatigue and sleep under large summer temperature differences. *Environ Res* 2015 Apr;138:17–21.
- [48] Rifkin DI, Long MW, Perry MJ. Climate change and sleep: A systematic review of the literature and conceptual framework. *Sleep Med Rev* 2018;42:3–9.
- [49] Wu ZH, Stevens RG, Tennen H, North CS, Grady JJ, Holzer C. Sleep quality among low-income young women in Southeast Texas predicts changes in perceived stress through hurricane Ike. *Sleep* 2015;38(7):1121–8.
- [50] Hoag JR, Wu H, Grady JJ. Impact of childhood abuse on adult sleep quality among low-income women after Hurricane Ike. *Sleep Health* 2015;1(4):293–9.
- [51] McKibben JB, Fullerton CS, Ursano RJ, Reissman DB, Kowalski-Trakofler K, Shultz JM, et al. Sleep and arousal as risk factors for adverse health and work performance in public health workers involved in the 2004 Florida hurricane season. *Disaster Med Public Health Prep* 2010;4(1):S55–62.
- [52] Alderman K, Turner LR, Tong S. Assessment of the health impacts of the 2011 summer floods in Brisbane. *Disaster Med Public Health Prep* 2013;7(4):380–6.
- [53] Zhen R, Quan L, Zhou X. Fear, negative cognition, and depression mediate the relationship between traumatic exposure and sleep problems among flood victims in China. *Psychol Trauma* 2018;10(5):602–9.
- [54] Psarros C, Thelertis C, Economou M, Tzavara C, Kioulos KT, Mantoukakis L, et al. Insomnia and PTSD one month after wildfires: evidence for an independent role of the “fear of imminent death”. *Int J Psychiatry Clin Pract* 2017;21(2):137–41.
- [55] Regens JL and Mould N. Prevention and treatment of traumatic brain injury due to rapid-onset natural disasters. *Front Publ Health*. 2014;2:28. Review.
- [56] Koubi V. Climate change and conflict. *Annu Rev Pol Sci* 2019;22(1):343–60.
- [57] Hsiang SM, Marshall B. Climate, conflict, and social stability: what does the evidence say? *Clim Change* 2014;123(1):39–55.
- [58] Hsiang SM, Burke M, Miguel E. Quantifying the influence of climate on human conflict. *Science* 2013;341(6151):1235367.
- [59] Mach KJ, Kraan CM, Adger WN, Buhaug H, Burke M, Fearon JD, et al. Climate as a risk factor for armed conflict. *Nature* 2019;571(7764):193–7.
- [60] Sander JW. The epidemiology of epilepsy revisited. *Curr Opin Neurol* 2003;16:165–70.
- [61] Thijs RD, Surges R, O'Brien TJ, Sander JW. Epilepsy in adults. *Lancet* 2019;393(10172):689–701. Review.
- [62] World Malaria Report 2019. Available: World Health Organization, Geneva. <https://www.who.int/publications/i/item/world-malaria-report-2019>.
- [63] WHO, World Health Organization. Climate change and human health. Geneva, 2009. (<http://www.who.int/globalchange/en>.)
- [64] Dasgupta S. Burden of climate change on malaria mortality. *Int J Hyg Environ Health* 2018;221(5):782–91.
- [65] Kim YM, Park JW, Cheong HK. Estimated effect of climatic variables on the transmission of *Plasmodium vivax* malaria in the Republic of Korea. *Environ Health Perspect* 2012;120(9):1314–9.
- [66] Martens P, Kovats RS, Nijhof S, de Vries P, Livermore MTJ, Bradley DJ, et al. Climate change and future populations at risk of malaria. *Global Environ Change* 1999;9(1):89–107.
- [67] Paaajmans KP, Blanford S, Bell AS, Blanford JI, Read AF, Thomas MB. Influence of climate on malaria transmission depends on daily temperature variation. *Proc Natl Acad Sci U S A* 2010;107(34):15135–9.
