The deep history of obesity and metabolic disease: The past informs the present, and the present informs the past.

Online symposium
and
networking event

Wednesday 26 May 2021

INFORMATION PACK

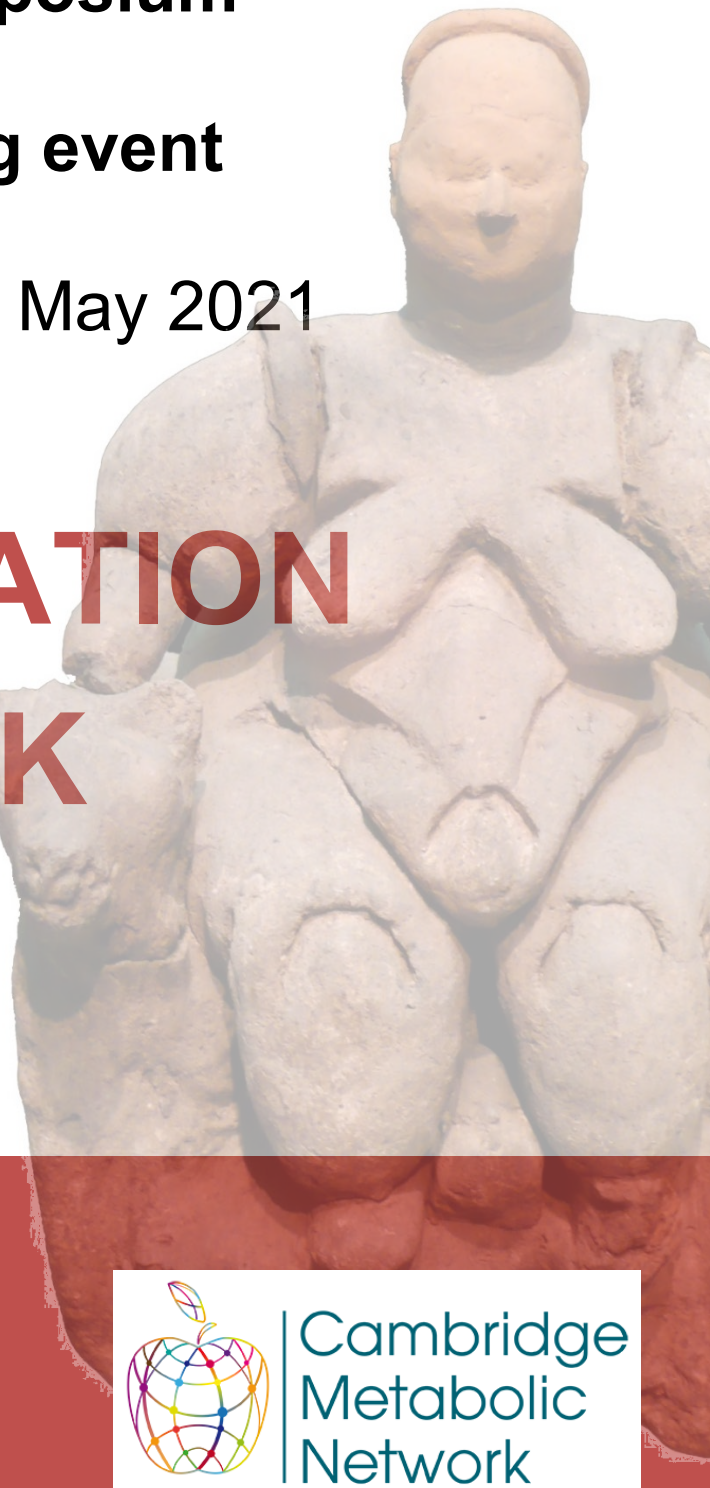

Image: Seated Woman of Çatalhöyük, Museum of Anatolian Civilizations, Ankara, Turkey, c. 6000 BC, Credit: Nevit Dilmen via Wikimedia commons under CC-BY3.0 Unported licence

UNIVERSITY OF CAMBRIDGE
Department of Archaeology

Cambridge Metabolic Network

Contents

Foreword

Welcome to our online symposium and networking event.

We had hoped to have been able to meet face-to-face, but whilst the pandemic has prevented us from doing so, it has also created an exciting opportunity allowing over 200 participants from all over the globe to join us in the virtual world.

We often assume that obesity and associated metabolic problems and diseases (e.g., type 2 diabetes, cardiovascular diseases) were rare until the last century, and largely the preserve of the wealthy and privileged in the past.

While an increase in rates of obesity and metabolic disorders in recent decades is undeniable, the assumption that this is a largely recent phenomenon underpins our current understanding, shaping how we research causes and treatment and wider societal perspectives on body size. However, depictions of obese people date back over 20,000 years to our hunter-gatherer predecessors and historical records attest the antiquity of metabolic disorders over millennia.

New theoretical perspectives that recognise the role of early life conditions and intergenerational factors in shaping lifelong metabolism, body size and composition suggest that in the past, metabolic disorders may have been more common than we currently recognise.

Developments in metabolomics, proteomics, lipidomics, genetics, and new lines of archaeological investigation, as well as insights from evolutionary perspectives and from animal models offer immense potential to revisit our understanding of, and evidence for, obesity and related conditions in the human past.

This interdisciplinary event, organised by the Cambridge Metabolic Network in collaboration with the Department of Archaeology, aims to draw together perspectives on obesity and metabolism from deep history to the present day. We hope it will provide a forum for exchange of ideas across disciplines to stimulate new perspectives on how the past can inform the present, and the present can inform the past.

Ultimately, the aim is to improve our understanding of the causes, prevention and treatment of metabolic disorders.

Professor Sir Stephen O'Rahilly
Chair – Cambridge Metabolic Network

Dr Emma Pomeroy
Department of Archaeology, Cambridge

Cambridge Metabolic Network

UNIVERSITY OF CAMBRIDGE
Department of Archaeology

Harassment, trolling, and unethical or abusive behaviour

The organisers have taken reasonable steps to ensure that issues such as trolling, hacking, abusive behaviour and comments will be dealt with swiftly and appropriately should they arise.

