RACMEM Québec 2022

Recent Advances & Controversies in the Measurement of Energy Metabolism

Centre des congrès de Québec — October 6-9, 2022

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Recent Advances & Controversies in the Measurement of Energy Metabolism (RACMEM)

RACMEM Québec 2022

Recent Advances & Controversies in the Measurement of Energy Metabolism

RACMEM is a forum for scientists from both academia and industry (nutritional/pharmaceutical) to meet and discuss the latest advances, controversies, and methodological issues related to the in-vivo assessment of energy expenditure and substrate oxidation in humans and animals.

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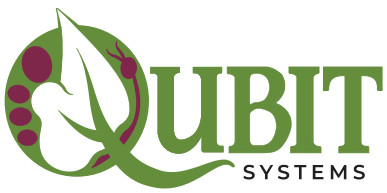

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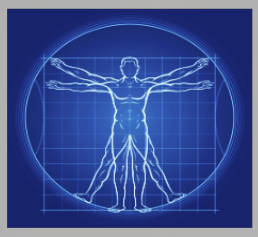

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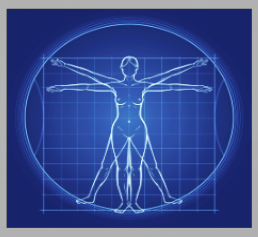

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- Columbia University, New York, NY USA
- University of Hohenheim, Stuttgart, Germany
- Christian-Albrecht University, Kiel, Germany
- University of Oslo, Oslo, Norway
- Pennington Biomedical Research Institute, Baton Rouge, LA, USA
- Ruijin Hospital Jiao Tong Univ. School of Medicine, Shanghai China

Current lab builds

- University of Leipzig, Leipzig, Germany
- Shanghai Institute for Biological Sciences, Hangzhou, China
- University of Louisville, Louisville, Kentucky USA
- Shandong University, Jinan, China

Additional information available upon request

Invited Speakers

Audrey Berguoignan, PhD, French National Center for Scientific Research (CNRS) & Pluridisciplinary Institute Hubert Curien (IPHC) University of Strasbourg

I am a Director of Research and lead a Joint International Research Laboratory between the CNRS IPHC in Strasbourg, France and the University of Colorado, Division of Endocrinology. Our research group conducts an interdisciplinary research program to understand the respective contribution of ecological, biological, socio-cultural and anthropological factors in the regulation of energy balance, weight and metabolic health. Our approach combines clinical research with unique models (e.g. remoted pre-industrial populations, hibernating mammals, prolonged fasting) and paradigms in extreme environments (e.g. space,) aiming to better understand both the determinants and mechanistic underpinnings of weight regulation and metabolic health. We further combine different state-of-the-arts methods to study energy and nutrient metabolism including whole-room calorimetry, indirect calorimetry, doubly labeled water method, radio-labelled and stable isotopic tracer techniques, accelerometry-based physical activity monitors, and *in vitro* experiments in cell cultures.

I am also a member of the Journal of Physiology (London) Editorial Board, a member of the Scientific Council of the French Space Agency, an expert in nutrition and metabolism for the French and European Space Agencies, and the Co-Chair of the Sedentary Behavior Council of the International Society for Physical Activity & Health (ISPAH).

Prof. **Denis P. Blondin** is an Assistant Professor and holder of a GSK Research Chair in Diabetes in the Faculty of Medicine and Health Sciences at the Université de Sherbrooke and researcher at the CHUS research centre. His research mainly focuses on tissue-specific energy metabolism in response to environmental or pharmacological stimuli and their impacts in obesity, type 2 diabetes and non-alcoholic fatty liver disease using a unique integration of medical imaging (PET and MRI), high-resolution respirometry, stable isotopic tracers and indirect calorimetry. His research is currently funded through NSERC, FRQS and FRQNT and is the recipient of a Fonds de recherche en santé du Québec Junior 1 Scholarship. His research team is now currently also investigating whether lifestyle interventions can be optimized based on circadian metabolic rhythmicity to prevent type 2 diabetes, as part of a Netherlands-Canada Type 2 Diabetes Research Consortium funded by ZonMw, the Dutch Diabetes Research Foundation, Health-Holland and CIHR.

Kevin M. Brindle, D. Phil., is Professor of Biomedical Magnetic Resonance at the University of Cambridge and a Senior Group Leader in the Cancer Research UK Cambridge Institute. He got his BA (Biochemistry,1978) and D. Phil (1982) in Oxford, before becoming a Royal Society University Research Fellow in 1986. He moved to a lectureship in Manchester in 1990 and in 1993 to a lectureship in Cambridge, where he became Professor in 2005. He was elected a Fellow of the Academy of Medical Sciences in 2012, a Fellow of the European Academy of Cancer Sciences in 2014, a Fellow of the International Society of Magnetic Resonance in 2020 and a Fellow of the Royal Society in 2020. He was President of the European Society for Molecular Imaging in 2018 and was awarded the European Society of Molecular Imaging Award in 2013 and the Gold Medal of the World Molecular Imaging Society in 2014.

Dr. **Alexandre Caron** is an Assistant Professor in the Faculty of Pharmacy at Université Laval. Dr. Caron holds the Canada Research Chair in NeuroMetabolic Pharmacology. His research focuses on the pathophysiological mechanisms that alter brain-organs communication in metabolic diseases and aims to identify new molecular and pharmacological targets to improve energy and glucose metabolism. After obtaining his PhD in Physiology-Endocrinology in 2015, Dr. Caron joined the laboratory of Dr. Joel Elmquist (University of Texas Southwestern Medical Center) first as a Diabetes Canada Postdoctoral Fellow and then as a Banting Postdoctoral Fellow. His postdoctoral work aimed at understanding how the central leptin-melanocortin system controls adipose metabolic and endocrine functions. In 2019, Dr. Caron received the NIDDK K99/R00 Award to study the sympathetic regulation of liver metabolism under the mentorship of Drs. Joel Elmquist and Shawn Burgess. In 2020, he came back home to the great White North to establish a laboratory dedicated to understanding how the nervous system controls energy and glucose metabolism.

Dr. **André Carpentier** is the Canada Research Chair in Molecular Imaging of Diabetes and professor and endocrinologist-lipidologist in the Departments of Medicine, Faculty of Medicine at the *Université de Sherbrooke*. He is the Scientific Director of the Centre de recherche du CHUS since December 2020. He was the director of the Province of Quebec Research Network on Cardiometabolic Health, Diabetes and Obesity (CMDO Network - https://www.rrcmdo.ca/en/) from 2012-2021 and is the new scientific co-lead of Diabetes Action Canada (https://diabetesaction.ca/). His research interests include: 1) the role of postprandial fatty acid metabolism in the development of type 2 diabetes and cardiovascular diseases; 2) the investigation of brown adipose tissue metabolism in humans; and 3) the anti-diabetic mechanisms of bariatric surgery. Dr. Carpentier has published more than 180 peer-reviewed manuscript publications cited over 16,500 times (H index 55). He is the recipient for multiple awards, including the 2011 Diabetes Young Investigator Award of the Canadian Society of Endocrinology and Metabolism, the CDA/CIHR Young Investigator Award in 2012 and the Canadian Lipoprotein Conference Physician-Scientist Award in 2014. He has been elected Fellow of the Canadian Academy of Health Sciences (FCAHS, 2015).

Kong Chen, PhD MSCI, is a trained biomedical engineer and a clinical investigator (PhD and MSCI both from Vanderbilt University in Nashville Tennessee). Started working on a metabolic chamber in 1993, he was recruited to the NIH in 2006 to build the intramural metabolic research program in Bethesda Maryland. He is currently a senior clinical investigator and co-directs the Metabolic Clinical Research Unit at the NIH Clinical Center. Kong's research focus is to understand physiological mechanisms of regulating energy balance and body weight in humans and to advance sensor technologies and analytical methods to monitor energy metabolism, body composition, physical activity, and sleep.

Abdul G. Dulloo studied at University of London (UK) for a Bachelor degree in Physiology and a PhD degree in Nutrition, followed by a 2-year postdoctoral research fellowship at Harvard Medical School in Boston (USA). He subsequently worked as a research associate in Physiology at University of Geneva in Switzerland before joining the University of Fribourg (Switzerland) as a lecturer in Physiology and Nutrition, and establishing the Laboratory of Nutritional Energetics and Body Composition Regulation. His current research interests in metabolic health (obesity & sarcopenic obesity, diabetes and cardiovascular risks) in Switzerland and in his native island of Mauritius encompass the following themes:

• Phenotyping for thrifty metabolic traits that predispose to obesity & cardiometabolic diseases

• Bioactive food ingredients as modulators of thermogenesis, fat oxidation and lean-fat partitioning

• Body composition dynamics and risks for sarcopenia in diabetes-prone people of Mauritius island

Marc-Emmanuel Dumas is Chair in Systems Medicine, jointly appointed between the Department of Metabolism, Digestion and Reproduction and the National Heart and Lung Institute at Imperial College London. He is head of the Section of Biomolecular Medicine, a 15-strong PI section which hosts state-of-the-art equipment dedicated to metabolomics (5 600 MHz NMR and 24 GC, LC and imaging MS systems), crystallisation science and tissue culture. He founded and is director of Imperial's Microbiome Network, a cross-faculty multidisciplinary network of excellence made of >60 PIs and their groups to consolidate research, teaching and public engagement activities around the microbiome. He is also a CNRS investigator and group leader at the European Genomic Institute for Diabetes in Lille, France and holds an Adjunct Professorship at McGill University's Genome Innovation Centre and Department of Human Genetics in Montréal, Canada. Research led by Professor Dumas focusses on the role of microbial metabolites in metabolic diseases to better understand the key challenges in integrative metabolism, blending metabolomics, genomics and microbiomics in human studies, animal models and cell-based assays. He focusses on the role of the microbiome in metabolic and cardiorespiratory diseases as well as in chronic inflammation, including neuroinflammation, and certain types of cancers.

Yosuke Yamada is Head of Section of Exercise Guideline, Department of Physical Activity Research at National Institutes of Biomedical Innovation, Health and Nutrition, Japan. He received his PhD in Human and Environmental Sciences at Kyoto University, Japan. He studied the doubly labeled water technique under Prof. Dale A. Schoeller at Nutritional Science, University of Wisconsin – Madison in 2009. His main research area is body composition, energy metabolism, and water turnover.

Dr. **François Haman**'s research deals with all aspects of human energetics. It focuses on how humans orchestrate metabolic fuel selection to improve chances of survival and increase performance in adverse environmental conditions such as changing climates and important modifications of dietary behavior. From mechanisms to applications, his work aims to establish principles that dictate fuel use and provide strategies to improve health/performance or chances of survival using alterations in dietary behaviors or physical training. Current work integrates a number of state-of-the-art metabolic methodologies to quantify human responses to climate change (heat/cold) and to provide dietary strategies to reduce the prevalence of obesity and obesity related diseases in First Nations communities of Northwestern Ontario.

Dr. **Mary-Ellen Harper** is the Director of the Ottawa Institute of Systems Biology (https://med.uottawa.ca/oisb/), and is also the Director of the NSERC-funded Metabolomics Advanced Training and International Exchange (MATRIX) graduate training program, based at Universities of Ottawa, McGill and Montréal http://www.matrixmetabolomics.ca.

Dr. Mary-Ellen Harper's research focuses on mitochondrial energetics – and specifically the mechanisms that impact the efficiency of energy transduction pathways in mitochondria. Beyond the implications for energy storage vs. energy release as heat, changes in the efficiency of energy conversion can affect oxidative stress and cell signaling. There are thus repercussions for the development and possible treatment of many diseases. Experimental approaches span from molecular *in vitro* studies, to mouse models, and to integrative translational studies in patient populations. She and her group have published over 200 peer-reviewed papers cited over 17,300 times.

Steven B. Heymsfield, M.D. is Professor and Director of the Body Composition-Metabolism Laboratory at the Pennington Biomedical Research Center of the Louisiana State University System in Baton Rouge. He is on the visiting faculty at Harvard Medical School and a former Professor of Medicine at Columbia University, College of Physicians and Surgeons. Dr. Heymsfield has published more than 700 peer-reviewed papers covering topics such as obesity, malnutrition, cancer, cachexia, body composition, and caloric expenditure. His contributions to the study of human nutrition led to the TOPS Award from The Obesity Society (TOS), the Rhoads Award from the American Society of Parenteral and Enteral Nutrition (ASPEN), the Robert H. Herman Memorial Award, American Society of Nutrition (ASN), and the George Bray Founders Award from TOS. Dr. Heymsfield is past president of ASPEN, ASN and TOS. He was recently appointed as an Amazon Scholar.

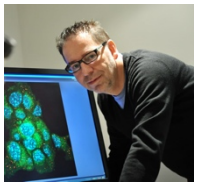
Leanne Hodson received her PhD from the University of Otago, New Zealand. She was awarded the Girdlers-Health Research Council of New Zealand Career Development Award to come and work with Professors Frayn and Karpe, University of Oxford. In 2011, she was awarded a British Heart Foundation (BHF) Intermediate Basic Science Research Fellowship and in 2015 she received a BHF Senior Basic Science Research Fellowship, which she has recently renewed. Her work focuses on issues pertinent to human metabolic health including the effect of obesity and obesity-related diseases, such as non-alcoholic fatty liver disease. Her work utilises a combination of human *in vivo*, *ex vivo* and *in vitro* models along with stable-isotope metabolic tracer methodologies, to provide insight into pathways that could be targeted to improve human health. Her expertise has

been recognised across different disciplines when she was awarded the Cuthbertson Medal from the Nutrition Society in 2017 and the Starling Medal from the Society of Endocrinology in 2018.

Lawrence Kazak completed his PhD at the University of Cambridge, MRC Mitochondrial Biology Unit, and post-doctoral work at the Dana-Farber Cancer Institute and Harvard Medical School. Lawrence joined McGill University as an Assistant Professor in 2018. His lab is focused on defining the molecular control of energy expenditure using thermogenic fat as a model system.

Mathieu Laplante, PhD, completed his graduate studies at Université Laval [2002-2007], where he developed an expertise in physiology, focusing his attention on metabolic tissues and the regulation of systemic glucose/lipid metabolism. During his postdoctoral training [2007-2011] at the Whitehead Institute for Biomedical Research (MIT), he studied the mTOR signaling pathway in relation to metabolism and cancer. Over these years, he generated several mouse models to study the role of mTOR in health and disease. At the end of 2011, he established his own laboratory at Université Laval. His research now focuses on the identification and characterization of novel proteins and secreted factors controlling metabolism and cell proliferation.

Dr. **Paul MacLean** Ph.D. is a tenured Professor at the University of Colorado School of Medicine with 25years of experience studying obesity and its metabolic complications. He has specific interests in the biological drivers of weight regain after weight loss, exercise as a strategy for weight loss maintenance, and understanding how obesity affects key aspects of women's health. Dr. MacLean's research in women's health has included studies of mammary gland development and its function during lactation, perinatal metabolic programming, the menopausal transition, and the risk for breast cancer. He is dedicated to building and supporting the broader research and educational enterprise on the CU Anschutz Medical Campus through the Colorado Nutrition Obesity Research Center, the Colorado Clinical Translational Science Institute, and the University of Colorado Cancer Center. Over the past 17years at the University of Colorado, Dr. MacLean has leveraged their resources to develop the next generation of scientists who will advance the treatment of obesity and its complications.



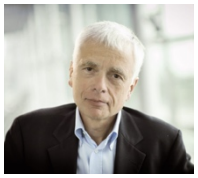
Dr. **André Marette** is a Professor of Medicine and researcher at the Heart and Lung Institute Hospital Center, and at the Institute of Nutrition and Functional Foods at Laval University. He holds a research Chair on the pathogenesis of insulin resistance and cardiovascular diseases (CVD).

Dr. Marette is an international renowned expert on the pathogenesis of insulin resistance and CVD and his research has advanced the understanding of the physiological and molecular mechanisms of inflammation, and opened new possibilities for prevention and treatment and type 2 diabetes and CVD. He is studying how nutrition and food ingredients can modulate the gut microbiota to protect against obesity-linked intestinal inflammation, fatty liver disease and type 2 diabetes. His research is funded by several Funding agencies in Canada (CIHR, NSERC, CFREF, Weston Fnd), in Quebec (FRQS, FRQNT) and in the US (NIH). He is holding a CIHR/Pfizer partnered Chair and a CIHR Foundation scheme grant and is a member of the Belgium Royal Academy of Medicine.

His research work has been published in >300 papers, reviews and book chapters and he was invited to give more than a hundred lectures at various national & international conferences in the last 10 years. He served as Editor-in-Chief for the *Am J Physiol: Endo & Metab.* from 2016-2022 and has authored two books in the last few years. Dr. Marette has received several awards for his work including the prestigious Charles Best Award and Lectureship from the University of Toronto for his overall contribution to the advancement of scientific knowledge in the field of diabetes.

Edward Melanson PhD, is a Professor of Medicine in the Division of Endocrinology, Metabolism and Diabetes, and Division of Geriatric Medicine. He is the Assistant Director of the Energy Balance Core Lab of the Colorado Nutrition and Obesity Research Center (NORC). In this capacity, he oversees the operation of the whole-room calorimeter, and is the director of the newly established Doubly Labeled Water Core Laboratory. The primary areas of research in Dr. Melanson's lab are 1) Understanding how lifestyle interventions, particularly adoption of regular exercise and alterations in sleep, impact physical activity, sedentary behavior, and health outcomes; 2) Developing new methods for assessing energy expenditure and physical activity in free-living humans, and 3) Studying the effects of endogenous sex steroids on bionergetics and metabolism. Dr. Melanson is also a co-investigator on the Colorado Clinical Center for the study of Molecular Transducers of Physical Activity Consortium (MoTrPAC) – Colorado Clinical Center, which will develop a national resource of the molecular responses to physical activity to advance the understanding of the mechanisms by which physical activity improves health. He is also a co-investigator on the Study pf Parkinson's Disease in Exercise Phase 3 Clinical Trial (SPARX3), the first randomized control trial designed to investigate the effects of moderate- and high-intensity aerobic exercise on disease progression in untreated patients with Parkinson's disease.

Associate Professor **Jennifer Miles-Chan** is Director of the Human Nutrition Unit at the University of Auckland, New Zealand - Australasia's only long stay residential nutrition facility with the capability of conducting diet-controlled interventions in order to demonstrate cause and effect relationships between diet, health and disease. Jennifer is an integrative physiologist whose research is focused on nutritional energetics and the regulation of body composition. Her experience covers a diverse range of settings: including a solid background in pre-clinical models and molecular analyses, clinical intervention studies, and experience in more epidemiological-type investigations. Jennifer is the Principal Investigator for the Metabolic Health Programme of the High Value Nutrition National Science Challenge, with her current research focused on two broad areas: (i) deciphering inter-individual variability in energy balance, and how this relates to inequities in our risk for metabolic disease; and (ii) prevention and treatment of metabolic disease in "at risk" population groups, including overweight and obesity, metabolic dysregulation, and type 2 diabetes – in other words, identifying why some of us are more susceptible to obesity and metabolic disease than others, and how we might be able to tailor prevention and treatment strategies accordingly.



Prof.Dr.med. **Manfred J. Müller** is as Gastroenterologist, Professor$_{em}$ of Human Nutrition and Internal Medicine and Venia legend for Biochemistry, Internal Medicine and Human Nutrition at the Institut für Humanernährung und Lebensmittelkunde (Institute of Human Nutrition and Food Science) Christian-Albrechts-Universität zu Kiel, Kiel. He authored of more than 650 papers published in peer-reviewed journals. His scientific interests are: control of energy expenditure and energy balance, functional body composition, prevention of obesity.

Jan Nedergaard is professor emeritus of physiology at The Department of Molecular Biosciences, The Wenner-Gren Institute, Stockholm University. Since 1975, his scientific efforts have concentrated on understanding the function and physiological significance of brown adipose tissue. He has played a role in the establishment of present basic concepts in brown adipose tissue research: - that brown adipocyte precursors are principally different from white adipocytes in that they display a myogenic gene expression phenotype (2007); - that the absence of brown adipose tissue is sufficient to cause or aggravate obesity (2009); - that existing radiological data implied that brown adipose tissue is present and active in adult humans (2007), – and that the gene expression profile observed in UCP1-expressing cells in white adipose depots is so distinct from that of classical brown adipocytes that these cells/depots should be considered to be of a different nature (“brite” or “beige” adipocytes) (2010). He is presently advocating the use of thermoneutrality for valid translation of mouse data to human conditions (2018), in metabolism – but also generally in clinically relevant mouse research models, and through this demonstrating that human brown adipose tissue is indeed of the same nature as classical mouse brown adipose tissue (2019). He has been dean of Biological Sciences at Stockholm University and is a Fellow of the Royal Swedish Academy of Sciences.

François Péronnet, Emeritus Professor at the Université de Montréal, obtained a Ph.D. in Physiology from the University of Montreal (1980) where he pursued his academic career as member of the Kinesiology department between 1976-2007, except for a two-year period (1996-98) spent at the Université Joseph Fourier (Grenoble, France) in the Laboratoire de bioénergétique fondamentale et appliquée. Trained in integrative physiology, his interest lies in the interplay of support systems that sustain energy release at rest and exercise by providing a steady flow of energy substrates and oxygen, and avenues for waste products to be recycled or excreted: the cardiovascular and pulmonary systems; energy substrate release, transport and oxidation, and fuel selection, with a particular focus on the oxidation of energy substrates ingested during prolonged exercise using indirect respiratory calorimetry and stable isotope tracer techniques.

Guy Plasqui is Associate Professor at the Department of Nutrition and Movement Sciences of Maastricht University

My research area is human energy metabolism with a special focus on physical activity. The goal is to integrate both nutritional and physical activity behavior to come to a better understanding of the regulation of human energy metabolism in health and disease. Unravelling the complex dynamics between different lifestyle and environmental factors on human energetics and health requires well controlled laboratory experiments using metabolic chambers together with measurements in daily life using wearable technologies and stable isotopes. Innovation and instrument validity in wearable sensor technologies is also a key part of my research. I run the indirect calorimetry and body composition facilities of the Metabolic Research Unit Maastricht (MRUM), including four room calorimeters as well as the stable isotope laboratory for doubly labelled water studies.

I have obtained national and international funding from both governmental and private sources (amongst others, The Netherlands Organisation for Health Research and Development ZonMW, Dutch Ministry of Defence, Rijksdienst voor ondernemend Nederland (RVO), Eurostars, Regieorgaan SIA, Nuffic, Ministry of National Education of Indonesia, National Health and Medical Research Council Australia, IMEC, Philips Research, Pfizer, Maastricht Instruments, Redustim).

Herman Pontzer, Ph.D., Professor of Evolutionary Anthropology and Research Associate Professor of Global Health at Duke University, investigates how our deep, 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 discoveries that have challenged the way we think about diet, exercise, metabolism, and health. Dr. Pontzer's book, *Burn*, published in March, 2021.

Anne Raben (AR), has a PhD in food science and nutrition, and is professor at the Department of Nutrition, Exercise and Sports, University of Copenhagen and senior researcher at the Steno Diabetes Center Copenhagen, Denmark. AR has solid research experience within the role of different lifestyle factors for the prevention and treatment of obesity, type-2 diabetes, (T2D) and cardiovascular diseases. Especially dietary patterns, and more specifically quantity and quality of dietary protein (plant vs animal), vegetarian vs omnivorous diets, and carbohydrates (eg added sugar, dietary fibre, glycemic index, non-caloric sweeteners) have been in focus. The research has been done through numerous short- and long-term randomized controlled trials, including a wide specter of fasting and postprandial outcomes to get a complete picture of the physiological regulation and interplay between substrates and hormones, including subjective (eg appetite) and objective measures (eg glucose, insulin, GLP-1). AR was Project Coordinator of the multinational EU FP7 project "PREVIEW" (www. www.preview.ning.com) focusing on the role of protein and glycemic index and types of exercise for development of T2D in people with pre-diabetes. AR now co-coordinates the EU-project SWEET (www.sweetproject.eu). AR manages a research group of 5-10 employees, has >200 scientific publications and an H-index of 57.

Dr. **Eric Ravussin** is a Boyd Professor at Louisiana State University. He received his PhD in human physiology at the University of Lausanne, Switzerland. Dr. Ravussin is an internationally recognized translational investigator in obesity and diabetes research. His research now focuses on the molecular basis of obesity and its co-morbidities. His studies are aimed at understanding the molecular mechanisms that determine the inter-individual variability in energy expenditure, fat oxidation and energy balance in response to caloric restriction, increased or decreased physical activity, overfeeding or physiological conditions such as puberty, pregnancy, or menopause. His latest research is in the field of aging with an emphasis on the impact of caloric restriction on human biomarkers of aging and longevity. Dr. Ravussin has published more than 590 peer reviewed manuscripts in the field of obesity, type 2 diabetes, and aging. He has an h index of 113 and has mentored more than 60 postdoctoral fellows.

Leanne M. Redman, is a Professor in the Division of Clinical Sciences and Associate Executive Director at Pennington Biomedical Research Center in Baton Rouge, Louisiana. Her expertise is in human physiology as it relates to the quantification of energy balance, in both controlled and free-living conditions in humans. The epicenter of her work has been in the design and conduct of controlled clinicals trials in humans where diet and physical activity are manipulated and studied in terms of body weight and energy stores. Overall, her research is conducted with the goal to understand the mechanisms of body weight regulation to promote healthy aging across the lifespan, as well as to develop and test inventions for effective prevention and treatment of obesity and its comorbidities. Dr. Redman directs the Reproductive Endocrinology and Women's Health Laboratory. The lab conducts extramurally funded studies in pregnant women (and their infants) and women with infertility with the goal to understand the impact of obesity and metabolic health on women and obesity risk in offspring. Dr. Redman is also substantially involved in the scientific development, training, and mentoring of postdoctoral fellows and early career investigators. She is the Chief Academic Officer at Pennington Biomedical and leads the Division of Scientific Education. She has published more than 200 research articles, reviews, and book chapters around energy metabolism, insulin sensitivity, obesity, calorie restriction, exercise, and maternal/infant physiology.

Dr. **Denis Richard** is Professor in the Department of Medicine at Université Laval. He is the Director of the *Université Laval* Research Chair in Obesity. He is an expert in the neuronal and hormonal circuitries and pathways involved in energy balance regulation (control of food intake and energy expenditure). He pioneered research on the neurobiology of obesity in Canada. His main research interests are (i) the role of the neurosystems (melanocortins, melanin-concentrating hormone, endocannabinoids, mechanistic target of rapamycin, endozepines) in the control of food intake and energy expenditure; (ii) the role of the sympathetic nervous system in the control of brown adipose tissue (BAT) thermogenesis and in the activity / expression of the uncoupling protein 1 and other BAT proteins in rats and humans; (iii) the mechanisms whereby gastrointestinal hormones and bariatric surgery influence energy balance regulation; (iv) the role of the UCP2 in energy metabolism. Dr. Richard was the Director of Research at the *Institut universitaire de cardiologie et de pneumologie de Québec* (IUCPQ) from 1999 to 2022.

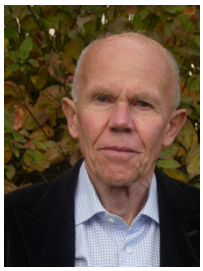
Vera Schrauwen-Hinderling is Professor of metabolic imaging with special focus on magnetic resonance spectroscopy at the Department of Radiology and Nuclear Medicine, Department of Nutrition and Movement Sciences, Maastricht University Medical Center, Maastricht, The Netherlands.

I use non-invasive magnetic resonance spectroscopy (MRS) to investigate the etiology of insulin resistance in type 2 diabetes. My research focuses on the causes and consequences of fat storage in heart, liver and muscle, with a particular focus on the balance between oxidation and storage. To this end, me and my team have set up cardiac, hepatic and skeletal muscle ^{1}H-MRS, ^{31}P-MRS and ^{13}C-MRS protocols to investigate substrate storage and energy metabolism *in vivo*. Using these tools, we reported reduced *in vivo* mitochondrial function in T2DM patients and we showed that lipid content and oxidative capacity in the heart and skeletal muscle are modulated by endurance training and acute exercise and that high concentrations of FFA- as seen in diabetes - lead to increased fat storage in skeletal muscle, heart and liver. Next to standard MRS measurements, my team also invests time and energy in method development and we showed that acetylcarnitine is detectable with ^{1}H-MRS and that levels are inversely related to insulin resistance. Furthermore, we set-up a new method to determine the relative amount of SFA, MUFA and PUFA in the liver. I combine my appointment at the Maastricht University Medical Center with an appointment at the German Diabetes Center, where I am heading the Metabolic Imaging group.

Shigeho Tanaka, PhD., Professor at the Faculty of Nutrition, Kagawa Nutrition University. He graduated from the Faculty of Education, the University of Tokyo and earned his Ph.D. from the Graduate School of Education. After working as a research assistant at the University of Tokyo, he became an assistant professor and an associate professor at Ibaraki University. In 2000, he studied under Dr. C Bouchard at the Pennington Biomedical Research Center (Baton Rouge, LA, USA) for ten months as a visiting scientist. After returning to Japan in 2001, he moved to the National Institute of Health and Nutrition to set up the human calorimeters and to be engaged in research on energy requirements and served as Head and/or Chief of Department of Nutrition and Metabolism. Since April 2020, he is a professor at Kagawa Nutrition University.

Dr. Tanaka's main research area is evaluation of energy expenditure, including prediction of basal metabolic rate, physical activity (e.g., NEAT, accelerometry, and questionnaire), and total energy expenditure. He has studied mainly adults including older adults and diseased but has also studied growth and development in children since he was a university student.

Professor **Angelo Tremblay** obtained his PhD in Physiology in Laval University, Quebec City, and is currently a professor in the Department of Kinesiology in this university. His investigations are mostly oriented towards the study of factors influencing energy balance in humans with the intent to improve obesity management. Recently, his research has been focused on the study of non-traditional determinants of obesity such as short sleep duration, low calcium/dairy intake, insufficient vitamin intake, suboptimal feeding behaviors, demanding cognitive effort and persistent organic pollutants. He is holder of the Canada Research Chair in Environment and Energy Balance.



Klaas R. Westerterp is professor of Human Energetics in the Faculty of Health, Medicine and Life Sciences and the School of Nutrition & Translational Research in Metabolism (NUTRIM) at Maastricht University, The Netherlands. He did his PhD at the University of Groningen, performed a three-year postdoc at Stirling University in Scotland, and a two-year postdoc at the University of Groningen and the Netherlands Institute of Ecology (NIOO, KNAW) in order to work on flight energetics in birds. In 1982 he became senior lecturer and subsequently full professor at Maastricht University in the department of Nutrition and Movement Science. Here his field of expertise is energy metabolism, physical activity, food intake and body composition, and energy balance under controlled conditions and in daily life. He currently is editor in chief of European Journal of Applied Physiology.

Prof. dr. **Margriet S. Westerterp Plantenga** is Professor of Food Intake Regulation in Humans at Maastricht University, Faculty of Health, Medicine, Life Sciences, Nutrim, The Netherlands.

Her research focuses on the neuro-endocrinology of food-intake, as well as energy expenditure, substrate oxidation, and the role of circadian rhythm and sleep in the perspective of obesity and its co-morbidities. Margriet Westerterp-Plantenga participated in several European projects, such as Diogenes, Full4Health, and PREVIEW. In 2019 she received the distinguished career award of the Society of the Study of Ingestive Behavior. She is Associate Editor of the International Journal of Obesity, and has been a member of several scientific committees and of the Faculty Board of the Faculty of Health, Medicine, and Life sciences of Maastricht University.

Dr **Lori Zeltser** graduated from Princeton University in 1989 and received her Ph.D. from The Rockefeller University in 1996. She completed her postdoctoral training in the laboratories of Andrew Lumsden at Kings College London and Claudio Stern and Tom Jessell at Columbia University. In 2007, she started her research program at the Naomi Berrie Diabetes Center at Columbia, and she is currently an Associate Professor in the Department of Pathology and Cell Biology. She is the Co-Director of Columbia's Nutritional and Metabolic Biology PhD program and the Director the NIDDK-funded Diabetes Research Center's Advanced Tissue and Imaging Core.

The Zeltser laboratory studies how developmental influences impart lasting effects on body weight regulation. They are defining how interactions between genetic, environmental and dietary factors across the lifespan affect the maturation and function of circuits regulating food intake and energy expenditure. This research is yielding new insights into developmental processes in the central and peripheral nervous system that regulate susceptibility to childhood obesity and anorexia nervosa.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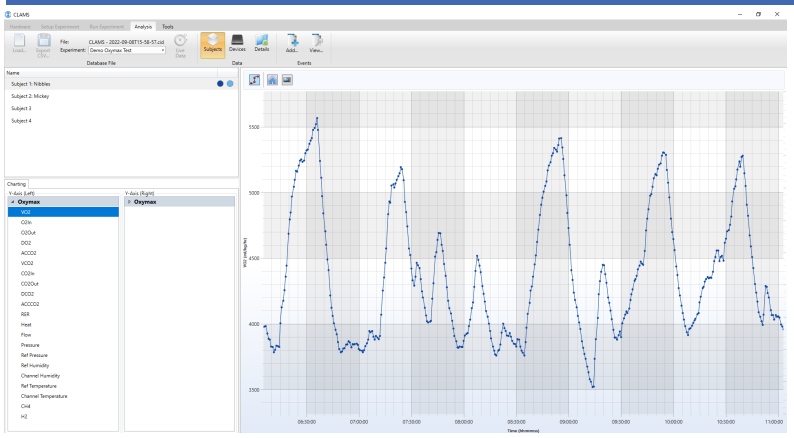

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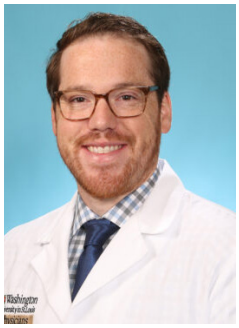
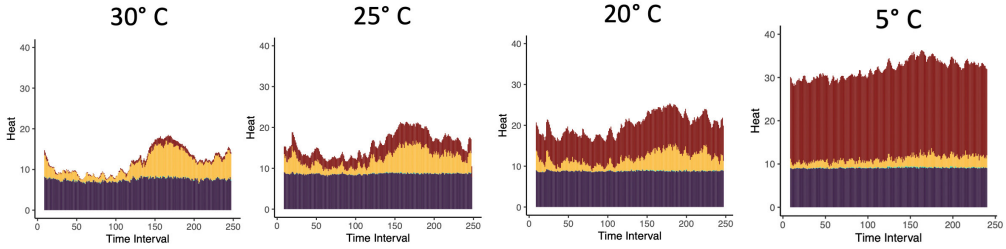
- Interactive experiment setup with drag & drop subject placement
- User friendly interface for managing roster, adding/viewing events, and activating cages
- Enhanced live view of raw data and key biomarkers

Upcoming webinar: CLAM*bake* algorithm



Jonathan R. Brestoff, MD, PhD
Assistant Professor, Pathology & Immunology
Washington University School of Medicine in St. Louis
@BrestoffLab

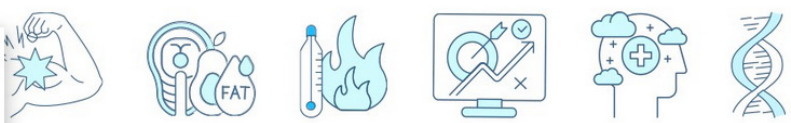


Join us with Dr. Jon Brestoff to discuss a quick, automated, and repeatable way to breakdown total energy expenditure into four specific categories by baking your CLAMS data.

