The ketogenic diet for epilepsy is a curate’s egg. On the positive side of the ledger a dietary intervention, as compared to a neuroactive pharmaceutical, offers the possibility of a more subtle nudge to the epileptic nervous system with a lower probability of side effects. On the negative, an intervention that drastically changes such a core human behaviour as eating promises (and delivers) extreme challenges with compliance. As an intervention with roots in antiquity the diet is a prime candidate for rational, evidence-based modifications to improve its efficacy and applicability. If such modifications are successful, the ketogenic diet might even overtake pharmaceutical treatments as the first line treatment for many presentations of epilepsy.1 Recently, tantalising discoveries have suggested that such modifications could target the gut microbiome, an apparent key player in the causal chain leading from the ketogenic diet to anti-seizure changes in the brain.2 Two research papers by Mu et al. published recently in eBioMedicine3,4 make valuable progress in the direction of ketogenic diet optimization, in the specific case of infantile spasms syndrome. Their findings are particularly noteworthy for their direct clinical implications, but also advance our understanding of particular mechanisms of the ketogenic diet in infantile spasms.

The first of these publications3 reveals that a variety of mechanistically-overlapping gut microbiome-based manipulations are capable of suppressing infantile spasms in the brain injury neonatal rat model. These manipulations included the ketogenic diet itself (observed here and elsewhere to significantly adjust the microbiome), a 3-day broad spectrum oral antibiotic (observed here and elsewhere to significantly adjust the microbiome), and fecal microbial transplants from ketogenic diet-fed rats. The clinical possibility of adjusting the ketogenic diet with antibiotics or another microbiome intervention is apparent, and the distinctions between these three related interventions suggest an improved probability of translational relevance.

Recapitulating these seizure-suppressing effects in other contexts will also be helped by knowledge of the chain of events between intervention and effect. Mu et al.’s first paper indicates that the tryptophan/kynurenine/serotonin system forms part of this chain, observing a shift away from kynurenine and towards the production of hippocampal kynurenic acid. Recapitulating this shift via an antagonist of indoleamine 2,3-dioxygenase 1 or via the antibiotic minocycline (which inhibits kynurenine formation) also recapitulated the effects on spasms. Looking forward, it remains to be seen whether this pathway is necessary as well as sufficient for the success of the ketogenic diet.

Some clinical questions also remain. The first steps might be exploring the generalizability of these microbiome and kynurenine-related interventions to other models of infantile spasms and other types of epilepsy, as well as determining the optimal point of intervention along the causal chain. Excitingly, one might also consider expediting a human study: while we must use caution in extrapolating from model to human and in exploring the promise of microbiome interventions, the particular context of the ketogenic diet is perhaps the strongest example of a gut microbiome-to-brain robust causal association.

The companion piece by Mu et al.1 leans further to the clinical side and in doing so provides a striking finding of potential immediate use. When employed in infantile spasms syndrome (as a common recourse in the case that pharmacological approaches fail),5 the ketogenic diet can damage the developing and under-protected liver.6 This was abundantly the case in the authors’ neonatal rat model, in which severe hepatic steatosis presented with a discolored liver, a near-uniform increase in liver triglyceride and malondialdehyde, and several other indicators. This visual and metabolic phenotype was robustly reversed by co-administration of a probiotic blend along with the ketogenic diet. Although (understandably) not further explored by the authors, the implications for mechanistic intervention in the gut microbiome and kynurenine metabolism appear at least as substantial as the pathological findings in the ketogenic diet-fed rats. Further human studies could provide conclusive evidence of the generalizability of these microbiome manipulations to the clinical setting.

Commentary on “Seizure modulation by the gut microbiota and tryptophan-kynurenine metabolism in an animal model of infantile spasms” and “Probiotics counteract hepatic steatosis caused by ketogenic diet and upregulate AMPK signaling in a model of infantile epilepsy”

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2022.103833, http://dx.doi.org/10.1016/j.ebiom.2022.103835
E-mail address: cian.mccafferty@ucc.ie
© 2022 Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

www.thelancet.com Vol 78 Month April, 2022
authors in this publication, it is noteworthy that the probiotic blend independently also lowered seizure score. The immediate clinical relevance of the prevention, by two dietarily-safe probiotics, of a significant side effect of the ketogenic diet on the immature liver, is evident. The authors also provide a plausible explanation of how these effects occur: shifting lipid metabolism towards oxidation, via phosphorylated AMP-activated protein kinase (pAMPK) upregulation and inflammatory cytokine modulation. It must be noted that this potential mechanism is not explored via positive or negative manipulation, and so demonstration of its necessity, sufficiency (or otherwise) for the prevention of hepatic steatosis awaits future research. Together these pieces of original research may help us adapt Johnny Mercer’s advice: mitigate the negatives and accentuate the positives of the ketogenic diet. Observations that probiotics can positively modify the weight-loss effects of a very-low-calorie ketogenic diet, and that yogurt can protect the liver in obese mice, are encouraging. We can and should aim towards tailored treatments for epilepsy that leverage the complex effects (and potential effects of the microbiome) on the excitability of the brain, and the twin findings of Mu et al. should provoke both clinical adjustments and renewed mechanistic enquiry to that end.

Contributors
CMC was responsible for conceptualization, writing, and reviewing.

Declaration of interests
The author has no relevant interests to declare.

References
1 Kossoff EH, Zupec-Kania BA, Auvin S, et al. Optimal clinical management of children receiving dietary therapies for epilepsy: updated recommendations of the international ketogenic diet study group. Epilepsia Open. 2018;3(2):175–192.
2 Olson CA, Vuong HE, Yano JM, Liang QY, Nusbaum DJ, Hsiao EY. The gut microbiota mediates the anti-seizure effects of the ketogenic diet. Cell. 2018;173(7):1728–1741.e13.
3 Mu C, Nkpoor N, Tompkins TA, Rho JM, Scantlebury MH, Shearer J. Probiotics counteract hepatic steatosis caused by ketogenic diet and upregulate AMPK signaling in a model of infantile epilepsy. eBioMedicine. 2022 10583. February.
4 Mu C, Cheudhary A, Mayengbam S, et al. Seizure modulation by the gut microbiota and tryptophan-kynurenine metabolism in an animal model of infantile spasms. eBioMedicine. 2022 10583. January.
5 Pavone P, Palizzi A, Marino SD, et al. West syndrome: a comprehensive review. Neurol Sci. 2020;41(12):3547–3562.
6 Lyons L, Schoeler NE, Langan D, Cross JH. Use of ketogenic diet therapy in infants with epilepsy: a systematic review and meta-analysis. Epilepsia. 2020;61(6):1261–1281.
7 Gutierrez-Rejos C, Hernandez-Garcia C, Garcia-Almeida JM, et al. Effect of probiotic supplementation in a very-low-calorie ketogenic diet on weight loss achievement and gut microbiota: a randomized controlled pilot study. Mol Nutr Food Res. 2019;63(19):e1900167.
8 Lasker S, Rahman MM, Parvez F, et al. High-fat diet-induced metabolic syndrome and oxidative stress in obese rats are ameliorated by yogurt supplementation. Sci Rep. 2019;9(1):10096.
9 Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: medical treatment of infantile spasms. Report of the guideline development subcommittee of the american academy of neurology and the practice committee of the child neurology society. Neurology. 2012;78(24):1974–1980.
10 Darch H, McCafferty CP. Gut microbiome effects on neuronal excitability & activity: implications for epilepsy. Neurobiol Dis. 2022;65:105629.