Whilst we welcome discussion, debate, networking and engagement within the symposium, participants should conduct themselves with professionalism, showing all other participants respect, courtesy and consideration. Any form of harassment, discrimination and bullying is unacceptable and will not be tolerated.

If a session is compromised, such as through abusive behaviour, we will remove those attendees and potentially end the session if necessary.

By registering for or speaking at this event, you are agreeing to adhere to this statement.

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Programme

09.45-10.00 Professor Sir Stephen O'Rahilly (Cambridge, UK) - Welcome and introduction

10:00-10.30 Dr Giles Yeo (Cambridge, UK) **-** 'Paleo-fantasy'

10.30 - 11.30 Markers of metabolic disease both past and present

Chairs: Professor Sir Stephen O'Rahilly and Antonia Hufnagel *(Cambridge, UK)*

- **Professor Matthew Collins** (Cambridge, UK) - Can the past shine a light on metabolic health?
- **Dr Richard Kay** (Cambridge, UK) - Peptidomics: dragging plasma insulin analysis out of the dark ages
- **Dr Albert Koulman** (Cambridge, UK) - Measuring metabolites to understand nutrition and malnutrition
- **Professor Mike Murphy** (Cambridge, UK) - Modern metabolomics and mitochondrial biology

11.30 – 11.45 BREAK

11.45 - 12.45 Flash Talks from submitted abstracts

Chair: Professor Matthew Collins *(Cambridge, UK)*

12.45 – 14.00 LUNCH AND NETWORKING OPPORTUNITIES

14.00 – 14.45 Environments, genotypes and phenotypes in the aetiology of metabolic disorders

Chairs: Professor Sue Ozanne and Dr Alex Mörseburg *(Cambridge, UK)*

- **Professor Peter Shepherd** (Auckland, New Zealand) - The CREBRF R457Q variant: An example of a population specific gene variant impacting on obesity and type-2 diabetes risk
- **Dr Eleanor Raffan** (Cambridge, UK) - Lessons on obesity biology from man's best friend
- **Professor Jonathan Wells** (London, UK) - A life-course and intergenerational perspective on obesity and diabetes before agriculture

14.45 – 15.00 BREAK

15.00 – 15.45 Past and present perspectives on the link between metabolic and infectious diseases

Chairs: Dr Giles Yeo and Dr Emma Pomeroy *(Cambridge, UK)*

- **Professor Sir Stephen O'Rahilly** (Cambridge, UK) **-** Obesity and COVID-19
- **Dr Sarah Inskip** (Leicester, UK) - Assessing the relationship between stable carbon and nitrogen isotope ratios and tuberculosis infection in past populations

15.45 – 16.15 Dr Herman Pontzer (Duke University, North Carolina, USA)
Healthy as the Hadza: Diet, Activity, and Metabolism in Hunter-Gatherers and other Subsistence Communities

16.15 – 16.30 Closing remarks

16.30 - 17.00 Networking

Speaker Biographies

(in alphabetical order)

Professor Matthew Collins

Matthew Collins is a Niels Bohr Professor at the University of Copenhagen and McDonald Professor in Palaeoproteomics at Cambridge University. Prior to joining Cambridge he was Professor of Biomolecular Archaeology at the University of York where he founded BioArCh, a collaboration between the departments of biology, chemistry and archaeology (BioArCh: Biology, Archaeology, Chemistry). His research focuses on the persistence of proteins in ancient samples, using modelling to explore the racemization of amino acids and thermal history to predict the survival of DNA and other molecules. Using a combination of approaches (including immunology and protein mass spectrometry) his research detects and interprets protein remnants in archaeological and fossil remains.

Dr Sarah Inskip

Sarah Inskip is a researcher based at the University of Leicester interested in the integration of data obtained from archaeological human skeletal remains with historical and modern health narratives. She undertook her MA in Osteoarchaeology at the University of Southampton, and after this, her doctoral research focused on activity-related skeletal changes and the emergence of Islamic identity in Southern Iberia (700-1200AD). During this time, she also became interested in understanding the origins and spread of Hansen's Disease (leprosy) in England through the use of osteological and biomolecular methods. She is currently the PI on the UKRI-FLF project Tobacco, Health and History, which takes an interdisciplinary approach to assess how the arrival and commodification of tobacco in the 16th century altered disease patterns in Western Europe, including tuberculosis, cancers, vitamin deficiencies and dental disease.

Dr Richard Kay

Richard Kay joined the Wellcome-MRC Institute of Metabolic Science (IMS-MRL) in 2016 to set up a peptidomics facility to support gut hormone peptide research. Prior to 2016 he worked at LGC in Fordham (just outside Cambridge) developing quantitative mass spectrometric methods to measure peptide drugs in preclinical and clinical studies to GLP and GCP standards. Since joining the IMS-MRL, he and his team have developed a world class peptidomics laboratory, and have published many papers on plasma insulin and plasma peptidomics analysis.

Dr Albert Koulman

Albert Koulman studied pharmaceutical science in Groningen (the Netherlands) and did his PhD in natural product analysis. At the end of his PhD, Albert started working on metabolomics and since then worked on plants, fungi, sheep and cows. In 2007 he moved to Cambridge and his work shifted to humans and model systems, developing methods focussed on lipid metabolism and nutritional biomarkers. By developing and applying analytical methods, he has contributed to more than 100 publications. Currently he heads the core Metabolomics and Lipidomics Laboratory as well as the Nutritional Biomarker Laboratory at the University of Cambridge.

