

Alternative Substrates in the Critically Ill Subject (ASICS): A Randomised Pilot Study to Assess the Safety, Feasibility, Tolerability and Metabolic Profiling of a Novel Ketogenic Feed

SUPPLEMENTARY INFORMATION

Angela McNelly¹, Anne Langan², Danielle E. Bear^{3,4}, Alexandria Page⁵, Tim Martin⁵, Fatima Seidu⁵, Filipa Santos⁵, Kieron Rooney⁶, Kaifeng Liang¹, Simon J Heales⁷, Tomas Baldwin⁸, Isabelle Alldritt⁹, Hannah Crossland⁹, Philip J. Atherton⁹, Daniel Wilkinson⁹, Hugh Montgomery^{10,11}, John Prowle^{1,5}, Rupert Pearse^{1,5}, Simon Eaton⁸ and Zudin A. Puthuchear^{1,5*}

¹William Harvey Research Institute, Faculty of Medicine & Dentistry, Queen Mary University of London, ²Department of Dietetics, Adult Critical Care Unit, Royal London Hospital, London, ³Department of Nutrition and Dietetics St Thomas' NHS Foundation Trust, London, ⁴Department of Critical Care, Guy's and St. Thomas' NHS, London, ⁵Adult Critical Care Unit, Royal London Hospital, London, ⁶Department of Critical Care, Bristol Royal Infirmary, Bristol, ⁷Genetic & Genomic Medicine Department, UCL Great Ormond Street Institute of Child Health, London, ⁸Developmental Biology & Cancer, UCL Great Ormond Street Institute of Child Health, London, ⁹Centre of Metabolism, Aging & Physiology (COMAP), MRC-Versus Arthritis Centre for Musculoskeletal Aging Research & NIHR Nottingham BRC, University of Nottingham, Nottingham, ¹⁰University College London (UCL), ¹¹UCL Hospitals NHS Foundation Trust (UCLH), National Institute for Health Research (NIHR) Biomedical Research Centre (BRC), London.

***CORRESPONDENCE TO**

Dr Zudin Puthuchear
Critical Care and Perioperative Medicine Research Group,
Adult Critical Care Unit,
Royal London Hospital,
London, E1 1BB
United Kingdom
Email: z.puthuchear@qmul.ac.uk