- [68] Postels DG, Birbeck GL, Valim C, Mannor KM, Taylor TE. Seasonal differences in retinopathy-negative versus retinopathy-positive cerebral malaria. *Am J Trop Med Hyg* 2013;88(2):315–8.
- [69] Hajjion PL, Mwakikunga BW, Mathanga DP, Feresu SA. Seasonal variation of malaria cases in children aged less than 5 years old following weather change in Zomba district, Malawi. *Malar J* 2017;16(1):264.
- [70] Waruiru CM, Newton CR, Forster D, New L, Winstanley P, Mwangi I, et al. Epileptic seizures and malaria in Kenyan children. *Trans R Soc Trop Med Hyg* 1996;90(2):152–5.
- [71] Nougouou EB, Koko J, Druet-Cabanac M, Assengone-Zeh-Nguema Y, Launay MN, Engohang E, et al. Cerebral malaria and sequelae epilepsy: first matched case-control study in Gabon. *Epilepsia* 2006;47(12):2147–53.
- [72] Nougouou EB, Dulac O, Poudiouou B, Druet-Cabanac M, Dicko A, Mamadou Traore A, et al. Epilepsy as a consequence of cerebral malaria in area in which malaria is endemic in Mali, West Africa. *Epilepsia* 2006;47(5):873–9.
- [73] Ngugi AK, Bottomley C, Kleinschmidt I, Wagner RG, Kakooza-Mwesige A, Aengibise K, et al. Prevalence of active convulsive epilepsy in sub-Saharan Africa and associated risk factors: cross-sectional and case-control studies. *Lancet Neurol* 2013;12(3):253–63.
- [74] Mewara A, Goyal K, Sehgal R. Neurocysticercosis: A disease of neglect. *Trop Parasitol*. 2013;3(2):106–13. Review.
- [75] WHO, World Health Organization. 2019, Taeniasis/cysticercosis Report. <https://www.who.int/news-room/fact-sheets/detail/taeniasis-cysticercosis>.
- [76] Vezzani A, Fujinami RS, White HS, Preux PM, Blümcke I, Sander JW, Löscher W. Infections, inflammation and epilepsy. *Acta Neuropathol*. 2016;131(2):211–34. Review.
- [77] Hotez PJ. Human parasitology and parasitic diseases: heading towards 2050. *Adv Parasitol* 2018;100:29–38.
- [78] Whitehorn J, Yacoub S. Global warming and arboviral infections. *Clin Med (Lond)* 2019;19(2):149–52.
- [79] Sergi C, Serra N, Colomba C, Ayanlade A, Di Carlo P. Tuberculosis evolution and climate change: How much work is ahead? *Acta Trop* 2019;190:157–8.
- [80] Rossati A. Global warming and its health impact. *Int J Occup Environ Med* 2017;8(1):7–20.
- [81] Bouchama A and Knochel JP. Heat stroke. *N Engl J Med*. 2002;346(25):1978–88. Review.
- [82] Hanna EG, Tait PW. Limitations to thermoregulation and acclimatization challenge human adaptation to global warming. *Int J Environ Res Public Health* 2015;12(7):8034–74.
- [83] Knochel JP, Reed G. Disorders of heat regulation. In: Narins RG, editor. Maxwell & Kleeman's clinical disorders of fluid and electrolyte metabolism. New York: McGraw-Hill; 1994. p. 1549–90.
- [84] Lee WG, Huh SY, Lee JH, Yoo BG, Kim MK. Status epilepticus as an unusual manifestation of heat stroke. *J Epilepsy Res* 2017;7(2):121–5.
- [85] van Zeijl JH, Mullaart RA, Galama JM. The pathogenesis of febrile seizures: is there a role for specific infections? *Rev Med Virol* 2002;12(2):93–106.