Professor Mike Murphy

Mike Murphy received his BA in chemistry at Trinity College, Dublin in 1984 and his PhD in Biochemistry at Cambridge University in 1987. After stints in the USA, Zimbabwe, and Ireland he took up a faculty position in the Biochemistry Department at the University of Otago, Dunedin, New Zealand in 1992. In 2001 he moved to the MRC Mitochondrial Biology Unit in Cambridge, UK (then called the MRC Dunn Human Nutrition Unit) where he is a programme leader. Murphy's research focuses on the roles of reactive oxygen species in mitochondrial function and pathology. In particular he has pioneered the targeting of bioactive and probe molecules to mitochondria *in vivo*. This general methodology is now widely used. Prominent mitochondria-targeted compounds are antioxidants, such as MitoQ, which protects against oxidative damage in ischaemia-reperfusion injury. Murphy and Rob Smith developed MitoQ as an oral drug which has been used in two Phase II trials so far. This work established mitochondria as a relevant drug target and opened up the field of mitochondrial pharmacology. The Murphy group has gone on to create MitoSNO, a mitochondria-targeted nitric oxide donor which is now being developed as a potential therapy for cardiac ischaemia-reperfusion injury, and MitoG to treat diabetes. Recently his work has extended to determining the mechanism by which mitochondria produce free radicals during ischaemia-reperfusion injury in heart attack and stroke. Murphy is Professor of Mitochondrial Redox Biology at the University of Cambridge, a Wellcome Trust Investigator, an MRC Investigator, an honorary research Professor at the University of Otago, New Zealand, a recipient of the Keilin Medal from the Biochemical Society, an honorary Fellow of the Royal Society of New Zealand and a Fellow of the Academy of Medical Sciences (FMedSci). He has published more than 390 peer reviewed papers, which have garnered more than 50,000 citations and he has an h-index of 117.

Professor Sir Stephen O'Rahilly

Stephen O'Rahilly's research has been concerned with the elucidation of the fundamental mechanisms underlying obesity, insulin resistance and Type 2 diabetes and the translation of those discoveries into improvements in patient care. His work has uncovered several previously unrecognised genetic causes of these diseases including some that are amenable to specific treatments. He graduated in Medicine from University College Dublin in 1981. From 1982 to 1991 he undertook postgraduate clinical and research training in general medicine, diabetes and endocrinology in London, Oxford and Harvard. In 1991 he obtained a Wellcome Trust Senior Clinical Fellowship and established his laboratory at the University of Cambridge. In 1996 he was appointed to a newly created Chair of Metabolic Medicine and in 2002 to the Chair of Clinical Biochemistry and Medicine. He is Co-Director of the Wellcome-MRC Institute of Metabolic Science (IMS), the establishment of which he led. Within the IMS, he is Director of the MRC Metabolic Diseases Unit and the Metabolic Research Laboratories of the University of Cambridge. He is also Scientific Director, NIHR Cambridge Biomedical Research Centre, Honorary Consultant Physician at Addenbrooke's Hospital, a Fellow of Pembroke College, Cambridge and an Associate Faculty Member of the Wellcome Sanger Institute. He has undertaken a substantial body of public service work for research charities, educational institutions and governmental organisations in the UK, Ireland and elsewhere.

He has won many awards including the Heinrich Wieland Prize, the Inbev Baillet Latour Prize, the Zülch Prize, the European Hormone Medal, the first EASD/Novo Nordisk Foundation Diabetes Prize for Excellence and the Banting Medal for Scientific Achievement. He gave the Harveian Oration of the Royal College of Physicians, London, in 2016. He was elected to the Royal Society in 2003, a Foreign Associate of the National Academy of Sciences USA in 2011, is an Honorary Member of the German Society for Internal Medicine

and the Royal Irish Academy. He also holds honorary Doctorates from the Universities of Dundee, Warwick, Buckingham, University College Dublin and the Royal College of Surgeons in Ireland. He was appointed Knight Bachelor in 2013.

Dr Herman Pontzer

Herman Pontzer is Associate Professor of Evolutionary Anthropology and Research Associate and Professor of Global Health at Duke University, North Carolina, USA. His interest is in investigating how our species' evolutionary past shapes our lives today. His team conducted the first measurements of daily energy expenditure in traditional hunter-gatherers and in non-human apes, with findings that have challenged the way we think about diet, exercise, metabolism, and health. Dr Pontzer's new book, *Burn: The Misunderstood Science of Metabolism*, was published in March 2020.

Dr Eleanor Raffan

Eleanor Raffan is a vet and scientist who studies spontaneously occurring disease in veterinary species to improve understanding of obesity and related diseases. Having initially worked as a GP vet and in specialist referral practice she has focussed mainly on research since 2010, currently leading a research group as Lecturer in Systems Physiology at the Department of Physiology, Development and Neuroscience at the University of Cambridge.

Professor Peter Shepherd

Professor Peter Shepherd is based at the University of Auckland. The main focus of his lab's research is on cell signalling pathways in metabolic disease and cancer but more recently has been involved in a nationwide research programme in Aotearoa/New Zealand investigating how population specific genetic factors might affect the trajectory of metabolic disease in Polynesian peoples.

Professor Jonathan Wells

Jonathan Wells is Professor of Anthropology and Paediatric Nutrition at ICH. His empirical work is primarily focused on the causes and consequences of variability in paediatric body composition, i.e., lean and fat mass accretion. Many of his current studies are in low- and middle-income countries, investigating how life-course exposure to the double burden of malnutrition shapes the risks of non-communicable disease in later life, and how improved nutrition can reduce those risks. To help interpret empirical data, he has developed an evolutionary perspective on human nutrition, growth and development.

Dr Giles Yeo

Giles Yeo got his PhD from the University of Cambridge in 1998, after which he joined the lab of Prof Sir Stephen O'Rahilly, working on the genetics of severe human obesity. Giles Yeo is now a programme leader at the MRC Metabolic Diseases Unit in Cambridge and his research currently focuses on the influence of genes on feeding behaviour & bodyweight. In addition, he is a graduate tutor and fellow of Wolfson College, and Honorary President of the British Dietetic Association. Giles is also a broadcaster and author, presenting science documentaries for the BBC's 'Horizon' & 'Trust Me I'm A Doctor'. His first book 'Gene Eating' was published in December 2018, and his second book 'Why Calories Don't Count' comes out in June 2021. Giles was appointed a Member of the Order of the British Empire (MBE) in the Queen's 2020 birthday honours for services to 'Research, Communication and Engagement'.

