Project Details	
Project Code	CMD27Ba Koumanov
Title	Fat Quality as a Determinant of Cardiometabolic Risk During Ketogenic Diets
Research Theme	Cardiometabolic Disease
Project Type	Wet lab
Summary	Very-low carbohydrate ketogenic diets (KDs) can improve body weight and blood glucose but often raise LDL-cholesterol levels, thereby increasing cardiovascular risk. A key unknown is whether the saturated to polyunsaturated fat ratio in a KD, affects cardiovascular risk. This PhD project will investigate how the fat quality in a KD affects cardiovascular health in a 4-week human trial and gain mechanistic understanding of how the body adapts to such diets using genetic epidemiology and cell culture models. The goal is to determine whether altering fat quality can deliver KD benefits without increasing LDL-cholesterol, improving safety and cardiometabolic health.
Description	Very low carbohydrate ketogenic diets (KDs) are increasingly used to manage body weight and blood glucose. Despite these benefits, typical KDs often raise atherogenic lipoproteins, including LDL cholesterol (LDL-C) and ApoB, potentially increasing cardiovascular disease (CVD) risk. In moderate carbohydrate diets, the ratio of saturated (SFA) to polyunsaturated fatty acids (PUFA) is a major determinant of LDL-C through regulation of hepatic LDL-receptor abundance (https://doi.org/10.1016/j.atherosclerosis.2023.117433). Whether this SFA:PUFA ratio similarly influences lipoprotein responses within ketogenic diets is unclear. If modifying fat quality could preserve glycaemic benefits while preventing LDL-C elevation, this would offer a safer nutritional strategy for the general population. Recent work (Hengist et al. DOI:10.1016/j.xcrm.2024.101667) demonstrated that in healthy individuals, a KD induced weight loss and reduced fasting glucose, but also increased LDL-C and ApoB concentrations. These findings suggest that while KDs may benefit individuals with metabolic dysfunction, they may pose risks for healthy populations. This raises several key questions: 1. How does the SFA:PUFA ratio within a KD affect LDL-C, ApoB, and lipoprotein particle characteristics? 2. Does fat quality in KD influences other CVD risk factors such as glycaemic control or blood pressure? 3. What mechanisms link dietary fat composition to atherogenic response to a ketogenic diet? 4. Does altering SFA:PUFA ratio ultimately change CVD risk? These questions have gained urgency following a recent report showing extensive liver transcriptome rewiring in response to KD, driven by fatty acid signalling and potentially linked to cancer risk (DOI:10.1038/s41586-024-07781-7). Understanding how fat quality shapes metabolic and molecular responses to KD is therefore essential for evaluating the safety and public health relevance of such diets. This forms the basis of the proposed PhD project, which integrates human intervention, mechanistic cell culture studies, and genetic epidemiology. Aim and Objectives

	Aim: To investigate how KDs affect cardiovascular health in healthy individuals and to uncover the mechanisms by which the body adapts to different fat compositions in KDs. Objective 1(O1): Determine how manipulating dietary fat quality (SFA vs PUFA) within a KD influences cardiovascular risk markers (primary outcome). Secondary analyses will use Mendelian randomisation to assess whether gene expression changes induced by diet causally influence CVD risk. Exploratory analyses will examine sex specific responses. Objective 2(O2): Characterise whole-body, tissue-level, and cellular adaptations to different fat qualities within KDs, identifying mechanistic pathways that explain changes in lipoprotein metabolism and metabolic health. Experimental Plan Human Study (O1) A 4-week randomised parallel-group nutritional intervention will be conducted in healthy adults (≥18 years). Forty participants will be recruited and randomised to one of two KDs: high-SFA or high-PUFA. Groups will be sex balanced. Measurements will be taken at baseline and after 4 weeks, including physiological assessments, blood sampling, and adipose and skeletal muscle biopsies. Blood plasma and serum will be analysed for insulin-sensitivity and cardiovascular risk markers. PBMCs will be isolated to quantify LDL-receptor transcript and protein levels. Muscle and adipose biopsies will undergo bulk RNA sequencing and proteomics to assess adaptations of metabolic pathways, including LDL-receptor regulation and AMPK–MNK–eIF4E signalling. Mitochondrial respiration will be measured to evaluate metabolic adaptation to KD. The PhD candidate will contribute to study design, ethics submission, and protocol refinement, with opportunities to tailor aspects of the intervention to their scientific interests. Genetic Epidemiology (O1) Under the supervision of Prof Vincent (University of Bristol), the student will receive training in Mendelian randomisation and genetic epidemiology. They will analyse RNA-seq data from the human study and integrate these results with large human genetic datasets to test causal relationships between diet induced gene expression changes and cardiometabolic outcomes. This training will take place within the MRC Integrative Epidemiology Unit, providing exposure to world-leading expertise. This component allows the student to shape mechanistic hypotheses based on causal inference, guiding subsequent experimental work. In Vitro Cell Culture Studies (O2) To dissect mechanisms underlying dietary fat-driven adaptations, the project will use established cellular models representing insulin-sensitive tissues: 3T3L1 adipocytes, C2C12 myotubes, and liver models developed in collaboration with Prof David Tosh (Bath), including iPSC-derived hepatocytes and 3D liver organoids. These models will be exposed to nutrient conditions mimicking high-SFA or high-PUFA ketogenic diets. Analyses will focus on insulin signalling, glucose uptake, lipid metabolism, LDL receptor regulation, and broader nutrient-responsive

	pathways. This will allow detailed mechanistic interpretation of human findings and help construct an integrated model of how fat quality shapes metabolic responses during KD. The PhD student will have freedom to select specific pathways or hypotheses to pursue, using human and genetic data to refine mechanistic experiments. Training and Opportunities for Student Leadership Across all components, the student will have substantial autonomy to steer the project. They will gain experience in human clinical research, molecular biology, cell culture, transcriptomics, proteomics, mitochondrial physiology, and genetic epidemiology. The project provides a unique interdisciplinary environment bridging nutrition, metabolism, molecular mechanisms, and causal inference.
Can be completed part time?	No
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