Supplementary Results

Recruitment and Retention

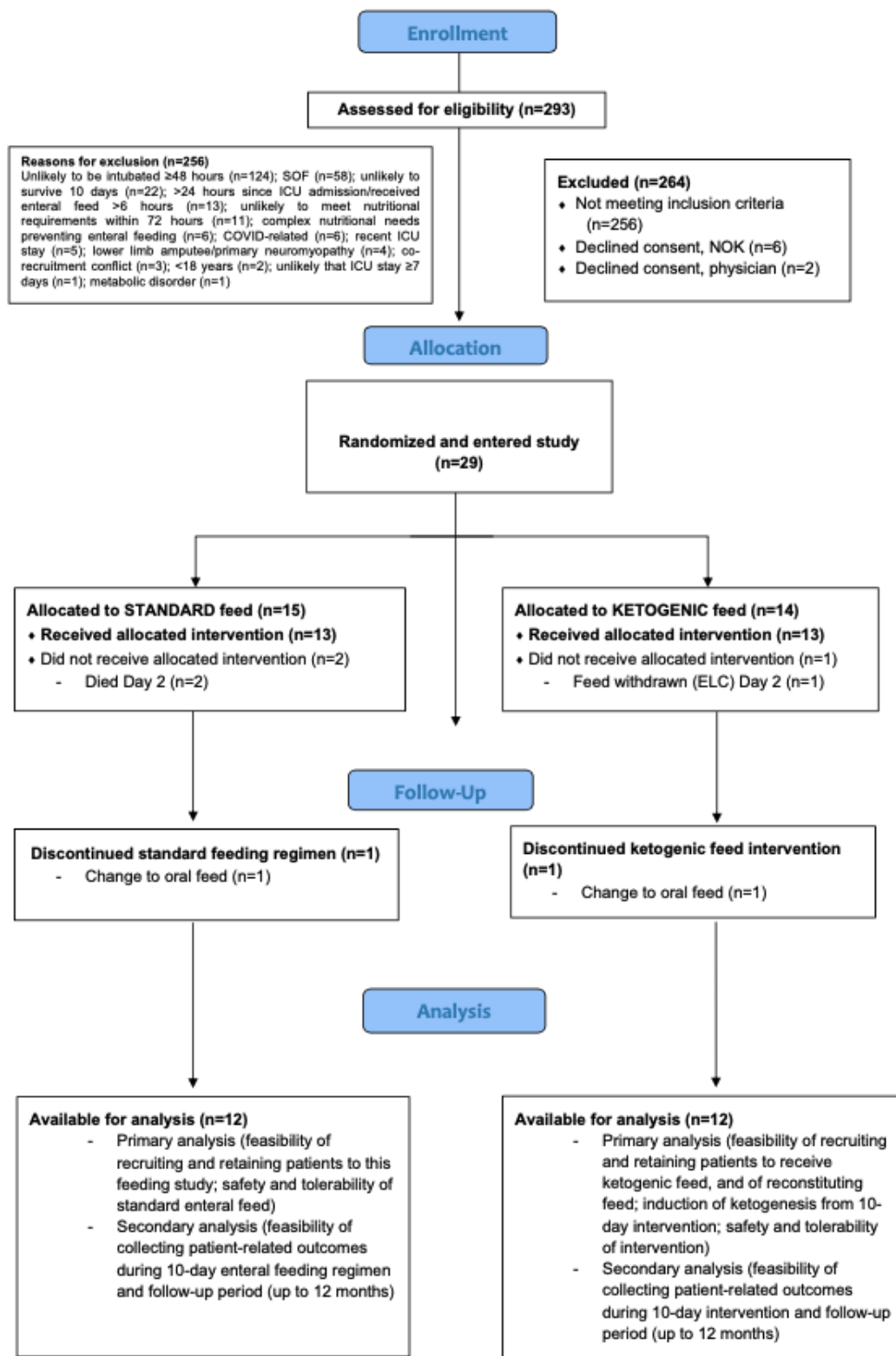


Figure S1: Consort flow diagram

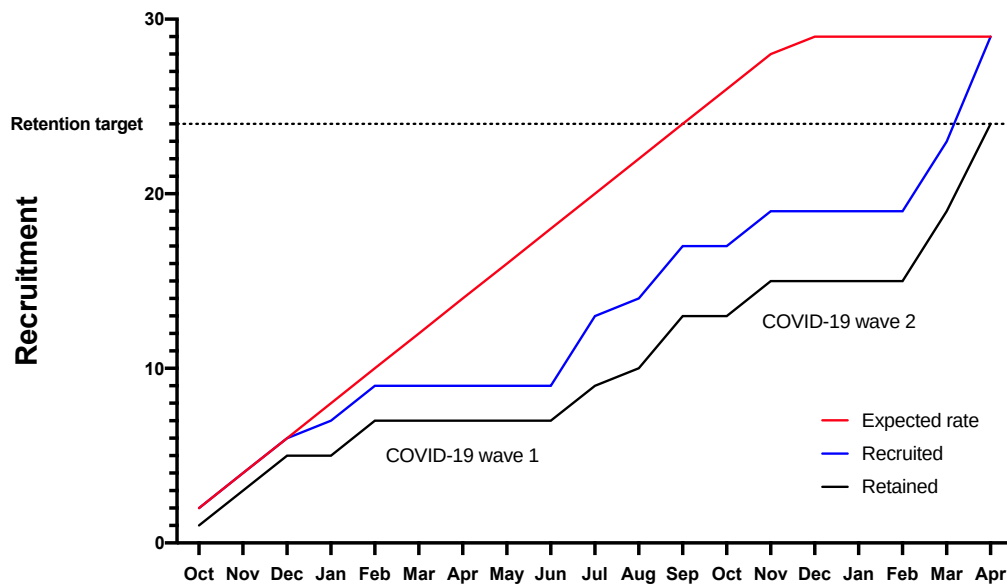


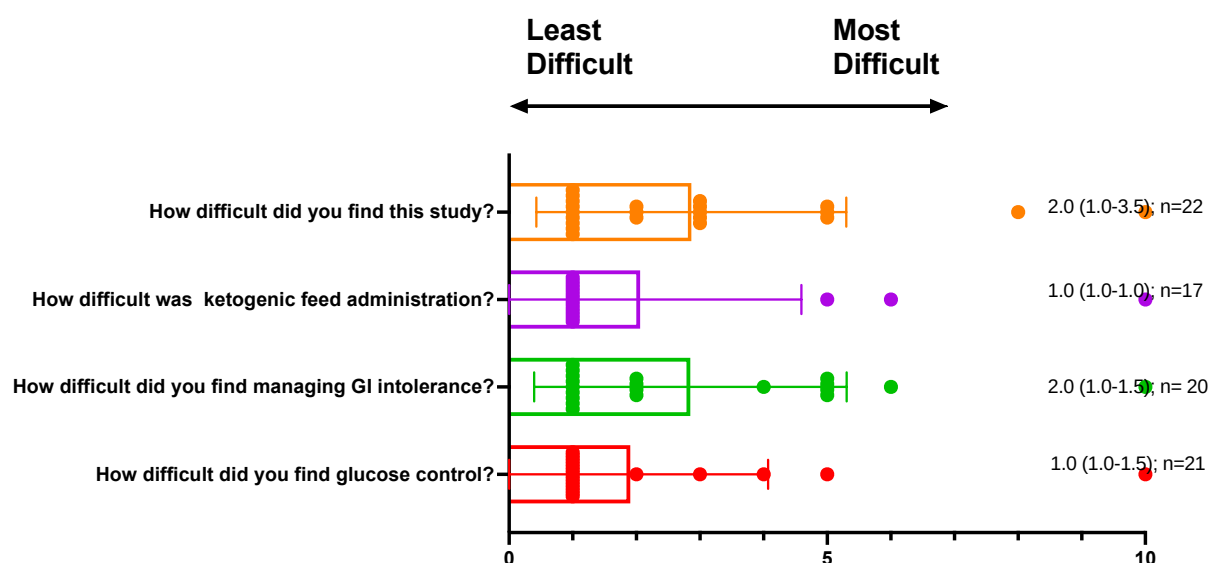
Figure S2: Recruitment rates and the effects of COVID-19 waves during the pandemic

Site	No. Screened	No. Recruited (%)	No. Retained (%)
RLH	258	27	23
BRI	35	2	1
TOTAL	293	29 (9.9)	24 (8.2)

Table S3: Recruitment across both sites. No.=number; RLH=Royal London Hospital
BRI=Bristol Royal Infirmary

Withdrawal reason	Ketogenic Feed Arm (n=14) No. (%)	Standard Feed Arm (n=15) No. (%)
ICU d/c<7d (died)	0	2
Feed withdrawn (ELC)	1	0
Feed change to oral	1	1
Total	2 (14.3)	3 (20)

Table S4: Reasons given for premature withdrawal of participants. ICU= Intensive Care Unit;
d/c<7d=discharged in less than 7 days; ELC=End of life care.

Acceptability and Feasibility

“Lack of pharmacists on study meant people were coming to me all day”

“4 Hour bags were inconvenient and increased work load, 24-hour bag was better”

Figure S3: Staff questionnaire data on feasibility and acceptability of delivering the intervention
Data are median (Inter-Quartile Range) scores from n=23. Variation in data come from the multi-disciplinary sample population i.e. not all members of the team were involved in all aspects of the study

Safety data

Serious Adverse Event summary	Outcome
Brain stem death due to trauma-related dissection of carotid arteries	Unrelated
Death from pulmonary embolism and biventricular failure	Unrelated
Metabolic acidemia secondary to hyperchloremia and dapagliflozine	Unrelated; Clinicians stopped dapagliflozine and continued ketogenic feed
Death from chest sepsis	Unrelated

Table S5: Severe Adverse Events and trial related outcomes.