- [86] Feenstra B, Pasternak B, Geller F, Carstensen L, Wang T, Huang F, et al. Common variants associated with general and MMR vaccine-related febrile seizures. *Nat Genet* 2014;46(12):1274–82.
- [87] Hee Woo J, Bin OhS, Hyuk Yim C, Hye Byeon J, Eun BL. Impact of weather on prevalence of febrile seizures in children. *J Korean Child Neurol Soc* 2018;26(4):227–32.
- [88] Fletcher EV, Kullmann DM, Schorge S. Alternative splicing modulates inactivation of type 1 voltage-gated sodium channels by toggling an amino acid in the first S3–S4 linker. *J Biol Chem* 2011;286(42):36700–8.
- [89] Verbeek NE, Wassenaar M, van Campen JS, Sonsma A, Gunning B, Knoers N, et al. Seizure precipitants in Dravet syndrome: What events and activities are specifically provocative compared with other epilepsies? *Epilepsy Behav* 2015;47:39–44.
- [90] Mei D, Cetica V, Marini C, Guerrini R. Dravet syndrome as part of the clinical and genetic spectrum of sodium channel epilepsies and encephalopathies. *Epilepsia* 2019;60(3):S2–7.
- [91] Steel D, Symonds JD, Zuberi SM, Brunklaus A. Dravet syndrome and its mimics: Beyond SCN1A. *Epilepsia* 2017;58(11):1807–16. Review.
- [92] Kang JQ, Shen W, Macdonald RL. Why does fever trigger febrile seizures? GABA_A receptor gamma2 subunit mutations associated with idiopathic generalized epilepsies have temperature-dependent trafficking deficiencies. *J Neurosci* 2006;26(9):2590–7.
- [93] Trivisano M, Pietrafusa N, Terracciano A, Marini C, Mei D, Darra F, et al. Defining the electroclinical phenotype and outcome of PCDH19-related epilepsy: A multicenter study. *Epilepsia* 2018;59(12):2260–71.
- [94] Battaglia A, Filippi T, South ST, Carey JC. Spectrum of epilepsy and electroencephalogram patterns in Wolf-Hirschhorn syndrome: experience with 87 patients. *Dev Med Child Neurol* 2009;51(5):373–80.
- [95] Hildebrand MS, Phillips AM, Mullen SA, et al. Loss of synaptic Zn²⁺ transporter function increases risk of febrile seizures. *Sci Rep* 2015;5:17816.
- [96] May P, Girard S, Harrer M, et al. Rare coding variants in genes encoding GABA_A receptors in genetic generalised epilepsies: an exome-based case-control study. *Lancet Neurol* 2018;17(8):699–708.
- [97] Voets T, Droogmans G, Wissenbach U, Janssens A, Flockerzi V, Nilius B. The principle of temperature-dependent gating in cold- and heat-sensitive TRP channels. *Nature* 2004;430(7001):748–54.
- [98] Caterina MJ. Transient receptor potential ion channels as participants in thermosensation and thermoregulation. *Am J Physiol Regul Integr Comp Physiol*. 2007;292(1):R64–76. Review.
- [99] Ghosh A, Kaur N, Kumar A, Goswami C. Why individual thermo sensation and pain perception varies? Clue of disruptive mutations in TRPVs from 2504 human genome data. *Channels (Austin)* 2016;10(5):339–45.
- [100] Athanasios G, Carroll K, Majeed A, Sander JW. The epidemiology of the comorbidity of epilepsy in the general population. *Epilepsia* 2004;45(12):1613–22.
- [101] McArthur K, Dawson J, Walters M. What is it with the weather and stroke? *Expert Rev Neurother* 2010;10(2):243–9.
- [102] Mostofsky E, Wilker EH, Schwartz J, Zanobetti A, Gold DR, Wellenius GA, Mittleman MA. Short-term changes in ambient temperature and risk of ischemic stroke. *Cerebrovasc Dis Extra*. 2014 22;4(1):9–18.