- **Basal metabolic rate**
- **Thermogenesis**
- **Physical activity**
- **Thermic effect of food**

Coming this fall, hosted by InsideScientific. **Visit our booth for advance registration.**

Exercise **Metabolism** **Behavior** **Neuroscience**



To hear about all the latest metabolic research trends, follow us on: LinkedIn

General Information

Registration Desk

Except for exhibitor who will receive their badge in advance via email, all badges will be distributed on site. For admission to the sessions, posters, exhibits, and receptions, you must have your official conference badge. Certificates of Attendance and Participation must be requested by writing to racmem2022@criucpq.ulaval.ca.

Registration Desk Schedule

Day	Date	Time			
Thursday	6 oct, 2022	from	17:30	to	19:15
Friday	7 oct, 2022	from	7:00	to	10:15
Saturday	8 oct, 2022	from	8:00	to	10:15

Oral Presenters

All speakers must go to the IT Desk located at the back of room 2000A (plenary hall) soon as possible to upload your presentation and review your presentation and become familiar with the equipment that will be in the session room. Note that you will NOT be able to use your own computer or upload your presentation in the session room.

Support document for your presentation should be in a PowerPoint format (9:16) saved on a USB stick to facilitate the transfer. We ask that to upload your presentation at least at the break before the session you are scheduled to speak at. Speakers for the Friday morning should go to the IT Desk upon their arrival on site at least 30 minutes before the start of your talk.

Poster Presentations

All posters must be displayed throughout the event. See the Move-In and Move-Out schedule bellow. Please stand next to your poster during the 2 designated poster sessions:

- Friday, October 7 from 12:00 to 13:15
- Saturday, October 8, from 18:30 to 20:00.

Only the student presentations will be evaluated (schedule to come). Each presentation is allowed 3 minutes plus 2 minutes for questions.

Move-in

Day	Date	Time			
Thursday	6 oct, 2022	from	17:30	to	19:00
Friday	7 oct, 2022	from	7:00	to	10:15

Move-out

Day	Date	Time			
Sunday	9 oct, 2022	from	11:30	to	14:30

The meeting does not take responsibility for posters that are not removed on time.

Viewing Sessions Online

Remote attendees can view sessions via the link they will get by email. The recordings of the sessions will be available until December XX, 2022 using the link that will be provided after the event.

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Test	Specification	Method
Oxygen-^{18}O	≥98atom%	MS
Oxygen-^{17}O	<2atom%	MS
Oxygen-^{16}O	<2atom%	MS
Copper	<1 ng/L	ICP-MS
Calcium	<1 ng/L	ICP-MS
Iron	<0.1 ng/L	ICP-MS
Zinc	<1 ng/L	ICP-MS
Potassium	<1 ng/L	ICP-MS
Sodium	<2 ng/L	ICP-MS
Magnesium	<1 ng/L	ICP-MS
Ammonium	<1 ng/L	IC
Chloride	<1 ng/L	IC
Bromide	<1 ng/L	IC
Fluoride	<1 ng/L	IC
Sulfate	<1 ng/L	IC
Nitrate	<1 ng/L	IC
Iodide	<1 ng/L	IC
Phosphate	<1 ng/L	IC
pH	5.5-8.0	pH meter
Conductivity	<0.3mS/m	Conductivity meter
Total Organic Carbon	<5 ng/L	TOC analyzer
Standard Plate Count	<1 /mL	Membrane Filter
Pyrogenicity	<0.25EU/mL	LAL
Appearance	Clear,Colorless, No visible object	Visual Check

Low Enriched Products

Test	Specification	Method
Oxygen-^{18}O	10-12atom%	MS
Oxygen-^{17}O		MS
Oxygen-^{16}O		MS
Conductivity	<15	Conductivity meter
pH	6.0-8.0	pH meter
Appearance	Clear,Colorless, No visible object	Visual Check

TAIYO NIPPON SANSO
The Gas Professionals

TAIYO NIPPON SANSO Corporation
Stable Isotope Div.
Toyo Bldg.1-3-26 Koyama Shinagawa-ku,Tokyo 142-8558 JAPAN
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http://stableisotope.tn-sanso.co.jp E-mail:isotope@ml.sanso.co.jp

Exhibitor and Sponsor Information

Please be sure to visit with the company representatives during the poster sessions and breaks.

Platinum Sponsors

The Gairdner Foundation is proud to sponsor RACMEN 2022 as part of its partnership with Fonds de recherche du Québec for the promotion of science culture and achievement in the province of Québec. The Gairdner Foundation was established in 1957 with the main goal of recognizing and rewarding international excellence in fundamental research that impacts human health. Annually, seven prestigious awards are given: five Canada Gairdner International Awards for biomedical research, one John Dirks Canada Gairdner Global Health Award, specifically for impact on global health issues, and two Momentum Awards, which recognizes mid-career investigators. The awards have been presented to 402 laureates from more than 40 countries, and 96 of those have gone on to receive the Nobel Prize. But, beyond the awards, Gairdner hosts various outreach events to inspire the next generation of researchers and facilitate open scientific discourse to better educate the public, understand the problems we face, and work together to find solutions. Learn more about Gairdner's upcoming events at gairdner.org and follow them on social media @GairdnerAwards.

Novo Nordisk is a leading global healthcare company, founded in 1923 and headquartered in Denmark. Our purpose is to drive change to defeat diabetes and other serious chronic diseases such as obesity and rare blood and endocrine disorders. We do so by pioneering scientific breakthroughs, expanding access to our medicines, and working to prevent and ultimately cure disease. Novo Nordisk employs about 49,300 people in 80 countries and markets its products in around 170 countries. Novo Nordisk's B shares are listed on Nasdaq Copenhagen (Novo-B). Its ADRs are listed on the New York Stock Exchange (NVO). For more information, visit novonordisk.com, Facebook, Twitter, LinkedIn and YouTube.

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FONDATION
INSTITUT UNIVERSITAIRE
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ET DE PNEUMOLOGIE
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The primary goal of the Fondation IUCPQ is to promote and support the work of the Institut universitaire de cardiologie et de pneumologie de Québec- Université Laval which mission is focused on the health of the people affected by cardiovascular and respiratory disease as well as obesity.

The Fondation IUCPQ is also aiming at promoting healthy lifestyles.

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Nestlé Health Science empowers healthier lives through nutrition. As a global leader in the science of nutrition, we nourish those who need extra care, fill nutrition gaps and provide innovative products for a healthier future, enabling customers and patients with choices to help them live their healthiest lives

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Maastricht Instruments BV is a company originating from the engineering department of the Faculty of Health, Medicine & Life Sciences of the Maastricht University Medical Center+. The company is founded in 1998 and has grown into a specialized high-tech company providing high demanding customers with innovative technical solutions in the field of life sciences and medical devices.
Maastricht Instruments is a strategic company of Maastricht UMC+ and is providing customers all over the world with novel research equipment such as indirect calorimetry equipment, room calorimeters, wearable healthcare solutions (devices, apps and data processing software) and sample preparation equipment.

WE'RE HELPING PEOPLE WITH DIABETES LEAD HEALTHIER, HAPPIER LIVES. As a global leader in diabetes care, Abbott is constantly working to deliver the highest quality products and unwavering support to our customers. Consistent and accurate glucose monitoring is the foundation of any diabetes management plan so we're committed to continuous improvement in the way patients and professionals measure, track and analyze glucose levels.

The CMDO Network is a group of research teams working in Quebec on CardioMetabolic health, Diabetes and Obesity funded by the Fonds de recherche du Québec - Santé (FRQS). The network's mission is to develop research on CMDO themes, to transmit knowledge and to promote the health and quality of life of Quebecers. It supports promising projects, from basic and clinical research to the population, which require a wide range of expertise and multicentre scientific and clinical platforms. Through the development of provincial but also international funding programs involving young investigators, as well as patient-partnership and student training within these initiatives, the CMDO Network promote the recruitment and success of talented young investigators and the emergence of a new generation of high-quality scientists.

Lilly was founded in 1876 by Colonel Eli Lilly, who was committed to creating high-quality medicines that met real needs in an era of unreliable elixirs peddled by questionable characters. His charge to the generations of employees who have followed was this: "Take what you find here and make it better and better."

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Bronze Sponsors

Chez nous, on opère en mode coopération parce que pour se surpasser, il est essentiel de collaborer.
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Bausch Health Companies Inc. (NYSE/TSX: BHC) is a global diversified pharmaceutical company whose mission is to improve people's lives with our health care products. We develop, manufacture and market a range of products primarily in gastroenterology, hepatology, neurology, dermatology, international pharmaceuticals and eye health, through our approximately 90% ownership of Bausch + Lomb Corporation. **Bausch Health, Canada Inc.'s** prescription treatment portfolio is focused on dermatology, gastrointestinal, cardio-metabolic and allergy conditions. Bausch Health also has two manufacturing facilities for prescription pharmaceuticals in Canada, in Laval, Quebec, and Steinbach, Manitoba. More information can be found at the Company's website at **www.bauschhealth.ca**."

Composé de six axes de recherche et de professionnels aux expertises variées, le Centre de recherche du CHUS se démarque par son approche intégrée qui regroupe la recherche fondamentale, épidémiologique et évaluative.

La proximité qu'a le Centre de recherche avec l'Hôpital Fleurimont, l'Hôtel-Dieu de Sherbrooke, la Faculté de médecine et des sciences de la santé de l'Université de Sherbrooke, l'Institut de pharmacologie de Sherbrooke et le pavillon de recherche appliquée sur le Cancer est le fruit de plusieurs collaborations.

Grâce à cette synergie, un phénomène de transfert des connaissances s'opère, menant à la création de succès présents et futurs. Des succès qui sont le reflet de la passion et du travail acharné de nos chercheurs, membres du personnel de recherche, et étudiants gradués. Ensemble, ils ont des impacts positifs et réels pour l'amélioration de la santé.

Depuis 1980, le Centre de recherche du CHUS conjugue l'audace, l'excellence et la créativité pour innover et relever avec brio les nombreux défis rencontrés en recherche. Il s'agit d'un milieu stimulant dans lequel le partenariat, la synergie et la diversité sont essentiels afin de favoriser un SAVOIR porteur d'ESPOIR!

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COSMED is the world-leading manufacturer of gold-standard Resting Energy Expenditure (REE), Cardio Pulmonary Exercise Testing (CPET), and the PEA POD and BOD POD Body Composition Systems, which provide highly accurate assessments of fat and fat-free mass throughout the lifespan. Key products include the portable Q-NRG™ Indirect Calorimeter, the Quark™ RMR Indirect Calorimeter, and the user-friendly OMNIA software suite. With OMNIA™, users can easily compare, integrate, and share subject data either in a standalone or large network environment.

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Supporters

Event Sponsors

At this year's RACMEM, we have attempted to create several mentorship and discussion opportunities for Trainees or Early Career Investigators to meet with established academics.

The Gairdner Foundation is sponsoring the Coffee Chats on Friday October 7th, 7:00 – 8:00 and Saturday October 8th, 7:00 –8:00, as well as the Women in Science Lunch session on Saturday October 8th, 12:00 – 13:00.

Gairdner Coffee Chat / Meet a Professor: The Coffee Chats are designed for Trainees or Early Career Investigator to create an opportunity to grab a coffee and light food and meet either individually or in small groups with Professors. If you are a trainee or early career investigator.

Women in Science consists in a Panel Discussion and Exchange with the emphasis of Women in Science. First, there will be a 30 min panel discussion with Pr Leanne Redman, Pr Mary-Ellen Harper, Pr Natalie Michael, and Pr Audrey Bergouignan, led by Pr. Hannah Pallubinsky. This panel discussion is open to all attendees. Following this panel discussion, there will be a 30 min small-group exchange between investigators and trainees. This small group discussion is reserved for women.

Safety Protocols

In-person attendees are asked to wear a protective mask while attending the conference. If you do not have access to a mask, a limited supply of complimentary masks will be available at the registration desk in Hall 2000. Hand sanitizers will be available in some locations.

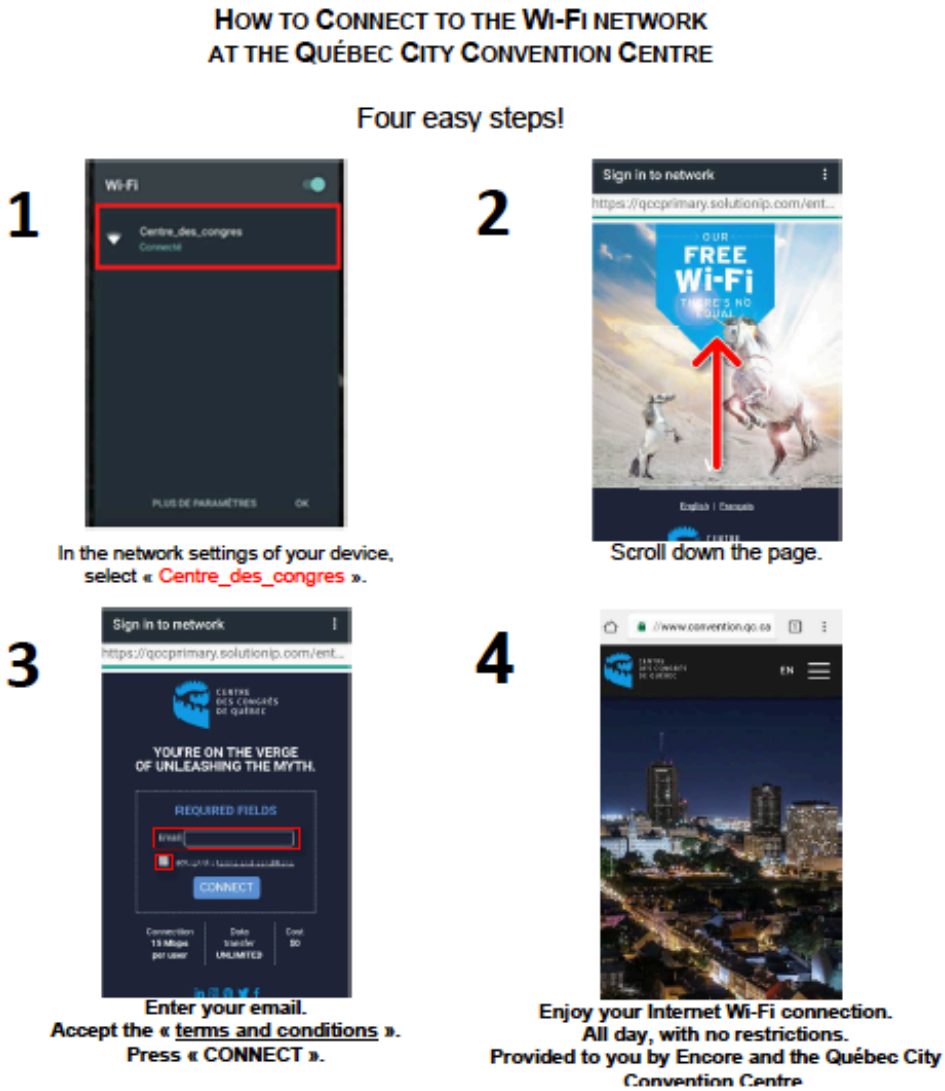
Meals

Unless otherwise specified, meals are not included in the conference registration fee. Meals included are as follows:

- Friday, October 7 from 12:00 to 13:15: Box Lunches
- Saturday, October 8 from 12:00 to 13:00: Box Lunches
- Saturday, October 8 at 20:00 in Room 2000D: Banquet Dinner

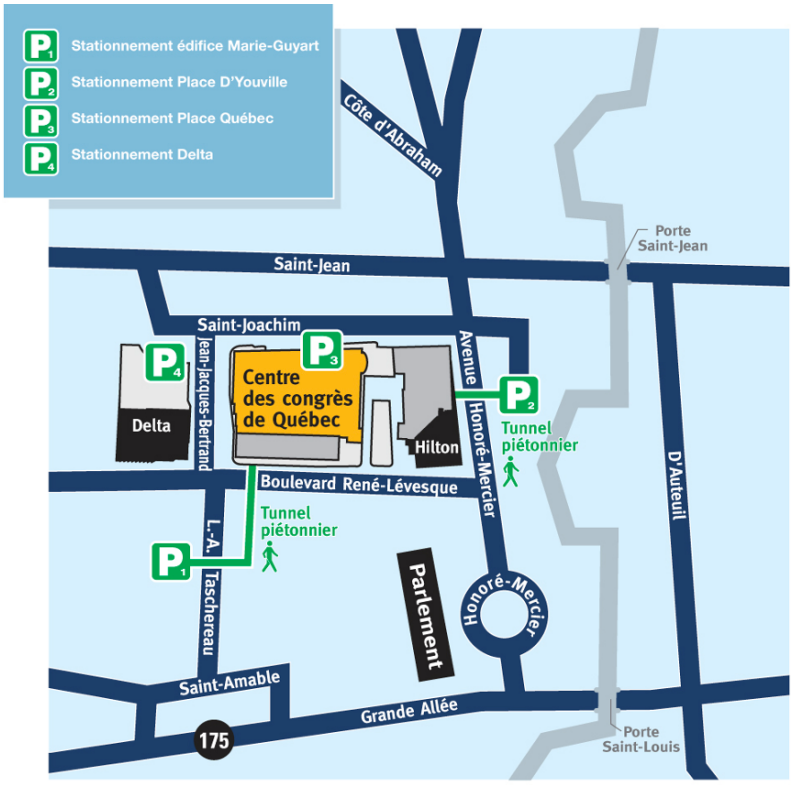
Internet Access

Complimentary Wi-Fi is available at the Québec City Convention Centre. Here's how to connect:



Parking

A few parking options are available in the area ($).



Code of Conduct

RACMEM fosters an international community and provides an opportunity to discuss scientific advances and form new collaborations. RACMEM values your attendance and wants to make your experience productive and inspiring by fostering an open exchange of ideas in a professional setting.

Diversity and Inclusion

RACMEM is committed to promoting equality, diversity, and inclusion to create greater opportunity for any individual to fulfill their scientific potential, irrespective of their background, gender, or circumstances. This diversity leads to innovation by attracting the widest possible talent to the community and fostering a greater diversity of ideas, approaches, and perspectives. The Organizing Committee aims to select speakers and session chairs that represent the breadth and diversity of the discipline and conference participants. RACMEM especially encourages the Committee to select excellent speakers from groups traditionally underrepresented in science.

Social Media/Photos/Video Policy

Live tweeting of presentations is allowed unless the speaker explicitly opts out by stating so at the start of their talk. With the exception of the first slide of the presentation, it is prohibited to take any photos of any PowerPoint. Taking or sharing photos or videos of posters is permitted only with the presenter's consent during the assigned poster session. Taking photos of posters while the presenter is not present is strictly prohibited.

Schedule of Event

THURSDAY OCTOBER 6th

17:30 — 19:30 **WELCOME RECEPTION**

Dinner on your own in Québec City

FRIDAY OCTOBER 7th

MORNING

08:00 — 08:15 **WELCOME TO QUÉBEC CITY!**

Introductory Remarks
Denis RICHARD — Canada

08:15— 08:30 **WELCOME TO RACMEM 2022**

Contribution of RACMEM to Energy Metabolism
Ed MELANSON — USA

08:30 — 10:30 **PET/CT, MRI AND ISOTOPIC TRACERS IN ENERGY METABOLISM AND HOMEOSTASIS**

SIEMENS Healthineers

Chairs: Denis BLONDIN & Anja BOSY-WESTPHAL

O-01 – MR Spectroscopy and Imaging of Fat Deposition in Organs
Vera SCHRAUWEN-HINDERLING — Netherlands

O-02 – Using MRI and Stable-Isotope Tracers to Image and Phenotype Liver Metabolism
Leanne HODSON — United Kingdom

O-03 – Body Composition Changes and Homeostatic Control of Resting Energy Expenditure During Weight Loss
Manfred J MÜLLER — GERMANY

O-04 – Emerging Technologies to Image Tissue Metabolism
Kevin K BRINDLE — United Kingdom

10:30 — 11:00 **PAUSE / SPONSOR EXHIBITION**

11:00 — 11:45	**THE SHAPES (AND MOVES) OF TRACERS: APPLYING POSITRON EMISSION TOMOGRAPHY TO ENERGY METABOLISM** (O-05)

André CARPENTIER — Canada

Chair: *Denis RICHARD*

12:00 — 13:15	**LUNCH / POSTER SESSION 1 / SPONSOR EXHIBITION**

AFTERNOON

13:15 — 15:15	**ENVIRONMENT CONDITIONS AND ENERGY METABOLISM/HOMEOSTASIS**

Chairs: Laura WATSON & Kong CHEN

O-06 – Modifying Thermogenic Pathways in Cold Exposed
François HAMAN — Canada

O-07 – Tailoring diets and housing temperature to improve the translatability of pre-clinical models to investigate hepatic and cardiovascular complications of obesity
André MARETTE — Canada

O-08 – Human Adaptation to Deep Space Environment and Understanding the Pathophysiology of Sedentary Behaviour
Audrey BERGOUIGNAN — France - USA

O-09 – Energy Metabolism in Severe Exercise
Guy PLASQUI — Netherlands

15:15 —15:45	**PAUSE**

15:45 — 17:45	**ENERGY METABOLISM/HOMEOSTASIS IN MOTHERS, CHILDREN AND ADOLESCENTS**

Chairs: Margriet WESTERTERP-PLANTENGA & Lori ZELTSER

O-10 – Energy Homeostasis in Pregnant and Postpartum Women
Leanne M REDMAN — USA

O-11 – Energy Expenditure in Women: The Effects of Oestrogens and Exercise
Ed MELANSON — USA

O-12 – Energy Homeostasis in Children and Adolescents
Shigeho TANAKA — Japan

O-13 – Intra-Adipose Sex Steroid Hormone Metabolism and Human Visceral Obesity
André TCHERNOF — Canada

18:00 — 19:30 **PUB NIGHT at THE HILTON (optional)**

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LES PRIX CANADA GAIRDNER AWARDS

EVENING

Dinner on your own

SATURDAY OCTOBER 8th

MORNING

08:00— 10:00 **HEAT-PRODUCING ORGANS, ORGANITES AND PATHWAYS**

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Chairs: François HAMAN & Leanne HODSON

O-14 – Mechanisms of Adaptive Thermogenesis Driving Catch-up Fat During Weight Regain
Abdul DULLOO — Switzerland

O-15 – Examining Futile Cycles as Recruitable Forms of Heat Production – Is it Fruitless?
Denis BLONDIN — Canada

O-16 – Regulatory Thermogenesis: UCP1 and Beyond
Lawrence KAZAK — Canada

O-17 – mTOR System in Brown Fat Thermogenesis
Mathieu LAPLANTE — Canada

10:00 — 10:30 **PAUSE / SPONSOR EXHIBITION**

10:30 — 12:00 **SHORT ORAL COMMUNICATIONS 1**

Chairs: Vera SCHRAUWEN-HINDERLING & André CARPENTIER

O-18 – Changes in Brain Energy Metabolism During Aging and at the Onset of Alzheimer Disease: Recent Developments with Ketone and FDG PET, Functional Connectivity, and Diffusion Imaging
Stephen CUNNANE — Canada

O-19 – The Acute Effects of a Single Dose of Anti-Obesity Drugs on Human Basal Metabolic Rate
Samuel LaMUNION — United States

O-20 – Underappreciated Role of the Histaminergic System in the Control of Energy Balance
Natalie J MICHAEL — Canada

O-21 – Effects of Time-Restricted Feeding on Energy balance: A Cross-Over Trial in Healthy Subjects
Shija PAN— China

O-22 – Impact of Endogenous vs. Exogenous Ketones on Energy Expenditure in Healthy Participants
Franziska A HÄGELE — Germany

O-23 – Combined α- and β-adrenergic Receptor Activation Triggers Thermogenesis by the Futile Creatine Cycle
Janane RAHBANI — Canada

12:00 — 13:00 **LUNCH / SPONSOR EXHIBITION**

12:00 — 13:00 **GAIRDNER's WOMEN IN SCIENCE (optional)**

Chair: Hannah PALLUBINSKY

Panel discussion (30 min) – Open to all

Panelists: Audrey BERGOUIGNAN, Mary-Ellen HARPER, Natalie J MICHAEL, and Leanne REDMAN

Breakout small groups discussions (30 min) – Limited to women

AFTERNOON

13:00 — 15:00 ENERGY METABOLISM/HOMEOSTASIS IN OBESE INDIVIDUALS

Chair: Angelo TREMBLAY

O-24 – Thermogenic Flexibility in Response to Weight Loss and Regain
Paul S MACLEAN — USA

O-25 – Permanence of Thermogenic Changes Induced by Weight Loss in Obese Individuals
Eric RAVUSSIN — USA

O-26 – Mitochondria and their Role in the Interindividual Variability in Weight Loss and Exercise Response
Mary-Ellen HARPER — Canada

O-27 – Low Capacity to Oxidize Fat and Body Weight
François PÉRONNET — Canada

15:00 — 15:30 PAUSE / SPONSOR EXHIBITION

15:30 — 17:00 SHORT ORAL COMMUNICATIONS 2

Chairs: Herman PONTZER & Paul MACLEAN

O-28 – Tuning and Validation of a Closed-Loop Control System for Air Flow to Improve Accuracy of Whole-Room Indirect Calorimeters During Dynamic Metabolic Studies
Paolo PIAGGI — United States

O-29 – Practical Application and Considerations for Doubly Labeled Water Assessment in Infants
Emily FLANAGAN— United States

O-30 – Determination of Energy Expenditure in Professional Cyclists Using Power Data: Validation Against Doubly Labelled Water
Maartje COX — The Netherlands

O-31 – Utility of Schofield Equations for Estimating Resting Energy Expenditure in a West African Population
Amy LUKE — United States

O-32 – Sex Differences in Free-living Total Daily Energy Expenditure and Physical Activity in Adults Successfully Maintaining Weight Loss
Annie CALDWELL — United States

O-33 – Inter-Individual Variability of Human Thermoregulation: Towards Personalized Ergonomics of the Indoor Thermal Environment
Yann RAVUSSIN — Switzerland

17:00 — 18:30 **Update on Doubly-Labelled Water**

TAIYO NIPPON SANSO
The Gas Professionals

Chair: Shigeho TANAKA & John SPEAKMAN

O-34 – Physical Activity and Body Composition during Growth and in Later Life
Klaas WESTERTERP (on behalf of the IAEA DLW database group) — Netherlands

O-35 – Human Water Intake: Great Variation Associated with Environmental and Lifestyle Factors
Yosuke YAMADA (on behalf of the IAEA DLW database group) — Japan

O-36 – Total Energy Expenditure and Body Composition in Populations across the Socioeconomic Spectrum
Herman PONTZER (on behalf of the IAEA DLW database group) — USA

18:30 — 20:00 **COCKTAIL / POSTER SESSION 2 / SPONSOR EXHIBITION**

EVENING

20:00 — 23:00 **BANQUET**

Hosted by Denis BLONDIN & François HAMAN

SUNDAY OCTOBER 9th

MORNING

08:00— 09:30 **ENERGY METABOLISM/HOMEOSTASIS: NOVEL AND INNOVATIVE APPROACHES**

Lilly

Chair: Jose GALGANI

O-37 – Developing New Tools to Study Sympathetic Regulation of Brown Adipose Tissue Function
Lori ZELTSER — USA

O-38 – Chemogenetics to Approach the Adrenergic Control of Liver and Adipose Tissues
Alexandre CARON — Canada

O-39 – Metabolomics of cardiometabolic diseases: potential markers of pre-morbidities for Covid-19
Marc-Emmanuel DUMAS — UK

09:30— 11:00 **CHANGES IN ENERGY BALANCE DURING HIGH PROTEIN DIETS — THE PREVIEW STUDIES**

Chairs: André CARPENTIER and François HAMAN

O-40 – Circadian Rhythm Parameters and Physical Activity Differentially Associated with Cardiometabolic Risk Factors in the Controlled Respiratory Chamber vs. The Free-Living Condition – A PREVIEW Lifestyle Study
Margriet WESTERTERP-PLANTENGA — Netherlands

O-41 – Protein as a Source for Body-Weight Maintenance — The Role of Quantity and Quality (The PREVIEW Study)
Anne RABEN — Denmark

O-42 – PREVIEW Population Studies: What Do we Learn About Energy Balance
ANGELO TREMBLAY — Canada

11:00 — 11:30 **PAUSE / SPONSOR EXHIBITION**

11:30— 13:00 **ASSESSING ENERGY EXPENDITURE AND THERMOGENESIS: A RELENTLESS CHALLENGE**

Chairs: Mary Ellen HARPER & Ed MELANSON

O-43 – Unraveling Inter-Individual Variability in Energy Metabolism
Jennifer MILES-CHAN — New-Zealand

O-44 – Measurement of Cold-Induced Thermogenesis
Kong CHEN — USA

O-45 – Measuring at or Below Thermoneutrality — A Persistent Debate
Keep your mice warm!
Jan NEDERGAARD and *John SPEAKMAN* — Sweden and UK (45-minute debate)

13:00 **CONCLUDING REMARKS PLUS THANKS**

Angelo TREMBLAY

Abstract – Oral Presentations

O-01 MR Spectroscopy and Imaging of Fat Deposition in Organs

Vera SCHRAUWEN-HINDERLING — Netherlands

Magnetic resonance spectroscopy (MRS) is a valuable tool to investigate substrate storage and energy metabolism in vivo. The non-invasive nature and the absence of ionizing radiation make it very suitable for repeated measurements to monitor metabolic changes real time in vivo. The application of MRS can thus be used to get insights in the etiology of insulin resistance in type 2 diabetes. Next to studying the dynamics of ectopic fat storage in heart, liver and muscle, by ^{1}H-MRS, ^{31}P-MRS can be used to quantify high-energy metabolites, such as ATP in the liver and to monitor Phosphocreatine kinetics in skeletal muscle during exercise. The PCr recovery kinetics yield information on the maximal oxidative capacity of muscle, while the PCr kinetic at the start of exercise (on-kinetics) bear information about the ability to activate oxidative metabolism and thereby reflect mitochondrial inertia. ^{13}C-MRS can be used to monitor liver glycogen fluctuations. The regular depletion of liver glycogen was suggested to be critical to maintain metabolic health. Using these tools, we reported reduced *in vivo* mitochondrial function in T2DM patients and we showed that lipid content and oxidative capacity in the heart and skeletal muscle are modulated by endurance training and acute exercise and that high concentrations of FFA- as seen in diabetes - lead to increased fat storage in skeletal muscle, heart and liver. Next to standard MRS measurements, my team also invests time and energy in method development and we showed that acetylcarnitine is detectable with ^{1}H-MRS and that levels are inversely related to insulin resistance. Furthermore, we set-up a new method to determine the relative amount of SFA, MUFA and PUFA in the liver and proton-observed, carbon-edited sequences to observe ^{13}C lipids with high sensitivity and ^{31}P editing sequences to quantify NAD^+ and NADH. I combine my appointment at the Maastricht University Medical Center with an appointment at the German Diabetes Center, where I am heading the Metabolic Imaging group.

O-02 Using MRI and Stable-Isotope Tracers to Image and Phenotype Liver Metabolism

Leanne HODSON — United Kingdom

The liver is a key metabolic organ that undertakes a multitude of physiological processes. It serves as an intermediary organ between exogenous (dietary) and endogenous energy supply to extrahepatic organs, with hepatocytes rapidly transitioning back and forth between the metabolic tasks of energy storage and supply. Given its pivotal role in regulating systemic metabolism, perturbations in hepatic metabolism can impact on metabolic disease risk. An example, is the accumulation of intra-hepatocellular triglyceride (IHTG), which likely results from an imbalance between fatty acid delivery to the liver, hepatic fatty acid synthesis and fatty acid removal (via oxidation or export as triglyceride (TG)) from the liver. Insulin is the main regulator of all these processes; insulin resistance has profound effects on liver fat metabolism. By using a combination of models (*in vivo, ex situ* and *in vitro*) in combination with methodologies such as stable isotope tracers and magnetic resonance imaging and spectroscopy (for *in vivo* studies), there is the potential to gain insight into intra-hepatocellular lipid metabolism. This talk will review the insights gained from undertaking studies using these models and methodologies and discuss how phenotype, metabolic and nutritional state may alter hepatic fatty acid partitioning. It will also review if the metabolic complications of NAFLD go beyond total IHTG quantity.

O-03 Body Composition Changes and Homeostatic Control of Resting Energy Expenditure During Weight Loss

Manfred J MÜLLER — GERMANY
Steven HEYMSFIELD – USA

Starting with Francis Benedict's seminal study on ‚Human vitality and efficiency under prolonged restricted diet', mass-independent changes in energy expenditure, i.e., metabolic adaptation (or adaptive thermogenesis, AT) to weight loss has been studied for more than 100yrs. Today, AT is still a hot research topic. AT may impede weight loss, impact maintenance of body weight (bw) and predispose to weight (fat) re-gain. Whether AT is a transient or persistent phenomenon is contradictory. Finally, as a mechanism of energy conservation AT may impact longevity.

Metabolic adaptation relates to all components of daily energy expenditure (i.e., resting and non-resting energy expenditure; REE, NREE) which again are inter-related. Weight loss is associated with decreases in fat mass (FM) and fat free mass (FFM) as well as changes in their anatomical and molecular compositions. With weight loss, up to 40% of the decrease in EE remains unexplained by changes in organ and tissue masses. During a controlled 3wk semi-starvation protocol healthy young normal weight men lost a mean of 6kg bw with decreases in FM and FFM of 18.9 and 5.2%, respectively. Concomitantly REE and NREE decreased by 173 and 103kcal/d. Adjusting decreases in REE for changes in (i) FFM or (ii) FFM plus its anatomical composition AT was calculated to be 116 (i) or 83kcal/d (ii). About 50% of the mass-independent decrease in REE could be explained by decreases in glomerular filtration rate, hepatic urea production, heart rate and body temperature. As to the kinetics of weight loss, AT becomes manifest within 3d of semistarvation. The early response is called 'nonspecific AT'. This relates to the early weight loss associated decreases in FFM and insulin secretion, negative fluid balance and loss of intracellular water and the increase in plasma glucagon levels. With ongoing and linear weight loss, the decrease in FM exceeds the corresponding decrease in FFM. There is a further moderate mass-independent decrease in REE (=specific AT) which is associated with lipid mobilization. During weight maintenance after weight loss, AT mainly refers to NREE and is associated with decreases in the plasma levels of leptin and T3 as well as the reduced activity of the sympathetic nervous system (SNS).

It is evident that during different phases of weight loss and weight maintenance AT (although it is of a similar magnitude) is explained differently where changes in the anatomical and molecular composition of FFM and FM impact AT related to the REE component of daily energy expenditure.

In conclusion,

- different systems of the body function together to excute homeostatic control mechanisms.
- Changes in body composition impact the REE-component of AT.
- AT should be seen in a greater context of metabolic adaptation (i.e., mobilization of glycogen and lipids).
- AT is likely not large enough in magnitude to be able to prevent weight loss and to explain weight regain after weight loss.
- For future studies, there is need of an appropriate conceptualization of AT.

O-04 Emerging Technologies to Image Tissue Metabolism

Kevin K BRINDLE — United Kingdom

Molecular imaging is likely to play an increasingly important role in predicting and detecting tumor responses to treatment and thus in guiding treatment in individual patients. Nuclear spin hyperpolarization increases sensitivity in the ^{13}C magnetic resonance experiment by >10,000x. This unprecedented increase in sensitivity has allowed ^{13}C magnetic resonance imaging of injected hyperpolarized ^{13}C labelled cell substrates in vivo and, more importantly, the kinetics of their metabolic conversion into other cell metabolites. We have used this

imaging technique, which has translated to the clinic, to detect tumor treatment response, to monitor disease progression and to investigate the tumor microenvironment (reviewed in [1]).