Speaker Abstracts

(in order of sessions)

Opening Keynote – Dr Giles Yeo
'Paleo-fantasy'

Paleo, so named because it supposedly mimics the diet of indigenous populations prior to the agricultural revolution, is a popular diet with a backstory that is epic in time-scale. Its premise is that for the vast majority of human existence, we subsisted as hunter-gatherers, until the agricultural revolution some 12,000 years ago, which brought about huge changes to our diet. Since diet-related illnesses are responsible for much of the chronic and non-communicable disease burden today, and no evidence of such conditions can be seen in the Palaeolithic skeletal record, the blame for our contemporary woes must lie with the post-agricultural diet. Hence, the solution must surely be to shift back to a pre-agricultural, so-called 'ancestral', subsistence. In this talk, I will discuss why, while the paleo movement is nothing more than fantasy, it still has such a large and evangelical following.

10.30 - 11.30 Markers of metabolic disease both past and present

Professor Matthew Collins (Cambridge, UK) - Can the past shine a light on metabolic health?

Danish astronomer Tycho Brahe was large. His bone collagen isotopes suggest a rich diet, and his death followed 'another' large banquet in Prague in 1601. Careful analysis of his skeleton exhumed in 2010 suggested a causal link between his rich diet and mortality. Tycho was special, not only because he was in receipt of an astronomical amounts of research funding (1% of GDP for his observatory on the island of Veen in the Øresund), but because he is one of a handful of ancient skeletons who have been diagnosed with Metabolic Syndrome based upon skeletal analysis.

Only 7% of those that have ever lived are alive today. Many of those that have passed, lived lives of great inequality, and some lived on what seem to be extraordinarily narrow diets. This presentation will provide a broad overview of what tools we are using to explore health and diet in the past. At present we lack a clear picture of the prevalence of obesity and whether it was indeed confined historically to the 'elites' of the population. This gap in our knowledge prevents a more comprehensive understanding of health, inequality, and the role of food production. Can modern studies help illuminate the past and can the past can shed light metabolic health?

Dr Richard Kay (Cambridge, UK) - Peptidomics: dragging plasma insulin analysis out of the dark ages

The methods used to quantify circulatory insulin and C-peptide have almost exclusively employed immunological based approaches, using pairs of antibodies to detect the peptides in plasma or serum. The marriage of liquid chromatography and mass spectrometry (LC-MS) has enabled an alternative approach to insulin analysis. LC-MS methods are now available that can quantify endogenous insulin and differentiate it from its synthetic variants. Whilst the focus of LC-MS methodologies have been on synthetics, its application to C-peptide and proinsulin processing intermediates has not been fully explored. We demonstrate that LC-MS

approaches can help explain spurious C-peptide immunoassay determinations, and aid in clinical diagnoses where aberrant insulin levels are involved.

Dr Albert Koulman (Cambridge, UK) - Measuring metabolites to understand nutrition and malnutrition

In this talk I will highlight the development of cutting-edge analytical methods to measure specific metabolites and nutrients to understanding metabolism and nutrition. The current technical challenge is to comprehensively analyse all metabolites and lipids (aka metabolomics and lipidomics), which demands developments in experimental design, sample preparation, analysis, data processing and bioinformatics. These approaches can help us to understand what a healthy response is to a diet and when it is moving to malnutrition. I will also show how long-term effects of early life nutrition can be measured and how this can help us to understand how the body adapts to its future environment.

Professor Mike Murphy (Cambridge, UK) - Modern metabolomics and mitochondrial biology

Over the past decade mitochondrial function and dysfunction have turned out to be so central to biomedical questions that we are no longer surprised to read papers where mitochondria are involved in pathways as diverse as innate immunity, oxygen sensing and response to viral infections. Consequently, we want to know more about how mitochondria function and go wrong in vivo. Furthermore, as mitochondria are cropping up in so many human pathologies there is a growing interest in developing therapies focussed on preventing mitochondrial damage. In both these areas the changes in core mitochondrial metabolites seem to be critical. Here I will survey some recent developments in our understanding of how mitochondrial metabolites may contribute to health and disease.

11.45 - 12.45 Flash talks from submitted abstracts

Abstract No:	**1**
Presenting Author	**Miss Miranda Evans**
Position	PhD Student
Affiliation	Department of Archaeology, University of Cambridge
Co-authors	Francesca Mazzilli (Cambridge Archaeological Unit), Oscar Aldred (Cambridge Archaeological Unit), Benjamin Neil (Cambridge Archaeological Unit), Chris Evans (Cambridge Archaeological Unit), Richard Hagan (BioArCh, Department of Archaeology, University of York), Matthew Collins (McDonald Institute for Archaeological Research, University of Cambridge and The GLOBE Institute, Faculty of Health and Medical Sciences, University of Copenhagen), Jessica Hendy (BioArCh, Department of Archaeology, University of York)
Abstract Title	**Eating on the Edge of the Empire: The Proteomics of Pottery in Roman Britain**
Abstract	What we eat is intrinsic to our health, yet cuisine is one of the most intangible aspects of the archaeological record. The detection of cuisine is often based on rare cases of exceptionally well preserved food remains, assumptions regarding the function of ceramic vessels, or on textual evidence usually written for and by the elite. Proteomics has the ability to detect ingredients with tissue and taxonomic specificity, and in some cases food preparation practices. Ceramics are one of the most robust and ubiquitous finds in the archaeological record. In this pilot investigation a proteomic approach was used to investigate the dietary proteins preserved in ceramics, their residues and dental calculus at the Romano British site of Northstowe, in an attempt to better characterise diet and cuisine on the edge of the Roman Empire.