- [103] Lichtman JH, Leifheit-Limson EC, Jones SB, Wang Y, Goldstein LB. Average temperature, diurnal temperature variation, and stroke hospitalizations. *J Stroke Cerebrovasc Dis* 2016;25(6):1489–94.
- [104] Vogelaere P, Pereira C. Thermoregulation and aging. *Rev Port Cardiol*. 2005;24(5):747–61. Review.
- [105] Sen A, Jette N, Husain M, Sander JW. Epilepsy in older people. *Lancet*. 2020;29:395(10225):735–48.
- [106] Baccini M, Kosatsky T, Analitis A, Anderson HR, D'Ovidio M, Menne B, et al. Impact of heat on mortality in 15 European cities: attributable deaths under different weather scenarios. *J Epidemiol Community Health* 2011;65(1):64–70.
- [107] Strine TW, Kobau R, Chapman DP, Thurman DJ, Price P, Balluz LS. Psychological distress, comorbidities, and health behaviors among U.S.

- adults with seizures: results from the 2002 National Health Interview Survey. *Epilepsia* 2005;46(7):1133–9.
- [108] Téllez-Zenteno JF, Matijevic S, Wiebe S. Somatic comorbidity of epilepsy in the general population in Canada. *Epilepsia* 2005;46(12):1955–62.
- [109] Bell GS, Peacock JL, Sander JW. Seasonality as a risk factor for sudden unexpected death in epilepsy: a study in a large cohort. *Epilepsia* 2010;51(5):773–6.
- [110] Sisodiya SM, Scheffer IE, Lowenstein DH, Free SL. Insight Why should a neurologist worry about climate change? *Lancet Neurol* 2019;18(4):335–6.
- [111] Shmueli S, Sisodiya SM, Gunning WB, Sander JW, Thijs RD. Mortality in Dravet syndrome: A review. *Epilepsy Behav* 2016;64(Pt A):69–74.
- [112] Cooper MS, McIntosh A, Crompton DE, McMahon JM, Schneider A, Farrel K, et al. Mortality in Dravet syndrome. *Epilepsy Res* 2016;128:43–7.
- [113] Kane JC, Ventevogel P, Spiegel P, Bass JK, van Ommeren M, Tol WA. Mental, neurological, and substance use problems among refugees in primary health care: analysis of the Health Information System in 90 refugee camps. *BMC Med* 2014;12:228.
- [114] Manjunath R, Davis KL, Candrilli SD, Ettinger AB. Association of antiepileptic drug nonadherence with risk of seizures in adults with epilepsy. *Epilepsy Behav* 2009;14(2):372–8.
- [115] Faught E, Duh MS, Weiner JR, Guérin A, Cunningham MC. Nonadherence to antiepileptic drugs and increased mortality: findings from the RANSOM Study. *Neurology* 2008;71(20):1572–8.
- [116] Parnas J, Flachs H, Gram L, Würtz-Jørgensen A. Excretion of antiepileptic drugs in sweat. *Acta Neurol Scand* 1978;58(3):197–204.
- [117] Cohn DF. Is there a climatic influence on the blood level of anticonvulsive drugs? *Med Hypotheses* 1982;8(4):427–30.
- [118] Avakian GN, Oleinikova OM, Lagutin IuV, Khromykh EA, Bogomazova MA, Delger AB, et al. Season fluctuations of carbamazepine and valproate concentration in patients with epilepsy. *Zh Nevrol Psikhiatr Im S S Korsakova* 2013;113(11):34–9 [Article in Russian].
- [119] Baxendale S. Seeing the light? Seizures and sunlight. *Epilepsy Res* 2009;84(1):72–6.
- [120] Ramgopal S, Thome-Souza S, Loddenkemper T. Chronopharmacology of anti-convulsive therapy. *Curr Neurol Neurosci Rep* 2013;13(4):339.