Exchange of hyperpolarized ^{13}C label between lactate and pyruvate frequently decreases following successful treatment and can provide an early indication of treatment response. Since PET measurements of tumour uptake of the glucose analog 2-([^{18}F]fluoro)-2-deoxy-D-glucose uptake (FDG-PET) are already used in the clinic for treatment response monitoring we have investigated what advantages the hyperpolarized ^{13}C experiment might have. We showed in a human colorectal xenograft model[2], and in patient-derived xenograft models of breast cancer[3] that successful treatment resulted in an early decrease in lactate labelling, whereas there was no change in FDG uptake. We have also used hyperpolarized [1-^{13}C]pyruvate to investigate glycolytic metabolism in patient derived xenograft (PDX) models of glioblastoma, which showed significant metabolic heterogeneity between tumours derived from different patients[4]. Some clinical results in breast cancer[5] and glioma patients[6] will be presented. Although we have used hyperpolarized [U-^{2}H, U-^{13}C]glucose to image glycolysis in murine tumour models[7] the method does not provide a quantitative measurement of glycolytic flux and moreover would be difficult to implement clinically because of the short ^{13}C hyperpolarization lifetime in vivo (~10 s). More recently we have shown that we can use dynamic ^{2}H MRI to provide quantitative measurements of tumour glycolytic flux following injection of d-[6,6'-$^{2}H_2$]glucose[8]. These showed that glycolytic flux was heterogeneous in a murine tumour model and that this showed a rapid decrease following successful tumour treatment. We had shown previously that we could detect tumour cell death in vivo by imaging the conversion of hyperpolarized [1,4-$^{13}C_2$]fumarate to [1,4-$^{13}C_2$]malate. We have shown more recently that this can also be accomplished by ^{2}H imaging with [2,3-$^{2}H_2$]fumarate[9,10].

1 Brindle, K. M. *J. Amer. Chem. Soc.* 137, 6418-6427 (2015).
2 Hesketh, R. L. *et al. Cancer Research* 79, 3557-3569 (2019).
3 Ros, S. *et al. Cancer Cell* 38, 1-18 (2020).
4 Mair, R. *et al. Cancer Res* 78, 5408-5418 (2018).
5 Gallagher, F. A. *et al. Proceedings of the National Academy of Sciences* 117, 2092-2098 (2020).
6 Zaccagna, F. *et al. Radiology: Imaging Cancer* 4, e210076 (2022).
7 Rodrigues, T. B. *et al. Nat Med* 20, 93-97 (2014).
8 Kreis, F. *et al. Radiology* 294, 289-296 (2020).
9 Hesse, F. *et al. Proceedings of the National Academy of Sciences* 118, e2014631118 (2021).
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O-05 The Shapes (and Moves) of Tracers: Applying Positron Emission Tomography to Energy Metabolism

André CARPENTIER

Positron emission tomography (PET) is a very powerful tracer technique that allows organ-specific measurement of the uptake and/or metabolism of a wide range of energy substrates. In addition to the well-known PET glucose tracer analog 18F-fluorodeoxyglucose (18FDG), PET metabolic tracers include fatty acids, amino acids, cetones, acetate, oxygen, and others. Over the past 15 years, we have developed a series of methods using these techniques combined with classical stable isotopic methods to detail energy metabolism in the postprandial state and during cold exposure in humans. These new techniques that resolve energy substrate tracer kinetics in 3D in the human body have allowed us to shed new light onto the roles played by white and brown adipose tissues in energy homeostasis. In this presentation, I will review these methods and key results we obtained and discuss the potential physiological and clinical relevance of our findings.

O-06 Modifying Thermogenic Pathways in Cold Exposed

François HAMAN — Canada

During cold exposure in humans, increases in heat loss are compensated fully or partially by increases in metabolic heat production via shivering (ST) and nonshivering thermogenesis (NST). In this context, the total amount of heat produced by an individual in an attempt to maintain core temperature is highly regulated for a

given cold stress level. However, the respective contribution of ST and NST to produce this heat is extremely variable between individuals and seems related to one's NST potential. Indeed, current evidence suggests that the contribution of NST by the activation of brown adipose tissue is associated with a reduction in ST. These effects become even more evident following cold acclimation protocols known to stimulate NST. Specific cold acclimation protocols have been shown to reduce ST by as much as 30% while heat production remained unchanged. Such regulation of these thermogenic processes are of great scientific and clinical relevance. However, the quantification of both whole body NST and ST is extremely complex and unfortunately, is highly inconsistent between cold exposure studies. Much work remains to better understand how ST and NST are regulated in the cold but little will be achieved without some level of standardization in the measurement of thermogenic processes. Such research is critical in order to consider strategies to either reduce its role to improve occupational performance and optimize chances of survival in cold climates.

O-07 Tailoring diets and housing temperature to improve the translatability of pre-clinical models to investigate hepatic and cardiovascular complications of obesity

André MARETTE — Canada

Pre-clinical models of obesity, type 2 diabetes (T2D) and cardiovascular diseases (CVD) have been developed and studied for many years. However, they often poorly represent all aspects of these chronic inflammatory diseases and their full blown cardiometabolic complications, hampering clinical translatability. For example, diet-induced mouse models of NAFLD develop very slowly (> 5 months) with inconsistent disease traits often lacking key features of NASH such as fibrosis and hepatocellular hypertrophy. Alternative models are either diet-deficient or chemically induced resulting in extreme liver and whole-body phenotypes generally not resembling human pathophysiology. The same is true regarding cardiovascular complications such as calcified aortic valve stenosis (CAVS), which is common in humans with obesity and T2D but not frequent in most pre-clinical models, even after 6 months on CVD-promoting western-type diets. This is key considering that NAFLD has been recently reported to be a strong and independent risk factor for heart failure in a meta-analysis of mutiple human cohort studies with ~11 million individuals (Mantovani A, *et al*. *Gut* 2022). It is therefore critically important to develop new preclinical models of NAFLD and CAVD. I will show some of our recent work that have identified key dietary components as well as ambient temperature as key factors that are critically important to accelerate and/or increase the severity of NAFLD and CAVD. We found that tailoring diet and housing temperature to better mimick human conditions improve the translatability of pre-clinical obesity models for NASH and CAVD, even removing sexual differences in disease risk, thus offering new and better tools to evaluate potential drug candidates for those severe complications with an unmet clinical need.

O-08 Human Adaptation to Deep Space Environment and Understanding the Pathophysiology of Sedentary Behaviour

Audrey BERGOUIGNAN — France - USA

Physical inactivity, i.e., not reaching the recommended level of physical activity and sedentary behaviours, i.e., sitting time have been associated with increased risk for common metabolic diseases and early mortality. Recent epidemiological data suggest that high volumes of sedentary behaviours are detrimental for metabolic health, even in the presence of regular exercise, i.e., moderate to vigorous physical activity (MVPA). This suggests that the health effects of sedentary behaviours are independent from those of exercise. However, experimentally testing this hypothesis is complicated because of the difficulty in disassociating sedentary behaviours from physical activity. Bedrest studies, a traditional space science model, can offer new insights. In some bedrest studies, an exercise training protocol has been used to counteract the harmful effects of inactivity. While bedrest induces an inactive and sedentary state, exercise with bedrest represents a unique model of sedentary yet physically active people. In this presentation, I will share data from dry immersion studies (another space analog model) and bedrest studies to better understand the pathophysiology of physical inactivity and sedentary behaviours. I will also present data from bedrest with and without exercise to examine

the complex relationships between exercise, non-exercise activity, SB and health outcomes. Finally, I will present novel data on the metabolic adaptations to space from the ENERGY experiment that was conducted in astronauts who spent 6 months onboard the International Space Station.

O-09 Energy Metabolism in Severe Exercise
Guy PLASQUI — Netherlands

O-10 Energy Homeostasis in Pregnant and Postpartum Women
Leanne M REDMAN — USA

In 2005, the IOM published dietary reference intakes for pregnant women. At that time the committee was only able to rely on four studies of 'well-nourished' pregnant women (BMI 18.5 to 25 kg/m^2) with doubly labeled water to measure free-living energy expenditure (TDEE). The median change in TDEE was 8 kcal per week and the average energy deposition was 180 kcal per day. The 2009 IOM committee evaluating the guidelines for weight gain in pregnant women, adopted the 2005 DRI recommendations (EER pregnant = EER non-pregnant + 8 KKW + 340 trimester 2 or 452 trimester 3) and stated, *"…keep in mind that these amounts are for women who were a normal weight before pregnancy. If you are overweight or obese, you may need fewer extra calories."* To address this gap, our group conducted the first study to assess energy balance physiology in pregnant women with obesity. For women with recommended weight gain (5 – 9 kg), they accumulated 7.0±0.8 kg of fat-free mass, which included fetal growth (2.7±0.1 kg), and a loss of fat mass (-2.5±0.8 kg). TDEE increased from 2664±119 to only 2984±121 kcal/d. Women with recommended weight gain maintained a negative energy balance (-125±52 kcal/d) during pregnancy compared to women with excess weight gain who increased their energy intake (345±42 kcal/d). To achieve weight gain recommendation, the change in EI during the second and third trimester would need to be -25±46 to 93±46 kcal/d for women with obesity. The 2005 DRI equations significantly over-estimated TDEE for pregnant women with obesity (+313±39kcal/d, p<0.001) and even more so for women who are Black (B: +422±55, W: +186±55kcal/d, p=0.003). With the high prevalence of obesity in reproductive-age women, and the disproportionate increase in their adverse pregnancy outcomes, energy requirements specific to women with obesity are needed to inform evidence-based interventions to promote recommended weight gain.

O-11 Energy Expenditure in Women: The Effects of Oestrogens and Exercise
Ed MELANSON — USA

In rodents, loss of estradiol (E_2) reduces brown adipose tissue (BAT) activity. Whether E_2 impacts BAT activity in women is not known. Thus, we measured BAT oxidative metabolism and glucose uptake were measured in premenopausal and postmenopausal women at room temperature (RT) and during acute cold exposure using computed tomography/positron emission tomography (PET/CT). Measures were repeated in a subset of premenopausal women after suppressing ovarian function for 6 months. At RT, there was no difference in the BAT oxidative index between premenopausal and postmenopausal women. During cold exposure, the BAT oxidative index increased more in premenopausal women. To isolate the effects of E_2 from age, a subset of premenopausal women underwent 6 months of ovarian suppression using a pharmacological approach. Following the suppression period, cold-stimulated BAT activity was nearly completely suppressed in these women. These data provide evidence that postmenopausal women have a lower capacity to stimulate BAT

thermogenesis. Combined with our preliminary data in premenopausal women following suppression of ovarian function, these data suggest that BAT metabolic activity in women is related to estrogen status.

O-12 Energy Homeostasis in Children and Adolescents
Shigeho TANAKA — Japan

School-aged children and adolescents have higher organ-tissue metabolic rates, in addition to new tissue accumulation. Therefore, a much higher energy metabolism for body size is observed during growth. Nevertheless, positive energy balance can occur even during growth. Lifestyle habits established at younger ages may be carried over into later years, making overweight/obese children more likely to become obese in later life.

Physical activity is related to energy balance, but the cause-effect relationship between physical activity and overweight/obesity is still unclear. Summer vacation is a period when children's energy balance is most likely to be upset and it has been reported that many children tend to become overweight/obese during summer vacation. Therefore, summer vacation may be one of the best opportunities to examine the causes of energy imbalance, including physical activity, sleep and diet, although the mechanism has not been sufficiently clarified yet.

We developed activity monitors which can discriminate non-ambulatory physical activity from ambulatory activity, which provide much more accurate prediction of activity intensity of activities in daily life, with the revised algorithm for children. We will introduce some results obtained by the objective methods.

O-13 Intra-Adipose Sex Steroid Hormone Metabolism and Human Visceral Obesity
André TCHERNOF — Canada

O-14 Mechanisms of Adaptive Thermogenesis Driving Catch-up Fat During Weight Regain
Abdul DULLOO — Switzerland

The recovery of body weight after substantial weight loss (or growth retardation) has often been shown in humans and other mammals to be accompanied by an accelerated rate of fat deposition (catch-up fat) - in part attributed due to a high metabolic efficiency for fat recovery. Such thrifty (energy conservation) metabolism for catch-up fat probably had evolutionary survival value as it contributes to the rapid restoration of survival capacity conferred by the rapid recovery of the fat reserves in preparation for the next period of food scarcity. Nowadays, however, it contributes to the ‘metabolic adaptation’ or ‘adaptive thermogenesis’ that facilitates obesity relapse after slimming, and to the disproportionately high rate of fat recovery (with lean tissue recovery lagging behind) that is often encountered during nutritional rehabilitation after malnutrition and disease cachexia or during catch-up growth.

This presentation reviews our search for mechanisms underlying this thrifty catch-up phenotype within the framework of an ‘adipose-specific control of thermogenesis’, with the focus on energy conservation mechanisms operating in the skeletal muscle through alterations in its fast-to-slow fiber composition and contractile properties, mitochondrial compartments and rates of substrate (futile) cycling, and in its local metabolism of thyroid hormones. The case is put forward that whereas adaptive thermogenesis during weight loss results primarily from a suppressed neuro-hormonal system that comprises circulating insulin, leptin, thyroid hormones and the sympathetic nervous system, the adaptive thermogenesis driving catch-up fat

operates primarily through peripheral resistance to the actions of this neuro-hormonal network - with emerging evidence pointing to a key role for altered skeletal muscle thyroid hormone deiodination.

O-15 Examining Futile Cycles as Recruitable Forms of Heat Production – Is it Fruitless?
Denis BLONDIN — Canada

Humans demonstrate a remarkable ability to adjust their metabolism in response to various acute and long-term stressors. Indeed, our early research interests aimed at improving operational performance of armed forces personnel in cold environments provided the impetus to examine whether heat generating mechanisms could be altered to increase the use of fatty acids and reduce the reliance on shivering. Brown adipose tissue became an ideal target to help reduce the reliance on disruptive bursts of shivering and increase the reliance on more abundant fuel sources. Our work and the work of others has demonstrated that this tissue is remarkably responsive to repeated cold exposures in humans, increasing both its apparent mass and its oxidative capacity. This increased oxidative capacity is counterbalanced by an improved coupling of oxidative phosphorylation in skeletal muscle, resulting in a transfer of one form of non-shivering thermogenesis from muscle to BAT. Whether other forms of muscle non-shivering thermogenesis, such as calcium cycling, are present and altered in response to repeated cold exposures in humans remains unknown. In the process of examining BAT in humans, we have also discovered an important contribution of the glycerolipid-fatty acid cycle. This is a cycle that we have demonstrated to be upregulated in response to mild cold exposure, except in men with type 2 diabetes. This cycle also accounts for a significant proportion of the increase in energy expenditure observed in men given a high dose of the beta-3 adrenergic receptor agonist, Mirabegron, demonstrating a promising energy dissipating target to increase energy expenditure. Pre-clinical work continues to highlight the metabolic importance of stimulating these energy consuming substrate cycles, but further work is needed to determine the presence and relevance of these cycles in humans. This presentation will highlight the current state of knowledge of various energetically costly cycles described in the literature with particular attention focused on their activation and relevance in humans.

O-16 Regulatory Thermogenesis: UCP1 and Beyond
Lawrence KAZAK — Canada

Noradrenaline regulates cold-stimulated adipocyte thermogenesis. Aside from cAMP signaling downstream of β-adrenergic receptor (βAR) activation, how noradrenaline promotes thermogenic output is still not fully understood. Here, we show that coordinated α_1-adrenergic receptor (α_1AR) and β_3AR signaling induces the expression of thermogenic genes of the futile creatine cycle, and that EBFs, ERRs, and PGC1α are required for this response *in vivo*. Noradrenaline triggers physical and functional coupling between the α_1AR subtype (ADRA1A) to $G\alpha_q$ to promote adipocyte thermogenesis in a manner that is dependent on the effector proteins of the futile creatine cycle, creatine kinase b (CKB) and tissue-nonspecific alkaline phosphatase (TNAP). Combined $G\alpha_q$ and $G\alpha_s$ signaling selectively in adipocytes promotes a continual rise in whole-body energy expenditure, and CKB is required for this effect. Thus, the ADRA1A-$G\alpha_q$-futile creatine cycle axis is a key regulator of facultative and adaptive thermogenesis.

O-17 mTOR System in Brown Fat Thermogenesis
Mathieu LAPLANTE — Canada

Introduction. Brown adipose tissue (BAT) serves as a key heat-producing organ that impacts body temperature in mammals. Upon cold stimulation, activation of the sympathetic nervous system (SNS) acutely activates triglyceride breakdown, fatty acid oxidation and thermogenesis in BAT. Chronic cold exposure also triggers a well-defined transcriptional program required to sustain heat production in brown adipocytes. The mechanistic target of rapamycin (mTOR) is a serine/threonine kinase that controls several biological processes to promote

anabolism, growth, and proliferation. This kinase is part of two complexes termed mTOR complex 1 (mTORC1) and 2 (mTORC2). In response to nutrients and growth factors, these complexes phosphorylate various effectors to increase the synthesis of the macromolecules needed to support growth. Over the last years, the mTOR signaling pathway was reported to impact BAT function in rodents. However, the precise mechanisms regulating mTOR signaling in BAT remain elusive. DEP-domain containing mTOR-interacting protein (DEPTOR) was identified in 2009 as a novel factor interacting with both mTORC1 and mTORC2. Because DEPTOR binds and represses mTOR kinase activity, this protein was originally characterized as an inhibitor of both complexes. The ability of DEPTOR to rewire mTOR signaling has been shown to affect several metabolic processes in mice including the regulation of energy balance, liver metabolism, and white fat cell development. However, the impact of DEPTOR on BAT development and function has never been tested. **Results.** Here, we identify BAT as the tissues showing the highest expression of DEPTOR in mice. We show that DEPTOR levels are dynamically regulated upon acute and chronic cold exposure. Studies *in vitro* indicate that DEPTOR is highly induced during brown adipocyte development and that its depletion impairs brown preadipocyte differentiation. The adipogenic defect linked to DEPTOR loss is associated with impaired mTOR signaling and lower expression of key adipogenic regulators. To test the importance of DEPTOR for BAT development and thermogenesis *in vivo*, DEPTOR was conditionally deleted from preadipocytes or mature brown fat cells by crossing DEPTOR floxed mice with either *Myf5*-Cre or *Ucp1*-Cre^{ERT2} mice. Here, we show that conditional deletion of DEPTOR slightly reduced the expression of adipogenic and lipogenic genes but did not impact BAT recruitment and thermogenesis in mice. **Conclusions.** Our observations indicate that DEPTOR plays a positive role in brown fat adipogenesis *in vitro*, but that its expression is dispensable for BAT formation, recruitment, and thermogenic activation in mice.

O-18 Short Oral Presentation

Changes in Brain Energy Metabolism During Aging and at the Onset of Alzheimer Disease: Recent Developments with Ketone and FDG PET, Functional Connectivity, and Diffusion Imaging

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BACKGROUND: The brain is commonly considered to be fueled almost exclusively by glucose. This perception has arisen primarily because the studies have been done with participants on carbohydrate-rich diets and with the PET tracer for glucose metabolism – ^{18}F-fluordeoxyglucose (FDG). For over 50 years, ketones (acetoacetate and beta-hydroxybutyrate) have been known to replace declining glucose availability to the brain during starvation but their role in fuelling the brain under normal circumstances is still poorly understood. We developed a ketone PET tracer – ^{11}C-acetoacetate (^{11}C-AcAc) – to quantify brain ketone metabolism in healthy older people, Alzheimer disease (AD) and mild cognitive impairment (MCI), and assess the response to ketogenic interventions.

METHODS: ^{11}C-AcAc is administered first, followed by a wash-out period, and then FDG, with both scans completed with 120 min. Arterialized blood is collected to calculate the *cerebral metabolic rate* and *influx rate* of ketones (CMRk and K_{ketone}) or glucose (CMRg and K_{FDG}) expressed as mmol/100 g/min and min^{-1}, respectively. Volumetric, resting state functional, and diffusion MR images are acquired within a few days of the PET scan. Images are analyzed using PMOD® software.

RESULTS: Based on n>300 dual tracer PET scans: (i) healthy aging is associated with 7-8% lower *capacity* to take up FDG (K_{FDG}), primarily in the frontal cortex. (ii) MCI is associated with 9-10% lower K_{FDG}, primarily in the cingulate cortex. (iii) AD is associated 15-20% lower K_{FDG} in several cortical regions. (iv) No change in K_{Ketone} regionally or globally in the brain has been observed in any of these groups. (v) CMRk increases linearly as plasma ketone concentration. (vi) While in nutritional ketosis, the additional ketones spare brain glucose uptake in healthy adults, i.e., brain glucose uptake actually *declines* with higher ketone availability. (vii) While consuming a ketogenic drink based on medium chain triglyceride, myelin integrity and functional connectivity

improve in MCI in relation to the brain uptake of ketones in specific white matter tracts and functional networks, respectively. Some of these results have been confirmed by other groups using PET and other methods.

DISCUSSION: Our results demonstrate that the vulnerability of the aging brain to impaired glucose uptake is not observed with brain ketone uptake. The reason that ketones improve cognition in MCI is a least partly because they rescue (bypass) deteriorating brain glucose metabolism.

Acknowledgements: Supported by CIHR, CFI, FRQS, Alzheimer Association USA, Alzheimer Society Research Program (Canada), Nestlé Health Science, and Université de Sherbrooke.

O-19 Short Oral Presentation

The Acute Effects of a Single Dose of Anti-Obesity Drugs on Human Basal Metabolic Rate

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Background: Obesity develops when energy intake exceeds energy expenditure (EE) over a prolonged period. Anti-obesity drugs are commonly designed to reduce energy intake while some may impact the shared autonomic nervous system pathways which could stimulate or suppress EE. However, their effects on EE are not well investigated. Thus, we conducted a placebo-controlled, double-blind, randomized cross-over study to determine the acute effects of four FDA-approved anti-obesity drugs on basal metabolic rate (BMR) under controlled conditions. **Methods**: Fourteen lean male subjects (28.0±3.9 years, BMI 22.8±1.2 kg/m^2, body fat percentage 19.7±5.1%) were recruited to be measured on six separate visits in a thermoneutral (27.1±0.5°C) whole-room indirect calorimeter from 8:00 AM to 12:00 PM following an overnight fasted inpatient stay, all with an outpatient washout period between visits (12.1±8.6 days). During each visit, a single dose of the following drugs was administered in randomized order: placebo, caffeine (300 mg, positive control), phentermine (37.5 mg), topiramate (200 mg), Qsymia (phentermine 15 mg/topiramate 92 mg), and naltrexone (100 mg). We hypothesized that, compared to placebo, BMR would be altered by ≥5% (increase or decrease) for each of the medications to be considered clinically meaningful. Additionally, we explored changes in secondary outcomes including resting respiratory quotient (RQ), resting heart rate (HR), mean arterial pressure (MAP), self-reported hunger, free-fatty acids, and catecholamines (epinephrine and norepinephrine). Mixed-effects analyses controlling for multiple comparisons were used to compare each drug to placebo. **Results**: Compared to placebo, the positive control agent caffeine significantly increased BMR by (Mean±SD) 3.6±2.4% (1.20±0.1 vs 1.28±0.12 kcal/min; p=0.039) and MAP by 2.7± 1.6% (90.4±4.3 vs. 94.8±6.0 mmHg; p=0.003). Phentermine significantly increased resting HR compared to placebo (61.0±8.9 bpm) both by itself (69.0±11.3 bpm or 6.0±3.4%; p<0.0001) and in Qsymia (66.6±8.0 bpm, or 3.8±1.9%; p<0.0001). Additionally, compared to placebo, Qsymia significantly decreased plasma norepinephrine by 14.6± 9.1% (633.3±208.6 vs 480.8±153.8 pg/mL p=0.014). No other significant changes in BMR, resting RQ, epinephrine, FFA, or self-reported hunger were detected with any treatments. **Conclusions:** Unlike the positive control caffeine, a single dose of the anti-obesity drugs we tested did not acutely alter BMR or hunger, although some physiological changes in heart rate and norepinephrine were detected. When administered chronically, these drugs reportedly suppress appetite to reduce energy intake and promote weight loss, however additional research is needed to better understand their potential long-term impact on metabolic adaptation.

O-20 Short Oral Presentation

Underappreciated Role of the Histaminergic System in the Control of Energy Balance

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Histaminergic neurons of the tuberomammillary nucleus (TMN) are well recognized for their role in regulating arousal and wakefulness. These neurons also have projections to numerous hypothalamic nuclei involved in regulating energy balance. Evidence indicates that melanocortin 4 receptors (MC4R), key regulators of energy homeostasis, are expressed within the TMN. However, interactions between the melanocortin and histaminergic systems have received limited attention. Therefore, we aimed to determine whether the melanocortin system influences the activity and function of TMN neurons expressing histidine decarboxylase (HDC), the sole enzyme required for histamine synthesis. Whole-cell patch-clamp electrophysiology in combination with in vivo chemogenetic experiments were used to determine if HDC neurons receive metabolically relevant information via the melanocortin system. Our data revealed that MC4R agonism excites a subset of HDC neurons via a presynaptic glutamatergic mechanism. In vivo chemogenetic inhibition of HDC neurons strikingly enhanced the anorexigenic effects of intracerebroventricular administration of a melanocortin receptor agonist. These findings identify a functional interaction between the melanocortin and histaminergic systems, and suggest that histaminergic neurons act as a 'brake' to restrain the effects of melanocortin system activation. Together these data provide a novel mechanism by which HDC neurons detect and integrate changes in metabolic status and demonstrate an underappreciated role of the histaminergic system in the regulation of energy balance.

O-21 Short Oral Presentation

Effects of Time-Restricted Feeding on Energy balance: A Cross-Over Trial in Healthy Subjects

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Time-restricted feeding (TRF) has been recently reported as an effective dietary intervention for weight reduction, implying a negative energy balance, without restricting nutrient intake. However, the energy balance alteration caused by TRF remains unclear. This on-going study is a randomized controlled clinical trial using a within-subject cross-over design. Currently, twelve healthy, normal weight volunteers (age: 24 +/- 2.3 years; BMI: 21.9 +/- 1.71 kg/m2; N=5 males, 7 females) were studied under a rigorous control for calorie intake, physical activity as well as the sleep-wake cycle to evaluate energy balance systematically. Each participant consumed an isocaloric diet within either a 5.5-hour TRF or 11-hour control feeding schedule. All energy intake and excretions were traced, collected and accessed by bomb calorimetry. Energy expenditure (kcal) and substrate oxidation (g) were monitored in a whole room indirect calorimeter. Repeated measures ANOVA and linear-mixed model were applied to compare the effect of TRF on macronutrients homeostasis. Our preliminary results show that TRF increased fecal energy loss by 22.7% (Δ = 32.25 +/- 9.33 Kcal, p = 0.005) with an increasing tread for urinary energy loss of 4.5 % (Δ = 6.67 +/- 3.14 kcal, p = 0.058) without a change in energy expenditure compared to the control feeding schedule. The consequence was a negative energy balance (Δ = -45.95 +/- 19.00 kcal, p = 0.034) during TRF intervention, which was equal to -2.6 % of total energy intake. This model could explain the majority of weight loss in previous long-term isocaloric TRF studies. Furthermore, metabolic flexibility, 24-hour blood glucose and heart rate were also increased during TRF intervention. Taken together, our findings may unravel the mystery of how TRF regulates energy balance, supporting the use of TRF as an alternative dietary strategy for weight loss.

O-22 Short Oral Presentation

Impact of Endogenous vs. Exogenous Ketones on Energy Expenditure in Healthy Participants

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Background: Oral ketone supplements may mimic the beneficial effects of endogenous ketones on energy metabolism as ß-hydroxybutyrate (BOH) has been proposed to increase energy expenditure and improve body weight regulation.

Methods: Seven healthy adults (4 women, 3 men; 24.2 ±2.8 y; BMI 23.6 ±2.7 kg/m^2) participated in a randomized cross-over trial with four 24h-interventions in a whole room indirect calorimeter with a physical activity level of 1.65: (1) isocaloric formula diet (ISO, 47% carbohydrates, 40% fat, 13% protein), endogenous ketone production due to (2) total fasting (FAST) or (3) isocaloric ketogenic formula diet (KETO, 3% carbohydrates, 89% fat, 8% protein) and (4) exogenous ketones (3x12.9 g ß-hydroxybutyrate, BOH as ketone salts) provided with an isocaloric formula diet (EXO). Serum-BOH levels (15 h iAUC), 24 h-BOH excretion, total energy expenditure (TEE) and sleeping energy expenditure (SEE) were measured.

Results: Compared to ISO, KETO led to higher BOH levels and EXO led to higher BOH excretion (both $p < 0.05$). Neither BOH levels nor BOH excretion differed between EXO and KETO or FAST and KETO. TEE and SEE were higher with KETO compared to FAST (TEE +149 ±90 kcal/d, SEE +123 ±78 kcal/d, both $p < 0.05$) as well as compared to ISO (TEE +110 ±54 kcal/d, SEE +199 ±96 kcal/d, both $p < 0.05$) and EXO (TEE +161 ±84 kcal/d, SEE +295 ±98 kcal/d, both $p < 0.05$). No differences in TEE or SEE were observed between EXO and ISO.

Conclusion: Endogenous ketones produced under isocaloric conditions of a ketogenic diet, in contrast to caloric restriction during fasting, led to higher energy expenditure compared to isocaloric control. Supplementation of exogenous ketone salts did not increase energy expenditure compared to isocaloric control and thus could not mimic the effects of a ketogenic diet.

O-23 Short Oral Presentation

Combined α- and β-adrenergic Receptor Activation Triggers Thermogenesis by the Futile Creatine Cycle

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Noradrenaline regulates cold-stimulated adipocyte thermogenesis. Aside from cAMP signaling downstream of β-adrenergic receptor (βAR) activation, how noradrenaline promotes thermogenic output is still not fully understood. Furthermore, while the transcriptional mechanisms regulating *Ucp1* are well-characterized, the transcriptional regulation of UCP1-independent thermogenesis is largely unknown. Here, we show that coordinated α-adrenergic receptor (αAR) and βAR signaling induces the expression of thermogenic genes of the futile creatine cycle, and that EBFs, ERRs, and PGC1α are required for this response *in vivo*. Noradrenaline triggers physical and functional coupling of α_{1A}AR (ADRA1A) to $G\alpha_q$ to promote thermogenesis through the futile creatine cycle. Combined fat-selective $G\alpha_s$ (activated by βARs) and $G\alpha_q$ (activated by αARs) signaling elevates whole-body energy expenditure to a greater extent than either signaling pathway alone in a manner that is largely dependent on an effector protein of the futile creatine cycle, CKB. Combined $G\alpha_q$ and $G\alpha_s$ signaling in adipocytes is critical for adaptive thermogenesis. Thus, the ADRA1A:$G\alpha_q$: futile creatine cycle axis is a key regulator of facultative and adaptive thermogenesis

O-24 Thermogenic Flexibility in Response to Weight Loss and Regain
Paul S MACLEAN — USA

O-25 Permanence of Thermogenic Changes Induced by Weight Loss in Obese Individuals
Eric RAVUSSIN — USA

Even if it is well accepted that body weight settles at a level at which energy expenditure (EE) balances energy intake (EI), the role of EE in the control of body weight has been much debated. There are at least three lines of evidence pointing to the role of EE in regulating body weight: 1) Studies in the Pima Indians have clearly shown that EE (and fat oxidation) are both genetically determined and that a low relative EE (and/or a low fat oxidation) is associated with significant weight gain; 2) In response to acute episodes of overfeeding or fasting, Piaggi et al identified "thrifty" and "spendthrift" phenotypes associated with resistance or ease of losing weight during caloric restriction; Data from the Weight Control Registry showed that individuals engaging in regular physical activity are more likely to be successful at maintaining significant weight loss.

Although most patients with obesity can achieve weight loss of 10% or more, a large majority struggles to maintain a reduced body weight over months or years. Many have argued that the primary contributor to weight regain is energy intake rather than expenditure. However, some have hypothesized that part of the failure to maintain weight loss is that negative energy balance triggers a slowing of metabolic rate called "metabolic adaptation". Such decrease in resting metabolic rate (RMR) is larger than what would be expected from the loss of metabolic mass and partially explain the resistance to further weight loss and the propensity to weight regain.

Leibel et. al reported significant metabolic adaptation after weight loss that persisted for years after weight loss. An even larger metabolic adaptation was observed in participants of the "Biggest Loser" competition. Furthermore, despite some important weight regain over the next 6 years (>70% of initial weight loss), these individuals were still quite "thrifty" in term of metabolism.

In my presentation, I will address the role of metabolic adaptation in the speed of weight loss, the maintenance of weight loss (or lack of), and the pace of weight regain. The overall impact of metabolic adaptation on energy balance may be rather small (~6% of daily EE) but the variance among individuals is considerably larger. As we initially proposed, an impaired EE can only explain a small fraction of the observed weight gain. Therefore, a low RMR may also be a marker for either enhanced hunger or impaired satiation and therefore hyperphagia. Confirming such hypothesis, caloric restriction was shown to impact circulating mediators of appetite after weight loss with an elevation of orexigenic signals and a reduction of anorexic signals, and that even one year later.

O-26 Mitochondria and their Role in the Interindividual Variability in Weight Loss and Exercise Response
Mary-Ellen HARPER — Canada

Current paradigms for forecasting weight loss in response to energy restriction have general validity but a subset of individuals with obesity fail to respond well, despite documented diet adherence. A better understanding of the variability in response to obesity treatments (*i.e.,* dietary, exercise, pharmacological or surgical), will allow better personalised approaches for the treatment of distinct obesity phenotypes.

Our previous findings show that patients in the lowest 20% for rate of weight loss in the first 6 weeks of a hypocaloric diet (diet-resistant) have distinct plasma proteomes, less type I muscle fibres, lower oxidative gene transcriptomes, and lower muscle mitochondrial function (*e.g.*, proton leak uncoupling, and fatty acid oxidation) compared to the top 20% of patients for rate of weight loss (diet-sensitive), leading to the

hypothesis that exercise may be an effective treatment when diet alone is insufficient. We thus examined the efficacy of exercise training on muscle mitochondrial function and metabolome characteristics in women having a documented history of minimal diet-induced weight loss.

From over 5000 patient records from the Ottawa Hospital Weight Management Program, we reviewed 228 files to identify baseline characteristics in those classified in the top or bottom 20% for weight loss in the first 6 weeks of the 900 kcal/day meal replacement program. A subset of 20 women identified as diet-resistant (DR) or diet sensitive (DS) then underwent a 6-week supervised, progressive, combined aerobic and resistance exercise intervention. Findings showed that DS had higher fasting insulin and triglycerides, greater abdominal *vs*. gluteofemoral adiposity, and a greater number of ATP-III criteria for metabolic syndrome. In DR women, the exercise intervention improved body composition, *vastus lateralis* mitochondrial content, length and metabolism, with minimal effects in DS. In-depth analyses of muscle metabolomes revealed distinct group- and intervention- differences, including decreases in serine-associated sphingolipid synthesis (*e.g.,* ceramides) correlation network in DR women following exercise training. Proton leak uncoupling in myofibres was lower in DR than DS (main effect). Protein levels of adenine nucleotide translocase (ANT), which can cause proton leak uncoupling, were lower in DR than DS (main effect).