Abstract No:	2
Presenting Author	**Dr Claire Meek**
Position	Senior Clinical Research Associate & Group Leader
Affiliation	Wellcome-MRC Institute of Metabolic Science, University of Cambridge
Co-authors	Samuel Furse, Laura C Kusinski, Alison Ray, Huw EL Williams, Albert Koulman, Claire L. Meek
Abstract Title	**The next generation: influence of lipid metabolism on spermatozoa structure and function**
Abstract	Male fertility, as manifest by the quality of spermatozoa, is closely linked to metabolic health, but the mechanisms underlying this association remain unclear. We aimed to describe lipid species abundance across three compartments (spermatozoa, seminal fluid and blood serum) and to identify any differences in states of male subfertility. Methods: Men under preliminary investigation for subfertility were recruited at an NHS clinic to an approved prospective observational study. Men had venesection (n=60) and provided a semen sample (n=30), subject to strict acceptance criteria, for analysis of spermatozoa count and motility. Blood serum, spermatozoa and seminal fluid were frozen for later batch lipidomics analysis. Results: Spermatozoa and seminal fluid were comparable in lipid composition, but showed marked differences with the blood lipidome. Spermatozoa had high abundance of ceramides, certain polyunsaturated fatty acids (C20-22), and certain phospholipids (sphingomyelin, phosphoethanolamines and related plasmalogens) and low abundance of phosphatidylcholines, cholesterol and triglycerides. Spermatozoa with low motility maintained concentration gradients of fewer lipid species between blood and spermatozoa compartments. Conclusions: Spermatozoa are abundant in multiple lipid species which contribute to a rigid cell membrane, likely essential for propulsion and optimal fertility. Lipid metabolism across three compartments shows reduced regulation in states of male subfertility.

Abstract No:	3
Presenting Author	**Dr Kate Lee**
Position	Research Fellow
Affiliation	University of Auckland
Co-authors	Sanaz Vakili (University of Auckland) Professor Peter Shepherd (University of Auckland)
Abstract Title	**A mouse model of Māori and Pacific-specific CREBRF gene variant.**
Abstract	A Māori and Pacific-specific coding-SNP in the CREBRF gene rs373863828 is associated with a significant increase in BMI and yet paradoxically, a decreased incidence of T2D. The mechanism by which this variant drives these physiological associations is unknown. CREBRF is involved in regulation of bZip transcription factors that are ubiquitously expressed and have roles in several key cellular processes. Our in vitro work has confirmed the variant changes levels of CREBRF-regulated mRNA, indicating perturbation in these pathways. As glucose metabolism is regulated by the synchronous activities of many organs; we need a whole-body model system to study this variant and we have therefore developed a mouse model in the C57BL/6J background. Considering the effects of the variant are subtle, we hypothesised more pronounced phenotypes may manifest over a lifetime. We have done initial characterisation on older (20-month) mice and show the R457Q mice to have lower fat to lean ratio in body composition and in males this is accompanied by increased grip strength and rotarod performance. In addition, we observe lower serum myostatin levels. Glucose metabolism was also affected. These models will be useful for studying the molecular mechanisms by which the CREBRF variant can confer metabolic protection.

Abstract No:	4
Presenting Author	**Dr Mark Tomás McAuley**
Position	Senior Lecturer
Affiliation	University of Chester
Co-authors	N/A
Abstract Title	**The nexus between obesity, cholesterol metabolism and evolution**
Abstract	The population of the world is ageing. Despite this demographic shift in favour of older people, morbidity among this group is high. Obesity is emerging as a significant determinant of health within older people. Obesity has a pleiotropic effect on metabolism. However, the impact obesity has on cholesterol metabolism requires greater recognition. Disrupted cholesterol metabolism increases our risk of cardiovascular disease (CVD). CVD is a classic example of a disease which is the clinical manifestation of a decline in the force of natural selection which occurs during ageing. The aim of this talk is to critically discuss the nexus between obesity, cholesterol metabolism, and evolution. In so doing I will reveal the impact of this tri-directional relationship for healthy ageing.

Abstract No:	5
Presenting Author	**Dr Gerard Bryan Gonzales**
Position	Assistant Professor
Affiliation	Wageningen University
Co-authors	Debbie Thompson and the CHANGE consortium
Abstract Title	**Metabolic consequences of childhood severe undernutrition during adulthood**
Abstract	Child undernutrition and adult non-communicable diseases (NCDs) are major public health problems. While convincing evidence links prenatal undernutrition with increased risk of NCDs, less is known about the long-term sequelae of childhood undernutrition. In a recent systematic review, we found that severe undernutrition or famine during childhood is associated with increased risk of cardiometabolic NCDs, suggesting that developmental plasticity extends beyond prenatal life. However, the mechanisms driving this increased risk remains unknown. To understand these mechanisms, we evaluated the (targeted) metabolomic profiles of survivors of childhood severe undernutrition 7 years (ChroSAM cohort, Malawi) and 30 years (LION cohort, Jamaica) after they have been treated and nutritionally stabilized. In the ChroSAM cohort, although the metabolome was not distinguishable from controls in multivariate analysis, we found that lean mass among childhood undernutrition survivors is lower than controls and was significantly mediated by plasma tryptophan concentrations. On the other hand, adult undernutrition survivors in the LION cohort have distinct metabolic profiles that suggest reduced β-oxidation and greater risk of type 2 diabetes (BCAAs, KT ratio, urea cycle metabolites) compared with controls. These indicate that early childhood undernutrition exposure has long-term metabolic consequences that may worsen with age and require targeted clinical management.

Abstract No:	6
Presenting Author	**Mr Ruairidh Macleod**
Position	Graduate student
Affiliation	Department of Archaeology, University of Cambridge; The Globe Institute, University of Copenhagen; Genetics, Evolution and Environment, University College London
Co-authors	Matthew Collins, Department of Archaeology, University of Cambridge; The Globe Institute, University of Copenhagen
Abstract Title	**Rock Solid Evidence: Lithiasis as a source of biomolecular data, in particular from sperm whales**
Abstract	Evidence of commensal microbial communities and metabolism is severely limited in the archaeological record so far, though one potential data source is in lithiasis pathologies where mineralised internal calculi may effectively preserve relevant biomolecules. We will discuss metagenomic data from DNA sequencing of ambergris as an example of this. Ambergris is a fecalith produced by sperm whales that is highly valued in perfumery, though the underlying mechanism for its production remains enigmatic. We will also discuss our attempts to identify microbial roles within the synthesis of ambrein, the primary component of ambergris, and the implications of our approach for future research.