Days/events reported, No. (% total days/events)	High GRV*	Vomiting**	Diarrhoea (3-days) ^a	Diarrhoea (daily) ^b	Prokinetic Use	Hypoglycaemia [^]	Hyper-glycaemia ^{^^}
STANDARD ENTERAL FEED (n=15)	25(19.8)	7 (5.5)	8 (53.3)	54 (42.9)	29 (22.8)	2 (1.6)	73 (57.5)
KETOGENIC ENTERAL FEED (n=14)	19 (17.3)	9 (8.1)	10 (76.9)	54 (53.5)	23 (20.7)	0 (0.0)	29 (26.9)

Table S6: Adverse events *Days with Gastric Residual Volume ≥ 300 mls; [^]Blood glucose ≤ 3.9 mM; **Days with any vomiting (>10 mls); ^{^^}Blood glucose ≥ 10 mM; ^aThree-day episodes of Bristol Stool Score T6 or T7; ^bDays with Bristol Stool Score T6 or T7. GRV=Gastric Residual Volume.

	Events reported, No. (%)		Mean (95% CI)	
	AKI	Metabolic acidosis	Base Excess	Bicarbonate
STANDARD ENTERAL FEED (n=15)	1 (6.6)	0 (0.0)	1.78 (2.61-0.95)	26 (16.8-25.2)
KETOGENIC ENTERAL FEED (n=14)	1 (7.1)	2 (14.3) [#]	-1.68 (-1.01- -2.35)	22.6 (23.3-21.9)

Table S7: Adverse events [#]Deemed by clinical team to be related to the ketogenic feed. AKI=Acute Kidney Injury.

Nutritional Medium Chain Triglyceride concentrations and micronutrient delivered

<i>Day</i>	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
Mean (%)	44.4	53.6	62.1	69.1	77.1	76.3	76.1	74.5	73.9	74.0
MCT										
<i>upper level</i>	52.8	61.9	69.9	78.4	86.1	86.4	88.1	87.3	84.3	83.8
<i>lower level</i>	36.0	45.4	54.2	59.9	68.1	66.1	64.1	61.7	63.5	64.2

Table S8: Concentrations of Medium Chain Triglycerides delivered per day as part of the ketogenic feed. Data are mean % (95%CI) of estimated energy requirements.

Micronutrient	Ketogenic Arm	Control Arm
<i>Vitamin A (μgRE)</i>	9060	9379
<i>Vitamin D (μgRE)</i>	50	124
<i>Vitamin E (mg)</i>	110	147
<i>Vitamin C (mg)</i>	600	825
<i>Vitamin B1 (mg)</i>	14	14
<i>Vitamin B2 (mg NE)</i>	16	17
<i>Niacin (mg)</i>	180	324
<i>Vitamin B6 (mg)</i>	20	17
<i>Folic Acid (μg)</i>	2000	2616
<i>Vitamin B12 (μg)</i>	13	29
<i>Biotin (μg)</i>	1500	486
<i>Pantothenic Acid (mg)</i>	60	52
<i>Vitamin K (μg)</i>	200	644
<i>Calcium (mg)</i>	2000	7907
<i>Phosphorus (mg)</i>	1450	5849
<i>Iron (mg)</i>	140	132
<i>Magnesium(mg)</i>	1000	2190
<i>Zinc (mg)</i>	150	115

<i>Iodine (μg)</i>	1500	1337
<i>Copper (μg)</i>	10000	12900
<i>Manganese (mg)</i>	10	27
<i>Chromium (μg)</i>	250	657
<i>Selenium (μg)</i>	550	655

