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

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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 aims 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.

Keywords: Global warming, emergency, seizure, temperature, extreme weather events, public health

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 Organisation (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 recognised 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 (REF). 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- of 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°-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 parameterisation within individual models and model simulations. Consequently, there are significant uncertainties associated with regional and local climate responses to greenhouse gas forcing. Nonetheless, climate modelling 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, increase in seizure development or deterioration of seizure control by enhancement of seizure precipitants or disruption of drug delivery and the potential indirect consequences, co-morbidities or Sudden Unexpected Death in Epilepsy (SUDEP) related to climate change were evaluated with the current literature in 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 associatedeconomic consequences are huge [26-27], amounting to 0.5% of the overall global burden of disease [27-28], disproportionately greater amongst 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; reported quality of life is much lower amongst 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 day-time 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 characterised.

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]. Whilst 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.

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].

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 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 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* [92-93, 95-96, 98].. Variants in genes causing the mainly rare, severe, fever-sensitive epilepsies can also be found in the more common epilepsies [99-100].

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 [101]. The cold-sensitive channels TRPM8 and TRPA1 and the heat-sensitive channel TRPV1 are activated at 15°C, 17°C and 40°C, respectively [102]. High encoding-gene variability among the TRP vanilloid subgroup (TRPV family) members has been reported [103]. 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, whilst 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 [104]. 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 [105-106]. Abrupt weather changes may increase blood viscosity, blood pressure and platelet reactivity [107-108]. 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 [109]. The majority of weather-related excess mortality is attributable to cardiovascular and respiratory disorders [110], which are common epilepsy comorbidities (respectively 2.5 and 2.9-fold increased risk for people with epilepsy) [111-112]. Climate change could also heighten the risk of Sudden Unexpected Death in Epilepsy (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 [113], rising temperatures could increase seizure frequency, and therefore SUDEP risk, especially in some fever-sensitive epilepsies, such as Dravet syndrome [114], conditions already associated with a particularly high risk of SUDEP under current temperature conditions [115-116]. The displacement of people due to climate change will be associated with reduced health care provision, as epilepsy is amongst the most common neurological conditions in refugee camps [117]. Displacement and supply chain disruption can interrupt medication provision sincenon-adherence (here enforced) increases seizure risk [118], and thus increases SUDEP risk [119].

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. [120] 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 [121], with a decrease in serum levels at the end of summer due to an increase of perspiration. A study from Russia among 107 people with epilepsy, who received either valproic acid or carbamazepine, found that the serum levels of carbamazepine and

valproate were significantly lower in spring compared to autumn [122]. 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 [123]. Endogenous circadian rhythms may contribute to seizure patterns, with ASM chronotherapy suggested as a method to optimize seizure control in selected people with epilepsy [124]. 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 [125]. 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 [126]; 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% [127]. 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 [128]. While the summary of product characteristics of phenobarbital states that it should be stored below 25°C and in a dry place [129], no such recommendations are found for other ASMs. The SARS-CoV-2 pandemic has highlighted the vulnerability of current supply chains [130-131]. 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 [132].

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

Brain (cortex) and core body temperatures closely follow each other [133]. 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 [133]. Core (skin) and brain temperatures measured in normothermic immature rats were on average 2.8°C higher in the brain than the core [134]. 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 [135]. Dysregulation of body temperature has been reported in Dravet syndrome [136]; the human reflex epilepsy "hot-water epilepsy" is characterised by seizures triggered by bathing with hot water, or pouring hot water on the head during bathing, as typically occurs in certain cultures [137]. 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 [138]. 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 [139]. 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 minutes compared to animals with lower (39°C, 40°C) core body temperatures following a 20-minute period of fluorothyl-induced status epilepticus [140]. 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 [141]. 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 [142] or L-type Ca^{2+} channels [143] 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-1β and TNF, overshoot their homeostatic threshold [144]; and hyperventilation-

induced alkalosis, which, when occurring during hyperthermia, may promote neuronal excitability and seizures [145-146].

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 [147]. 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 [148]. 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) [148]. 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 [149]. 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 [150-151]. Seizure threshold in electrically-induced kindling, the most widely used model for focal epilepsy, did not change between different calendar months [152]. 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 [153]. 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 [154]. 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 [155]. 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 [155]. 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, behavioural or pharmacological characteristics are classified as either pharmacological/chemical or genetic [156], 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

behavioural arrest [157]. 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 behavioural characteristics among the main GAERS colonies present in institutes in Melbourne, Strasbourg, Istanbul and Grenoble [158]; 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.

Other models and in vitro studies

The zebrafish model is efficient for high-throughput drug therapy screening, especially for genetic epilepsies [159]. Temperature can regulate susceptibility in zebrafish to a PTZ-induced seizure [160]. 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 pharmacological blockade of these channels resulted in seizure reduction, whilst GABA re-uptake inhibitors, or TRPV1 antagonists, failed to modulate electrographic seizures [142]. Overall, experimental evidence from a commonly-used vertebrate model organism suggests that changes in temperature are sufficient to trigger electrographic and behavioural 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 [161]. 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 [162]. 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 [163-165].

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 suggests 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 recognised 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 [166]. 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 genetic to global political levels.

Work on human genetics and fever-sensitive epilepsies shows 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 [167], 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 [168-170], they have been neglected in most experimental studies, including those of epilepsy [155]. 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 [171], 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 [172].

The evidence that we are facing a climate emergency, with its multiple attendant consequences, is amongst the strongest for any scientific observation ever [173]. Detailed projections and evaluations also clearly demonstrate the impending sizeable impacts on health and healthcare [174]. 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 [175], but its global reach and impact show that global challenges happen, need to be anticipated for preparedness, analysed 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 countriessince 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.

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Appendix 1.

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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 (*SCN1B*, *SCN1A*)
	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-1β, TNF)
Induction of hyperventilation	Alkalosis