Abstract No:	7
Presenting Author	**Dr Denes Stefler**
Position	Senior Research Fellow
Affiliation	Department of Epidemiology and Public Health, University College London
Co-authors	Daniel Brett - School of Slavonic and East European Studies, University College London, London, United Kingdom; Eszter Sarkadi Nagy - Department of Nutritional Epidemiology, National Institute of Pharmacy and Nutrition, Budapest, Hungary; Ewa Kopczynska - Institute of Sociology, Jagiellonian University, Krakow, Poland; Stefan Detchev - Department of History, South-West University, Blagoeavgrad, Bulgaria; Sofia Malyutina - Novosibirsk State Medical University Novosibirsk, Russia; Ruzena Kubinova - National Institute of Public Health, Prague, Czech Republic; Andrzej Pajak - Department of Epidemiology and Population Studies, Jagiellonian University Collegium Medicum, Krakow, Poland; Anne Peasey; Hynek Pikhart; Martin Bobak - Department of Epidemiology and Public Health, University College London, London, United Kingdom.
Abstract Title	**Traditional Eastern European diet and its relationship with mortality: results from the HAPIEE study**
Abstract	**Background.** Cardiovascular disease (CVD) and cancer mortality rates in Eastern European countries are among the highest in the world. Although unhealthy diet is an important risk factor, traditional eating habits and their health effects in this region have not yet been explored. This analysis assessed the relationship between traditional dietary pattern and mortality from all-causes, CVD and cancer in Eastern European population-based cohorts. **Methods.** The traditional Eastern European diet was characterised based on dietary habits of rural communities who lived in the 1950s and 60s. Data from the Health, Alcohol and Psychosocial factors in Eastern Europe multi-centre prospective cohort study was used to assess the relationship between the traditional Eastern European diet score and mortality outcomes. **Results**. In multivariable adjusted models, participants with high adherence to the traditional Eastern European diet had significantly higher risk of all-cause (HR 1.20; 95% CI 1.05-1.38) and CVD deaths (1.32; 1.05-1.64) compared to those with low adherence. The association with cancer mortality was not significant (1.12; 0.90-1.40). **Conclusion.** Our results suggest that traditional eating habits may contribute to the poor health status, particularly the high CVD mortality rates, of populations in Eastern Europe. Adequate public health nutritional interventions in this region are essential.

Abstract No:	8
Presenting Author	**Dr Simon Stoddart**
Position	Reader in Prehistory
Affiliation	Department of Archaeology, University of Cambridge
Co-authors	Bruno Ariano, Giovanna Bagnasco, Caroline Malone, Rowan McLaughlin, Eoin Parkinson, Ronika Power, Jay Stock and Jess Thompson
Abstract Title	**Obesity in Neolithic Malta and Iron Age Etruria. Rhetoric or Reality?**
Abstract	Third millennium BC Malta is renowned for the artistic representation of human obesity. From precisely the same period, we have a biological data source from the disarticulated remains of c. 900 individuals (now analysed for pathology, isotopes and aDNA) and direct sources for their diet. The artistic representations suggest one reality whereas the human remains (even accounting for a variation on the osteological paradox) and food remains suggest another. We pose the same problem for first millennium BC Etruria, where the inhabitants were described by the Romans, their rivals, as obesus (obese) or pinguis (fat). We have artistic representation of the ancient Etruscans looking well fed, but presentation of the Etruscans as overweight was probably a deprecatory characterisation by their political rivals and conquerors. The Etruscans are known for their cemeteries, so if osteological evidence could provide answers, this would be the solution, alongside evidence of their food remains. We will very briefly present the scientific and artistic evidence for these alternative perspectives in these two distinctive societies of the ancient past and ask for assistance in finding osteological and other signatures of ancient obesity from these richly preserved ancient societies.

Abstract No:	9
Presenting Author	**Mr Jens Lund**
Position	PhD Student
Affiliation	Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
Co-authors	Zachary Gerhart-Hines, Christoffer Clemmensen, Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
Abstract Title	**The Overlooked Role of Energy Excretion in Human Body Weight Regulation**
Abstract	Introduction: While obesity propensity seems to be driven primarily by an increase in appetite, food intake-controlled overfeeding studies suggest that weight gain resistance might be a trait characterized by elevated energy expenditure and/or increased energy excretion. Aim: By reviewing the literature, we explored if variations in fecal and urinary energy loss play a physiologically relevant role in modulating human energy homeostasis. Observations: Since the 1980s, bomb calorimetry studies have consistently shown that fecal energy loss varies from around 1 – 11% in healthy humans. In the context of overfeeding, this can correspond to a fecal energy excretion of around 80 kcal/d in some individuals versus around 500 kcal/d in others. This marked difference significantly alters the relative level of overfeeding and could theoretically have a profound long-term impact on human fat mass. Perspectives: Calorie excretion via feces represents an understudied aspect of energy balance biology and is potentially a component that protects some individuals from obesity. Interestingly, animal studies have reported reductions in digestive efficiency in response to an elevated energy intake. This combined evidence highlights the need for future studies exploring whether increased calorie excretion is an evolutionary conserved mechanism against adiposity.

Abstract No:	10
Presenting Author	**Dr Amélie Beaudet**
Position	Lecturer
Affiliation	Department of Archaeology, University of Cambridge, Cambridge, UK
Co-authors	N/A
Abstract Title	**How did the human brain metabolism evolve?**
Abstract	Biological features and behaviours such as dietary flexibility, developmental plasticity and technological capabilities enabled our ancestors to accommodate changing environments. Cognitive abilities involved in these adaptive strategies are hypothesised to correlate with complex cerebral organization and prolonged brain maturation. However, these come at considerable cost. Besides the significant amount of energy invested by the mother during foetal and early postnatal brain growth, adult modern human brains require 20-25% of the basal metabolic rate for maintenance. Accordingly, the emergence of a human-like brain organization and growth pattern in the hominin lineage should have occurred concomitantly with substantial changes in brain metabolism. This project aims to track time-related variation in fossil hominin cerebral blood flow rate to understand how energetic demands of the brain evolve. Our preliminary results demonstrate that brain cost in Australopithecus, the putative ancestor of the genus Homo, is about three times lower than in extant humans (i.e., 6.0-7.5% of its basal metabolic rate). These results support a late emergence of the human-like brain metabolic pattern in the hominin lineage. Future analyses will tentatively relate these changes to fundamental behavioural innovations and dietary shift, such as stone-tool-assisted consumption of meat.

