Project Details	
Project Code	MRCNMH24Ex Weightman Potter
Title	Can nutritional intervention unlock better outcomes after traumatic brain injuries? Investigating brain blood flow and cellular metabolism regulation by ketones following head impacts.
Research Theme	Neuroscience & Mental Health
Summary	This project will investigate the efficacy of ketogenic supplements to improve cognition and brain blood flow regulation after concussive or sub-concussive head impacts. The approach will be from petri dish to person and allow you to learn a range of skills. In people you will measure head impacts over a season of sport and examine the effect of dietary supplements. You will also explore how ketones alter brain cells using in vitro and ex vivo models.
Description	Head accelerations, such as during contact sports, are associated with an increased risk of neurodegenerative disease. The underlying mechanisms linking head accelerations to neurodegeneration are poorly understood, but alterations in brain blood flow and energy metabolism are believed to play a crucial role. Neurovascular coupling (NVC), the connection between brain blood flow and neural activity, is disrupted after one season of contact sport, and acute changes in NVC are also observed following concussion. In neurodegenerative conditions like Alzheimer's disease, impaired glucose uptake by the brain contributes to cellular dysfunction and death. This metabolic deficit is closely tied to changes in inflammatory signalling. Ketogenic dietary interventions, such as medium-chain triglyceride (MCT) supplementation, improve cognition in individuals with cognitive impairment and Alzheimer's disease. However, the potential of ketogenic supplements to enhance brain function and recovery after brain injuries, as well as their impact on NVC and cognitive performance in contact sports, remains unexplored. Project hypothesis: Ketogenic supplements enhance recovery from head acceleration-induced brain injury by improving NVC and cognitive function through anti-inflammatory and metabolic-supporting properties. Aim 1: Test how ketones in vitro modulate metabolic and inflammatory responses of microglia to noxious stimuli. Hypothesis: β-hydroxybutyrate (BHB) supplements microglial metabolism and dampens the pro-inflammatory phenotype following classical or TBI-like stimuli. Methods: Human microglia will be exposed to a sham, TBI-like extracellular milieu, or a classical inflammatory stimulus with and without BHB. Conditioned media will be analysed using cytokine array panels and validated with targeted ELISAs. Intracellular inflammatory signalling pathways will be assessed by immunoblotting. Mitochondrial and glycolytic metabolic parameters will be measured in the microglia with the Seahorse XFe96 system in response to inflammatory stimuli and BHB. Once the student has learnt these skills the student can focus their efforts on their interests within inflammation and metabolism using their preferred techniques and investigate different cell types, such as astrocytes or neurons. The student may expand the project by using ex vivo slices of living brain tissue from rodents, diversifying their skill set. Aim 2: Evaluate the impact of head acceleration load during a season of contact sports on NVC and cognitive function in humans. Hypothesis: Head acceleration load impairs NVC and cognitive performance.

	Baseline cognition and NVC will be assessed in the pre- mid- and end-of-season for contact and non-contact sport players. Head acceleration load will be measured using wearable accelerometers. Once trained in transcranial Doppler measurements on humans, the student can explore different aspects of NVC and investigate blood flow regulation in response to various physiological stimuli. Aim 3: Test the efficacy of ketogenic dietary supplementation to improve symptom recovery in people after acute head acceleration events. Hypothesis: MCT-oil-induced elevations in plasma ketone levels improves recovery in cognitive function and NVC following acute head impacts. Participants identified in aim 2 who experience head acceleration events above a predetermined threshold will undergo repeated assessments of NVC and cognition within 72 hours of the event and after 1 and 2 weeks to capture the recovery timeline. Participants will be assigned to either the MCT or long-chain triglyceride supplement groups. The student will design the supplement implementation protocol, determining the dosage and frequency. They may also consider implementing different dietary strategies in conjunction with the supplements. Furthermore, the student will be responsible for setting the threshold for inviting participants for further NVC and cognitive testing.
Supervisory Team	
Lead Supervisor	
Name	Dr Paul Weightman Potter
Affiliation	Exeter
College/Faculty	Health and Life Sciences
Department/School	Clinical and Biomedical Sciences
Email Address	p.weightman-potter2@exeter.ac.uk
Co-Supervisor 1	
Name	Dr Bert Bond
Affiliation	Exeter
College/Faculty	Health and Life Sciences
Department/School	Sport and Health Sciences
Co-Supervisor 2	
Name	Professor Keith Stokes
Affiliation	Bath
College/Faculty	Department for Health
Department/School	Centre for Health and Injury and Illness Prevention in Sport
Co-Supervisor 3	
Name	Dr Stephen West
Affiliation	Bath
College/Faculty	Department for Health
Department/School	Centre for Health and Injury and Illness Prevention in Sport