Thus, exercise preferentially enhances skeletal muscle metabolism and improves body composition in women with a history of minimal diet-induced weight loss. The role of ANT-mediated proton leak uncoupling in DR and DS obesity requires further investigation.

O-27 Low Capacity to Oxidize Fat and Body Weight

François PÉRONNET — Canada

It has been suggested that fat accumulation and weight gain could be favored by a low intrinsic capacity to oxidize fat (low fat oxidation hypothesis of weight gain). This hypothesis is based on the assumption that in subjects ingesting for some days a diet with a stable FQ, the RQ reflects a low intrinsic capacity to oxidize fat. This assumption is not valid. In this situation, the 24-h RQ is entirely determined by the FQ and the energy and mass balances (positive, negative, or equal to zero), which are dictated by the laws of conservation of mass and energy and the RQ/FQ concept, and thus are totally independent of any characteristic of the subject, including the genetic makeup and a purportedly capacity to oxidize fat. As for the fasting RQ, it mainly depends on the availability of CHO, which in turn depends on the FQ and the energy balance the previous days. In line with these observations directly derived from first principles, because of the constraints of the laws of conservation of mass and energy, and as shown in an animal model, there is no evidence that any intervention that will increase fat oxidation without increasing EE will favor weight loss in negative energy balance. Numerous studies have also examined the arguments in support of the low fat oxidation hypothesis, i.e., that the RQ is higher in obesity prone than in obesity resistant subjects and that the higher the RQ at baseline, the larger the future weight gain. A review of these studies shows that the experimental results do not provide any convincing experimental evidence in support to this hypothesis.

O-28 Short Oral Presentation

Tuning and Validation of a Closed-Loop Control System for Air Flow to Improve Accuracy of Whole-Room Indirect Calorimeters During Dynamic Metabolic Studies

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Although whole-room indirect calorimeters (WRIC) are accurate and reproducible tools to assess human energy metabolism, some technical challenges need to be tackled to ensure high levels of accuracy of individual O_2 consumption (VO_2) and CO_2 production (VCO_2). Dynamic control of air flow rate may allow CO_2 concentration inside the WRIC to promptly achieve the midpoint of an analyzer calibration curve (~0.4-0.5% for

a 0-1% range CO_2 analyzer) to increase accuracy of VCO_2 and respiratory exchange ratio (RER) estimates. We report results using an automatic, proportional-integrative-derivative (PID) feedback control system for inflow rate implemented in one push calorimeter at the NIDDK in Phoenix, Arizona.

A precision gas blender infused N_2 and CO_2 into the respiratory chamber for 24 h with static and dynamic infusion profiles mimicking VO_2 and VCO_2 changes during resting and non-resting conditions. Conditions for air inflow rate during infusion tests included constant (30-45-60 L/min) and time-variant rates set by a PID controller based on CO_2 concentration inside the chamber. Results were compared based on errors between measured vs. expected values for VO_2, VCO_2, RER, and metabolic rate (MR) simulated by gas infusions.

Compared to constant inflow conditions, the PID controller allowed both a faster rise time from baseline CO_2 concentration and long-term maintenance of a stable CO_2 concentration inside the WRIC, resulting in more accurate VCO_2 estimates (mean hourly error, PID:−0.9%, 60 L/min=−2.3%, $p<0.05$) during duplicate static infusions. During dynamic infusions (n=8) mimicking acute exercise conditions, the PID controller achieved smaller errors for VCO_2 (mean: −0.6% vs. −2.7%, p=0.02) and RER (mean: 0.5% vs. −3.1%, p=0.02) compared to the constant 60 L/min condition, with no differences for VO_2 (p=0.97) and MR (p=0.76) errors.

PID control of inflow rate leads to improved WRIC performance and more accurate metabolic measurements during dynamic metabolic studies.

O-29 Short Oral Presentation

Practical Application and Considerations for Doubly Labeled Water Assessment in Infants

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Assessment of energy expenditure from birth is fundamental to understanding the biological origins of health and disease. Doubly labeled water (DLW) is the gold-standard method to measure free-living total daily energy expenditure (TDEE). TDEE is calculated from changes to isotopic enrichment in bodily fluids, including urine and saliva. Inherent complexities of infant subjects increase the likelihood of erroneous data. Therefore, we conducted a method development study to determine best practices of the application of DLW in infants including the feasibility of using saliva versus urine in DLW protocols and data outcomes between the two biospecimens.

Infants aged one to three months completed a 7-day DLW study. Following collection of baseline saliva and urine samples, infants received a single oral dose of DLW (0.1g ^2H_2O at 99.98% ^2H and 1.6g 10% ^{18}O kg/body weight) in the laboratory. Three post-dose samples (3-hour and 5-7 days) were collected. Samples were analyzed at Baylor College of Medicine (saliva) and Pennington Biomedical (urine).

Twenty-eight infants provided saliva samples and 7 additionally provided urine. In total, 11 (39.3%) salivary sets contained ≥1 erroneous samples and 9 (32.1%) were invalid. Invalid data were non-physiological (n=6), inadequate volume (n=2), and inadequate dosing (n=1). Salivary data tended to have less errors with older age (68±11 vs 60±14 days). One set of urine samples were invalid (14%). Urinary and salivary obtained TDEE were positively correlated (r=0.8, p=0.04) with no proportional bias. Salivary TDEE tended to be higher (saliva:400±56 vs urine:364±67 kcals/day, p=0.06).

In infants, TDEE can be obtained from saliva or urine, yet erroneous data is greater with salivary samples. Importantly, dosing procedures remain constant regardless of collection method. Given that the International Atomic Energy Agency recommends saliva for infant assessment in low resource settings, special considerations are warranted to ensure accurate and adequately powered data from infant DLW studies.

O-30 Short Oral Presentation

Determination of Energy Expenditure in Professional Cyclists Using Power Data: Validation Against Doubly Labelled Water

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Purpose

Accurate determination of total daily energy expenditure (TDEE) in athletes is important for optimal performance and injury prevention, but there is insufficient information to accurately determine TDEE in-field. We therefore developed an approach to determine TDEE in professional cyclists based on power data.

Methods

21 male professional cyclists participated in this study. The following parameters were measured to create a model for step-by-step calculations of TDEE: 1) basal metabolic rate (BMR), 2) the relation between power output and energy expenditure (EE) during an incremental cycling test, which was used to determine EE during exercise (EE_E) based on the measured power output, and 3) TDEE using doubly-labelled water (DLW). A non-exercise physical activity level (PAL) value was obtained by subtracting BMR and EE_E from TDEE.

Results

Measured BMR of male cyclists was 7.9 ± 0.8 MJ/day, which was significantly higher than predicted by the Oxford equations. Mean TDEE obtained with DLW was 31.7 ± 2.8 MJ/day and 27.3 ± 2.8 MJ/day during the Vuelta a España and Ardennes classics, while EE_E obtained from the power-energy relationship was 21.1 ± 0.8 MJ/day and 27.9 ± 3.7 MJ/day, respectively (Figure 1). Non-exercise PAL values were 1.3 and 1.8 for the Vuelta and Ardennes classics, respectively.

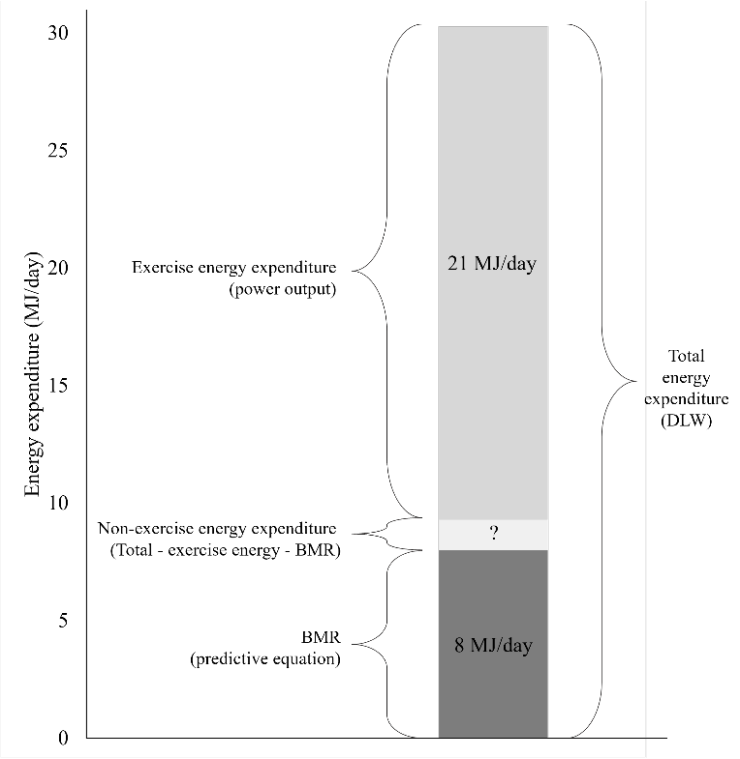

Figure 1 Schematic representation of the proposed step-by-step approach to determine energy expenditure.

Conclusion

The proposed approach leads to a more accurate estimation of EE than the use of a generic PAL value in

combination with BMR predictive equations developed for non-elite athletes, and is also relatively easy to implement in practice. This in turn can improve nutritional strategies in professional cyclists.

Keywords: Physical activity level; Professional cyclists; Indirect calorimetry; Energy expenditure; Endurance athletes

O-31 Short Oral Presentation

Utility of Schofield Equations for Estimating Resting Energy Expenditure in a West African Population

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Resting energy expenditure (REE) is an important component of the calculation of energy requirements in both clinical and non-clinical settings. In much of the world, however, measurement of REE is not possible owing to both expense and inaccessibility of indirect calorimetry. In such settings, utilization of prediction equations based on easily measured anthropometric factors is necessary. The accuracy and utility of widely used equations have not been examined in low-income countries, however. For this analysis, we compared measured REE with REE predicted using the Schofield equations in a large sample of individuals of Yoruba ethnicity living in southwest Nigeria. In the rural community of Igbo-Ora, Oyo State, data were collected from a convenience sample of 1336 individuals aged 13-85 years and approximately 50% female. REE was measured following an overnight fast (>10 hours) using a Delta Trac II indirect calorimeter (Viasys Medical Systems, Palm Springs, CA). Prior to all measurements, the Delta Trac was calibrated using gas of known concentration, and alcohol burns were performed monthly; the unit operated with a variance of less than 2% over the study period. Age, sex, height, weight, fat-free mass, and fat mass were also collected on all participants. Predicted REE was calculated using the age- and sex-specific equations from Schofield (Schofield, Schofield, and James, 1985) which included weight and height. Of the participants, the majority were between 19-60 years of age (68.8%), while 13.3% were 18 or below, and 17.9% were over 60. The sample, as a whole, was relatively lean with a mean body mass index of 22.0 and percent body fat of 25.4%. Mean (±SD) measured REE, unadjusted, was 5.77 ± 0.85 MJ/d (1378 ± 204 kcal/d); mean predicted REE was 5.93 ± 0.76 MJ/d (1417 ± 182 kcal/d). The mean difference between measured REE and predicted REE was 0.17 ± 0.56 MJ/d (40 ± 133 kcal/d), i.e. <3% difference between measured and predicted. This variance did not differ by age, sex or mean REE. These results illustrate a slight overestimation of REE when predicted using age- and sex-specific Schofield equations. The 2.5-2.9% overestimation was consistent across the age span from teens to the elderly and for both sexes. In conclusion, the Schofield equations for calculating age- and sex-specific REE from height and weight provide reasonable estimates of REE in settings where direct measurement using indirect calorimetry is not feasible.

O-32 Short Oral Presentation

Sex Differences in Free-living Total Daily Energy Expenditure and Physical Activity in Adults Successfully Maintaining Weight Loss

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Background: Prior research suggests high physical activity (PA) levels are associated with successful weight loss maintenance. Globally, females have lower self-reported and device-measured PA levels than males, but whether these sex differences are apparent among successful weight loss maintainers (WLM) is not clear. Our

objective was to examine sex differences in free-living total daily energy expenditure (TDEE) and PA in successful WLM as compared to non-weight reduced controls.

Methods: Weight stable adult males and females (n=104) were recruited in three groups: WLM (maintaining ≥13.6kg weight loss for ≥1yr); normal weight controls (NC, similar to post-weight loss body-mass-index of WLM); and controls with overweight/obesity (OC, similar to pre-weight loss body-mass-index of WLM). Resting energy expenditure (REE) was measured with indirect calorimetry, total daily energy expenditure (TDEE) was measured with doubly labeled water, and body composition was measured via dual X-ray absorptiometry. PA energy expenditure (PAEE) was calculated as TDEE – REE - thermic effect of food (estimated as 10% of TDEE). Steps/day, and mins/day in sedentary, light-intensity PA and moderate-to-vigorous-intensity PA (MVPA) were measured using activPALs over 7 days. Sex differences were assessed with sex × group interaction terms and within-group contrasts in linear regression models. To investigate sex differences in TDEE and PAEE independent of body composition differences, fat-free mass and fat-mass were included as covariates. Least square mean estimates and 95% confidence intervals (adjusted for body composition where relevant) are presented in Table 1.

Table 1. Least square mean estimates and 95% confidence intervals across 3-groups in females and males.

		WLM				NC				OC				Sex-difference omnibus *p*-value
		n	Mean	95% CI		n	Mean	95% CI		n	Mean	95% CI		
TDEE (kcals/day)	Females	21	**2400****	2235	2566	25	**1999****	1847	2150	25	**2484****	2333	2636	0.06
	Males	11	**3012****	2784	3241	12	**3027****	2808	3246	10	**3122****	2882	3362	
$TDEE_{Adjusted\ for\ Body\ Composition}$ (kcals/day)	Females	21	**2674**	2525	2823	25	2482	2312	2653	25	**2700****	2524	2876	**<0.001**
	Males	11	**2283**	2023	2542	12	2529	2311	2747	10	**2200****	1901	2499	
PAEE (kcals/day)	Females	21	802	672	932	24	**562****	440	684	23	635	511	759	0.064
	Males	11	928	749	1108	12	**995****	823	1167	9	739	541	938	
$PAEE_{Adjusted\ for\ Body\ Composition}$ (kcals/day)	Females	21	**919****	785	1053	24	789	633	944	23	**883****	725	1041	**0.004**
	Males	11	**431****	198	663	12	637	442	833	9	**286****	6	566	
Sedentary (mins/day)	Females	16	**585***	536	633	23	596	556	637	20	634	591	678	0.376
	Males	10	**706***	645	768	11	643	585	702	7	707	633	781	
Light PA (mins/day)	Females	16	**293****	249	337	23	282	245	319	20	**247***	208	287	0.113
	Males	10	**137****	81	193	11	225	172	278	7	**123***	56	190	
MVPA (mins/day)	Females	16	98	86	111	23	73	62	83	20	52	41	64	0.66
	Males	10	87	71	103	11	66	51	81	7	54	35	73	
Steps/day	Females	16	12857	11167	14546	23	9619	8210	11028	20	6726	5215	8237	0.338
	Males	10	10512	8375	12649	11	8815	6777	10853	7	7378	4823	9933	

Bold: within-group sex-difference $p<0.05$

***Bold**: within-group sex-difference $p<0.01$

****Bold:** within-group sex difference $p\leq0.001$

TDEE: Total daily energy expenditure; PAEE: Physical activity energy expenditure (TDEE - resting energy expenditure – Thermic Effect of Food [10% of TDEE]); kcals: kilocalories; mins: minutes

Results: Patterns of TDEE and PAEE (adjusted for body-composition) across the 3 groups were significantly different between sexes ($p<0.001$ and $p=0.004$, respectively). Among females, NC had lower adjusted TDEE than WLM ($p=0.004$) and OC ($p=0.041$). Conversely, in males, NC had higher adjusted TDEE than WLM ($p=0.052$) and OC ($p=0.013$). Within WLM and OC, adjusted TDEE was higher in women than men ($p=0.018$ and $p=0.002$, respectively), as was adjusted PAEE ($p=0.001$ and $p<0.001$). WLM females exhibited less sedentary time than WLM males ($p=0.003$) and higher levels of light-intensity PA ($p<0.001$). Differences in MVPA or steps/day were not statistically significant.

Conclusions: Female WLMs had higher body composition adjusted TDEE and PAEE, more light-intensity PA, and less sedentary time than male WLMs. Our findings suggest weight loss maintenance in females may require higher levels of PAEE relative to males, and higher PA levels relative to population averages than males. To sustain weight loss in females, novel approaches and additional support will likely be needed to increase PA and PAEE.

O-33 Short Oral Presentation

Inter-Individual Variability of Human Thermoregulation: Towards Personalized Ergonomics of the Indoor Thermal Environment

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Indoor temperature maintenance represents a large portion of the energy used in buildings and reducing dependence on energy-intensive thermal conditioning systems would benefit our fight against climate change as well as potentially have positive effects on human physiology/psychology. Thus, instead of conditioning spaces, the shift towards targeted conditioning of people is necessary. New technologies can now assimilate various inputs into building thermal controls with the potential to directly integrate physiological parameters from individuals living/working in the buildings. Yet the data to adequately model metabolic rate in individuals under various normal daily activities is still lacking. It is within this context that a synergistic collaborative effort between the *Laboratory of Integrated Comfort Engineering* (ICE) headed by Dr. Khovalyg at the EPFL and the *Laboratory of Energetics and Advanced Nutrition* (LEAN) headed by Dr. Ravussin at the UNIFR has been undertaken to try to integrate human physiology with building HVAC systems. The synergism between these two labs will take advantage of the ICE research facility in which the indoor environment can be controlled in a modular manner all while obtaining metabolic, physiological, and psychological data from subjects undertaking normal living/working tasks.

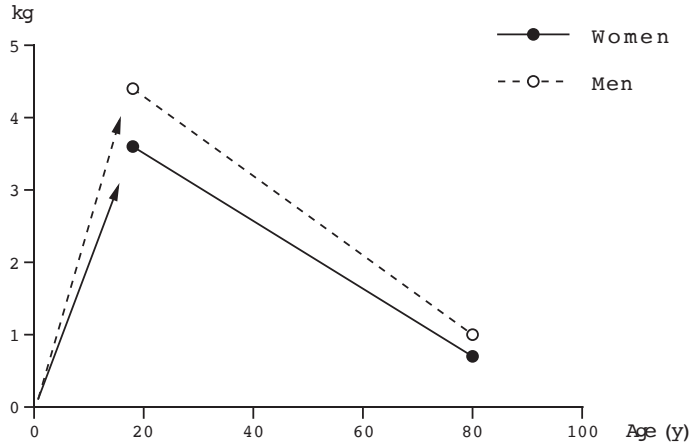
In the first round of experiments, we examined physiological (e.g. metabolic rate, heart rate) and psychological (e.g. alertness, cognitive performance) changes during multiple normal day activities (e.g., standing up, eating a meal, low-level activity) in a "normal" population at thermoneutrality (23-24^{o}C), cold (16^{o}C), and warm (32^{o}C) temperatures both during the summer and winter seasons (Khovalyg & Ravussin, Obesity, *in press*). Large inter-individual differences amongst the subjects are demonstrated on multiple measured parameters and suggest that these differences will need to be integrated as input into future personalized temperature control systems. The second round of experiments is more office-centric and includes similar measurements while doing sitting work (typing), and standing work, while the meal is standardized. We will present our data related to these studies in terms of inter-individual variability of the metabolic rate and further overview metabolic rate models available from the literature and discuss their drawbacks when it comes to individuals' dynamic metabolism. In addition, we will present our future outlook on how to capture humans' dynamic metabolism using invasive and non-invasive approaches and use them to decrease the operational energy of buildings and potentially positively impact human metabolic health parameters (e.g. by impacting brown adipose tissue or creating thermal environments more conducive to higher mental concentration levels).

O-34 **Physical Activity and Body Composition during Growth and in Later Life**

Klaas WESTERTERP (on behalf of the IAEA DLW database group) — Netherlands

The doubly labelled water method is the indicated method to measure total energy expenditure (TEE) under free-living conditions. The method was first described in 1955, initially applied for the measurement of energy expenditure in small animals, and subsequently validated for energy expenditure assessment in humans in 1983. The method typically allows assessment of human energy expenditure over intervals of at least a week. Here, data on TEE measurements with doubly labelled water are presented, accompanied by measurements of resting energy expenditure (REE), to allow calculation of physical activity level (PAL = TEE/REE).

TEE increases with body size. PAL is not decreased in overweight and obese participants. However, body movement is lower in overweight and obese participants, despite similar activity energy expenditure. Exercise training increases exercise economy, especially in untrained participants. Larger body size limits high-intensity activity, and exercise training has little or no long-term effect on energy balance. Physical activity increases fat-free mass during growth under age 18 year. Older age counteracts the positive association of physical activity with fat-free mass as illustrated in the figure below, showing fat-free mass difference between a sedentary participant PAL 1.5) and a physically active participant (PAL 2.0), as a function of age.



Physical activity is a determinant of body composition as reflected in peak-fat-free mass.

O-35 Human Water Intake: Great Variation Associated with Environmental and Lifestyle Factors
Yosuke YAMADA (on behalf of the IAEA DLW database group) — Japan

Water is essential for survival, but one in three individuals worldwide (2.2 billion people) lack access to safe drinking water. Water intake requirements largely reflect water turnover, the water used by the body each day. We investigated the determinants of human water turnover in 5,604 people aged 8 days to 96 years from 26 countries using isotope tracking (2H) methods. Age, body size, and composition were significantly associated with water turnover as were physical activity, athletic status, pregnancy, socioeconomic status, and environmental characteristics (latitude, altitude, air temperature, and humidity). People in countries with low human development index (HDI) had higher water turnover than people who lived in countries with high HDI. Based on this extensive dataset we provide equations to predict human water requirements in relation to anthropometric, economic, and environmental factors.

O-36 Total Energy Expenditure and Body Composition in Populations across the Socioeconomic Spectrum
Herman PONTZER (on behalf of the IAEA DLW database group) — USA

Population differences in obesity are due to a mismatch between energy intake and expenditure, but the role of each is unclear. Using objectively measured energy expenditure data from the IAEA Doubly Labelled Water Database, we compared total energy expenditure (TEE), basal energy expenditure (BEE), activity energy expenditure (AEE) and physical activity level (PAL) across populations grouped by socioeconomic development: hunter-gatherer, horticulturalist, or low, middle or high Human Development Index (HDI) ranking (n = 5,743 for TEE and n=1,901 for BEE, AEE and PAL). TEE adjusted for age, sex, fat-free mass, and fat mass was 3.0% higher in High HDI compared to Mid HDI ($p = 0.004$) but equivalent to Hunter-gatherer, and significantly lower than Low HDI or Horticulturalists (5.2% and 10.6%, respectively; $p<0.001$). PAL and adjusted AEE in High HDI were at or above levels measured in Mid HDI, Low HDI, and Horticulturalist populations. No inverse association between TEE and body fat was observed in any model. Obesity in more socioeconomically developed and industrialized populations appears to derive primarily from increased energy intake rather than decreased expenditure.

O-37 Developing New Tools to Study Sympathetic Regulation of Brown Adipose Tissue Function
Lori ZELTSER — USA

Cold or adrenergic stimulation of brown adipose tissue (BAT) induces thermogenesis and improves glucose tolerance in mice and humans. Cold-induced activation of BAT is diminished in the context of obesity and aging.

However, the nature of the primary impairment in sympathetic signaling in these conditions remains a matter of debate. A major obstacle to resolving this issue is the dearth of tools to directly modulate and measure SNS signaling in BAT. The seminar will highlight progress and failures in assembling a toolkit to study sympathetic regulation of brown adipose tissue function.

O-38 Chemogenetics to Approach the Adrenergic Control of Liver and Adipose Tissues
Alexandre Caron — Canada

Chemical genetics, also known as chemogenetics, is an approach use to genetically engineer receptors that interact with previously unrecognized small molecule chemical actuators. This approach has been used to create modified GPCRs, called Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), that can only be activated by clozapine-N-oxide (CNO) and compounds with similar structure. Originally developed to control neuronal activity, DREADDs are emerging as key tools for selective pharmacological control of GPCR signaling in any cell type or organ. These tools offer the potential to stimulate GqPCR (using the DREADD receptor hM3Dq), GiPCR (using the DREADD receptor hM4Di) and GsPCR (using the DREADD receptor rM3Ds).

Recently, we reported the generation of a novel chemogenetic approach allowing acute stimulation of GPCR signaling in adipocytes. This innovative model revealed important, previously unappreciated complex interactions of GPCR signaling in adipose tissue and demonstrated the usefulness of chemogenetic technology to better understand adipocyte function. Stimulation of GsPCR signaling in adipocytes induced rapid and sustained hypoglycemia. These hypoglycemic effects were secondary to increased insulin release, likely consequent to increased lipolysis. Notably, we also observed differences in gene regulation and ex vivo lipolysis in different adipose depots. In contrast, acute stimulation of Gi signaling in adipose tissue did not affect glucose metabolism or lipolysis, but regulated leptin production. We also harnessed the power of chemogenetics to manipulate GPCR signaling in the liver with the objective of identifying key pathways regulating lipid and glucose homeostasis in hepatocytes.

In this lecture, I will discuss recent advances and controversies related to the use of chemogenetics to manipulate GPCR signaling, acutely and chronically, in metabolic organs.

O-39 Metabolomics of cardiometabolic diseases: potential markers of pre-morbidities for Covid-19
Marc-Emmanuel DUMAS — UK

The gut microbiome – the comprehensive set of bacterial genes in our guts – is now recognized as a key driver in the pathophysiology of obesity, type 2 diabetes and cardiometabolic diseases and their common low-grade inflammatory component. However, the signals sent by the gut microbes to the host remain elusive. Through machine learning and multivariate analysis of metabolomes and metagenomes our group identified clinically relevant and drug-deconfounded microbiome signatures for the progression along the cardiometabolic disease spectrum, paving the way for new hypotheses and elucidation of the mechanisms impacted by the gut microbiome.

O-40 Circadian Rhythm Parameters and Physical Activity Differentially Associated with Cardiometabolic Risk Factors in the Controlled Respiratory Chamber vs. The Free-Living Condition – A PREVIEW Lifestyle Study
Margriet WESTERTERP-PLANTENGA — Netherlands

The present sub-study of the PREVIEW intervention study investigated post-hoc associations between circadian-rhythm parameters, physical activity (PA) and cardiometabolic risk factors during one week in 91 free-living participants (age=56.6±10y; BMI=28.2;homeostatic-model-assessment-of-insulin resistance (HOMA-IR)=3.2±3.1) and during 48h in 38 participants in sedentary respiration-chamber conditions at Maastricht University (NCT01777893). Circadian-rhythm parameters (continuous wrist-temperature measurements), and

PA (accelerometry) were determined continuously; cardiometabolic risk factors (systolic and diastolic blood-pressure (SBP, DBP), heart rate (HR), plasma HDL-cholesterol-, LDL-cholesterol-, remnant cholesterol (RC)-, triacylglycerol (TAG)-, C-reactive-protein (CRP)-concentrations), were determined in the mornings in fasting conditions. Associations of circadian-rhythm parameters and PA with cardiometabolic risk factors were determined using factor-analyses followed by Pearson's correlations.

Values of cardiometabolic risk factors were similar, while circadian-rhythm parameters and PA differed significantly (P<0.05) between free-living and respiration-chamber conditions. In free-living conditions, parameters indicating a robust circadian-rhythm, associated inversely with SBP, DBP, CRP, and PA, and positively with plasma HDL-c-concentrations. PA associated inversely with HR and SBP, and positively with plasma HDL-c-concentrations. In the respiration-chamber condition, parameters indicating a robust circadian-rhythm associated positively with plasma HDL-c-concentrations, and inversely RC-, TAG-, CRP-concentrations, HR and PA; PA associated positively with HR.

In conclusion, (I) differences between circadian-rhythm parameters and PA lead to different associations of circadian-rhythm parameters, physical activity (PA) and cardiometabolic risk factors, between both conditions.

Obviously, firstly effects of a controlled high protein (HP) diet compared with a moderate protein (MP) diet on components of energy expenditure (EE), energy balance (EB), respiratory quotients (RQ), adaptive thermogenesis (AT), perception of hunger and satiety, concentrations of glucagon-like peptide-1 (GLP-1) and polypeptide YY (PYY) had been assessed in the 38 participants. participating in the respiratory chamber assessment at

Participants consumed a high-protein (HP) diet (***n***=20;13 women/7 men;age:64.0±6.2y; BMI:28.9±4.0kg/m^2) with 25:45:30% or a moderate-protein (MP) diet (***n*** = 18;9 women/9 men; age:65.1±5.8y;BMI:29.0±3.8kg/m^2) with 15:55:30% of energy from protein:carbohydrate:fat. In summary, results showed that EB (MP=0.2±0.9MJ/d;HP=−0.5±0.9MJ/d) and RQ (MP=0.84±0.02;HP=0.82±0.02) were reduced and REE (MP=7.3±0.2MJ/d compared with HP=7.8±0.2MJ/d) was increased in the HP group compared with the MP group (P<0.05). REE was not different from predicted resting energy expenditure REEp in the HP group, whereas REE was lower than REEp in the MP group (P<0.05). EB was positively related to AT (r_s=0.74;P<0.001) and RQ (r_s=0.47;P<0.01) in the whole group of participants. Additionally, HP versus MP reduced hunger perception, and hunger was inversely associated with PYY in the HP group (r=-0.7;p<0.01).

In conclusion, (II) a HP diet *vs.* MP diet led to a negative EB and counteracted AT ~34 mo after weight loss, in participants with prediabetes in the postobese state (1). Moreover, a HP *vs.* MP diet reduced hunger, which was associated with increased PYY concentrations (2).

1. Drummen et al.,J Nutr 2020;150(3):458-463.
2. Tischmann et al., Nutrients, 2019;11(10):226.

O-41 Protein as a Source for Body-Weight Maintenance — The Role of Quantity and Quality (The PREVIEW Study)

Anne RABEN — Denmark

The multinational PREVIEW project (PREVention of diabetes through lifestyle intervention and population studies In Europe and around the World) included a 3-y intervention study in 2,500 participants with prediabetes and data from large population studies (n=170,000). The main goal was to investigate if a high-protein, low-glycemic index (GI) diet was superior to a moderate protein, moderate GI diet for weight-loss maintenance and prevention of type-2-diabetes (T2D).

The intervention consisted of 2 months weight-loss phase followed by 34-months weight-maintenance phase with 2 diets and 2 physical activity programs in a 2x2 factorial design (NCT01777893). After 3 years there were no differences in weight-loss maintenance, prevalence of T2D, or other secondary outcomes between the 4 study groups (1). Due to this, and that maintaining target intake of protein and GI over 3 years was difficult, data were pooled and analysed as a longitudinal study.

Associations of changes in estimated and reported energy and protein intake with changes in HOMA-IR, HbA1c, and BMI were determined by linear mixed-model analysis (2). During weight-loss maintenance, an increase in protein intake and a decrease in energy intake were not associated with a decrease in HOMA-IR, beyond the associations with the decrease in BMI. The increase in estimated and reported protein intake were, however, associated with a decrease in HbA1c.

Animal-based food consumption was assessed from 4-day dietary records. Available-case analysis showed that each 10-g increment in processed meat, but not total meat, unprocessed red meat, poultry, dairy products, or eggs, was positively associated with weight regain (0.17 kg/y, P<0.001) and increments in waist circumference, HbA1c, and triacylglycerols (3). The associations of processed meat with HbA1c or triacylglycerols disappeared when adjusted for weight change. Fish and seafood consumption was inversely associated with triacylglycerols and triacylglycerol-glucose index, independent of weight change. Modelled replacement of processed meat with isoenergetic (250-300 kJ/d) dairy, poultry, fish and seafood, grains, or nuts was associated with -0.59, -0.66, -0.58, and -0.69 kg/y of weight regain, respectively (P<0.001) and significant improvements in HbA1c, and triacylglycerols.

Adherence to a plant-based diet was evaluated using a novel plant-based diet index, where all plant-based foods received positive and all animal-based foods received negative scores (4). The plant-based diet index was inversely associated with weight regain, but not with cardiometabolic risk factors. Nut intake was inversely associated with regain of weight and fat mass and increments in total cholesterol and LDL cholesterol. Fruit intake was inversely associated with increments in diastolic blood pressure, total cholesterol, and LDL cholesterol. Vegetable intake was inversely associated with an increment in diastolic blood pressure and triglycerides and was positively associated with an increase in HDL cholesterol. All associations with cardiometabolic risk factors were independent of weight change.

These results indicate that both quantity and source of dietary proteins matter in relation to cardiometabolic health effects in a 3-y weight loss maintenance period.

References
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O-42 PREVIEW Population Studies: What Do we Learn About Energy Balance

ANGELO TREMBLAY — Canada

The PREVIEW research project (www.preview.ning.com) was based on different work packages that included a multicentre intervention study and the access to large cohort studies. This global research endeavour has allowed to identify factors influencing energy balance and metabolic health in a cross-sectional context and to better understand variations in the response of energy balance to a low-energy diet. The combination of cohort analyses revealed a significant association between protein intake and pre-diabetes or diabetes which did not persist after adjustment for body mass index and waist circumference. In the multicentre component of the program, about 10% of participants were unable to achieve a sufficient negative energy balance to lose 8% of baseline body weight in two months. They appeared more vulnerable to stress, as reflected by their increased score of perceived stress and resting heart rate. Subsequent genetic studies revealed that the polymorphism of the glucocorticoid receptor gene is related to variations in visceral adipose tissue. Recent analyses focussing on mechanical energy efficiency showed that its variations are closely related to energy expenditure and balance as well as metabolic health. Genetic studies testing the potential influence of polymorphisms influencing uncoupling proteins and skeletal muscle enzymatic activity are currently performed to better understand this relationship.

O-43 Unraveling Inter-Individual Variability in Energy Metabolism

Jennifer MILES-CHAN — New-Zealand

"Variability is the law of life" (Sir William Osler). Indeed, despite exposure to the same environment, considerable variability is observed in susceptibility to obesity and metabolic disease, and conversely in the success of current treatment and prevention strategies. Understanding the factors underlying this variability presents opportunities to design more efficacious approaches. However, considerable knowledge gaps remain, particularly in relation to (i) non-exercise activity thermogenesis, and (ii) diet-induced thermogenesis – two energy expenditure compartments that may offer accessible targets for improving metabolic health in the context of a modern, sedentary lifestyle.

For many individuals, who do not participate in regular physical activity, non-exercise activity thermogenesis accounts for the vast majority of non-resting energy expenditure. Investigation of the energy cost of standardised activities, both isometric and dynamic reveals considerable heterogeneity. Comparing "responder" and "non-responder" phenotypes is shedding light on factors contributing to inter-individual variability and consequently metabolic disease risk, although robust methodologies to minimise measurement error remain a challenge.

Similarly, given that the majority of the day is spent in the postprandial state, variability in postprandial thermogenesis, even if small in scale, may accumulate over time to elicit a positive energy balance and subsequent weight gain. Indeed, the ability to appropriately shift substrate oxidation in response to nutrient availability (i.e., metabolic flexibility) is a key tenant of metabolic health. However, inter-individual variability related, for example, to sex and hormonal contraceptive use has been observed, suggesting a potential link between these factors and metabolic risk. Furthermore, metabolic disease, such as Type 2 diabetes, dysregulates energy sensing mechanisms and therefore is likely to itself affect energy expenditure within the postprandial period. However, experimental evidence in this area is lacking, and the time-course of such changes is largely unknown; begging the question as to whether hypothesised changes in postprandial thermogenesis are a cause, or rather a consequence, of the diseased state.