Abstract No:	11
Presenting Author	**Ms Nellissa Ling**
Position	PhD Student
Affiliation	University of Otago, New Zealand
Co-authors	Hallie Buckley, University of Otago, New Zealand Siân Halcrow, University of Otago, New Zealand
Abstract Title	**Gout and DISH in ancient populations of mainland East and Southeast Asia**
Abstract	Today, there is a high prevalence of joint conditions, gout and diffuse idiopathic skeletal hyperostosis (DISH), in the Asia-Pacific region. High prevalences of these conditions have also been found among ancient populations from the Pacific. However, there is a lack of knowledge of the occurrence of these conditions in prehistoric Asia, the people who are ancestrally linked to the Pacific. This study investigated the existence of gout and DISH among archaeological populations in Asia through a study of 321 adult skeletons from five archaeological sites, ranging from pre-Neolithic to the Iron Age (6000 to 1500 BP). To establish contributory factors to the development of these conditions, we investigated if early life stress, inferred through bone measurements, was related to gout and DISH development. Five cases of probable gout and three cases of possible DISH were found from two populations, Khok Phanom Di (Neolithic) and Non Ban Jak (Iron Age). Individuals with gout tended to have larger bone sizes, whereas individuals with DISH had some of the shortest long bone lengths. This study provides evidence for gout and DISH in mainland Southeast Asia and suggests that early life stress may not be a factor underlying gout development, but may be a contributing factor for DISH.

Abstract No:	12
Presenting Author	**Miss Josca Schoonejans**
Position	PhD researcher
Affiliation	Wellcome-MRC Institute of Metabolic Science, University of Cambridge
Co-authors	Blackmore HL, Ashmore TJ, Fernandez-Twinn DS, Ozanne SE, Wellcome-MRC Institute of Metabolic Science-Metabolic Research Laboratories, University of Cambridge
Abstract Title	**Maternal metformin intervention during obese pregnancy affects gonadal white adipose tissue biology in mouse offspring in a sex-specific manner**
Abstract	An obese diabetic intrauterine environment leads to increased risk of cardiometabolic disease. Metformin is used to treat gestational diabetes, but long-term studies investigating offspring effects are lacking. This study investigated white adipose tissue in offspring exposed to metformin in utero using a maternal diet-induced obesity model. Female C57Bl/6J mice were fed control (7% sugars, 3% fat) or high-fat diet (10% sugars, 20% fat) supplemented with condensed milk (55% sugars, 8% fat). Half of obese dams (Ob) were treated orally with metformin throughout pregnancy (Ob-Met). Offspring were weaned onto control diets. Male but not female 8-week-old Ob-Met offspring had increased adiposity compared to Con, with adipocyte hypertrophy, hyperplasia, insulin resistance and inflammation. By 12 months, both Ob and Ob-Met males had increased fat percentage and inflammation compared to Con. Although female 12-month-old Ob offspring had increased fat mass compared to Con, Ob-Met offspring showed even further increased adiposity, adipocyte hyperplasia, inflammation and insulin resistance. Intrauterine metformin did not correct adiposity in offspring of obese pregnancy and increased metabolic risk factors in a sex- and time-dependent manner. In males, metformin increased adiposity and adipose tissue dysfunction in young adult life, whereas in females this was not observed until 12 months of age.

14.00 – 14.45 Environments, genotypes and phenotypes in the aetiology of metabolic disorders

Professor Peter Shepherd (Auckland, New Zealand) - The CREBRF R457Q variant: An example of a population specific gene variant impacting on obesity and type-2 diabetes risk

Polynesia is a region covering hundreds of mainly small islands that are spread over an area of 25 million km^2. Despite this, related groups of Polynesian (Pacific peoples and Aotearoa/New Zealand Māori) and Oceanic peoples have populated virtually all of these islands over the last 2000-3000 years using their advanced seafaring skills. Factors associated with their migrations along with the later impacts of diseases brought by first contact with western societies has presented opportunities for the development of patterns of genetics that are enriched in or unique to these populations. The CREBRF R457Q variant is one such example. This is found at up to 30% MAF in these populations but absent in other populations globally. Several studies have shown that this variant is associated with a large increase in BMI and it has been suggested is associated with increased adiposity. Here we will present the work of a broad team of researchers in Aotearoa/New Zealand using human studies, transgenic animal models and cell based studies which together provide strong evidence that the CREBRF R457Q is not in fact an adiposity gene but is associated with a relative increase in lean mass instead. This would be more in line with the consistent finding that CREBRF R457Q is associated with a reduced risk of Type-2 diabetes despite the increase in BMI. However, this does not explain the high incidence of this gene variant in these peoples.

Dr Eleanor Raffan (Cambridge, UK) - Lessons on obesity biology from man's best friend

Dogs share many diseases with humans, and develop them whilst living in the same environments. Selective breeding has produced the extraordinary diversity seen between breeds - a side effect is that studying how genes link to disease is powerful in the species. We exploit those features to learn lessons about the fundamental control of body weight by studying pet dogs. I will outline recent studies in retriever breeds that demonstrate how a mutation in the gene POMC predisposes dogs to obesity by affecting both eating behaviour and energy expenditure, shedding light on a previously difficult to study area of the neurological control of appetite and explain how multi-breed studies illustrate the importance of genetically driven variability in appetite in controlling body weight.