Table S9 Mean total micronutrient delivery over the 10 day intervention period

Urinary Ketone Body Concentration

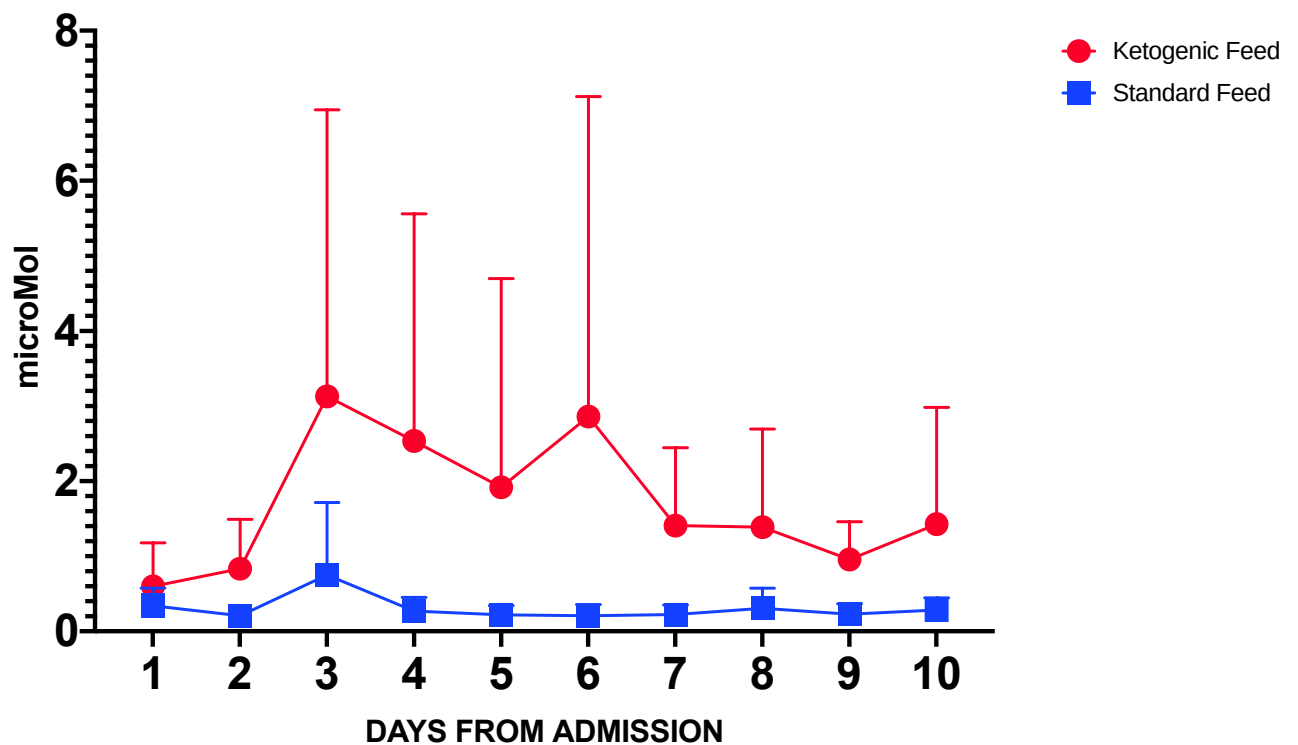


Figure S4: Urinary beta-hydroxybutyrate during the 10-day intervention. Red lines represent ketogenic feeding, and blue lines controls. N=14 subjects in the ketogenic arm and n=15 subjects in the control arm