Despite the current push towards personalised medicine, and increasing publication requirements for experimental data availability, the majority of studies continue to present overall means rather than individual-level data. Therefore, it is of the utmost importance that researchers carefully and comprehensively explore of inter-individual variability in response to standardised energetic challenges, to build a robust foundation upon which to recalibrate approaches to improve metabolic health.

O-44 Measurement of Cold-Induced Thermogenesis

Kong CHEN — USA

Cold-induced thermogenesis is a component of adaptive thermogenesis. It has intrigued scientists since Lavoisier (1780's). The measurement of this dynamic component is critical for determine the mechanism of action and potential window for targeting this component for intervention. In this talk, we will review the historical approaches to measure it, the theoretical model of thermal regulation and its characteristics and the challenges to quantify them, and our efforts to "map" resting energy expenditure (in the whole-room calorimeter) to a range of ambient temperatures (16-31^{o}C) in young lean men, young men with obesity, and young lean women to validate the thermal regulation models and quantify cold-induced thermogenesis. We found that the lower critical temperatures, the inflection point when cold-induced thermogenesis initiates, varied between three groups, and the average cold-induced thermogenesis at the lowest tolerable temperature was lower only in the young men with obesity. Many of the popular rationales to "justify" the myth that women are less cold tolerant than men were also being challenged by our data from this study.

O-45 Keep your mice warm!

Jan NEDERGAARD and *John SPEAKMAN* — Sweden and UK (45-minute debate)

Translationability – or rather – the *absence* of translationability – is presently a large concern in the transfer of both insights and medical treatments from preclinical (read: mouse) experiments to human application. There are likely many reasons for this, including the dominant use of a single, inbred mouse strain for nearly all metabolic experiments, the use of highly defined diets, the boredom of experimental mouse environments. However, one major factor that comparatively easily can be amended is the housing temperature. Standard housing temperatures for mice (≈ 20 °C) are pleasant for the staff – but much too cold for the mice. Mice at 20 °C have to keep their metabolism at nearly double the rate of mice at thermoneutrality, and much of their metabolism is thus constantly directed to supply the heat-producing organs (shivering muscle or non-shivering brown adipose tissue) with extra energy. But the fact that mice use less energy at thermoneutrality (30 °C) than at 20 °C does not necessarily indicate that they are more human-like in this condition. One formulation of being metabolically humanized is to ascertain that the mice use the same proportion of energy over basal metabolic rate as do normal humans: total daily energy expenditure is about 1.8 times basal metabolic rate in humans. Remarkably, when basal metabolic rate is carefully established in mice, it turns out that at thermoneutrality, this is exactly what the mice's daily energy expenditure is: 1.8 times their basal metabolic rate. Thus, this is a reasonable rationale to keep mice at thermoneutrality – and doing this will probably provide improved translational accuracy. It is at least clear that it will eliminate a series of both false positive and false negative outcomes of studies of agents affecting metabolic rate. False positive outcomes may result from agents inducing alterations in the insulative properties of the mice (skin, fur and circulation); metabolic effects of such alterations cannot occur at thermoneutrality. False negative outcomes are fundamentally more regrettable in that they may exclude the identification of e.g. agents that may increase metabolism. This is because at temperatures below thermoneutrality, the need for extra heat production to defend body temperature will overshadow any effect of any agent on basal metabolism. In addition to these outcomes, thermoneutrality may also affect many other metabolic parameters, such as the development of obesity, of liver disease, etc. Therefore: keep your mice warm!

Abstract – Posters

P-006 Short duration protocols for resting metabolic rate and exercise metabolic measurements utilizing whole room indirect calorimetry

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Background: Currently, 60-minutes is the shortest duration for resting metabolic rate (RMR) and exercise energetic (EXEE) measurements utilizing whole room indirect calorimetry (WRIC).

Objective: Validate 30 and 15-minute protocols for assessing RMR and EXEE, respectively, utilizing WRIC.

Methods: Ten propane burns were performed in the RMR (4,597 liters) and exercise (10,340 liters) WRIC's for 30 and 60-minutes to compare ventilation rates (V; liters/day) of oxygen (VO_2), carbon dioxide (VCO_2) and the respiratory quotient (RQ; VCO_2/VO_2), to that calculated by stoichiometry from burn rates (BR; g/minute). A larger burner was utilized to simulate EXEE. Furthermore, subject data from prior studies (RMR; 13 females/22 males, 37.7.6±13.8 years, BMI 25.3±4.9) and (EXEE; 2 females/13 males, 28.3±10.8 years, BMI 25.1±3.9) were recalculated to 24-hours for RMR, and 60-minutes for cycling EXEE (65% HR max). T-tests; ($p<0.05$) were performed (SPSS, version 27).

Results:

	RMR								
	Propane						Subjects (N=35)		
	30-minutes to 24-hours (N=10)			60-minutes to 24-hours (N=10)			30-minutes to 24-hours	60-minutes to 24 hours	<0.05
	Stoichiometry	WRIC	<0.05	Stoichiometry	WRIC	<0.05			
BR	0.1623	----------	-----	0.1684	----------	-----	----------	----------	-----
VO_2	594.4±39.3	597.0±55.8	0.91	617.1±42.8	621.2±52.1	0.85	401.2±83.9	397.9±85.8	0.26
VCO_2	356.9±23.6	356.5±25.4	0.97	370.3±25.7	370.5±27.2	0.98	329.9±66.8	326.4±67.1	0.17
RQ	0.60±0.00	0.60±0.02	0.87	0.60±0.00	0.60±0.01	0.81	0.84±0.05	0.84±0.04	0.09
RMR	2785.4±184.3	2746.1±247.8	0.69	2889.7±200.4	2855.5±235.2	0.73	1946.1±401.3	1929.2±409.8	0.22

	EXEE								
	Propane						Subjects (N=15)		
	30-minutes to 1-hour (N=10)			60-minutes to 1-hour (N=10)			15-minutes to 1-hour	30-minutes to 1-hour	<0.05
	Stoichiometry	WRIC	<0.05	Stoichiometry	WRIC	<0.05			
BR	0.6698	----------	-----	0.5664	----------	------	----------	----------	-----
VO_2	102.3±16.0	103.4±16.7	0.88	86.5±18.0	86.7±19.0	0.97	98.2±31.3	98.3±29.7	0.97
VCO_2	61.4±9.6	61.5±9.7	0.98	51.9±10.8	51.9±11.2	1.00	89.2±19.0	89.22±19.01	0.29
RQ	0.60±0.00	0.60±0.01	0.15	0.60±0.00	0.60±0.01	0.43	0.87±0.05	0.85±0.05	0.00
EXEE	479.0±75.0	475.6±76.8	0.92	404.9±84.4	399.3±87.2	0.89	530.5±125.6	533.3±112.5	0.75

Conclusions: Shorter protocols for RMR and EXEE are valid utilizing WRIC.

P-007 Adaptability of Whole Room Indirect Calorimetry for Determining the Energetics of Various Physical Activities

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Exercise energetics (EXEE; kcal) of running and/or cycling are usually measured in subjects with head gear connected to a metabolic cart. The head gear limits the types of EXEE that can be measured. Furthermore, subject discomfort and/or anxiety due to wearing the head gear can lead to errors in EXEE.

Advancements in instrumentation has improved sensor sensitivity and eliminated the need for drying sample gases during metabolic measurements. Recently, EXEE of numerous physical activities were determined by whole room indirect calorimetry (WRIC; interior volumes from 10,000 to 14,000 liters) in healthy subjects of various body weights (BW;kg) utilizing the Sable Promethion (model GA3m2/FG250) instrumentation (Sable Systems International, North Las Vegas NV). Metabolic parameters included the respiratory quotient (RQ:VCO_2/VO_2), glucose (g) and fat (g) oxidation. Results are as follows:

Activity	Minutes	Sex	BW	BMI	EXEE	RQ	Glu	Fat
Jazz drumming	25	M	84.1	24.6	125.0	0.73	0.3	12.8
Trumpet playing	40	M	98.2	34.0	100.8	0.85	1.6	3.1
Guitar playing	30	F	64.9	23.8	81.8	0.78	3.0	6.0
Opera singing	40	F	52.7	21.4	66.0	0.85	8.0	2.0
Yoga practice	30	F	59.6	22.8	243.1	0.93	55.2	2.1
Shadow boxing	30	F	66.8	25.2	267.0	0.88	43.2	6.9
Aerobic dancing	40	M	78.2	24.1	400.0	0.80	32.0	27.6
Step exercise	40	F	58.2	20.6	320.8	0.93	73.6	2.9
Half-marathon	77	M	61.9	21.9	1100.0	0.85	144.8	54.7
Tennis (forehand)	20	M	79.1	27.4	146.0	0.84	18.0	7.6
Tennis (backhand)	20	--	-----	------	135.4	0.86	19.6	5.8

Other metabolic measurements (not shown) included determination of VO_2 max. Furthermore, metabolic measurements can now be conducted and monitored remotely. In conclusion, the adaptability of WRIC has led to its use as an adjunct for enhancing the performance of all types of physical activities. Furthermore, there are two commercial WRIC's currently in operation.

P-008 The discovery of a potential therapeutic agent in regulating metabolic homeostasis

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Introduction: Obesity is characterized by the excessive accumulation of white adipose tissue (WAT). The expansion of WAT in obesity is linked to a rise in cell size (hypertrophy) and cell number (hyperplasia). Factors controlling the hyperplastic growth of WAT are not well characterized. Recently, ADIPOKINE-Y has been identified as a secreted protein produced by pre-adipocytes that promotes adipogenic commitment. Interestingly, *in vitro* experiments showed that ADIPOKINE-Y depletion impairs adipogenesis, while its overexpression induces it. Yet, the effects of ADIPOKINE-Y overexpression *in vivo* are still elusive.

Objective: Identify the effects of ADIPOKINE-Y overexpression *in vivo*.

Methods: Mice (adults and pups) were injected with adenovirus to overexpress ADIPOKINE-Y. These mice were then fed a chow or high-fat diet for 3 weeks and body weight measurement was followed. Glucose and insulin tolerance tests were performed. At the end of the study, tissues were collected, and several metabolic genes were measured. Blood metabolites were also analyzed.

Results: ADIPOKINE-Y overexpressing mice are viable and show normal food intake. ADIPOKINE-Y overexpression significantly reduced body weight and fat pad weight in both adults and pups. Moreover, glucose and lipid metabolic profiles were improved as glucose and triglyceride levels were significantly reduced in response to ADIPOKINE-Y overexpression. This observation was associated with an important improvement in glucose and insulin tolerance. Also, ADIPOKINE-Y overexpression was sufficient to reduce inflammation in adipose tissue and reduce the expression of genes involved in gluconeogenesis in the liver. Interestingly, when ADIPOKINE-Y overexpression faded away, the observed effects were lost. This indicates that these effects are reversible and directly dependent on ADIPOKINE-Y overexpression.

Conclusion: Collectively, our findings indicate that ADIPOKINE-Y could represent a new therapeutic agent to normalize body weight and improve glycemic and metabolic homeostasis in mice.

P-012 **NDIR CO2 analyser accuracy: the effect of linearisation**

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Objective:
Characterisation of and subsequent signal correction of CO2 gas concentrations used in calorimetry.

Methods:
Multiple concentrations of CO2 in air were delivered by a piston gas mixing pump. Air was from a CO2 free air dryer and CO2 from a cylinder. Corrections were applied for inaccuracies in the pump delivery. Variation in CO2 concentration from the air dryer was compensated for. Measured concentrations were compared to the theoretical concentration and a cubic correction curve derived. This curve is applied directly to our room calorimeter data.

Results:
The maximum magnitude of relative error at any 1 concentration was that of typical fresh air, 0.04%. Error of 6.9% before correction.

The maximum magnitude of relative error of the difference between any 1 concentration and that of fresh air was 3.97% before correction. After correction this reduced to 0.95%. Both of these were at a nominal concentration of 0.2% CO2.

The mean of relative errors in the difference between any 1 concentration and that of fresh air over the range 0.1% CO2 to 0.5% CO2 before correction was 2.95%. After correction this reduced to 0.13%.

Discussion:
NDIR gas analysers are inherently un-linear due to the relationship between absorption of radiation and amount of gas in the radiation path being an exponential function (Beer, Lambert law). The servomex analyser that we used for this test has an on-board linearisation circuit that brings the voltage output to a near linear relation with regard to the partial pressure of CO2 that is in the measurement cell. As can be seen from the results, it is far from perfect. By utilising external linearisation procedures, the error in the measurement can be significantly reduced.

P-014 SIZE DOES NOT MATTER: Validation of short duration RMR measurements in three different sized whole room indirect calorimeters

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Background: Metabolic carts with ventilated hoods are the most common method for measuring RMR.

Objective: Validate 30 and 60-minute RMR measurements in three different sized whole room indirect calorimeters (WRIC's).

Methods: Ten propane burns of 30 and 60-minutes each, were performed in three different sized WRIC's, to compare ventilation rates (V; liters/day) of oxygen (VO_2), carbon dioxide (VCO_2), respiratory quotient (RQ; VCO_2/VO_2) and RMR (kcal) to that calculated by stoichiometry from burn rates (BR; g/minute). All results factored up to 24-hours. T-tests and one-way ANOVA ($p<0.05$) were performed (SPSS, version 27).

Results

St. Luke's Hospital RMR_WRIC, New York, USA (4,500 liters)								
	30-minutes (BR=0.1623±0.0107)				60-minutes (BR=0.1684±0.0117)			
	Stoichiometry	WRIC	Delta %	p	Stoichiometry	WRIC	Delta %	p
VO_2	594.8±39.3	597.0±55.8	0.32±3.9	NS	617.1±42.8	621.2±52.1	0.6±2.5	NS
VCO_2	356.9±23.6	356.5±25.4	0.1±1.2	NS	370.3±25.7	370.5±27.2	0.0±0.8	NS
RQ	0.60±0.00	0.60±0.02	-0.2±3.1	NS	0.60±0.00	0.60±0.01	-0.2±3.1	NS
RMR	2785.4±184.3	2746.1±247.8	-1.5±3.5	NS	2889.7±200.4	2855.5±235.2	-1.2±2.1	NS
Medical University of Oslo RMR_WRIC, Oslo, Norway (7,600 liters)								
	30-minutes (BR=0.3293±0.0442)				60-minutes (BR=0.2280±0.0371)			
	Stoichiometry	WRIC	Delta %	p	Stoichiometry	WRIC	Delta %	p
VO_2	1207.0±162.0	1212.8±148.1	0.6±2.1	NS	835.6±135.9	840.1±136.3	0.5±1.1	NS
VCO_2	724.2±97.2	706.5±90.7	-2.4±1.2	NS	501.3±81.5	496.7±80.4	-0.9±0.0	NS
RQ	0.60±0.00	0.58±0.01	-2.8±1.6	<0.01	0.60±0.00	0.59±0.00	-1.4±0.5	<0.01
RMR	5652.0±758.8	5562.72±689.6	-1.5±1.8	NS	3912.9±636.4	3860.6±624.8	-1.3±1.1	NS
St. Luke's Hospital EX_WRIC, New York, USA (10,000 liters)								
	30-minutes (BR=0.1605±0.0294)				60-minutes (BR=0.1605±0.0294)			
	Stoichiometry	WRIC	Delta %	p	Stoichiometry	WRIC	Delta %	p
VO_2	588.3±107.7	587.7±103.1	-0.0±3.7	NS	588.3±107.7	589.7±108.9	0.3±2.9	NS
VCO_2	353.0±64.6	358.6±65.2	1.6±1.7	NS	353.0±64.6	362.2±67.5	2.6±1.2	NS
RQ	0.60±0.00	0.61±0.02	1.7±2.9	NS	0.60±0.00	0.62±0.02	2.5±2.6	<0.01

Conclusions: Accurate 30 and 60-minute RMR measurements were obtained in WRIC's up to 10,000 liters. These durations may be less taxing for vulnerable subjects, such as those with cancer or sarcopenia.

P-015 LOCATION LOCATION LOCATION: Differences in simulated metabolic measurements related to propane-burn setup positioning within the whole room indirect calorimeter

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Background: Propane burns are performed by placing the propane burn setup (balance, propane bottle and torch) in the Center of the whole room indirect calorimeter (WRIC). However, no one knows if a change in position of this set-up within the WRIC effects the metabolic results.

Objective: Observe any differences in simulated metabolic results as related to positioning of the set-up within the WRIC.

Methods: Five 8-hour propane burns were performed in the Exercise WRIC (10,000 liters) with the setup placed in the Center, Northeast, Northwest, Southeast and Southwest corners to compare the ventilation rates (V; liters/day) of oxygen (VO_2), carbon dioxide (VCO_2) respiratory quotient (RQ; VCO_2/VO_2) and energy expenditure (EE; kcal) to that calculated by stoichiometry from burn rates (BR; g/minute). The mean percent difference was taken across all metabolic parameters at each location and statistical differences determined by one-way ANOVA ($p<0.05$; SPSS, version 27).

Results: Mean percent differences across the Center, Northeast, Northwest, Southeast and Southwest corner locations for VO_2, VO_2, RQ and EE were 0.35, 0.43, 0.52, 0.18 and 0.45 %, respectively. Furthermore, no statistical differences existed between locations.

Center (BR=0.1652)			
Parameter	Stoichiometry	WRIC	Delta %
VO_2	201.84	202.46	0.40
VCO_2	121.61	121.61	0.00
RQ	0.60	0.60	0.00
EE	945.2	936.0	1.00
Northeast corner (BR=0.2163)			
VO_2	264.28	265.92	0.50
VCO_2	158.57	158.88	0.20
RQ	0.60	0.60	0.00
EE	1237.6	1224.0	1.00
Northwest corner (0.1662)			
VO_2	203.07	204.00	0.50
VCO_2	121.84	121.92	0.07
RQ	0.60	0.60	0.00
EE	950.9	936.0	1.50
Southeast corner (BR=0.2307)			
VO_2	281.14	283.20	0.70
VCO_2	168.68	169.44	0.40
RQ	0.60	0.60	0.00
EE	1316.5	1300.8	1.20
Southwest corner (BR=0.1622)			
VO_2	198.18	199.20	0.50
VCO_2	118.91	119.04	0.10
RQ	0.60	0.60	0.00
EE	928.0	916.8	1.20

Conclusions: It appears that the propane burn setup can be placed anywhere within the WRIC without effecting the metabolic results.

P-016 Substrate metabolism and metabolic flexibility in male astronauts onboard the International Space Station: The ENERGY study

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Metabolism being at the crossroad of multiple physiological functions, metabolic alterations induced by microgravity can affect astronaut's performance and health. Bedrest studies (space analog model) showed in healthy adults that simulated microgravity induces a shift in substrate use, i.e. decrease in fat oxidation in favor of carbohydrate use as fuel in both fasting and post-prandial states. This shift was associated with reduced metabolic flexibility (MF), i.e. the ability of the body to adjust substrate use to changes in substrates availability. Decreases in MF are known to favor ectopic fat storage, which contributes to insulin resistance and muscle atrophy; alterations commonly induced by microgravity. Substrate use and MF have however never been measured in space. Before and after at least three months on the international space station, carbohydrate and fat oxidation was measured by indirect calorimetry in fasting state and after a standardized

meal in 11 male astronauts (age=45.7[SD 7.7] years, BMI=24.3[2.1] kg/m²). MF was determined by the difference between maximal value of postprandial RQ and fasting RQ (ΔRQ). Food quotient (FQ) was calculated based on diet logs. Fat (FM) and fat-free mass (FFM) were measured by 2H2O dilution and daily physical activity by accelerometry. Three months in space increased fasting RQ and carbohydrate oxidation by 13% and 54%, respectively, and decreased fasting lipid oxidation by 75% ($p<0.01$ for all). A concomitant shift in diet composition was observed as indicated by the increase in FQ from 0.85(0.00) to 0.87(0.00) inflight ($P<0.001$). Spaceflight-induced changes in RQ adjusted on ground RQ were significantly associated with inflight FQ (partial R2=0.66; $P<0.01$). Although no change in postprandial nutrient oxidation nor in MF were noted on average, large inter-individual differences were noticed. Individual postprandial shift towards carbohydrate oxidation was inversely related to spaceflight-induced body composition changes with associations between FM changes and changes in postprandial carbohydrates ($R^2=0.55$; $P<0.01$), fat ($R^2=0.40$; $P<0.05$) oxidation and ΔRQ ($R^2=0.46$; $P=0.03$). Changes in postprandial carbohydrates and fat oxidation were positively ($R^2=0.41$; $P=0.05$) and negatively ($R^2=0.42$; $P=0.04$) associated with inflight aerobic exercise time, respectively. Changes in ΔRQ were positively associated with inflight resistive exercise ($R^2=0.43$; $P=0.04$) and changes in FFM ($P<0.01$). In conclusion, the shift in substrate oxidation observed during spaceflight may be essentially driven by diet modifications. Changes in postprandial substrates use and MF are associated with changes in body composition and exercise. A particular attention on nutrition and exercise prescriptions will be needed to prevent metabolic alterations during future spaceflights.

P-018 Novel Analytic Approach to Quantifying Exercise VO2 and VCO2 Offset Kinetics Using Room Calorimetry

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Due to their lower temporal resolution, whole-room calorimeters have traditionally been used to measure metabolism over long time periods, while the evaluation of on/off kinetics has been measured with metabolic carts. We present a strategy for room calorimeters that enables precise fitting of oxygen consumption (VO_2) recovery kinetics using the same monoexponential equation applied to cart data, by first adjusting for the slower response time of the room. We also introduce the kinetic measurement of carbon dioxide production (VCO_2). Eight young healthy men completed 12 total 30-minute treadmill walks inside a 32,500L whole-room calorimeter. Upon cessation of the walk, participants sat quietly for 1 hour of recovery. VO_2 and VCO_2 data were averaged in 15-s bins using a 2-min centered derivative, and a 2-step approach was applied to first identify the start point of recovery and second to determine the recovery kinetics (Fig. 1). Average values for VO_2 and VCO_2 were: time-delay = 57.5s (range 50-68s) and 59.1s (52-68s), recovery time constant = 95.5s (73.8 – 134.8s) and 113.2s (95.2 – 162.9s), and r^2 of monoexponential fit = 0.87 (0.79 – 0.95) and 0.94 (0.86 – 0.97), respectively. These results show that precise measurements of VO_2 and VCO_2 off-kinetics can be made using whole-room calorimeters. In addition, the lower variation about the fit (higher r^2) observed in the VCO_2 signal compared to VO_2 (Fig.1D vs. Fig. 1C) may yield greater measurement reliability, and thus supports further investigation into its use as an additional recovery measure. This insight will enable investigations into how

aging, inactivity, and disease impact recovery from bouts of activity in a pseudo-free-living setting which will provide critical insights into the role of whole-body energy metabolism in performance fatigability.

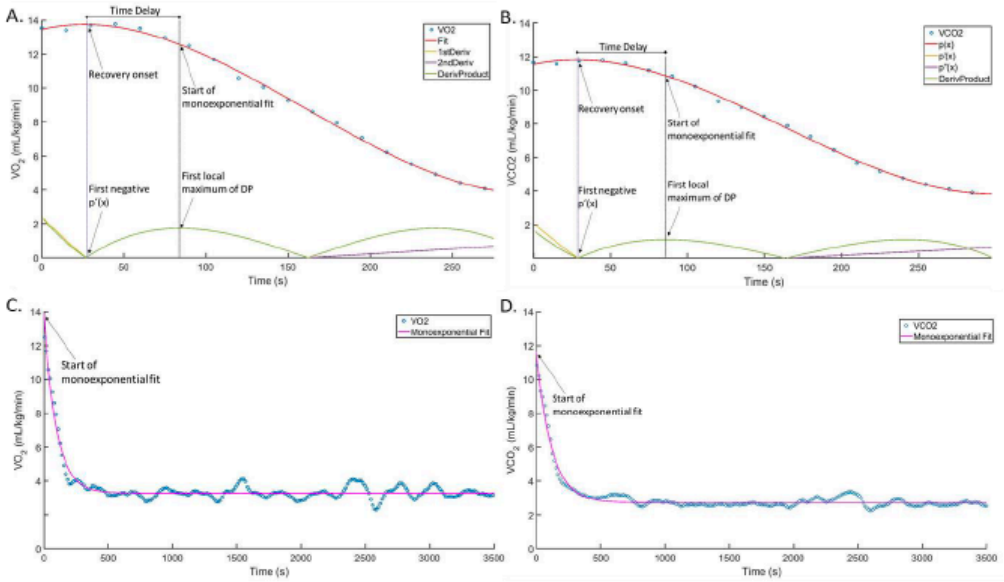

Figure 1. Recovery analysis of VO_2 and VCO_2 kinetics. A-B) Step 1: a third-order polynomial [$p(x) = ax^3 + bx^2 + cx + d$] was fit to VO_2 and VCO_2 from when the participant began sitting to the point where the rate began to plateau (defined as $\Delta<5\%$). The first [$p'(x)$] and second [$p''(x)$] derivatives of this polynomial, and their product [$DP = p'(x) * p''(x)$] were then calculated. The first negative point of $p'(x)$ represented the onset of recovery and the first local maximum of DP was used as the starting point of the monoexponential. The difference between the two points represented a time-delay metric. C-D) Step 2: the standard monoexponential equation [$(x) = \text{initial rate} - \Delta\text{rate} \cdot (1 - e^{(-x\ /\ \text{time constant})})$] was used to fit VO_2/VCO_2 from the first local maximum of DP through 1hr of recovery.

P-019 Impact of endogenous vs. exogenous ketones on glucose metabolism and subjective appetite in healthy participants

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Background: Oral ketone supplements may mimic the beneficial effects of endogenous ketones on appetite control and have been proposed to improve postprandial glycemia due to increased insulin secretion.

Methods: Seven healthy adults (4 women, 3 men; 24.2 ±2.8 y; BMI 23.6 ±2.7 kg/m^2) participated in a randomized cross-over trial with four 24h-interventions: (1) isocaloric formula diet (ISO) compared with endogenous ketone production due to (2) total fasting (FAST) or (3) isocaloric ketogenic formula diet (KETO) and (4) exogenous ketones (3 x 12.9 g ß-hydroxybutyrate, BOH as ketone salts) plus isocaloric formula diet (EXO). Serum-BOH levels (15h-iAUC), 24h-BOH excretion, subjective appetite (visual analogue scales), and parameters of glucose metabolism were measured. After the interventions, subjects consumed a standardized breakfast and *ad libitum* energy intake and interstitial glucose were monitored throughout the day.

Results: Compared to ISO, KETO led to higher postprandial BOH levels and EXO led to higher BOH excretion (both, $p<0.05$). Neither BOH levels nor BOH excretion differed between EXO and KETO or FAST and KETO. FAST and KETO lowered glucose and insulin levels and 24h-C-peptide excretion compared to ISO (all $p<0.05$), whereas no differences were observed between EXO and ISO or FAST and KETO. Parameters of glucose metabolism were lower with KETO compared to EXO (all $p<0.05$). The day after the interventions, glycemia during the standardized breakfast and throughout the day were 57-60% lower after EXO compared to FAST and

KETO (all p<0.05). Subjective appetite during the interventions and *ad libitum* energy intake thereafter did not differ between conditions.

Conclusion: In contrast to endogenous ketones in response to an isocaloric ketogenic diet, postprandial supplementation of ketone salts to an isocaloric diet had no immediate impact but a delayed effect on regulation of glucose metabolism. Neither endogenous nor exogenous ketones had an impact on subjective appetite.

P-021 Validation of energy expenditure and macronutrient oxidation measured by two new whole-room indirect calorimeters

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Objective: To validate two new whole-room indirect calorimeters according to Room Indirect Calorimetry Operating and Reporting Standards (RICORS 1.0).

Methods: For technical validation, 16 propane combustion tests were performed to determine accuracy and precision of energy expenditure (EE), ventilation rates of oxygen (VO_2), carbon dioxide (VCO_2), and RER (VCO_2/VO_2). For biological validation, eight participants (24.1 ±2.5 y; BMI 24.3 ±3.1 kg/m²) underwent four 24h-protocols under highly standardized conditions: (1) isocaloric sedentary, (2) fasting sedentary, (3) isocaloric active, and (4) fasting active. Reliability (CV) and minimal detectable changes (MDC) were calculated for 24h-EE, sleeping metabolic rate (SMR), activity energy expenditure (AEE), thermic effect of food (TEF), and macronutrient oxidation rates.

Results: Technical validation showed high reliability and recovery rates for VO_2 (0.75%; 100.8%), VCO_2 (0.49%; 100.6%) and EE (0.54%; 98.2%). Biological validation revealed CVs and MDCs for active conditions of 1.4% and 4.3% for 24h-EE, 1.7% and 5.9% for SMR, 30.2% and 38.4% for TEF as well as 5.8% and 10.5% for AEE. Mean CV and MDC for macronutrient oxidation rates was 9.9% and 22.9%.

Conclusion: Precision of 24h-EE and SMR was high, whereas it was lower for AEE and poor for TEF.

P-022 Energy expenditure response to high intensity low volume sprint interval exercise compared to moderate continuous exercise

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Objective: To assess total energy expenditure (TEE) and macronutrient oxidation following two different forms of exercise sessions compared to a non-exercise control session.

Methods: In a randomised, cross-over design, five healthy males completed three visits. Each visit consisted of a 15 hour period in a room calorimeter, preceded by either a High intensity low volume (HILV) or moderate intensity continuous (MIC)) exercise session or a control visit in which no exercise was performed (CNT). HILV consisted of 5 x 30 s sprints and MIC consisted of 40 min cycling at 60% VO_2max. During each visit participants

were fed in energy balance and a MMTT was conducted. TEE and substrate oxidation were calculated and blood samples were collected for insulin, glucose and glucagon-like peptide-1 (GLP-1) measurements. Resting energy expenditure (REE) was measured using ventilated hood indirect calorimetry immediately upon waking on day 2.

Results: There were no significant differences in TEE in the 15 hour period following exercise compared to CNT (mean diff; HILV 163.5kJ and MIC 267.5kJ). However, fat oxidation was higher following HILV than MIC (mean difference 46.8 KJ vs -504.5 KJ) compared to CNT. During the period of sleep following HILV, fat oxidation was higher compared to the control visit (mean diff 143.8 KJ P=0.454). There were also no significant differences in REE following each exercise. There were no significant differences in insulin, glucose or GLP-1 responses to MMTT between visits, however insulin and GLP1 were lower post HILV compared to CNT and MIC.

Discussion: The results suggest that a short but intense period of cycling exercise induces a similar metabolic response to a more conventional continuous exercise period. HILV exercise may also have the ability to encourage fat metabolism in the hours post exercise and therefore be a more appealing alternative for the general public.

P-024 A large interindividual variability in metabolic adaptation in non-exercise activity thermogenesis is observed after moderate weight loss in former elite athletes

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Objectives: Energy conservation may occur in non-exercise activity thermogenesis (NEAT) as a response to a weight loss (WL), identified as adaptive thermogenesis (AT). The aim of this study was twofold: 1) to investigate whether AT in NEAT occurs after WL, and 2) to explore the association between AT in NEAT with WL and body composition changes.

Methods: Ninety-four former athletes [mean±SD, age: 43.0±9.4y, BMI: 31.1±4.3kg/m^2, 34.0% females] were recruited and randomly assigned to intervention or control groups (IG, CG). The IG underwent 4 months of a WL phase; no treatments were administered to the CG. PA was measured using accelerometery and NEAT was predicted with a model including sample baseline characteristics. AT was calculated as $_{measured}NEAT^{4mo}{}_{(kcal/d)} - {}_{predicted}NEAT^{4mo}{}_{(kcal/d)} - {}_{measured}NEAT^{baseline}{}_{(kcal/d)} - {}_{predicted}NEAT^{baseline}{}_{(kcal/d).}$ Dual-energy x-ray absorptiometry was used to assess fat-free mass and fat mass.

Results: No significant differences were found in the IG for NEAT after the WL intervention (p>0.05), compared to the CG. Considering mean values, AT was not found for either group [estimated means (SE): IG: -41 (45) kcal/d; CG -24 (45) kcal/d, p>0.05]. However, inter-individual variability was large among both groups for AT in NEAT (IG: -656 to 281 kcal/d; CG: -313 to 331 kcal/d). No significant associations were found between AT in NEAT and changes in WL and body composition for both groups.

Conclusion: No energy conservation was observed in NEAT after moderate WL (mean values). Still, further studies are needed to clarify the mechanisms behind the large inter-individual variability in AT observed in NEAT to better implement lifestyle-induced WL interventions.

P-025 Energy expenditure and substrate utilization after acute body weight and body fat loss with hypocaloric diets in overweight men and women

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Objective: The purpose of this study is to examine the effects of acute weight loss on energy metabolism, energy expenditure and substrate utilization in overweight men and women. Methods: Twenty overweight men and women (10 men and 10 women, 41 ± 7 years old, 28.2 ± 2.4 kg/m^2) completed hypocaloric diets for 2 wk. Before and after the hypocaloric diets intervention, energy metabolism, total energy expenditure (TEE) and sleeping metabolic rate (SMR) and metabolic hormones were measured by whole-room human calorimeter for 24-h. Body composition, fat mass (FM) and fat free mass (FFM) were measured by dual energy X-ray absorptiometry. The subjects completed an appetite questionnaire every hour while in the calorimeter.

Results: Subjects lost body weight (-1.06 ± 0.11 kg, $p < 0.001$) and fat mass (-0.55 ± 0.12 kg, $p < 0.001$) throughout the interventions corresponding to an overall negative energy balance. Compared with baseline, the after the weight loss significantly decreased TEE (-68.0 ± 16.8 kcal/d, $p < 0.001$), SMR (-47.1 ± 21.3 kcal/d, $p < 0.001$), carbohydrate (CHO) oxidation (-15.4 ± 5.3 g/d, $p = 0.009$) and did not change fat oxidation (-0.8±3.8 g/d, $p = 0.885$) and protein oxidation (0.9 ± 6.4 g/d, $p = 0.893$). Furthermore, after weight loss, TEE per FFM ($p = 0.011$) and CHO oxidation per FFM ($p = 0.022$) coincided decreased significantly with increased T4 ($p = 0.044$) and decreased T4/T3 ratio ($p = 0.030$). Compared with before weight loss, fasting leptin levels ($p < 0.001$) were significantly decreased and average hunger sensation ($p = 0.040$) were significantly increased after the weight loss.

Conclusions: Short-term weight loss can also result in conservative changes in energy metabolism and appetite, causing weight regain. An understanding of the physiology during acute weight loss can support a weight loss strategy for obese individuals in the context of achieving and maintaining weight loss.

P-026 Using non-infrared spectroscopy to assess muscle oxygen uptake and its relationship to postprandial whole-body metabolism.