- [121] Spencer DC, Sun FT, Brown SN, Jobst BC, Fountain NB, Wong VS, et al. Circadian and ultradian patterns of epileptiform discharges differ by seizure-onset location during long-term ambulatory intracranial monitoring. *Epilepsia* 2016;57(9):1495–502.
- [122] Goh GH, Maloney SK, Mark PJ, Blache D. Episodic ultradian events-ultradian rhythms. *Biology (Basel)* 2019;8(1):pii: E15.
- [123] Cloyd J. Pharmacokinetic pitfalls of present antiepileptic medications. *Epilepsia* 1991;32(5):S53–65. Review.
- [124] Redmayne N, Robertson S, Kockler J, Llewellyn V, Haywood A, Glass B. Repackaged sodium valproate tablets—Meeting quality and adherence to ensure seizure control. *Seizure* 2015;31:108–11.
- [125] <https://www.medicines.org.uk/emc/product/5843/smpc>.
- [126] <https://www.newindianexpress.com/cities/chennai/2020/apr/30/grave-shortage-of-medicine-for-epilepsy-care-amid-covid-19-lockdown-2137239.html>.
- [127] <https://www.thebureauinvestigates.com/stories/2020-04-09/drug-shortages-put-worst-hit-covid-19-patients-at-risk>.
- [128] Kobayashi S, Endo W, Inui T, et al. The lack of antiepileptic drugs and worsening of seizures among physically handicapped patients with epilepsy during the Great East Japan Earthquake. *Brain Dev* 2016;38:623–7.
- [129] Sundgren-Andersson AK, Ostlund P, Bartfai T. Simultaneous measurement of brain and core temperature in the rat during fever, hyperthermia, hypothermia and sleep. *Neuroimmunomodulation* 1998;5(5):241–7.
- [130] Dubé C, Brunson KL, Eghbal-Ahmadi M, Gonzalez-Vega R, Baram TZ. Endogenous neuropeptide Y prevents recurrence of experimental febrile seizures by increasing seizure threshold. *J Mol Neurosci* 2005;25(3):275–84.
- [131] Pollandt S, Bleck TP. Thermoregulation in epilepsy. *Handb Clin Neurol* 2018;157:737–47.
- [132] Skluzacek JV, Watts KP, Parsy O, Wical B, Camfield P. Dravet syndrome and parent associations: the IDEA League experience with comorbid conditions, mortality, management, adaptation, and grief. *Epilepsia* 2011;52(2):95–101.
- [133] Bebek N, Gürses C, Gokyigit A, Baykan B, Ozkara C, Dervent A. Hot water epilepsy: clinical and electrophysiologic findings based on 21 cases. *Epilepsia* 2001;42(9):1180–4.
- [134] Ilbay G, Sahin D, Ates N. Changes in blood-brain barrier permeability during hot water-induced seizures in rats. *Neurol Sci* 2003;24(4):232–5.
- [135] Liu Z, Gatt A, Mikati M, Holmes GL. Effect of temperature on kainic acid-induced seizures. *Brain Res* 1993;631(1):51–8.
- [136] Lundgren J, Smith ML, Blennow G, Siesjö BK. Hyperthermia aggravates and hypothermia ameliorates epileptic brain damage. *Exp Brain Res* 1994;99(1):43–55.
- [137] Sarkisian MR, Holmes GL, Carmant L, Liu Z, Yang Y, Stafstrom CE. Effects of hyperthermia and continuous hippocampal stimulation on the immature and adult brain. *Brain Dev* 1999;21(5):318–25.
- [138] Hunt RF, Hortopan GA, Gillespie A, Baraban SC. A novel zebrafish model of hyperthermia-induced seizures reveals a role for TRPV4 channels and NMDA-type glutamate receptors. *Exp Neurol* 2012;237(1):199–206.