Plasma Fatty Acid Concentrations

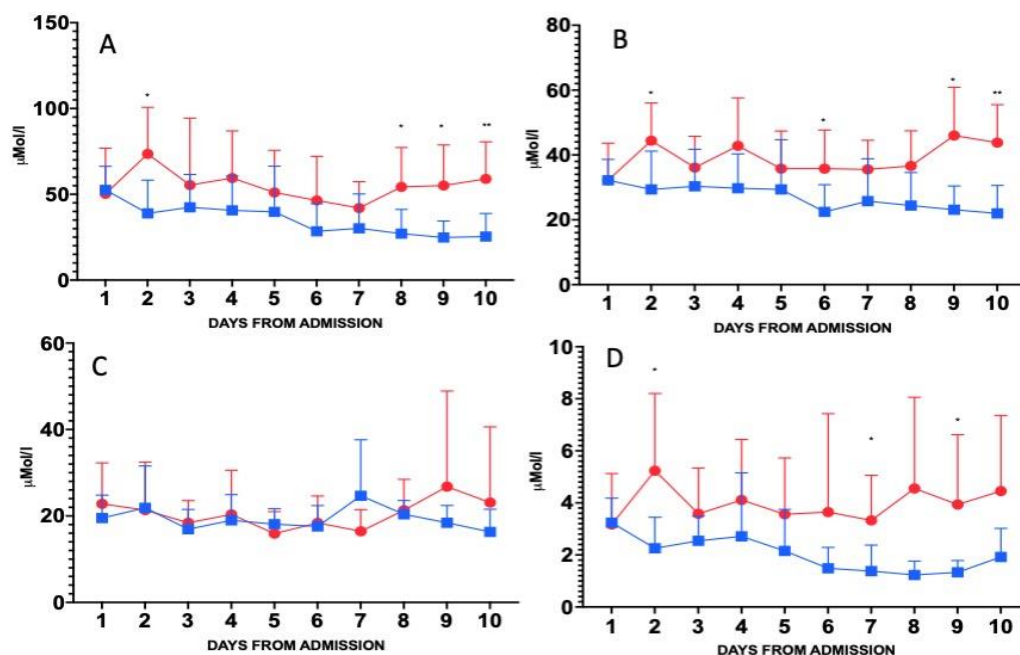


Figure S5: Octanoic acid (A), decanoic acid (B), and dodecanoic acid (C) in plasma during the 10-day intervention; octanoic:dodecanoic acid ratio (D). * $p < 0.05$, ** $p < 0.01$ between arms (Two-tailed Mann Whitney-U test). N=14 subjects in the ketogenic arm and n=15 subjects in the control arm

Glycaemic analysis.

The AUC of plasma glucose was higher in the control arm than in the intervention arm (367.8 vs. 316.9).

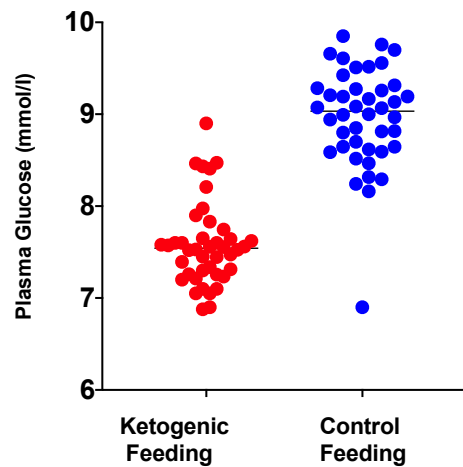


Figure s6: Raw plasma glucose data across both trial arms. 102 glucose readings in ketogenic arm vs 128 glucose readings in the control arm

Respiratory Quotients

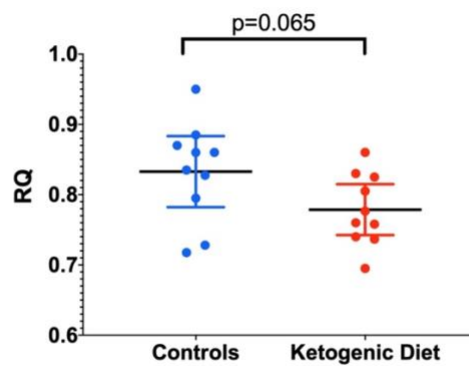


Figure S7: Respiratory Quotient (RQ) of a sub-group of patients receiving the ketogenic (red) and control (blue) feeds. n=9 controls, n=9 ketogenic feeding