Professor Jonathan Wells (London, UK) - A life-course and intergenerational perspective on obesity and diabetes before agriculture

Evolutionary perspectives on obesity have been dominated by genetic frameworks, but there is now compelling evidence that plastic responses within and across generations play a key role in its aetiology. This presentation will focus on potential biological mechanisms that could have driven ancient female obesity, as visualised during the palaeolithic through Venus figurines. I will emphasise (a) the role of climate and ecology in favouring variable levels of lean body mass, (b) the role of diet in stimulating fat deposition, (c) the role of social and ecological stress in shaping fat accumulation in different anatomical depots through the life-course, driving life-history trade-offs between metabolic health, reproduction and defence. Using these insights, I will suggest how the high levels of female body fat represented by the

Venus figurines could have occurred. The capacity of the placenta, to partially protect the fetus from physiological perturbations associated with maternal obesity and diabetes, suggests that these maternal phenotypes occurred sufficiently commonly to represent a selective pressure.

15.00 – 15.45 Past and present perspectives on the link between metabolic and infectious diseases

Professor Sir Stephen O'Rahilly (Cambridge, UK) - Obesity and COVID-19

Obesity has been reported to be strongly associated with poor clinical outcomes of COVID-19. In this talk I will discuss whether this interaction with obesity is specific for infection with the SARSCov2 virus and, if so, what possible mechanisms might underpin this. Infectious challenges have occurred throughout evolution with the current epidemic providing a unique opportunity to explore the interaction between an emerging infection and an over-nourished state.

Dr Sarah Inskip (Leicester, UK) - Assessing the relationship between stable carbon and nitrogen isotope ratios and tuberculosis infection in past populations

Tuberculosis is a chronic infectious disease that has affected humans for millennia and is a re-emerging health threat today. As well as causing primary and secondary infection in the body, most individuals with the disease suffer from metabolic wasting disease characterised by loss of body mass, especially of muscle. Even though tuberculosis can have a significant effect on metabolism, there has been little research exploring how stable isotope ratios that are informative about protein intake relate to TB infection in the past. This research aims to explore whether there is any relationship between stable isotope ratios of carbon and nitrogen as taken from collagen of rib and dentine samples and the presence of TB infection, as identified from skeletal lesions. We assess 260 men, women and children from Medieval Cambridge of which approximately 32 individuals have lesions consistent with TB infection. Overall, the results suggest a complex relationship where differences in socio-economic status, age of infection and disease duration are likely significant.

Closing Keynote - Dr Herman Pontzer (Duke University, North Carolina, USA) 'Healthy as the Hadza: Diet, Activity, and Metabolism in Hunter-Gatherers and other Subsistence Communities'

Hunter-gatherers and other small-scale subsistence communities are remarkably free of cardiovascular disease, diabetes, and other non-communicable disease, and are therefore used as models in public health. Yet the lessons drawn from these communities are often based on poor or outdated understanding of their lifestyle and physiology. Here, I discuss recent advances in the study of diet, daily activity, metabolic energy expenditure, and health drawn from field research with the Hadza hunter-gatherer community of northern Tanzania and other small-scale communities around the globe. These populations are physically active and also experience energetically costly pathogen burden, but their total daily energy

expenditures remain similar to more sedentary, aseptic, industrial populations. I discuss the implications of these results for tackling obesity and non-communicable disease in the developed and developing world.

PROGRAMME COMMITTEE

Miss Antonia Hufnagel, PhD student (Ozanne group), Wellcome-MRC Institute of Metabolic Science, Cambridge

Dr Alexander Mörseburg, Bioinformatician, Wellcome-MRC Institute of Metabolic Science, Cambridge

Professor Sue Ozanne, Professor of Developmental Endocrinology, Wellcome-MRC Institute of Metabolic Science, Cambridge

Dr Emma Pomeroy, Lecturer in the Evolution of Health, Diet and Disease, Department of Archaeology, Cambridge

Professor Matthews Collins and **Dr Giles Yeo** as above

Angela Lumsdon, Co-ordinator, Cambridge Metabolic Network

Cambridge Metabolic Network

The Cambridge Metabolic Network, is one of several Strategic Research Initiatives and Networks funded by the University of Cambridge to build on areas of existing research strength by bringing together a critical mass of expertise from across the University Schools and beyond. The four key aims of this approach are to:

- address large-scale inter-disciplinary research challenges
- strengthen research collaborations and knowledge transfer across disciplines
- increase research capacity and profile by providing a platform for large-scale funding applications, recruitment and international research partnerships
- enhance our ability to influence national and international research, policy and funding agendas.

Joining the Cambridge Metabolic Network is free and is open to Cambridge-based researchers, at any level of their career, with an interest in research relating to metabolism. The online researcher directory allows people to search for network members with interests or expertise in particular areas. We encourage everyone based in Cambridge and with an interest in metabolism to join us at Network events and we are always open to new ideas from our members.

www.metabolism.cam.ac.uk

Contact: Angela Lumsdon, Network Co-ordinator, aml95@medschl.cam.ac.uk

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UNIVERSITY OF CAMBRIDGE
Department of Archaeology

The Department of Archaeology at Cambridge brings together an extraordinary community of people committed to advancing and transforming our understanding of the past through innovative research and teaching. We aim to convey that knowledge to society today, in ways that will change ideas, contribute to vital wider conversations and help to navigate a wiser, more sustainable future. Our core comprises some 30 long-term academic staff, 30-40 rising post-doctoral researchers, and more than 15 administrative and technical staff. We engage with the archaeology of most regions of the world, from the fens of East Anglia to Antarctica, including Eurasia, Africa, the Americas and Oceania, as well as most periods of the past.

Through recent appointments we have grown our strength in next-generation archaeological (including material) science and computational analysis, supported by an extensive suite of well-equipped laboratories. In addition to world-leading centres for Heritage and Ancient Near Eastern and Egyptian Studies, we have an established and now rapidly growing strength in Biological Anthropology and human evolutionary studies, with research ranging from fossil hominins to the behaviour, culture and phenotype of living populations.

The Department includes several additional individually renowned institutions. The McDonald Institute for Archaeological Research is the hub for all postdoctoral researchers in archaeology and adjacent fields at Cambridge, and a centre for attracting large-scale external research funding. The Cambridge Archaeological Unit has had an immense influence on field archaeology nationally and internationally. The Duckworth Collection contains one of the largest collections of human remains in the UK. We collaborate closely with colleagues in the nearby Museum of Archaeology and Anthropology, as well as many others across the arts, humanities and sciences.

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