- [139] Radzicki D, Yau HJ, Pollema-Mays SL, Mlsna L, Cho K, Koh S, et al. Temperature-sensitive Cav1.2 calcium channels support intrinsic firing of pyramidal neurons and provide a target for the treatment of febrile seizures. *J Neurosci* 2013;33(24):9920–31.
- [140] Heida JG, Moshé SL, Pittman QJ. The role of interleukin-1beta in febrile seizures. *Brain Dev* 2009;31(5):388–93. Review.
- [141] Schuchmann S, Hauck S, Henning S, et al. Respiratory alkalosis in children with febrile seizures. *Epilepsia* 2011;52(11):1949–55.
- [142] Schuchmann S, Schmitz D, Rivera C, et al. Experimental febrile seizures are precipitated by a hyperthermia-induced respiratory alkalosis. *Nat Med* 2006;12(7):817–23.
- [143] Toman JE, Swinyard EA, Goodman LS. Properties of maximal seizures, and their alteration by anticonvulsant drugs and other agents. *J Neurophysiol* 1946;9:231–9.
- [144] Swinyard EA, Toman JE. Effects of alterations in body temperature on properties of convulsive seizures in rats. *Am J Physiol* 1948;154(2):207–10.
- [145] Löscher W, Fiedler M. The role of technical, biological and pharmacological factors in the laboratory evaluation of anticonvulsant drugs. VI. Seasonal influences on maximal electroshock and pentylenetetrazol seizure thresholds. *Epilepsy Res* 1996;25(1):3–10.
- [146] McNamara JO. Kindling model of epilepsy. *Adv Neurol* 1986;44:303–8.
- [147] Goddard GV. Development of epileptic seizures through brain stimulation at low intensity. *Nature* 1967;214(5092):1020–1.
- [148] Wlaź P, Löscher W. The role of technical, biological, and pharmacological factors in the laboratory evaluation of anticonvulsant drugs. V. Lack of seasonal influences on amygdala kindling in rats. *Epilepsy Res* 1993;16(2):131–6.
- [149] Ebert U, Rundfeldt C, Lehmann H, Löscher W. Characterization of phenytoin-resistant kindled rats, a new model of drug-resistant partial epilepsy: influence of experimental and environmental factors. *Epilepsy Res* 1999;33(2–3):199–215.
- [150] Shirazi M, Izadi M, Amin M, Rezvani ME, Roohbakhsh A, Shamsizadeh A. Involvement of central TRPV1 receptors in pentylenetetrazole and amygdala-induced kindling in male rats. *Neurol Sci* 2014;35(8):1235–41.
- [151] Löscher W, Fiedler M. The role of technical, biological, and pharmacological factors in the laboratory evaluation of anticonvulsant drugs. VII. Seasonal influences on anticonvulsant drug actions in mouse models of generalized seizures. *Epilepsy Res* 2000;38(2–3):231–48.
- [152] Onat FY, van Luijtelaar G, Nehlig A, Snead 3rd OC. The involvement of limbic structures in typical and atypical absence epilepsy. *Epilepsy Res* 2013;103(2–3):111–23.
- [153] Depaulis A and van Luijtelaar G. Genetic models of Absence epilepsy, in Models of seizures and epilepsy. Editors: Pitkanen A, Schwartzkroin PA, Moshe SL. San Diego, CA: Elsevier Academic Press 2006 233–248.
- [154] Powell KL, Tang H, Ng C, Guillemain I, Dieuset G, Dezsi G, et al. Seizure expression, behavior, and brain morphology differences in colonies of Genetic Absence Epilepsy Rats from Strasbourg. *Epilepsia* 2014;55(12):1959–68.
- [155] Griffin A, Krasiak C, Baraban SC. Advancing epilepsy treatment through personalized genetic zebrafish models. *Prog Brain Res* 2016;226:195–207.
- [156] Menezes FP, Da Silva RS. The influence of temperature on adult zebrafish sensitivity to pentylenetetrazole. *Epilepsy Res* 2017;135:14–8.