Metabophenotyping

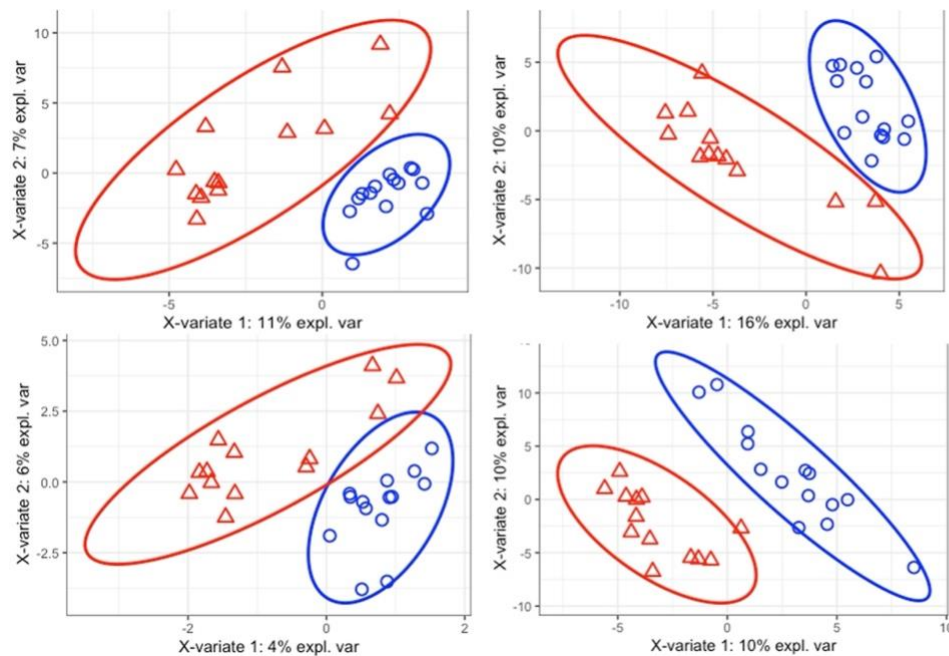


Figure S8: Sparse Partial Least Squares Discriminant analysis of patient randomised to ketogenic feeding on Day 1 (red triangle) and control feeding on day 1 (blue sphere). Clockwise from top right: polar positive, non-polar positive, non-polar negative, polar negative. Error rates are >20% (17%, 41%, 31% and 20% respectively), suggesting plot is overfitted and not true variance. N=14 subjects in the ketogenic arm and n=15 subjects in the control arm