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Non-invasive measures for assessing muscle metabolism are rising in popularity and may provide additional insight into the contribution of muscle to whole-body metabolic rate. However, it is unknown if these devices are sensitive enough to detect if changes in muscle metabolic rate or are related to changes at the whole-body level. We explored whether skeletal muscle metabolic rate ($m\dot{V}O_2$) and resting metabolic rate (RMR) in the postprandial state were related. 12 young healthy males and females completed the study (M9/F3; 22 (3.31) years, 176.08 (0.28) cm, 78.5 (0.28) kg). $m\dot{V}O_2$ was assessed with continuous-wave near-infrared spectroscopy (CW-NIRS) on the vasus lateralis during a high-fat meal challenge. RMR was measured for 20 minutes at baseline (0-min) and every 30-min during the 4-hour postprandial period. $m\dot{V}O_2$ was assessed immediately following each RMR assessment with three 30-second ischemic cuffs with 90 seconds of rest between cuffs. The average of the 3 $m\dot{V}O_2$ slopes was recorded. There were positive relationships between resting $m\dot{V}O_2$ ($OD \bullet sec^{-1}$) and RMR for the full high-fat meal challenge ($r = 0.347$; $P \leq 0.001$, $n = 12$), at baseline ($r = 0.699$; $P \leq 0.003$, $n = 12$), 30 minutes ($r = 0.621$; $P = 0.023$, $n = 12$), 60 minutes ($r = 0.608$; $P = 0.050$, $n = 12$), 90 minutes ($r = 0.399$; $P = 0.023$, $n = 12$) and 120 minutes ($r = 0.728$; $P = 0.007$, $n = 12$). These findings indicate that there is a significant relationship between skeletal muscle and whole-body metabolism following a high-fat meal challenge. CW-NIRS may be an additional way to assess differences in resting skeletal muscle metabolism kinetics and their contribution to whole-body metabolism during the postprandial period.

P-027 Metabolic health in individuals with low and high metabolic flexibility using a marker not influenced by fasting fuel oxidation and energy balance

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Background
Enhanced metabolic flexibility (MetF) is expected to predict better metabolic health. Nevertheless, the evidence supporting this notion is weak. In part, MetF is often approached through markers influenced by baseline fuel oxidation and energy balance. Moreover, classical assessment using euglycemic-hyperinsulinemic clamps may not represent physiological conditions. Here, we measured MetF with a marker independent of baseline fuel oxidation and energy balance representing the fasting-postprandial transition. Metabolic health was then compared in volunteers with contrasting MetF.

Methods
In 52 healthy volunteers (23/29 men/women; mean [SD] age: 34±9 years; BMI: 26±4 kg/m^2; body fat: 31±8%), fasting and postprandial respiratory quotient (RQ) and energy expenditure were measured hourly for 6 hours after two 3-h apart 75-g glucose doses. MetF was calculated as the 6-h incremental area under the curve in RQ (iAUC-RQ) adjusted for fasting RQ (by regression analysis) as they strongly correlated (r=-0.78; p<0.0001). This marker did not relate to energy balance (r=-0.01; p=0.97). For metabolic health, volunteers with high or low MetF were compared by t-test and Cohen effect size (d). ANCOVA tested the interaction of BMI and MetF in health markers.

Results
By design, fasting RQ was similar in the low and high MetF groups (0.85±0.07 and 0.85±0.08, respectively; p=0.84; d=0.05) whereas iAUC-RQ differed (28±14 and 48±19, respectively; p<0.0001; d=1.20). Groups were similar in sex, age, BMI and body fat (p=0.35-0.79; d=0.08-0.26). Similar fasting glucose (p=0.66; d=0.13), HDL (p=0.67; d=0.12), triglycerides (p=0.96; d=0.02), HbA1c (p=0.11; d=0.28), HOMA (p=0.60; d=0.15), and Matsuda (p=0.53; d=0.19) were noted. No interaction between BMI and MetF in any health marker was detected.

Conclusion
A marker of MetF to glucose independent of known confounders did not discriminate for metabolic health nor protected against BMI-related disturbances. This study does not rule out that MetF may confer future protection for metabolic health.

P-030 Exercise-Induced Metabolic Compensation; A Physiological Adaptive Response To Exercise Training

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Background and Aim: Exercise training intervention studies have shown that total energy expenditure (TEE) increases less than expected, and consequently less weight than predicted is lost. However, the physiological mechanisms for exercise-induced energy compensation remain unclear. The aims of this study were to identify changes in the volume of highly metabolic organs (liver, kidneys, and brain) and to identify changes in the metabolic efficiency that occur as a physiological adaptation to moderate exercise training.

Methods: Using a clinical trial protocol, 16 overweight (body mass index: 28.2±1.7 kg/m^2) men (n=8) and women (n=8) aged 37.9±4.4 years will be enrolled in a 3-month exercise intervention. Exercise will be performed at a moderate intensity of 20 kcal/kg/week, and all exercise sessions are supervised. The volume of highly metabolic organs is measured pre-and post-exercise intervention using magnetic resonance imaging

(MRI). A cycling ergometer with a varied workload (10W, 25W, and 50W) pre-and post-intervention is used to assess muscle metabolic efficiency adaptation. Changes in overnight sleeping metabolic rate (SMR), basal metabolic rate (BMR), and 4 hours post breakfast diet-induced thermogenesis (DIT) are evaluated by whole human room indirect calorimetry ("metabolic chamber"). In addition, free-living TEE is measured for ten days pre-and post-intervention by doubly labeled water. Data collection is still ongoing, and preliminary results will be presented at the conference.

We hypothesize that the compensatory mechanisms induced by chronic exercise may act at least partly by reducing the volume of metabolically active organs and thereby contribute to a decrease in BMR, improves the efficiency of skeletal muscle in low-intensity physical activity, and reduce the SMR and DIT, leading to a decrease in TEE.

P-032 Potential role of SDR in regulating the hepatic response to fasting

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Introduction: The liver is a critical hub for numerous physiological processes, including macronutrient metabolism, endocrine control of growth signalling pathways, lipid and glucose homeostasis, bile acid production, and amino acid metabolism. The metabolic flexibility of the hepatocytes in response to changes in energy and nutrients levels is essential to insure survival. Over the years, several proteins and signalling nodes have been identified as playing key roles in regulating the response of the liver to fasting. Despite these advances, new discoveries are constantly emerging and our understanding of the molecular mechanisms controlling this important biological process keeps evolving. Objective: The main objective of this project is to identify and characterize new proteins regulating liver metabolism in response to fasting. Methods: We used hepatocytes isolated by serial dilutions and obtained more than 30 new clonal lines. Interestingly, we found that some of these lines produced low glucose amounts (Low Lines) whereas others produced high amounts (High Lines). Hepatic glucose production was assessed in these clonal lines since it is a process that occurs during fasting. To identify the factors involved in this variability between these lines, we performed transcriptomic assays on High and Low lines, and obtained 25 new targets that could be potentially involved in hepatic glucose production. Results: Our first interesting candidate is a *short dehydrogenase reductase* (*SDR*) gene, whose expression is higher in High Lines versus Low Lines. This *SDR* gene encodes for a protein of unknown function. Our studies indicate that *SDR* is induced by fasting and PPARα, repressed by insulin, and that the SDR enzyme localizes to mitochondria. Knockdown of *SDR in vitro* decreases oxygen consumption and fatty acid oxidation, suggesting an involvement in mitochondrial metabolism. Conclusion: With our work, we hope to elucidate the role of SDR in regulating the hepatic response to fasting.

P-034 Inferring Metabolic Effects of Brown Adipose Tissue Activity in Samoans

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PET/CT scanning technology is the gold standard for measuring brown adipose tissue (BAT) activity in humans and has been an invaluable tool for understanding BAT's metabolic effects and potential health benefits such as decreased risk of weight gain and type II diabetes. To ensure the safe implementation of BAT manipulation as a health tool among different populations, additional data need to be collected across various populations, environmental conditions, and clinical contexts. While foundational work focused on cold- and temperate-climate populations, we set out to determine the metabolic effects of BAT in a warm-climate sample from Apia, Samoa (N=61, age: 31-54, female: 38). We used a field-based BAT activity-inferring protocol consisting of

comparing metabolic rate (kcal/day) and heat dissipation at room temperature and cold exposure (15-19°C) using breath-by-breath indirect calorimetry and thermal imaging of the supraclavicular area. We compared fasting glucose levels using a portable point of care device before and after cold exposure. Our findings show that changes in heat dissipation at the supraclavicular area, a superficial BAT location, between room temperature and cold exposure were significantly smaller than those in the sternum area, a non-superficial BAT location (control area), between exposures ($P < 0.001$). These results suggest that BAT was inferred in Samoan adults despite recording no change in metabolic rate between exposures ($P = 0.14$). Fasting glucose levels decreased significantly during the 30min of cold exposure ($P < 0.001$), reinforcing previous findings of BAT as a potential glucose disposal organ. Our results demonstrate the variation in metabolic effects of BAT activity between populations and emphasize the benefits of field-based BAT activity assessing protocols. This BAT-inferring method facilitates data collection in different, remote study environments allowing for greater data collection eventually resulting in a better representation of human variation in metabolic effects of BAT.

P-035 Impact of secretory adiposopathy on subcutaneous abdominal and omental adipose tissue characteristics in women of various age and adiposity

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Several anatomical and functional changes are observed with adipose tissue (AT) dysfunction, including impaired adipogenesis and lipid storage/mobilization, as well as adverse endocrine and inflammatory responses. One marker of AT dysfunction, secretory adiposopathy reflected by a low plasma adiponectin (A)/leptin (L) ratio, is commonly observed with increased BMI. Our objective was to examine the relationship of these circulating adipokines, and the plasma A/L ratio with AT metabolism in 67 women of varying age and adiposity (age: 40-62 years; BMI: 17-41 kg/m²). Body composition, regional AT distribution, and plasma A and L levels were determined. Lipolysis was measured in subcutaneous abdominal (SCABD) and omental (OME) adipocytes, under basal-, isoproterenol-, forskolin (FSK)- and dibutyryl-cyclic AMP (DcAMP)-stimulated conditions. Adipogenesis (C/EBP-alpha/beta/delta, PPAR-gamma2 and SREBP-1c) and lipid metabolism AT gene mRNA abundance (beta2-/beta3-ADR, HSL, FABP4, LPL and GLUT4) was assessed in both depots. When expressed per cell number, basal lipolytic rate and lipolysis stimulated by isoproterenol or DcAMP were higher in SCABD adipocytes ($0.0005 \leq p \leq 0.05$). Messenger RNA abundance of C/EBP-alpha, SREBP-1c and of genes coding for proteins involved in lipid metabolism were increased in the SCABD fat ($p \leq 0.005$). Analysis was performed considering tertiles of low vs high circulating A or L levels and A/L ratio. Women in the low adiponectinemia tertile showed higher lipolysis stimulated by isoproterenol or FSK, in OME fat cells ($0.005 \leq p \leq 0.05$), while those in the high leptinemia tertile displayed increased lipolytic response to isoproterenol in OME adipocytes, only ($p \leq 0.05$). Isoproterenol-stimulated lipolysis was enhanced in both SCABD and OME adipocytes ($0.005 \leq p \leq 0.05$) of women with a low A/L ratio. Expression of most transcripts coding for proteins related to lipid metabolism and some to adipogenesis was higher in SCABD fat of women with secretory adiposopathy. A reduced A/L ratio is more closely associated with an increased adipose cell lipolysis than each individual adipokine.

P-036 The Berlin-Buch whole-room indirect calorimeter: high accuracy and resolution for energy expenditure measurements

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We present a methodological overview of a respiration chamber at the Experimental and Clinical Research Center in Berlin, Germany. Since 2010, we run 750 study protocols with healthy subjects and patients with

various diseases. We routinely measure resting energy expenditure (REE), dietary-induced thermogenesis, and activity energy expenditure.

The chamber (length 2.5 m, width 2.0 m, height 2.2 m, total volume 11,000 L, net volume 9,900 L) is a room-in-room dry construction. Fresh air is pulled into the chamber at four entry points near the ceiling, is mixed by the air conditioning, and exits at four points in the middle of the opposite wall (pull calorimeter). The majority of measurements is done with a flow rate of 120 L/min, yielding a favorable time constant of 1.53 hours. The air conditioning achieves a mixing time constant of 30 times per hour or 2 min.

The gas analysis system consists of two paramagnetic O_2 sensors and two infrared CO_2 sensors, one for incoming and one for outgoing air samples. O_2 and CO_2 sensors are calibrated simultaneously before each measurement with a 360 sec calibration routine.

To verify the accuracy of $\dot{V}O_2$, $\dot{V}CO_2$, EE and respiratory exchange ratio (RER) measurements, the calorimetric system is validated every two weeks by 2 h acetone burning tests. Validation factors of 20 representative 2 h acetone burning tests were 1.14 ± 0.07 for $\dot{V}O_2$, 1.00 ± 0.02 for $\dot{V}CO_2$, 0.88 ± 0.05 for RER, and 1.11 ± 0.05 for EE.

The response time of the chamber, measured by 10 sec openings of the door, is 81 ± 1 sec for O_2 and 58 ± 2 sec for CO_2 (n = 24).

Three repeated 60 min REE measurements of one healthy woman showed a variability of 233.5 ± 4.5 ml/min for $\dot{V}O_2$ and 162.7 ± 3.0 ml/min for $\dot{V}CO_2$.

P-038 Comparison of equations for calculating total energy expenditure using the doubly labelled water method

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Objective: To assess the agreement and bias between the Schoeller[1] and the newly developed Speakman[2] equations for calculating total energy expenditure (TEE) using the doubly labelled water method, in multiple representative sample-sets of the UK population.

Methods: Data from 770 male and female participants aged 4 to 92 years, collected between 2008 and 2014 as part of the UK National Diet and Nutrition Survey Rolling Programme was used for the analysis. Using the dilution spaces for oxygen (N_o) and deuterium (N_d) and the rate constants for oxygen (K_o) and deuterium (K_d), rates of CO_2 production (rCO_2) and TEE were calculated using the method of Schoeller, applying a fixed space ratio of 1.030, and the newly developed equation of Speakman. The two methods were compared using linear regression and Bland-Altman analysis.

Results: A strong, significant association between the two equations was observed for both rCO_2 (r^2 = 0.995) and TEE (r^2 = 1.0) (both P<0.0001). With the Speakman equation, rCO_2 was a mean (SD) 3.8% (0.59) lower than with the Schoeller equation and TEE 2.7% (0.59) lower. We observed a positive proportional bias between equations in the estimates of both rCO_2 and TEE as indicated by the Bland-Altman plots (Figure 1).

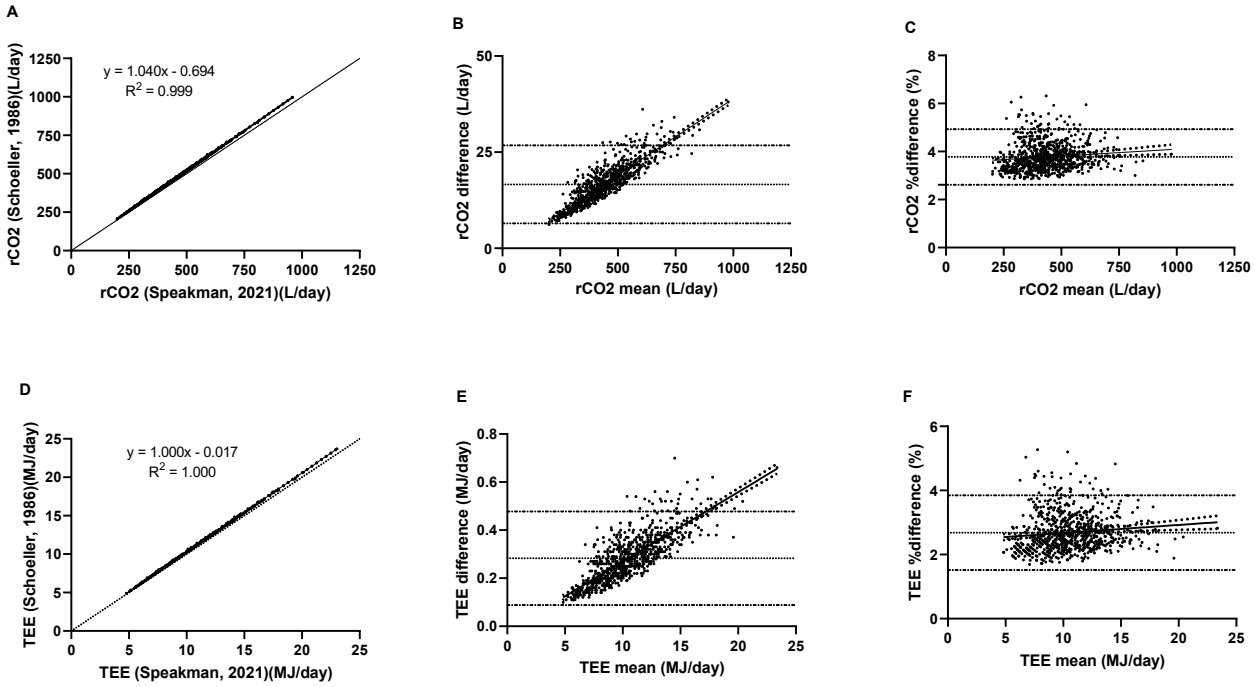

Figure 1. Comparison of CO_2 production rates (A-C) and total energy expenditure (D-E) calculated using the equations of Schoeller and Speakman.

Discussion: Estimates of rCO_2 and TEE were highly correlated, however, we observed a small but significant difference in both rCO_2 and TEE estimates between the two equations. In the original validation of this calculation a similar trend can be observed, but was not significant, likely due to the diversity of the data used. Using our large uniform dataset this bias is apparent. The introduction of a bias using the new equation should be considered when undertaking longitudinal studies.

[1]Schoeller DA, *et al. Am J Physiol* 1986; 250: R823-30.
[2]Speakman JR, *et al*. *Cell Reports Medicine* 2021; 2: 100203.

P-039 The impact of indoor carbon dioxide on human cognition and health

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There is increasing evidence that higher levels of carbon dioxide (CO_2) inside buildings are negatively associated with cognitive performance and the health of occupants. Many studies measure CO_2 to estimate indoor air quality because CO_2concentrations are strongly correlated with other substances such as volatile organic compounds (VOC). However, it is still unclear if the VOCs or CO_2 itself can cause such effects. As such, also studies performed in a respiration chamber could be affected by high CO_2 concentrations inside the chamber. This interdisciplinary project aims to contribute new insights by examining the effect of long-term exposure to CO_2 on the cognitive and metabolic responses of humans.

The study used a cross-over design, in which 20 healthy white-collar workers were exposed two test days of eight hours to either 0.08% CO_2 or 0.3% CO_2 in a respiration chamber. VOCs were filtered out from the air to examine the pure effect of CO_2. Cognition was measured using the CANTAB Cognition test, multiple price lists from economics literature, and a questionnaire to measure heuristic thinking. Physiological parameters such as oxygen consumption, heart rate, respiration rate, blood CO_2 concentration, blood pressure, and skin temperature were measured continuously.

Preliminary statistical analysis indicated no significant effect of CO_2 on results of the cognition tests in either of the domains of psychomotor control, executive functioning, and memory. Episodic memory tended to be worse during high CO_2 concentrations ($p = 0.085$), indicating that further analysis could reveal an effect on memory-related tasks. Also, preliminary results showed no significant effect on the health-related parameters.

These preliminary results indicate that studies need to distinguish between the effect of indoor CO_2 and VOCs on cognition. However, further analysis of the complete dataset needs to be done to examine more thoroughly the possible effects of indoor CO_2 on the above-mentioned outcomes.

P-041 A platform to measure murine interscapular Brown Adipose Tissue activity in real time

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Activation of interscapular brown adipose tissue (iBAT) induces thermogenesis and improves glucose tolerance in mice and humans. Approaches to study neural regulation of BAT activity in rodents historically involved either pharmacological or electrophysiological stimulation. Whereas the former method completely bypasses the nervous system by directly targeting the adipocytes, the latter stimulates both sympathetic and sensory nerves. Molecular, genetic and imaging tools have been used to modulate and measure the activity of brain circuits regulating iBAT function, but application of these tools in the peripheral nervous system has lagged behind. This has left a major gap in our understanding of neural regulation of iBAT activity. We are developing a toolkit that includes novel genetic tools and integrated in vivo physiological recordings to evaluate the impact of stimulating sympathetic inputs on iBAT activity in real time. Retrograde viruses are widely used to target projections from molecularly-defined neuronal populations to specific brain regions. However, until now these viruses have been working less well in the periphery. We are developing new viral serotypes to target chemogenetic or optogenetic tools to sympathetic neurons projecting to iBAT. In parallel, we developed an anesthetized preparation that combines temperature recordings from ultra-fast, sensitive implantable probes in several locations in the body with laser doppler imaging. This system permits the exploration of the temporal dynamics of iBAT activation following physiological (i.e. cold) and pharmacological (i.e. adrenergic receptor agonists and antagonists) manipulations. With these tools in hand, we are optimizing the application of chemogenetic and optogenetic approaches to modulate sympathetic inputs to iBAT. In the long term, combining these new techniques and tools will provide us with an unprecedented opportunity to examine many fundamental questions about the relationship between neural regulation of iBAT in the physiological and pathophysiological conditions.

P-042 Can accelerometers improve the calculation of the thermic effect of food in whole-room calorimeter studies?

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The thermic effect of food (TEF) is a component of total daily energy expenditure (TDEE) that is difficult to measure and there is no consensus on how to disentangle TEF from resting metabolic rate and spontaneous physical activity (SPA). Our objective was to test whether SPA from accelerometers could improve TEF calculation in whole-room calorimeter studies. Healthy men and women consumed two days of an energy- and macronutrient-balanced diet before completing two 23-hour visits in a whole-room calorimeter in randomized order: one visit included an energy-balanced diet ('fed') and one visit did not provide any food ('fasted'). Women completed both visits in the same menstrual cycle phase. Upright time in seconds from an activPAL accelerometer was summed in 15-minute bins and expressed as percent of time spent in SPA (%SPA); this value was regressed against measured energy expenditure to estimate energy expenditure from SPA. Measured TEF was calculated as the difference between TDEE on fed and fasted visits and used as the criterion to compare three methods of calculating TEF using activPAL data: 1. SPA-adjusted TEF (adj-TEF): difference in TDEE without SPA between visits, 2. 15h TEF: difference in energy expenditure obtained from linear regression and basal metabolic rate during waking hours in the fed visit, 3. 24h TEF: increase in TDEE above SPA and sleeping metabolic rate in the fed visit.

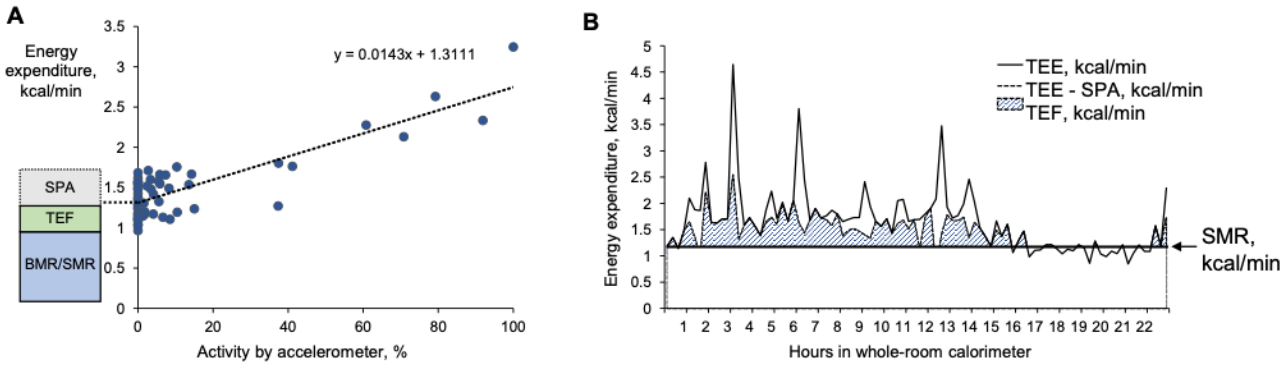

Figure 1. Energy expenditure and activity to calculate the thermic effect of food (TEF) in one subject. To adjust for spontaneous physical activity (SPA), % upright activity from accelerometers were regressed against energy expenditure in 15-minute bouts during waking hours; the resultant y-intercept is the combined energy expenditure from resting metabolic rate and TEF, **1A**. Using this model, adjusted TEF was calculated as the difference in total daily energy expenditure without SPA between fed and fasted conditions and 15h TEF was calculated as the difference in intercept-obtained energy expenditure and basal metabolic rate (BMR; measured 30 minutes directly after waking). 24h TEF was calculated as the increase in total energy expenditure (TEE) above SPA and sleeping metabolic rate (SMR; average energy expenditure during sleeping hours), **1B**. Adapted from: Tataranni *et al.*, American Journal of Clinical Nutrition 1995;61:1013-9.

Sixteen participants with both fed and fasted visits were included (50% women; age=27 ± 5 years; body mass index: 24.2 ± 3.2 kg/m^2). There were no differences in SPA expressed in absolute energy expenditure (fed: 435 ± 171 kcal/d, fasted: 401 ± 138 kcal/d, p=0.687) or percent of time spent in SPA (fed: 13.0 ± 3.0%, fasted: 13.0 ± 2.7%, p=0.980) between conditions. Mean TDEE on fed and fasted days was 2255 ± 343 and 2039 ± 252 kcal/d, respectively (p<0.001) and measured TEF was 216 ± 134 kcal/d, i.e., 9.2 ± 4.8% of fed TDEE. There were no differences between measured TEF and adj-TEF (195 ± 115 kcal/d, p=0.773; 8.5 ± 4.6%, p=0.687), 15h TEF (205 ± 134 kcal/d, p=0.774; 8.7 ± 4.8%, p=0.753), or 24h TEF (222 ± 115, p=0.688; 9.7 ± 4.3%, p=0.894) and there were no proportional biases.

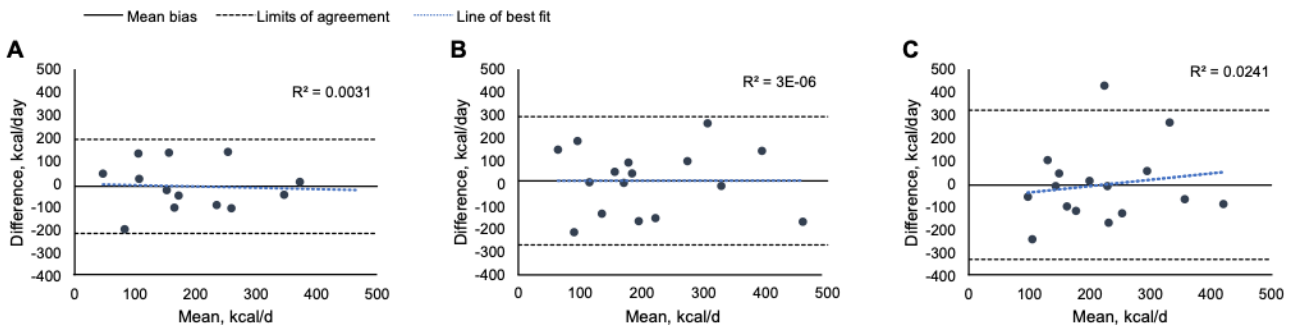

Figure 2. Bias and limits of agreement between measured thermic effect of food (TEF) and adjusted TEF (A), 15h TEF (B), and 24h TEF (C). Bias is the difference between measured and calculated TEF and limits of agreement are bias ± 1.96 standard deviations. R^2 represents the relationship between bias and mean (i.e., proportional bias).

Accelerometers can be used to accurately account for SPA and calculate TEF in whole-room calorimeter studies.

P-044 Response to short nutritional intervention predicts later susceptibility to obesity

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Aims: Murine strains differ in their propensity to obesity induced by high-fat diet (HFD) feeding. A/J mice, as compared with C57BL/6J (B6) mice, exhibit lower susceptibility to obesity. Despite the fact that response to acute nutritional intervention might predict later ability of organism to adapt, short-time exposure to HFD in A/J vs. B6 mice has not been studied yet. The aim of this study was to detect metabolic flexibility, at both whole-body and tissue level, in murine strains differing in susceptibility to obesity.

Methods: Male A/J and B6 mice at the age of 8 weeks were exposed to standard (STD) or HFD containing 60% of calories as fat for 3 days. They underwent oral glucose tolerance test (OGTT), insulin tolerance test (ITT), lipid tolerance test (LTT) or 4-days indirect calorimetry (Somedic, Sweden) either at laboratory temperature or at thermoneutrality, after 2-week- acclimatization to the respective temperatures. Alternatively, food intake was characterized or mice were euthanized after or during the 3rd day of dietary treatment. Plasma parameters, such as glycemia, TAG, insulin and leptin and expression of selected genes were characterized in epididymal white adipose tissue (eWAT).

Results: A/J mice after the short-term exposure to HFD as compared to B6 mice displayed healthier metabolic parameters, such as lower incremental AUC from OGTT and ITT and blunted increase in TAG levels after lipid load in LTT. The circadian rhythms in RQ and food intake were preserved after 3 days on HFD in A/J mice only. A/J mice also adapted to HFD by an increase in energy expenditure, resting metabolic rate (RMR) and body temperature (BT) both in mice pre-acclimated to laboratory temperature and thermoneutrality. As we did not detect any changes in heat losses through the tail as the main thermoregulatory organ in mice, we assumed higher body-temperature set point was set. We detected higher expression of genes for leptin and SOCS3 in eWAT and higher plasma leptin levels in A/J mice on HFD.

Conclusions: Our results document strain-specific difference in metabolic flexibility between A/J and B6 mice during short-term HFD-feeding. These difference predicts propensity to obesity later on during the life of the animals. Further studies are required to characterize contribution of various organs to the strain-specific metabolic phenotypes.

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P-045 Rôle de DEPTOR dans le développement et le fonctionnement du tissu adipeux brun

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Le tissu adipeux brun (TAB) augmente son volume et sa dépense énergétique pour produire de la chaleur en réponse au froid. Ce phénomène pourrait être un vecteur d'amélioration de la santé métabolique dans le cadre de l'obésité. *Mechanistic Target Of Rapamycin* (mTOR) fait partie des complexes protéiques mTORC1 & 2, indispensables pour le développement et le fonctionnement du TAB. *DEP domain containing mTOR-interacting protein* (DEPTOR) module l'activité de mTOR. L'expression de DEPTOR augmente dans les préadipocytes bruns se différenciant en adipocytes matures et dans le TAB de souris exposées au froid. Connaissant son influence sur mTOR, l'importance de DEPTOR dans le TAB reste à étudier.

In vitro, l'expression de DEPTOR a été supprimée dans les préadipocytes bruns puis leur différenciation a été étudiée. *In vivo*, DEPTOR a été supprimée chez la souris soit de façon constitutive dans les progéniteurs du TAB soit de façon induite dans les adipocytes bruns matures. Les souris ont ensuite été exposées pendant 6h ou 2 semaines à 10°C. Leurs températures rectales ont été mesurées pendant les premières heures d'exposition au froid. Après sacrifice, plusieurs gènes et protéines impliqués dans le métabolisme du TAB ont été étudiés.

In vitro, la perte de DEPTOR dans les préadipocytes bruns a entraîné une diminution significative de l'adipogenèse pendant leur différenciation. *In vivo*, la perte constitutive ou induite de DEPTOR dans le TAB n'a pas impacté les températures corporelles. Elle n'a pas non plus influé sur la différenciation ou l'adipogenèse dans le TAB au niveau génique. Par ailleurs, elle n'a pas modifié significativement l'activité de mTORC1 & 2 au niveau protéique.

En conclusion, les effets de la perte de DEPTOR observés *in vitro* ne sont pas retrouvés *in vivo*. Ceci pourrait être dû à l'apparition d'un mécanisme de compensation dans le TAB, reposant sur d'autres modulateurs en amont de la voie mTOR.

P-046 Impact of hepatic steatosis on myocardial, muscle and adipose glucose uptake in individuals without diabetes

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Background and aims: Hepatic steatosis (HS) is associated with an increased risk in cardiovascular mortality. We hypothesize that a decrease in myocardial glucose uptake may partly explain increased cardiovascular risk. We aimed to quantify glucose uptake in myocardium, adipose, and muscle in individuals without diabetes with and without HS.

Materials and methods: All consecutive patients without diabetes undergoing a whole body ^{18}[FDG]-PET-CT at CHU de Québec were included retrospectively if the PET-CT was negative for metastatic cancer or infection. Two groups were divided according to moderate-severe HS defined by hepatic density < 48 Hounsfield Units (HU) and subdivided according to BMI (>or < than 27 kg/m^2). Mean SUV (SUVm) adjusted on aortic SUVm were quantified in regions of interest (ROI) from myocardium, skeletal muscles, visceral and subcutaneous abdominal fat; and liver.

Results: Over 320 included patients; 64 were classified with HS. Myocardial ^{18}FDG was decreased in individuals with HS SUVm/a 1,22±0,98 vs 2,48±2,23; p-value <0,0001) and was also significantly lower in comparison to the same BMI category. There was a significant negative association between hepatic density and myocardial glucose uptake, but not with BMI. There was also a decreased ^{18}FDG uptake in subcutaneous (SUVm/a 0,16±0,07 vs 0,20±0,08; p-value 0.0001), visceral adipose tissue (SUVm/a 0,30±0,09 vs 0,41±0,13; p-value

<0,0001), and skeletal muscle (SUVm/a 0,32±0,05 vs 0,35±0,09; p-value 0,012) that were not significantly different according to BMI.

Conclusion: Independent of obesity, myocardial glucose uptake is decreased in individuals with hepatic steatosis, which could contribute to increased cardiovascular risk. This could reflect an increased myocardial insulin resistance and/or preferential utilization of fatty acids.

P-047 Living in Extremes: Energy metabolism of Nomadic Pastoralists

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IntroductionA study on the temperature adaptations of Tuvan nomadic pastoralists living in yurts was performed in January 2020. These nomads are unique, since they live in a region with extreme temperatures between summer (35 °C) and winter (-45 °C). During the wintertime, they are exposed to daily (indoor, outdoor) variation of temperatures up to 50°C! This multi-disciplinary study encompasses physiological, health, and sociological aspects in combination with the physics of the built environment.

Aim
Here we examine the effect of daily exposure to wintertime environmental temperature variations on body temperatures, energy expenditure, and physical activity.

Methods
Nomadic pastoralists (9 males, 3 females), living in Tuva (Siberia) were studied during 12 days in wintertime during normal daily activities. Field measurements encompassed continuously monitoring of indoor and outdoor temperatures, body temperatures (core temperature by BodyCap, skin temperatures by iButtons), energy expenditure by doubly labeled water technique, and physical activity (ActiGraph). Besides, under laboratory conditions resting metabolic rate (Metalyzer) was measured in thermoneutral and cold conditions.

Results
Preliminary results show frequent exposure to extreme temperatures, ranging from -38°C to -15°C (outdoors) and -8°C to +43°C (indoors). Skin temperature variations are mild, ranging from 31-38 °C for chest and shoulder. Resting metabolic rate (mean: 7.23 ± 1.11 MJ/d) and average daily metabolic rate (13.49 ± 1.33 MJ/d) were significantly higher compared to prediction equations from literature that are based on body mass or fat free mass. Their physical activity level was on average 1.91±0.36 with a relatively large range from 1.4 to 2.7 times BMR. This is in line with high levels of physical activity as assessed by accelerometry.

Discussion
Interesting is the large individual differences in energy expenditure in Tuvan nomads. A metabolic scope of more than 2.2xBMR in some individuals is of the level of athletes. The high level of physical activity and the extreme cold exposure are likely to both contribute to the greater than predicted average daily metabolic rate.

P-048 Effects of adding moisture into the whole room indirect calorimeter during testing on simulated metabolic results

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Background: No one has determined the effects of additional moisture added during metabolic testing.

Objective: Determine if raising the relative humidity from 25 to 65% within the whole room indirect calorimeter (WRIC) in a short amount of time affects simulated metabolic results.