- [157] Sun L, Gilligan J, Staber C, Schutte RJ, Nguyen V, O'Dowd DK, et al. A knock-in model of human epilepsy in *Drosophila* reveals a novel cellular mechanism associated with heat-induced seizure. *J Neurosci* 2012;32(41):14145–55.
- [158] Wang P, Saraswati S, Guan Z, Watkins CJ, Wurtman RJ, Littleton JT. A *Drosophila* temperature-sensitive seizure mutant in phosphoglycerate kinase disrupts ATP generation and alters synaptic function. *J Neurosci* 2004;24(19):4518–29.
- [159] Suchomelova L, Lopez-Meraz ML, Niquet J, Kubova H, Wasterlain CG. Hyperthermia aggravates status epilepticus-induced epileptogenesis and neuronal loss in immature rats. *Neuroscience* 2015;305:209–24.
- [160] Wang YY, Qin J, Han Y, Cai J, Xing GG. Hyperthermia induces epileptiform discharges in cultured rat cortical neurons. *Brain Res* 2011;1417:87–102.
- [161] Qu L, Leung LS. Effects of temperature elevation on neuronal inhibition in hippocampal neurons of immature and mature rats. *J Neurosci Res* 2009;87(12):2773–85.
- [162] IPCC 5th assessment report. Intergovernmental Panel on Climate Change. Climate change 2014: impacts, adaptation, and vulnerability. Working Group II contribution to the IPCC 5th assessment report – changes to the underlying scientific/technical assessment. <http://www.ipcc.ch/report/>.
- [163] Scheffers BR, De Meester L, Bridge TC, Hoffmann AA, Pandolfi JM, Corlett RT, et al. The broad footprint of climate change from genes to biomes to people. *Science* 2016;354(6313).
- [164] Nelson RJ, Demas GE, Klein SL, Kriegsfeld LJ. The influence of season, photoperiod, and pineal melatonin on immune function. *J Pineal Res* 1995;19(4):149–65. Review.
- [165] Bartsch H, Bartsch C, Mecke D, Lippert TH. Seasonality of pineal melatonin production in the rat: possible synchronization by the geomagnetic field. *Chronobiol Int* 1994;11(1):21–6.
- [166] Wong CC, Döhler KD, Atkinson MJ, Geerlings H, Hesch RD, von zur Mühlen A. Circannual variations in serum concentrations of pituitary, thyroid, parathyroid, gonadal and adrenal hormones in male laboratory rats. *J Endocrinol* 1983;97(2):179–85.
- [167] Harte-Hargrove LC, Galanopoulou AS, French JA, Pitkanen A, Whittemore V, Scharfman HE. Common data elements (CDEs) for preclinical epilepsy research: Introduction to CDEs and description of core CDEs. A TASK3 report of the ILAE/AES joint translational task force. *Epilepsia Open* 2018;3(1):13–23.

- [168] Scharfman HE, Galanopoulou AS, French JA, Pitkänen A, Whittemore V, Harte-Hargrove LC. Preclinical common data elements (CDEs) for epilepsy: A joint ILAE/AES and NINDS translational initiative. *Epilepsia Open* 2018;3(1):9–12.
- [169] Ripple WJ, Wolf C, Newsome TM, Barnard P, Moomaw WR. World Scientists' warning of a climate emergency. *Bioscience* 2020;70(1):8–12.
- [170] Watts N, Amann M, Arnell N, Ayeb-Karlsson S, Belesova K, Boykoff M, et al. The 2019 report of The Lancet Countdown on health and climate change: ensuring that the health of a child born today is not defined by a changing climate. *Lancet* 2019;394(10211):1836–78. Review.
- [171] French JA, Brodie MJ, Caraballo R, Devinsky O, Ding D, Jehi L, et al. Keeping people with epilepsy safe during the COVID-19 pandemic. *Neurology* 2020;94(23):1032–7.