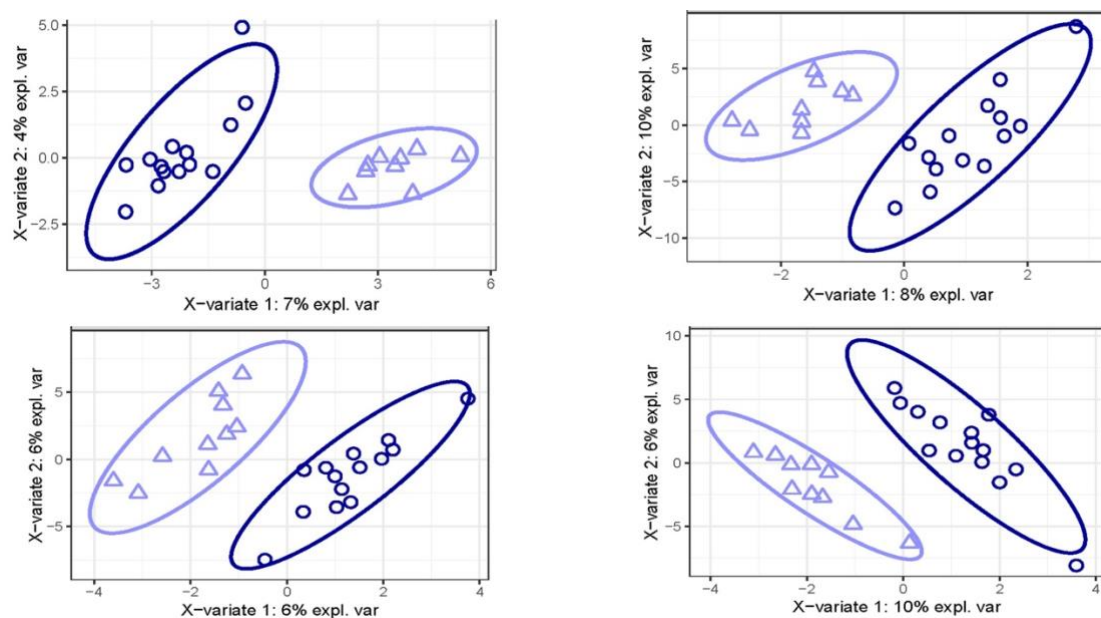


Figure S9: Sparse Partial Least Squares Discriminant analysis of patient randomised control feeding on Day 1 (blue sphere) and day 10 (blue triangle). Clockwise from top right: polar positive, non-polar positive, non-polar negative, polar negative. Error rates are mixed >20% (17%, 25%, 15% and 25% respectively), suggesting plot is at risk of overfitting a opposed to true variance. N=14 subjects in the ketogenic arm and n=15 subjects in the control arm

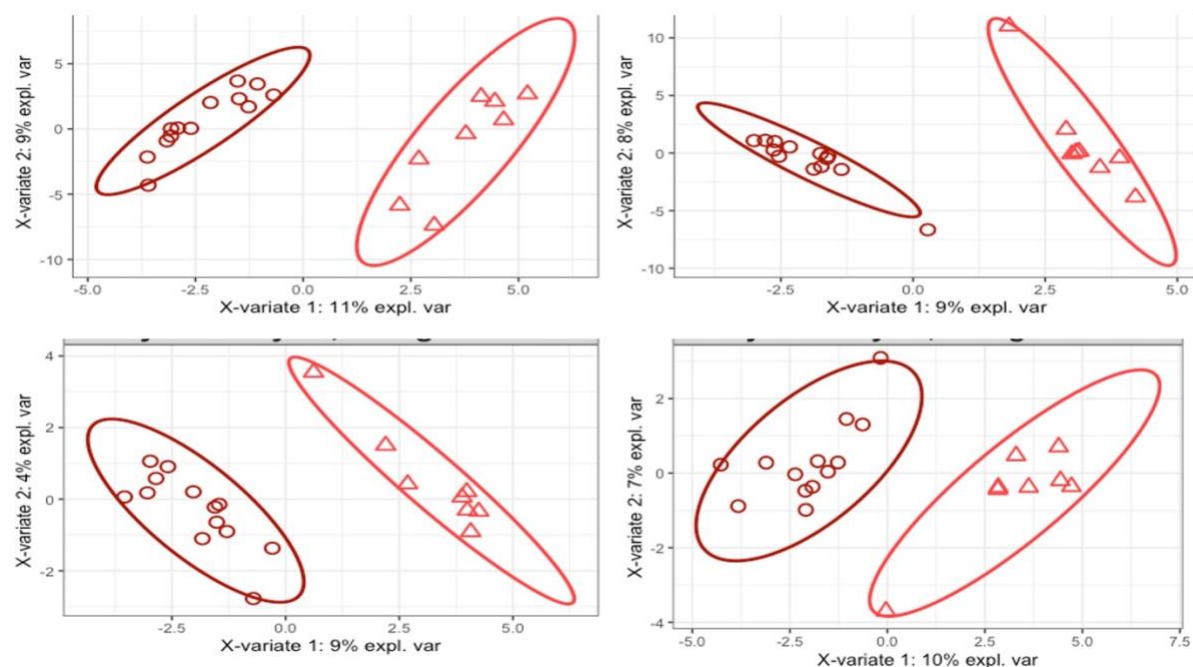


Figure S10: Sparse Partial Least Squares Discriminant analysis of patient randomised to ketogenic feeding on Day 1 (red sphere) and day 10 (red triangle). Clockwise from top right: polar positive, non-polar positive, non-polar negative, polar negative. Error rates are <20% (10%, 12%, 15% and 10% respectively), suggesting plot is result of true variance. N=14 subjects in the ketogenic arm and n=15 subjects in the control arm.

Supplementary References

1. Domingo-Almenara X, Siuzdak G. Metabolomics Data Processing Using XCMS. *Methods Mol Biol* 2020;**2104**:11-24.
2. Broadhurst D, Goodacre R, Reinke SN, et al. Guidelines and considerations for the use of system suitability and quality control samples in mass spectrometry assays applied in untargeted clinical metabolomic studies. *Metabolomics* 2018;**14**(6):72.