Methods: Continuous propane burns (two 10-hour, one 12-hour) were performed and subjected to different interventions (IN): IN# 1 = four-hours ambient air, followed by two- hours additional moisture added using a humidifier placed within the WRIC (22,000 liters), followed by four-hours ambient air, IN# 2 = four-hours ambient, four-hours added moisture (2+2), four-hours ambient, IN# 3 = similar to IN#1 but with the propane flame turned up for two-hours without additional moisture added. Ventilation rates (V; liters[TF1]) of oxygen (VO_2), carbon dioxide (VCO_2), respiratory quotient (RQ; VCO_2/VO_2) and energy expenditure (EE; kcal) were calculated from burn rates and compared to propane stoichiometry.

Results: Active injection of water vapor into the room resulted in large transient offsets in VO_2 (higher) and consequently RQ (lower) that lasted for several hours but had no impact on VCO_2. The transients are observed after correcting for the known "dilution" effect of water vapor pressure (WVP) on the O_2 sensor readings (water vapor dilution). From reverse calculation, it appears the transients could be caused by an underestimation in measuring true room WVP when the humidifier was active. Alternatively, an underestimation of the O_2 partial pressure in the room during humidification could yield the observed readings. In both cases, no physical mechanism could yet be identified that would lead to these hypothesized errors. The transients are independent of the absolute WVP in the room, as they have not been observed in the IN# 3 experiment, despite similar overall water vapor pressure in the humidification experiments.

P-049 Improving Quality Control Procedures for Isotopic Analysis in the DLW Method

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Background: The accuracy of the doubly labeled water (DLW) method is determined, in part, by the precision of the isotopic measurements. Quality control (QC) procedures are commonly based on instrument precision, i.e., duplicate measurements that differ more than instrument precision are typically subjected to a triplicate measurement, which increases operating costs. To optimize laboratory efficiency, we explored the impact of widening the QC criteria for accepting duplicates.

Methods: We screened an existing DLW data set of n=121 participants with urine samples collected on day 1 (pre dose, 4 and 5 hours post dose) and day 7 (4 and 5 hrs end dose) for all instances where given samples were analyzed more than twice. Isotopic enrichments were determined using Off-axis Integrated Cavity Output Spectroscopy. Triplicate analyses are performed when duplicate samples differ by more than 2 per mil for ^{2}H and 0.5 per mil for ^{18}O. We then applied wider QC criteria for accepting duplicate measures, and recalculated TDEE. We determined the effect of increasing the QC criteria to 5 and 10 per mil for ^{2}H and 1.5 and 2 per mil for ^{18}O. The QC criteria for the baseline (pre-dose) samples were not altered due to the importance of obtaining accurate measurements of background abundances. TDEE was calculated using the Speakman 2021 equation with the 2-point method. The original and recalculated TDEE were compared using a paired t-test.

Results: Widening the QC range for ^{2}H in the post-dose samples to 10 per mil and end-dose samples to 5 per mil produced similar mean TDEE results compared to the originally calculated TDEE (2684.3 ± 508.4 kcal/day vs. 2686.5 ± 511.5 kcal/day, $p < 0.001$), respectively, and there was a strong positive correlation with the originally calculated TDEE ($r = 0.9723$, $n = 121$, $p < 0.001$). Widening the QC range for the ^{18}O measurements produced unacceptable TDEE results.

Conclusions: Expanding the ^{2}H QC range to 10 per mil for post-dose samples and 5 per mil for end-dose samples provides similar TDEE results (within 2 kcals/day) compared to a QC range of 2 per mil. This provides insight for DLW labs to optimize their QC criteria and minimize analytical costs.

P-050 Acute effects of whole-body heat exposure on liver insulin sensitivity

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Recent evidence suggests that heat acclimation (HA) positively affects metabolic health in humans. HA has been shown to decrease fasting plasma glucose and insulin concentrations, inflammation markers, free fatty acids and cholesterol levels. In a previous study, we found that both rate of glucose disappearance and endogenous glucose production (EGP) decreased in a fasted state upon HA in overweight middle-aged men, which indicates improved liver metabolism. This suggests that beneficial effects of HA could at least partly be due to enhanced liver function, but underlying mechanisms remain uncertain. To gain better understanding of the metabolic effects of HA, this study aimed to assess the effect of *acute* whole-body heat exposure on liver insulin sensitivity, as well as parameters of metabolic health and thermoregulation in middle-aged overweight individuals.

11 overweight non-diabetic volunteers (n=6 male/5 female, 56.5±3.2y, BMI 29.6±1.8kg/m^2, fasting plasma glucose 5.6±0.4mmol/L) participated in this study. After a standardized dinner and overnight fast, participants underwent two times a 3-hour 1-step hyperinsulinemic-euglycemic clamp with a low dose of insulin (10mU/m^2/min) and primed-continuous intravenous infusion of [6,6-2H2]glucose (0.04mg·kg^{-1}·min^{-1}), during either heat exposure (H) or thermoneutrality (TN). Thermal exposure was applied with a water-perfused suit (39˚C (H); 32˚C (TN)). Rates of glucose appearance and disposal, EGP, plasma metabolites, hematocrit and parameters of thermoregulation (e.g. core body temperature, mean skin temperature) were assessed at baseline and during insulin stimulation.

To the best of our knowledge, this is the first study performing an insulin-clamp during thermal exposure. Preliminary results (N=8) show that core body temperature and mean skin temperature were successfully increased by 0.8±0.5˚C (p=.008) and 2.2±0.7˚C (p=.000) during H vs. TN in the insulin-stimulated stable period. As the analysis is ongoing, parameters of blood chemistry and stable isotope analysis will be presented at the conference.

P-051 Adcy9 expression in choroid plexus or endothelial cells modulates brown adipose tissue thermogenesis

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Adenylyl cyclase type 9 (Adcy9) is an enzyme involved in the synthesis of cyclic AMP from ATP. It has been shown in patients treated with dalcetrapib, a cholesteryl ester transfer protein inhibitor, that *ADCY9*polymorphisms modulate cholesterol efflux. Adcy9-null mice at the whole-body level also exhibit a higher body weight and adipose tissue volume. Adcy9 in endothelial cells (EC) is involved in the control of endothelium permeability through a cAMP signalling mechanism. In the choroid plexus (CP), Adcy9 may be involved in brain permeability to HDL particles. Our objective is to determine the role of Adcy9 expressed in the CP or EC on interscapular brown adipose tissue (iBAT), heart, liver and kidney energy metabolism. Mice with homozygous Adcy9 inactivation in CP (Adcy9CP$^{-/-}$), mice with heterozygous (Adcy9EC$^{+/-}$) or homozygous (Adcy9EC$^{-/-}$) Adcy9 inactivation in EC, and the respective wild-type (WT) mice were randomly exposed, in a

crossover design, to a thermoneutral (30°C) or cold (10°C) temperature acclimation for 7 days after hepatic Ldlr inactivation and 14-16 weeks of an atherogenic diet rich in cholesterol. Mice were then injected with [^{11}C]-acetate, [^{11}C]-palmitate and [^{18}F]-FDG followed with micro-positron emission tomography to determine organ-specific oxidative, non-esterified fatty acid and glucose metabolism, respectively. All mice had a decrease in body weight and glycemia after cold exposure without difference between groups. Compared to WT mice, Adcy9CP$^{-/-}$ mice had a significant decrease in cold-induced iBAT oxidative metabolism without change in iBAT glucose uptake, but with an increase in iBAT palmitate oxidation. These animals also displayed robust cold-induced increase in liver oxidative metabolism. Adcy9EC$^{+/-}$ mice have a higher cold-induced increase in iBAT oxidative metabolism than WT mice, but without change in iBAT glucose/palmitate metabolism. Our results suggest that Adcy9 CP expression stimulates iBAT thermogenesis from intracellular triglyceride utilisation, whereas heterozygous Adcy9 EC deletion may decrease iBAT oxidative metabolism.

P-052 Role of Malat1 in the response of skeletal muscle to exercise

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Objective: Metastasis-associated lung adenocarcinoma transcript 1 (Malat1) is a long non-coding RNA first associated with metastasis in lung cancer. A study performed in our laboratory demonstrated that Malat1 is upregulated in conditions of hypoxia through the CaMKK/AMPK/HIF1-α signaling pathway. Of note, during physical activity, a significant decrease in oxygen concentration is observed in skeletal muscle. Therefore, the objective of this project was to determine the role of Malat1 in response to exercise in skeletal muscle in mice. Methodology: Male and female mice Malat1$^{+/+}$ et Malat1$^{-/-}$ were housed individually in cages with or without a running wheel for 4 weeks. The distance traveled in the cage, running wheel activity, and Regularity Disruption Index (RDI), a behavioral change index, were recorded in real-time by the DVC Analytics system. Results: Male mice housed with a running wheel traveled a significantly greater distance in the cage than those without a running wheel ($p=0.005$), without any difference between genotypes. However, the distance traveled in the running wheel was significantly higher in male Malat1$^{-/-}$ than in Malat1$^{+/+}$ counterparts, in accordance with an increase in speed ($p=0.03$), specifically during the night ($p<0.001$), without affecting the RDI, either during the day or the night. On the contrary, females housed with a running wheel traveled a significantly lower distance in the cage ($p=0.007$). Moreover, female Malat1$^{-/-}$ mice traveled a significantly lower distance in the cage than their Malat1$^{+/+}$ counterparts ($p=0.04$). No significant differences were observed in the use of the running wheel between Malat1$^{+/+}$ and Malat1$^{-/-}$ females. Interestingly, female mice with running wheels had significantly lower RDI during the day ($p=0.03$), but higher RDI during the night ($p<0.001$). Conclusion: The loss of Malat1 in female mice did not affect voluntary physical exercise performance, while the loss of Malat1 in male mice induced higher volume and speed during voluntary physical exercise. The molecular mechanisms by which Malat1 affects skeletal muscle performance are yet to be studied.

Study funded by NSERC and the Quebec Research Network on Aging (RQRV).

P-053 Alpha linolenic acid-enriched diacylglycerol enhances postprandial dietary fat oxidation in humans

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Background and objective: Alpha-linolenic acid-enriched diacylglycerol (ALA-DAG) oil has beneficial effects on body weight and visceral fat area compared with conventional oil comprising mainly triacylglycerol (TAG). Although ALA-DAG increases fat utilization as energy in rodents, its effects in humans are not known. Here, we investigated the effect of ALA-DAG on fat metabolism in humans.

Methods: Seventeen men and women with normal weight and moderate obesity (BMI: 25.7 ± 2.0 kg/m^2, mean ± SD) participated in this randomized double-blind cross-over trial. Each participant was assigned to a 4-week

intervention period with administration of 2.5 g/day of ALA-DAG or ALA-TAG, followed by a 4-week washout period. At the end of the intervention period, postprandial dietary fat oxidation was measured as the recovery rate of ingested ^{13}C-labeled triolein to $^{13}CO_2$ in the breath.

Results: Dietary fat oxidation, assessed by the $^{13}CO_2$ recovery rate in the breath, was significantly increased by ALA-DAG consumption compared with ALA-TAG consumption (17.0 ± 4.5% and 14.1 ± 5.9%, respectively, $P < 0.05$). Additionally, ALA-DAG consumption significantly decreased visceral fat area compared with ALA-TAG (102.9 ± 51.9 cm^2 and 110.9 ± 51.7 cm^2, respectively, $P < 0.05$).

Conclusion: These results indicate that ALA-DAG consumption enhances postprandial dietary fat oxidation, which may partially explain its visceral fat area reducing effect.

P-054 Changing Aerobic Exercise Parameters Performed by Individuals Living with Obesity in order to Increase Exercise Responders; Studying Gut Microbiota Composition

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Obesity affects one in three Canadiens. Exercise is often recommended for improving weight loss as well as glycemic control. Despite a significant enhancement for some obese individuals, engagement in aerobic exercise does not result in significant glucose tolerance improvement for up to 80% of obese population who are termed "exercise non-responders". Quitting exercise, increased cardiovascular diseases risk, and substantial premature mortality are probable implications among these individuals. Increasing exercise intensity, duration, or volume might rescue this group, perhaps by enhancement of cardio-metabolic health, resulting in improved glucose tolerance. Moreover, previous studies have shown that exercise affects composition and function of gut microbiota which plays an important role in host metabolism and glucose homeostasis. However, effects of changing aerobic exercise (AEX) parameters on human gut microbiota with respect to its association with glucose handling have not been addressed till now. The aim of this project is to investigate how increasing intensity of AEX affects gut microbiota composition.

This is a multi-center parallel-group single blinded randomized controlled exercise trial, including 282 obese individuals. All middle-aged individuals living with obesity participated in a supervised AEX program according to the Canadian physical activity guidelines. Individuals trained 150 min of AEX based on 4.5 metabolic equivalent tasks (METs) counting for 675 METs-min/week during the initial 24 weeks. After 16 weeks, participants were randomized into status quo or higher intensity group (150 minutes of AEX at 6.0 METs for a total of 900 METs-min/week). Fecal samples were collected at 24 and 40 weeks from 10 individuals. Gut microbiota composition was quantified using next generation sequencing of 16S ribosomal RNA genes.

β-diversity analysis revealed *Vampirovibrio* increased significantly in the high intensity group at 40 weeks. However, alpha diversity and *Firmicutes/Bacteroidetes* ratio did not change significantly.

The results suggest that increasing AEX parameters induces changes in human gut microbiota composition. To understand the possible mechanisms through which exercise can affect the human gut microbiota composition, more studies are required.

Key words: obesity, aerobic exercise, exercise non-responders, high intensity aerobic exercise, gut microbiota

P-055 Middle-age, menopause, and energy expenditure

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Basal metabolism is thought to slow down in women from younger adulthood to midlife due to aging and, after menopause, changes in sex hormone levels. Metabolic rate decline is believed to mediate menopause-related fat accumulation. However, the evidence behind these claims is conflicting. Therefore, we investigated whether middle-aged women have lower fat-free mass (FFM) and fat mass (FM) adjusted resting energy expenditure (REE) and total energy expenditure (TEE) than younger women and whether their menopausal status or body fat percentage explains adjusted REE.

We measured REE and body composition of 120 women (age 17–59 years) with indirect calorimetry and dual-energy X-ray absorptiometry. We divided subjects into three age groups according to potential energy expenditure turning points. The first and second groups (n = 26 and 35) consisted of 17–21- and 22–38-year-old women. Middle-aged women (n = 59, age 42–59 years) formed the third group. Of them, 19 were pre- or perimenopausal, 30 were postmenopausal, and 10 were postmenopausal hormone therapy users. The sample included 16 daughter and middle-aged mother pairs. Ten pairs also had TEE measured with doubly labeled water. We used FFM and FM adjusted residuals as response variables.

We observed that middle-aged women had 126 kcal/d and 89 kcal/d ($P < 0.001$) lower residual REE than first and second group subjects. In the subsample partially controlled for genotype, mothers had 100 kcal/d ($P < 0.001$) lower residual REE but not residual TEE than their daughters. In middle-aged women, residual REE did not differ according to menopausal status but was positively associated with body fat percentage ($\beta = 0.38$, $P = 0.003$).

In conclusion, women have lower FFM and FM adjusted REE in midlife than in earlier adulthood, more likely due to aging than menopausal hormonal changes. Higher adjusted REE accompanies a higher body fat percentage in middle-aged women.

P-056 Metabolic flexibility during sleep

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Oxidized substrate is selected in response to changes in the nutritional and physiological state, and disrupted metabolic flexibility, or metabolic inflexibility, is associated with many pathological conditions including obesity and type 2 diabetes mellitus. RQ as a ratio of CO_2 production to O_2 consumption is an index free of body mass, and it is useful to compare individuals with varying body mass. It has been assumed that RQ is a gradually decreasing during sleep, suggesting a shift of oxidized substrate from carbohydrate to fat (Am J Physiol 295: E1009, 2008). However, indirect calorimetry of high time resolution (J Appl Physiol 106: 640, 2009) revealed that RQ decreased during the first half but increased during the second half of the sleep, suggesting that sleeping energy metabolism is not simply the result of prolonged fasting. Among individuals without obesity, individual differences in RQ become apparent during sleep, and it might serve as a window to gain insight into the early-stage pathogenesis of metabolic inflexibility. Transient decrease of RQ during sleep is shallower in older individuals compared with young individuals. Furthermore, there is a sex difference in the U-shaped time

course of RQ during sleep; the increase in RQ during sleep is earlier in women than in men (Sci Rep 11:17849, 2021). Interestingly, this sex-dependent U-shaped time course of RQ resembles the time course of core body temperature during sleep. Possible mechanism (melatonin and orexin system) and physiological significance (relation of energy metabolism and sleep quality) of sex-dependent U-shaped time course of RQ will be discussed.

P-057 Effects of dietary sulfur amino acid restriction on body weight, resting energy expenditure and substrate oxidation in men and women with overweight and obesity: Results from an 8-week double-blind randomized controlled trial

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Introduction: Dietary sulfur amino acid restriction (SAAR) in animals leads to decreased body weight and body fat, and increased energy expenditure and heat production resulting in a beneficial metabolic phenotype.

Aims: We aimed to investigate the effects of dietary SAAR on body weight and composition, resting energy expenditure (REE) and substrate oxidation in men and women with overweight and obesity.

Methods: Sixty-one subjects (35 women) were allocated by sex-stratified randomization to a dietary intervention with either low (SAAR, 2 g/d) or high (control, 5.5 g/d) content of sulfur amino acids for eight weeks. Body weight and composition were measured using a calibrated weight and dual X-ray absorptiometry. REE was measured using the newly built whole-room indirect calorimeter (7600 L, pull system) at the Department of Nutrition, University of Oslo, where subjects were seated in a comfortable recliner for 60 minutes. Sample gases from excurrent air (O_2, CO_2 and water vapor) were analyzed using a Promethion GA-3m2. Measurements were taken at baseline, after four and eight weeks. Outcome analyses were performed intention-to-treat (n = 59 analyzable) using baseline-adjusted linear mixed model regression.

Results: After 8 weeks, the SAAR group had lost more weight than controls (β vs controls 1.29 ± 0.45 kg, $p_{interaction}$ = 0.018) with similar decreases in body fat %, whereas no differences were observed between groups for REE, RQ, fat oxidation or glucose oxidation. Results in sex-stratified analyses were similar for body weight, body composition and REE, but men in the SAAR group had higher fat oxidation compared to controls after 8 weeks (β vs controls: 34.0 ± 19.1 g/d, $p_{interaction}$ = 0.019), whereas no differences were observed for women.

Conclusions: Despite greater weight loss in the SAAR group compared to controls, decreases in REE were similar after 8 weeks. In men, dietary SAAR increased fat oxidation compared to controls, whereas in women fat oxidation increased similarly in both groups indicating that some effects of dietary sulfur amino acids vary by sex. Further studies are needed to determine the potential sex specific effects of dietary SAAR.

P-058 Doubly labeled water-calibrated energy intake associations with mortality risk among older adults from the Kyoto–Kameoka Study

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Background: The body mass index (BMI) is closely related to the risk of death, and energy intake (EI) is essential for the maintenance of energy balance in weight control. However, self-reported EI has been shown to lead to a systematic underestimation.

Objective: To examine the association between biomarker-calibrated EI and BMI on overall mortality risk in older adults.

Methods: A prospective cohort study was performed using data of 8,051 (4,267 women and 3,784 men) Japanese older adults from Kyoto-Kameoka study in Japan. Calibrated EI was calculated from the estimated EI using a food frequency questionnaire and equation developed based on biomarkers. BMI was calculated using self-reported height and body weight. Mortality data were collected between July 30, 2011 and November 30, 2016. Statistical analysis was performed using the multivariable-adjusted restricted cubic spline model.

Results: During the median 4.75 years of follow up (36,552 person-years), a total of 661 deaths were recorded. In both women (hazard ratio [HR], 0.63; 95% CI, 0.41–0.98) and men (HR, 0.62; 95% CI, 0.44–0.87), after adjusting for confounders, the top quartile as compared with the bottom calibrated EI quartile showed a negative association with risk for all-cause mortality. The lowest HR for all-cause mortality was at 1,900-2,000 kcal/day in women and 2,400-2,600 kcal/day in men. However, after adjusting for BMI, there was no significant association between the calibrated EI and risk of death. These associations could not be confirmed in the uncalibrated EI. BMI, with or without adjustment for the calibrated EI, showed a negative association with mortality.

Conclusions: Calibrated EI showed a negative association with the risk of death but not uncalibrated EI. This may be mediated by an increase in body weight over time. Caution is required when interpreting the association between diet without adjusting for self-reported measurement error and outcomes.

P-059 Regulation of energy balance during a 21-day bedrest with and without resistive exercise training: the MNX bedrest study

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Body mass (BM) loss is commonly observed during spaceflights. Understanding its cause is critical for future long-term spaceflights. While exercise countermeasure is widely used to prevent spaceflights-induced physiological alterations, high volumes of exercise are associated with changes in body composition (BC). Bedrest studies (ground-based space analog model) showed that combined aerobic and resistive training elevated total energy expenditure (TEE). This greater TEE was not associated with concomitant increases in energy intake (EI), which induced negative energy balance (EB). Although resistive exercise is known to effectively prevent the microgravity-induced loss of body mass, its impact when performed alone on EB and BC has never been tested. This study aims to determine the evolution of TEE and its components and BC during a 21-day bedrest with a resistive+vibration exercise (RVE) countermeasure compared to a strict bedrest control condition (CNT). The vibration aims to increase muscles activity. We hypothesized that RVE will limit the loss of total and lean body mass in response to simulated microgravity, especially in lower body parts, while having minimum impact on TEE.

Twelve healthy male adults (aged 34.3[SD 8.4], body mass index=22.6[1.9]kg/m²) participated in a randomized cross-over trial consisting in 21-day strict bedrest without (CNT) or with an RVE countermeasure. At baseline

and after 21 days of bedrest, TEE, activity-related EE (AEE) and resting metabolic rate (RMR) were measured by combining doubly labeled water method and indirect calorimetry. Total, upper and lower body lean mass (LM) and fat mass (FM) were measured by DXA. Although EI was prescribed to match TEE and ensure FM maintenance, participants were allowed to ask for more or not finish their meals.

In both groups, TEE adjusted for LM and FM decreased during bedrest on average by 1.50MJ/d (through decrease in AEE). EI decreased on average by 1.84MJ/d; few leftovers being reported. This coupling between the changes in TEE and EI maintained stable EB and FM during the bedrest. BM dropped by 4.3%, mostly accounted for reduction in total body LM (muscle disuse). Leg mass loss was lower in the RVE group compared to CNT likely due to the leg-specific resistive exercise.

Although RVE had no significant impact on EB, it did not allow to maintain total LM and BM. Only loss of lower BM was partially prevented. Further studies are still warranted to optimize the exercise countermeasure for future missions, i.e. prevention of microgravity-induced physiological alterations while not inducing a negative EB.

P-060 Estimating Energy Cost of Body Weight Resistance Exercise Using a Multistage Exercise Test

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Introduction: Previous studies have investigated traditional resistance exercise using free weights or weight machines with high loads, there is relatively little information about exercise intensity (energy expenditure (EE) and energy cost) of body weight resistance exercise (BWRE). We recently estimated EE and METs for popular BWRE (e.g., the squat and push-up) with slow movement in young male and older adults using a recovery calculation method. However, the time course of postexercise VO_2 differed between the exercises, and in some cases, it is possible that EE was overestimated or underestimated. The purpose of this study were (1) to examine energy cost of energy cost (EE for a single repetition) of BWRE-slow (heel-raise, squat, and push-up) and (2) to extrapolate these findings to obtain an EE value for each of these exercises at 10 repetitions/min. Methods: Fifteen men aged 21–29 years performed 3 exercises (heel-raise, squat, and push-up) at different frequencies (1, 2, 3, 4, 5, and 6 repetitions/min). VO_2 was measured using indirect calorimetry; we then computed a simple linear regression between aerobic EE and repetition frequency. The slope coefficient in the regression represents the energy cost of those exercises; we compared the extrapolated EE for a frequency of 10 repetitions/min. Gross EE increased linearly with repetition frequency in all subjects (y=ax + b). Results and practical applications: Energy cost was significantly greater in the case of the push-up than in the case of the squat {squat: 0.50 ± 0.14 kcal (95% confidence interval [CI], 0.42–0.58); push-up: 0.77 ± 0.20 kcal (95% CI, 0.66–0.88); and the heel-raise elicited the lowest energy cost: 0.13 ± 0.04 kcal (95% CI, 0.11–0.15), Fig}. Extrapolated EE at 10 repetitions/min was 2.760.5 kcal (2.3 metabolic equivalents [METs]), 6.3±1.4 kcal (5.4 METs), and 9.2 ± 2.1 kcal (7.8 METs), respectively, according to the regression based on aerobic EE. Gross EE depends on height, weight, and muscle mass, although, if average young men performed 3 exercises (10 reps × 3 sets),

respectively, the gross EE is estimated to be 55 kcal. These results will be useful for health professionals in prescribing resistance exercise programs improving muscle fitness and considering for weight management.

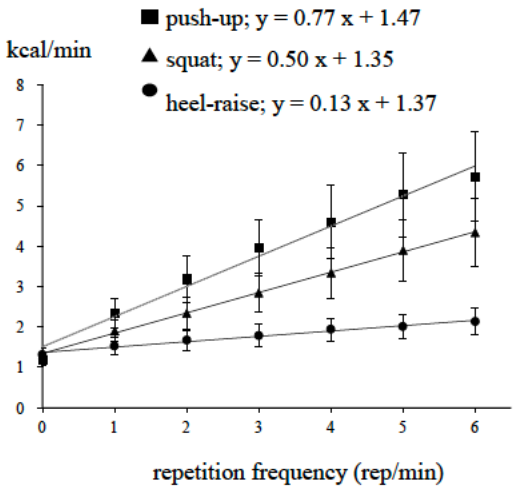

Fig 1

P-061 Protonophore treatment augments energy expenditure in mice housed at thermoneutrality

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Background: Sub-thermoneutral housing increases facultative thermogenesis in mice, which may mask the pre-clinical efficacy of anti-obesity strategies that target energy expenditure (EE). Here, we set out to quantify the impact of protonophore treatment on whole-body and tissue energetics in mice housed at a thermoneutral 30°C.

Methods: C57BL/6J mice (*n*=32, 16M/16F) were housed at 24°C for two weeks and were then transitioned to 30°C for a further four weeks. Following two weeks acclimation at 30°C, mice (*n*=16 per group, 8M/8F) received either normal (0 mg/L; Control [CTRL]) or supplemented (400 mg/L; 2,4-Dinitrophenol [DNP]) drinking water. This DNP dose was based on pilot experiments demonstrating increased total EE (TEE) with 400 mg/L, whilst minimizing reduced energy intake and wheel running observed with doses >400 mg/L. Mice were housed in metabolic cages to determine TEE and its components via respiratory gas exchange. Liver, brown adipose (BAT) and white adipose tissue (WAT) bioenergetics were assessed by high resolution respirometry.

Results: Transitioning all mice from 24°C to 30°C reduced TEE and basal EE (BEE) by 16% and 41%, respectively (both *P*<0.001). Body mass was similar between groups after 2 weeks of CTRL or DNP treatment. DNP treatment reduced percent body fat exclusively in females (CTRL, 5.3±0.4 vs. DNP, 2.3±0.3%; *P*=0.001). Compared to CTRL, TEE was 49% and 29% higher in DNP-treated males and females, respectively (both *P*<0.016), which was largely due to 60% and 27% higher BEE in DNP-treated males and females, respectively (*P*=0.002 and *P*=0.081, respectively). Absolute TEE of male and female (M: 9.3±0.7 and F: 9.5±0.6 kcal/day) mice housed at 30°C with DNP treatment remained lower compared to when mice were housed at 24°C in the absence of DNP (M: 11.1±1.0 and F: 9.6±1.6 kcal/day). Energy intake was 37% and 69% higher in male and female DNP-treated mice, respectively (both *P*<0.038). Oligomycin-insensitive leak respiration was similar between conditions in liver, BAT and WAT.

Conclusion: Protonophore treatment markedly increases BEE and thus TEE in male and female mice at 30°C. However, TEE of animals receiving protonophore treatment at 30°C was lower than their own TEE when

housed at 24°C, emphasizing that facultative thermogenesis must be considered when assessing anti-obesity drugs that target energy expenditure in mice.

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P-062 ABCB10, a novel regulator of metabolic inflammation

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Introduction: Uncontrolled inflammation triggers pro-inflammatory cytokines secretion and inappropriate immune response. Macrophages are important immune cells for the development of inflammation leading to insulin resistance and metabolic diseases. The macrophages' activity can be regulated by metabolic reprogramming, reactive oxygen species (ROS) and mitochondrial activity. We found a novel mitochondrial antioxidant system involved in these processes and regulated by the ATP Binding Cassette B10 (ABCB10). ABCB10 allows biliverdin export from the mitochondria to the cytosol where it is converted into the antioxidant, bilirubin. ABCB10 expression is increased in obesity, inhibiting physiological H_2O_2 signaling by increasing bilirubin levels which reduces mitochondrial function. Although ABCB10 expression is regulated during macrophages activation, its role on modulating macrophages functions and systemic inflammation in metabolic diseases remains unknown.

Objective: To determine how ABCB10 and bilirubin regulate mitochondrial function in macrophages.

Method: We used wild-type and ABCB10 myeloid-specific KO mice to remove ABCB10 in macrophages. We isolated the bone-marrow-derived macrophages (BMDM) and polarized them in pro-inflammatory macrophages (M1) or anti-inflammatory macrophages (M2). We analyzed transcriptomic levels and signaling pathways of pro- or anti-inflammatory markers. We analyzed mitochondrial function, glycolysis and redox changes in BMDM.

Results: Our preliminary results show that ABCB10 KO BMDM displayed lower p38 phosphorylation (Thr180 and Tyr182) in M1 macrophages suggesting less pro-inflammatory activity. Likewise, we demonstrated that ABCB10 KO BMDM decreased the transcriptomic expression of pro-inflammatory genes like *TNFα* and *IL-1β*, in response to LPS and IFN-γ treatment. Alternative macrophage activation (M2) by IL-4, measured with *Arg1* mRNA expression, was increased by ABCB10 deletion.

Conclusion: Our data suggest that ABCB10 deletion leads macrophages to an anti-inflammatory profile which could be harnessed to reduce inflammation.

P-064 Identification of a new E3 ubiquitin ligase involved in the regulation of hepatic metabolism in response to fasting

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The liver plays an important role in carbohydrate metabolism by storing and producing glucose. These functions change according to the body's nutritional status. Feeding state promotes glucose storage while fasting state induces glucose release. In case of obesity and diabetes, glucose is produced constantly which mimics the fasting state in healthy individuals. Hence, identifying new factors involved in the regulation of hepatic metabolism during fasting and feeding transition could provide a new perspective to better understand glucose metabolism in obese and diabetic patients.

To identify new factors involved in the control of liver metabolism during fasting, we analyzed datasets in which the hepatic response to fasting was characterized by microarray. This approach allowed us to identify

differentially expressed genes after different periods of fasting. We have defined a list of thirteen genes coding for proteins that have not been studied in this context so far. These genes could potentially be involved in the control of hepatic metabolism. Interestingly, qPCR validation revealed that most of the hit genes were regulated by fasting. The top gene in the list was “F-box only” (*Fbxo*). This gene encodes an E3 ubiquitin ligase that functions as a complex with “S-phase kinase-associated protein 1” (SKP1) and “Cullin 1” (CUL1) to ubiquitinate target proteins. We observed that *Fbxo* showed a significant increase after 6, 12 and 24 hours of fasting. Also, we observed a deregulation in *Fbxo* expression in obese and diabetic mouse models. To identify potential substrates of FBXO, we performed immunoprecipitation to pull down FBXO in the liver of fasting mice and samples were analyzed by mass spectrometry. Our results revealed that FBXO could interact with proteins already known to be involved in metabolic processes such as amino-acid starvation.

These preliminary data show that during fasting and feeding transition, FBXO is activated to rapidly modulate the expression of certain proteins by ubiquitination. This study suggests that FBXO could be deregulated in individuals with obesity and diabetes and provides a possible mechanism that plays a role in regulating hepatic metabolism in these patients.

P-065 Short-term physical inactivity triggers whole-body and skeletal muscle metabolic inflexibility and insulin resistance

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Physical inactivity is a recognized risk factor for the onset and progression of metabolic diseases such as type 2 diabetes. We showed that physical inactivity impairs metabolic flexibility, a core component of metabolic health defined as the capacity of the body to match substrate oxidation to fuel availability. This inflexibility was shown to precede glucose intolerance triggered by physical inactivity. The underlying biological mechanisms are however unknown. To determine the specific role of skeletal muscle in the development of whole-body metabolic inflexibility and insulin resistance induced by short-term physical inactivity, we used a space analog model of rapid deconditioning consisting of 5 days of dry immersion (DI) in 18 active, normal-weight men. Metabolic flexibility was assessed as changes in respiratory quotient measured by indirect calorimetry during 5h following a carbohydrates-rich breakfast. Physical inactivity reduced variance in respiratory quotient but increased variance in insulin in response to the standard meal. This indicates a lower shift in substrate use (-29%, $p<0.05$) despite greater changes in insulin concentration (2-fold increase, $p<0.01$), reflecting a lower metabolic flexibility. This was accompanied by a decrease in insulin sensitivity (5h post-prandial Insulin/Glucose: -34%, $p<0.001$). A decrease in quadriceps cross-sectional area (-3%, $p<0.05$) measured by MRI indicated muscle atrophy. In primary myotubes, the increase in fat oxidation in response to incremental fatty acids concentration and the suppression of fat oxidation in presence of increasing glucose concentration were both blunted after DI ($p<0.05$ for both). This reflects a muscle-autonomous impairment of metabolic flexibility. This was associated with a reduced *in vitro* insulin-stimulated glycogen synthesis (-20%, $p<0.05$) and Akt phosphorylation (-42%, $p<0.05$), indicating a lower insulin sensitivity. Our results suggest that short-term physical inactivity induces whole-body metabolic inflexibility and insulin resistance that are mirrored in skeletal muscle cells *in vitro*, thus indicating rapid imprinting of environmental changes in skeletal muscle.

P-068 Lack of light in the evening alters thermal and metabolic physiology during sleep

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Previous studies involving evening light exposure on thermoregulation and energy metabolism have reported the use of high intensities of bright white light, and dim light as control exposures. These studies have consistently indicated that bright light in the evening attenuate decrease in core body temperature and delays the circadian rhythm. However, little has been reported focusing on the effects of lack of light in the evening on thermal and metabolic physiology during sleep. Here we present a preliminary data on healthy male participants who underwent exposure to dim light (<10 lux) for 7 hours before bedtime under constant postural position and caloric intake. Core body temperature, EEG, and energy metabolism were continuously recorded in the metabolic chamber. Participants were instructed to remain sedentary during dim light exposure until their habitual bedtime with a sleep duration of 7 hours. Preliminary results showed that body temperature gradually decreased at the start of dim light exposure and reached nadir before or at sleep onset. Respiratory quotient, which has been reported to vary with circadian phase, reached nadir 2 hours after sleep onset. Previous studies have shown that minimum body temperature under non-dim light exposure tends to occur at around 5 hours after sleep onset in men. The extended exposure to dim light in the present study may either implicate a shift in body temperature rhythm to an earlier time, regulated in the SCN, or is the result of the direct responses to light on thermoregulation at the preoptic area. Further data collection is needed to understand the relationship between thermal and metabolic regulations in response to lack of light in the evening and how they may be linked to circadian physiology.

P-069 Exercise-induced reallocation of physical behaviors and its possible role on daily energy expenditure in humans

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Background: Increasing moderate-vigorous physical activity (MVPA) through exercise requires reallocating time from other(s) physical behavior(s). The increase in daily energy expenditure induced by exercise should depend on those reallocations. We aimed to determine the reallocations induced by endurance exercise in physically active subjects. We also searched for behavioral compensatory responses, and explored the effect of exercise on daily energy expenditure.

Methods: Fourteen subjects (8 women; median age 37.8 [IQR 29.9–48.5] years) exercised on Monday, Wednesday and Friday mornings (cycling MVPA, 65 min/session; "exercise days"), and avoided exercising on Tuesday and Thursday ("rest days"). Time spent on sleep, sedentary behavior, light-intensity physical activity, and MVPA was determined each day by accelerometers and logs. An energy expenditure index was computed considering the minutes spent on each behavior and fixed metabolic equivalents (MET): 1.0 MET for sleep, 1.25 MET for sedentary behavior, 2.25 MET for light-intensity physical activity, and 4.0 MET for MVPA. Thus, for example, exercise sessions represented an energy expenditure of 260 METmin (65 min x 4.0 MET). The minimum exercise-induced increase in daily energy expenditure expected was 0 METmin, in case 65 min of non-exercise MVPA were reallocated to exercise. Whereas the maximum increase expected was 195 METmin,

in case 65 min of sleep (65 min x 1.0 MET = 65 METmin) were reallocated to exercise: 260 METmin of exercise – 65 METmin of sleep = 195 METmin.

Results: All subjects had lower sleeping time and higher time on total (including exercise) MVPA on exercise days compared to rest days. Thus, on exercise vs. rest days, sleeping time was lower (490 [453–553] vs. 553 [497–599] min/day, respectively, *P*<0.001) and time on total MVPA was higher (86 [80–101] vs. 23 [15–45] min/day, respectively; *P*<0.001). No differences in other physical behaviors were detected. Notably, besides reallocations (i.e. less time in other behaviors), exercise also induced behavioral compensatory responses in some subjects (e.g. increased time on sedentary behavior in six subjects). Time reallocations and behavioral compensatory responses resulted in re-arrangements of physical behaviors that manifested in exercise-induced increases in daily energy expenditure ranging from 96 to 232 METmin.

Conclusion: Physically active subjects reallocated time from sleep to accommodate morning exercise. Yet exercise induced variable re-arrangements of physical behaviors, with some subjects manifesting behavioral compensatory responses. Individual time re-arrangements of physical behaviors may influence the outcomes of exercise interventions in the long-term, e.g. weight loss.

P-070 Humans in the Cold: Acute Increases in Hunger

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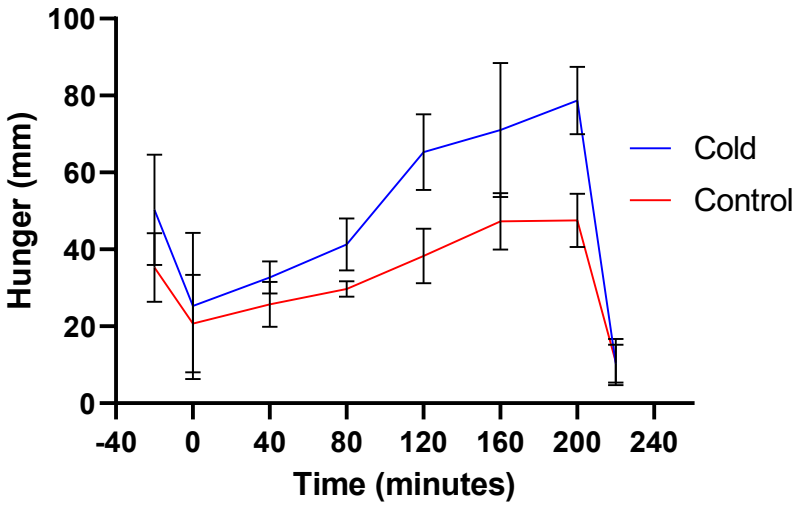
Purpose: Cold exposure (CE) has repeatedly been shown to increase energy expenditure, leading some scientists to believe that CE could be used for improving body weight regulation. However, the possible orexigenic effects of CE have not been documented, particularly in individuals living with obesity. The goal of this study is to measure the acute impact of CE on energy balance, focusing on energy intake and hunger.

Methods: Three individuals living with obesity underwent 90 minutes of CE in a liquid conditioned suit perfused with 10°C water, followed by 48 hours of direct energy intake measurement via food boxes. Subjective hunger was recorded at regular intervals throughout the testing day. Data collection is ongoing.

Results: As expected, CE caused a trending increase in energy expenditure compared to the control condition (176.1 ± 7.8 vs 148.1 ± 11.6 kcal, respectively). Initial data shows a near significant increase in area under the curve subjective hunger levels (p=0.054) as seen in the below figure, with a small difference in energy intake over the 48 hours between CE and control conditions (7183 ± 1270 vs 7079 ± 1389 kcal, respectively).

Conclusion: Early data shows trending increases in hunger of 57% following acute CE, a concern for the long-term negative energy balance needed to result in changes in body energy stores. However, further data is

needed to properly power statistical analysis.



P-071 Dynamic Gas Infusion-Based Determination Of Minimum Derivative Size For The Calculation Of VO2 And VCO2 In A Whole Room Calorimeter.

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Measurement of whole-body oxygen consumption (vO_2), carbon dioxide production (vCO_2), and energy expenditure (EE) by whole room calorimetry is becoming increasingly common. Signal post-processing can have significant implications on the interpretation and use of the data. Historically, studies that use whole room calorimeters have focused on long duration measurements, e.g., 24-h EE. Here we explore the effect changing derivative term has on the calculation of vO_2 and vCO_2 over 2-hour steady state and multiple 5-minute time-windows. We conducted four identical gas infusions in our 32,500L metabolic chamber. Inflow air was held constant at 70 $L*min^{-1}$ and inflow and outflow O_2 and CO_2 were sampled every 15s; N_2 and CO_2 were infused though used our precision, traceable gas blending system (MEI, Enida, MN, USA) to simulate vO_2 and vCO_2. The infusion protocol (Fig. 1) began with 2-h of simulated rest (1 MET, RER 0.75), followed by a dynamic portion with step changes every 5-min (2-5.5 METS 0.5 MET step with return to 1 MET for 5-min between stages, RER 0.75), and ended with a 30-min simulated treadmill walk (4.4 METS, RER 0.85) with three 'challenge periods' (5.0 METS, RER 0.85).

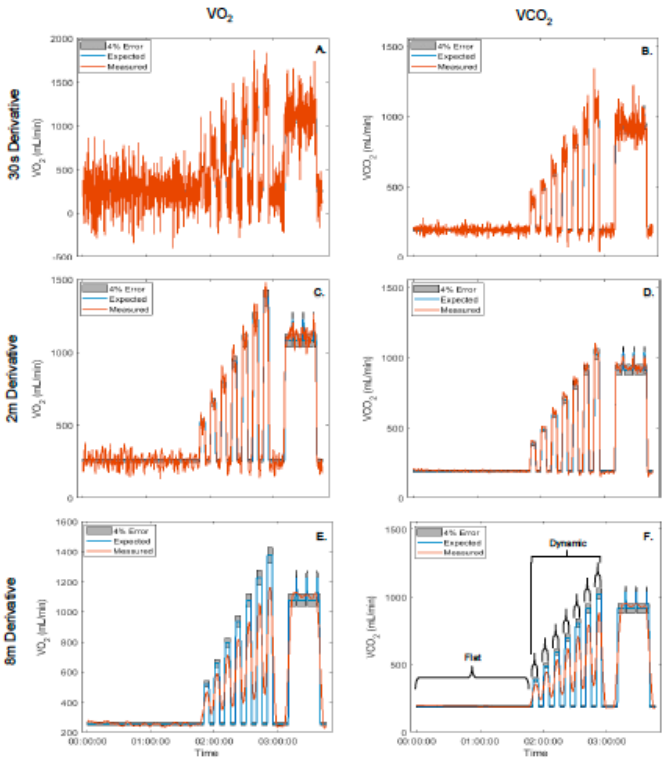

Figure 1. Calculated and expected gas exchange rates during an example infusion processed with different derivative sizes. Panel F. shows the portions used for "Flat" and "Dynamic" window analysis. VO_2, volume of oxygen consumed; VCO_2, volume of carbon dioxide produced.

vO_2 and vCO_2 were evaluated for: overall percent error, calculated as the difference in the areas under the curve (AUC) between the expected vs. the measured; and average absolute sample error (ABS), calculated as the average absolute percent difference between the measured and expected values at every time-point. Both AUC and ABS were evaluated across the different time-windows. Data were post processed using 0.5, 1, 2, 4, and 8-min center derivatives. Average results are reported. Our results (Table 1) show that both AUC and ABS varied with time-window, derivative size, and signal (vO_2 vs vCO_2). **INSERT TABLE 1 HERE*** These results indicate that the derivative term used in post-processing whole room metabolic chamber data should be tuned to the time-window of interest as both the AUC and ABS can be impacted. This is especially of concern if an investigation is interested in vO_2 or vCO_2 kinetics. These results suggests that whole room calorimetry is an appropriate tool for investigating both short and long time-windows of metabolic data and can be tuned to be responsive to rapid changes in metabolic rate.

P-072 Energy expenditure and energy intake during healthy pregnancies

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Objectives. During pregnancy, an indicator of energy expenditure (EE) and energy intake (EI) is gestational weight gain (GWG). However, very few study designs considered altogether EE, EI, and GWG. Moreover, there are misunderstood factors potentially associated with EE and EI variations in pregnancy such as eating, physical activity and sleep behaviours, diet quality, and lumbopelvic pain (LBPP). The aims of the study are to 1) quantify maternal EE, EI, and GWG at each trimester of pregnancy, 2) examine maternal EE, EI, and GWG

according to maternal pre-pregnancy body mass index (ppBMI) and 3) identify factors associated with maternal EE and EI during pregnancy.

Methods. As part of this prospective cohort pilot study, 40 nulliparous pregnant females will be recruited in Quebec City from early 2023 until mid 2024. At each trimester (T1: 9-13th, T2: 22-26th and T3: 33-37th gestational week), the following variables will be evaluated: a) Basal metabolic rate (BMR) will be assessed by indirect calorimetry using a ventilated hood system (Promethion Room Calorimetry System). Oxygen consumption and carbon dioxide production will be measured at several intervals and used to calculate BMR; b) participants will wear an accelerometer (Actigraph GT3X) during seven consecutive days to evaluate their physical activity levels. Total daily EE will be estimated using BMR and physical activity levels; c) EI will be assessed using three Web-based 24-hr dietary recalls (R24W), over a three-week period. Other maternal factors will be assessed: a) Body weight entries in the medical records to calculate the GWG; b) ppBMI calculated from self-reported body height and weight; c) diet quality derived from the R24W dietary intakes and assessed using the Healthy Eating Food Index (HEFI-2019); d) participants' eating behaviours (dietary supplements use, nausea, vomiting, food cravings and aversions, attitudes and behaviours towards food and restriction, disinhibition and susceptibility to hunger) from seven short food-related questionnaires; e) sleep quality and duration using the Pittsburgh Sleep Quality Index and f) limitations and symptoms linked to LBPP and its severity using the Pelvic Girdle Questionnaire and a visual analog scale.

Anticipated results. This project will lead to a better understanding of EE and EI variations during pregnancy in association with GWG, ppBMI, and factors such as maternal eating, physical activity and sleep behaviours, diet quality, and LBPP. These findings will strengthen the evidence required to adjust the approach in estimating maternal energy needs in future intervention studies and support the importance of individualized interventions.

P-074 Measuring urinary energy loss in community-dwelling and independent middle-aged and older adults

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Background: Understanding energy balance and the factors that influence them are important for nutrition research. Urinary energy loss is one of the factors that influence energy balance. However, to our knowledge, the data on urinary energy loss in middle-aged and older adults is fairly limited.

Objective: The present study examined urinary energy loss and the factors that influence them.

Methods: Participants were 19 Japanese individuals aged 60–90 years old (9 males and 10 females). One participant had diabetes, urinary energy loss was larger in the diabetes participant (274.0 kcal/d) than in all of the other participants (mean 84.9 kcal/d), and so we did not include the data of that participant in the analysis. Finally, data from 18 participants were included in the analysis. In this study, anthropometric data, physical activity data measured using a triaxial accelerometer, 24-h urine samples, and fasting blood samples were collected. Total energy expenditure (TEE) was measured using the triaxial accelerometer and the doubly labeled water (DLW) method (the data of TEE by DLW method is under analysis). TEE measured by the triaxial accelerometer was defined as equal to estimated energy intake (EI). The urine samples were freeze dried, and analyzed for energy with a bomb calorimeter. Thereafter, urinary energy loss per day was calculated from urinary volume and dried urinary energy. Urinary protein and urea nitrogen were analyzed. The blood samples

were analyzed creatinine, cystatin C, and urea nitrogen as renal function markers. The estimated glomerular filtration rate (eGFR) was calculated from sex, serum cystatin C concentrations, and age.

Results: Urinary volume was 1,839 ± 498 (mean ± SD) mL (range: 821–2,880 mL), and urinary energy loss per day was 84.9 ± 19.1 kcal/d (53.7–139.3 kcal/d). Urinary energy loss per day was significantly positively correlated with estimated EI (r=0.692) and anthropometric data [body weight (r=0.652) and abdominal circumference (r=0.516)]. Urinary energy loss per day divided by estimated EI did not relate to anthropometric data, physical activity data, and renal function markers. Urinary energy loss as a percentage of estimated EI was 4.9 ± 0.9% (3.1–6.4%).

Conclusions: The findings of the present study indicated that urinary energy loss per day was positively associated with estimated EI and that mean 4.9% of estimated EI was lost as urinary energy in the community-dwelling and independent middle-aged and older adults.

P-076 Dietary protein modulation of urea cycle mediates liver fatty acid oxidation

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We recently reported that feeding mice a diversified protein mix (PM) that better reflects dietary protein sources consumed by humans increases the deleterious metabolic effects of high fat high sucrose (HFHS) diets as compared to feeding casein (Cas) only. These effects were partly explained by microbiota metabolites, but other mechanisms remain to be elucidated to explain the impact of PM on acylcarnitine accumulation and insulin resistance in the liver. We believe that part of these effects are caused by the differential activation of the urea cycle during the catabolism of amino acids (AA), whose composition varies from source to source especially regarding their total nitrogen load. Furthermore, recent studies point to a link between urea cycle activation and liver oxidative stress through lipid metabolism. Objective: To establish whether protein sources and their AA composition alter hepatic metabolism and insulin resistance through the urea cycle. Methods: Urea cycle, oxidative stress and lipid metabolism enzymes of mice's liver fed either PM, Cas for 12 weeks or pork protein (PP) for 2 weeks in HFHS background have been measure as well as weight and fat mass gain. Results: Animals that were fed the PM diet had increased protein expression of the rate-limiting urea cycle enzyme Carbamoyl Phosphate Synthetase 1 (CPS1) and Arginosuccinate synthase 1 (ASS1). Since ASS1 has been linked to increased mitochondrial beta oxidation through increased AMP levels, we looked at the phosphorylation of Adenosine Monophosphate kinase (AMPK) and its downstream target Acetyl-CoA Carboxylase (ACC) and both were increased in HFHS PM-fed mouse livers as compared to livers of HFHS Cas-fed animals. This activation of the lipid oxidation pathway was also observed in HFHS PP-fed mice, compared to casein or soy proteins that resulted in significantly lower post prandial AA-derived nitrogen load. AMPK activation was also increased in the liver of PP-fed mice and was accompanied by increased gene expression of inducible nitric oxide synthase (iNOS) and increased reactive oxygen species accumulation as showed by dihydroethidium (DHE) staining. PP also recapitulated within only 2 week the significant increase in HFHS-induced body weight and fat mass gain observed with the PM diet. Conclusion: PM and PP- increase AA-derived total nitrogen load activating the urea cycle, leading to alterations in hepatic lipid metabolism, inflammation and oxidative stress in the liver. The interaction between protein AA composition and dietary fat load should be explored further to better understand its contribution to diet-induced insulin resistance.

P-077 Web-based analysis of indirect calorimetric data arising from metabolic phenotyping systems

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Indirect calorimetry is widely applied in pre-clinical and clinical research to quantify energy expenditure. While principles and technologies are well established, users would profit from a versatile tool for data exploration and analyses, including suitable statistical routines to account for differences in body mass and body composition. Therefore, we developed a standalone open-source web application framework for the analysis of indirect calorimetry data, arising typically from metabolic phenotyping systems. This web application can be deployed either to cloud infrastructures or to self-hosted services at departmental facilities providing full control and sovereignty over research data. By making use of a reactive graphical user interface users can for instance conduct a fast explorative data analysis, interactive visualization / plotting of analysis results and a in-depth analysis through established methods e. g. ANOVA / ANCOVA with regards to energy balance, total energy expenditure (TEE), resting metabolic rate (RMR) and activity energy expenditure (AEE). Since our code base is in R, one can readily make use of additional analysis packages as respR. Based on modular design, availability in public repositories, i. e. Github, and conformity with the FAIR principles, our application provides transparency, repeatability and reproducibility of analysis to the energy metabolism community. Through separation and modularization of the user interface from the backend code (providing the analysis tools) the application can be extended ad libitum. In particular we streamlined the user interface for rapid data analysis workflows (which can be saved for reproducibility and used as templates in subsequent analysis runs). When calculating RMR from indirect calorimetric measurements, activity-related data are instrumental to discern between RMR and AEE as main contributors to TEE. Lack of activity-related data thus jeopardizes the determination of RMR. Therefore, we added a novel functionality to the web application allowing for the extraction of RMR and AEE from indirect calorimetric measurements without the need for activity-related data. We used standardized data sets (containing activity data) to validate our novel method for calculating RMR without activity data. Input data provided in diverse formats can be consolidated into common file formats (CalR, Sable, TSE) and re-exported or analyzed with our framework, to be shared with collaboration partners. Export functionality of plotting results and high-quality graphics export have been directly embedded in the web application. By providing a holistic and open-sourced data analysis framework for indirect calorimetric data, we strive to improve trust and rigor of data analysis in the field of energy metabolism.

P-078 Circulating endocannabinoids: potentials determinants of metabolic function of white adipose tissue in human

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Introduction: The endocannabinoid system plays a role in white adipose tissue (WAT) metabolism, assuring the energy conservation through modulation of storage and mobilization of fatty acids (FA). To this regard, its hyperactivation in obese individuals is suspected of amplifying the development of obesity and promoting the onset of type 2 diabetes. Nevertheless, while plasmatic endocannabinoids (ECs) and their entourage compounds (ERCs) have primarily served as a biomarker of obesity and indirectly of dysmetabolism so far, their

potential physiological and pathophysiological roles on the metabolic function of WAT remains to be determined. Hypothesis: Fasting and postprandial plasma levels of 3 ECs and 6 ERCs will be higher in obese and pre-diabetic subjects and will be associated with dietary FA (DFA) storage capacity and/or mobilization of free fatty acids (FFA) in WAT. Method: Positron emission tomography with an analogue of saturated fatty acids, acid [^{18}F]-fluorothiaheptadecanoïque administered orally, as a radiotracer, allowed the measurement of the storage capacity in WAT and lean organs. Sequential intravenous administration of [7,7,8,8-^{2}H]-palmitate and [1,1,2,3,3-^{2}H]-glycérol allowed the measurement of the mobilization of FFA (i.e. intracellular lipolysis) by WAT. A validated liquid chromatography method coupled with tandem mass spectrometry was used to quantify ECs (2-AG, AEA, DHEA), ERCs (OEA, PEA, 2-OG, SEA, LEA, 2-LG) and arachidonic acid in fasting, 3h and 6h postprandial plasma of 20 healthy and prediabetic subjects in whom the metabolic function of WAT was measured using the above tracers. Results: Our preliminary results show that fasting and postprandial levels of plasmatic ECs and ERCs correlate with storage of DFA in WAT, but also in the heart and liver. Area under the curves (AUC) of postprandial kinetics of ECs and ERCs also correlate with postprandial AUC of FFA. Interestingly, AUC of 2-AG is increased in prediabetic men (p = 0,07) and strongly correlate with intracellular lipolysis of FFA (r = 0,95; p = 0,05). Conclusion: Taken together, these first results suggest that plasmatic ECs and some ERCs are associated with storage of DFA in WAT, but also in the heart and liver, as well as with mobilization of FFA by WAT.

P-080 Association between SARS-CoV-2 infection severity and circulating amino acid levels as markers of adiposity and altered metabolic profile in the Quebec COVID-19 Biobank (BQC19)

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Background: Compared to lean individuals, those living with obesity are at a greater risk of presenting severe symptoms when infected by the SARS-CoV-2 virus responsible for COVID-19. Circulating levels of some amino acids have been shown to be associated with obesity and metabolic alterations, notably leucine, isoleucine, valine and glutamate. Therefore, we hypothesized that the circulating levels of these amino acids would be associated with COVID-19 severity.

Methods: From the Quebec COVID-19 Biobank (BQC19), we selected participants with a positive COVID-19 qPCR test and for whom at least 1 plasma metabolomic measurement was available within 1 week of study inclusion. Disease severity was assessed at study inclusion using the World Health Organization criteria, as either mild, moderate or severe. We used logistic regression models to calculate the odds ratio (OR) of presenting severe vs mild and severe vs moderate symptoms associated with an increase in amino acid levels.

Results: Overall, 736 patients were considered, including 159 (22%), 353 (48%) and 224 (30%) with mild, moderate and severe symptoms, respectively. In the severe group, participants were older on average and the prevalence of male sex, diabetes and obesity was greater compared to the mild group. Among the 20 amino acids tested, 12 were significantly associated with the presence of severe vs mild and moderate symptoms. Leucine, isoleucine, valine and glutamate were all significantly associated with the prevalence of severe symptoms (OR ranging from 1.35 to 1.64, all p<0.05), but phenylalanine and tryptophan showed far stronger associations (OR: 4.14, 95%CI: 2.79-6.13, p: 1.5e-12 for phenylalanine and OR: 0.38, 95%CI: 0.29-0.50, p: 9.7e-13 for tryptophan). The association of phenylalanine and tryptophan with disease severity remained significant after adjustment for age, sex, obesity, and diabetes.

Conclusion: Among the amino acids known to be associated with obesity and metabolic alterations, phenylalanine and tryptophan levels were most strongly associated with COVID-19 severity. The pathophysiology of the association between circulating amino acids and COVID-19 warrants further investigation.

P-081 Probing cardiac and renal ketone metabolism in healthy adults: PET ketone imaging plus a ketone supplement in the fasted and fed state

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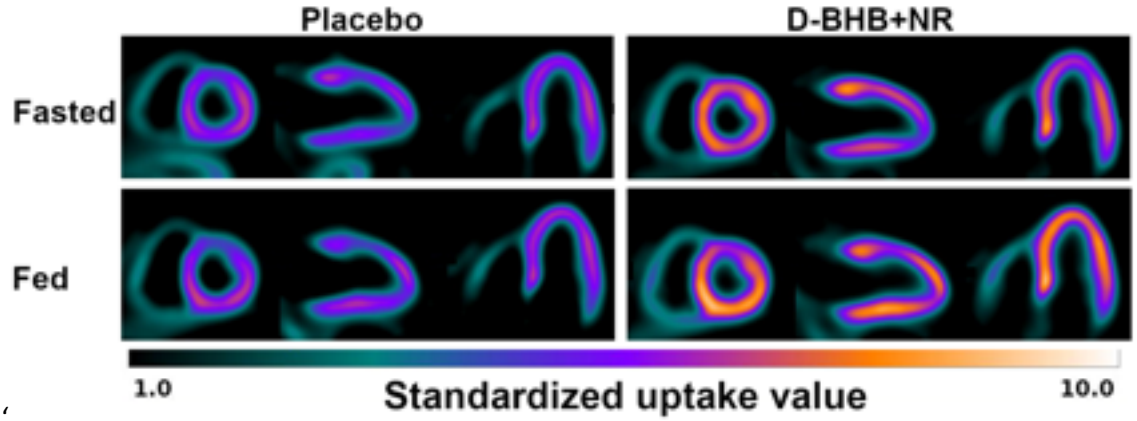
BACKGROUND: The heart and kidney rely mainly on free fatty acids and glucose to meet their high energy needs. Several nutritional strategies exist to increase blood ketones but it is unclear whether exogenous ketones could be significant metabolic fuels for the heart or kidney. Exogenous ketones may improve heart function in heart failure.

METHODS: Cardiac and renal ketone metabolism were assessed in healthy participants using dynamic positron emission tomography (PET) with the ketone tracer – ^{11}C-acetoacetate. Ten healthy participants were evaluated, each under four conditions: fasted, fed, fasted+ketones (fastedK), and fed+ketones (fedK). In the fed condition, participants consumed a liquid complete meal (Boost®) 20 minutes before imaging. In the ketone supplementation condition, participants took a supplement that combined 12 grams of D-beta-hydroxybutyrate and 500 mg of nicotinamide riboside (D-BHB+NR) 30 minutes before the PET scan. Plasma ketones were measured and kinetic modeling was performed to derive heart and kidney metabolic rate of ketone consumption ($MR_{ketones}$). Cardiac ejection fraction and left ventricular volume were also measured. Conditions were compared with a one-way repeated measures ANOVA, with a significance threshold of $p < 0.05$.

RESULTS: With or without a meal, D-BHB+NR significantly increased plasma ketones ([mean±SD]: fasted 0.2 ± 0.2 mM, fed 0.1 ± 0.4 mM, fastedK 1.5 ± 0.8 mM, fedK 1.5 ± 0.5 mM), and myocardial $MR_{ketones}$ ([all µmol/100 g/min]: fasted 0.06 ± 0.05, fed 0.02 ± 0.01, fastedK 0.39 ± 0.19, fedK 0.34 ± 0.11). After D-BHB+NR, left ventricular ejection fraction increased by about 5% (fasted 68 ± 4 %, fastedK 71 ± 3 %, fedK 72 ± 4 %) while end-systolic volume declined by 10-13% (fasted 30 ± 8 ml, fastedK 27 ± 7 ml, fedK 26 ± 9 ml). Preliminary data suggest ketones were consumed by the kidney in relation to their availability ([all µmol/100 g/min]: fasted 0.03 ± 0.03, fed 0.01 ± 0.004, fastedK 0.26 ± 0.19, fedK 0.19 ± 0.10).



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Ketone uptake by the healthy adult heart here’DISCUSSION: D-BHB+NR produced a 5-10-fold increase in both plasma ketones and MR_{ketone} in the heart and kidney, an effect that was independent of feeding state. A single acute dose of D-BHB+NR increased myocardial contractility on the basis of the higher left ventricular ejection fraction and lowered end-systolic volume, effects that could potentially be beneficial in the treatment of heart failure. The effects of ketone supplementation on kidney function warrant further investigation.
Acknowledgements: Supported by Nestlé Health Science, FRQS and the Université de Sherbrooke.

P-082 Accuracy and precision of four metabolic carts in comparison to Deltatrac II

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Objective: We determined the accuracy and precision of four commercially available metabolic carts (Q-NRG [Cosmed; Rome, Italy]; Omnical [Maastricht Instruments; Maastricht, The Netherlands]; Vyntus CPX [Vyaire; Hochberg, Germany]; and TrueOne 2400 [Parvo-Medics; Salt Lake City, USA]) compared to our institutional gold-standard (Deltatrac II [Datex-Ohmeda; Helsinki, Finland]).

Methods: *Experiment 1:* Over a 4-week period, we performed: (i) 20 combustions of 5g of pure ethanol and (ii) 20 infusions of pure gases (N_2 and CO_2) mimicking the combustion rates. *Experiment 2:* Over 10-day period, we performed daily gases infusions simulating: (i) different energy expenditure (EE) [1000, 1500 and 2000 Kcal/d at Respiratory Exchange Ratio (RER)=0.85] and; (ii) different RER (0.80, 0.85 and 0.90 at EE=1500 Kcal/d). Rates of oxygen consumption rate (VO_2) and carbon dioxide production (VCO_2) were measured, and EE and RER were calculated. The measured VO_2, VCO_2, EE and RER readouts were then computed as a percentage of the expected values.

Results: The measures obtained in *Experiment 1* are depicted in figure 1.

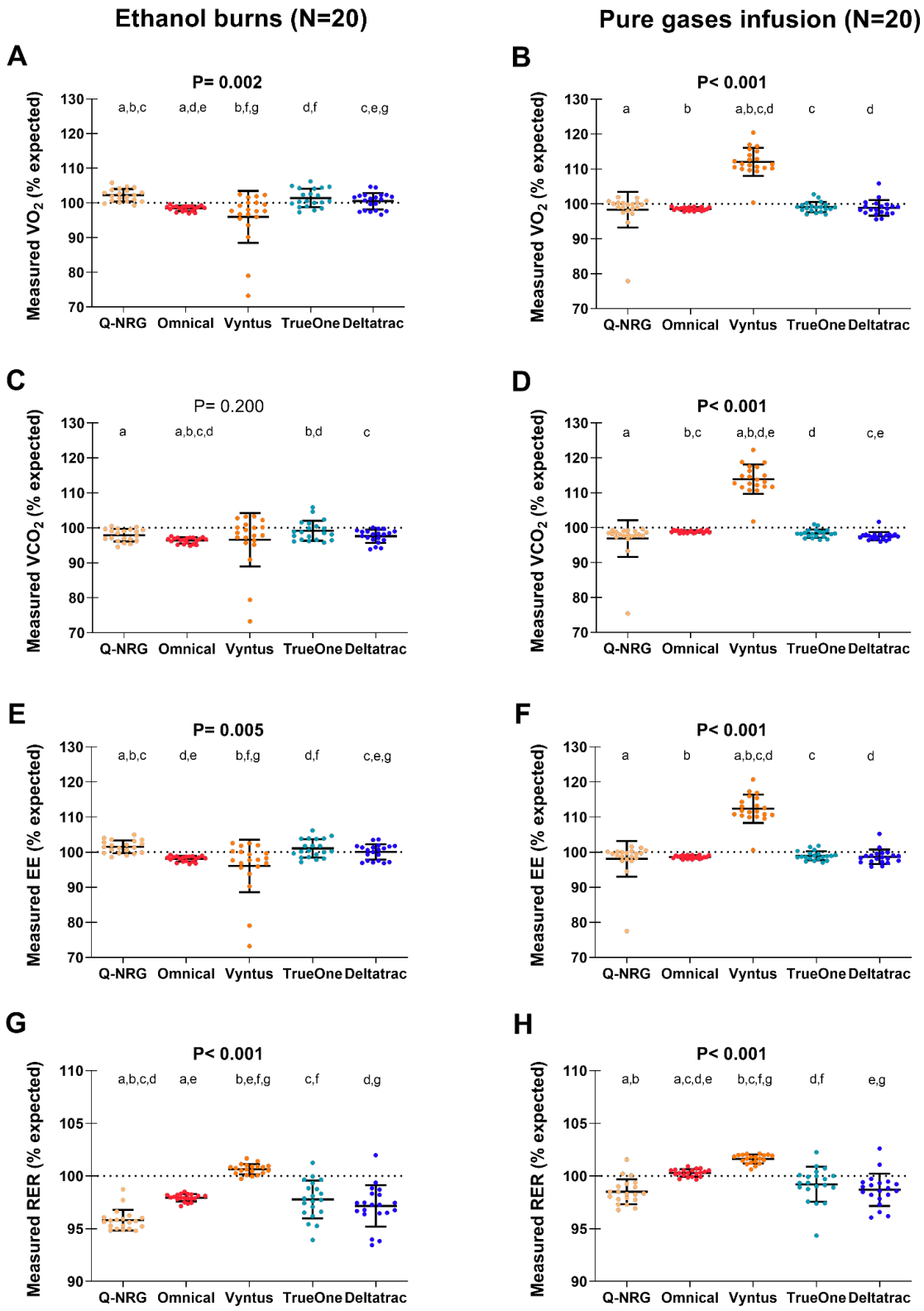

Figure 1. Measures of oxygen consumption (VO2), carbon dioxide production (VCO2), energy expenditure (EE) and respiratory exchange ratio (RER) during ethanol burns and pure gases infusions. Data are presented as mean (standard deviation). P-values from repeated measures analysis of variance (ANOVA). Similar letters represent between-carts differences as determined by post-hoc LSD analysis.

The five metabolic carts provided discrepant measures both when using combustion test or gases infusions. During combustion tests, the highest accuracies (i.e., the closest to 100% of the expected values) for VO_2 and VCO_2 were provided by the Deltatrac and the TrueOne, respectively. With gases infusions, the best accuracies for VO_2 and VCO_2 were provided by the TrueOne and the Omnical, respectively. Overall, the Omnical provided the most reproducible measures for all variables in both combustion and infusion tests. In *Experiment 2*, VO_2 and VCO_2 accuracies were impacted by the level of simulated EE and RER for all metabolic carts.

Conclusions: The five metabolic carts provided discordant measurements of VO_2 and VCO_2. Despite differences in accuracies among carts, Omnical seems to be the most precise instrument to measure both VO_2 and VCO_2.

P-083 Assessment Of Insulin Sensitivity By Continuous Glucose Monitoring And 24-H Urinary C-Peptide Excretion In Non-Diabetic Individuals

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Introduction: The gold standard method for *in vivo* assessing whole-body insulin sensitivity (IS) in humans is the hyperinsulinemic-euglycemic clamp. Unfortunately, implementing a clamp procedure is time consuming, labor-intensive, and expensive. We previously demonstrated that a simple measure of 24-h urinary C-peptide excretion conducted under controlled feeding conditions is a valid, surrogate marker of IS in non-diabetic adults. In this study, we hypothesized that the combination of 24-h continuous glucose monitoring (CGM) and 24-h urinary C-peptide excretion (24h-glycemia/C-peptide ratio) will be associated with IS as derived by the hyperinsulinemic-euglycemic clamp, and that it will be more strongly associated with IS than 24-h urinary C-peptide excretion alone.

Methods: Thirteen participants (7 women, 6 men; 52.2±13.8 years; BMI: 26.1±3.7 kg/m^2) completed a 24-h stay in an indirect calorimetry chamber wearing a CGM sensor (Dexcom G6 Pro) and all urine was collected. The 24-h urinary C-peptide excretion was computed from total urinary volume and C-peptide concentration (Immulite 2000 XPi). A fasting blood sample was collected upon leaving the chamber to measure glycemia and insulinemia. On a different day, the participants' IS was assessed by a 2-step hyperinsulinemic-euglycemic clamp. Insulin was infused for 180 min at 10mU/min/m^2 (low-dose) and 120 min at 80mU/min/m^2 (high-dose) with variable glucose infused to maintain plasma glucose at 90 mg/dL. Resting energy expenditure (REE) was assessed and utilized for adjusting the glucose infusion rate (GIR). Body weight and fat free mass were used instead of REE for sensitivity analyses. Further adjustments were made to account for small differences in glycemia during the clamp.

Results: Four surrogate markers of IS were computed: a) 24-h urinary C-peptide excretion; b) 24-h urinary C-peptide excretion adjusted for energy intake; c) 24h-glycemia/C-peptide ratio; and d) the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). All 4 markers were associated with GIR during low-dose insulin infusion, with 24h-glycemia/C-peptide ratio having the strongest association (Figure 1). Moreover, the 24h-glycemia/C-peptide ratio was the only marker of IS associated with glucose disposal rate during the high-dose clamp (Figure 1). Similar results were found when body weight or fat free mass were used instead of REE to adjust the GIR, or when the GIR was further adjusted for mean insulinemia.

Conclusion: The 24h-glycemia/C-peptide ratio is a promising marker of IS, providing better estimates than 24-h urinary C-peptide excretion alone or HOMA-IR. Future studies should explore the validity of this new marker in free-living conditions.

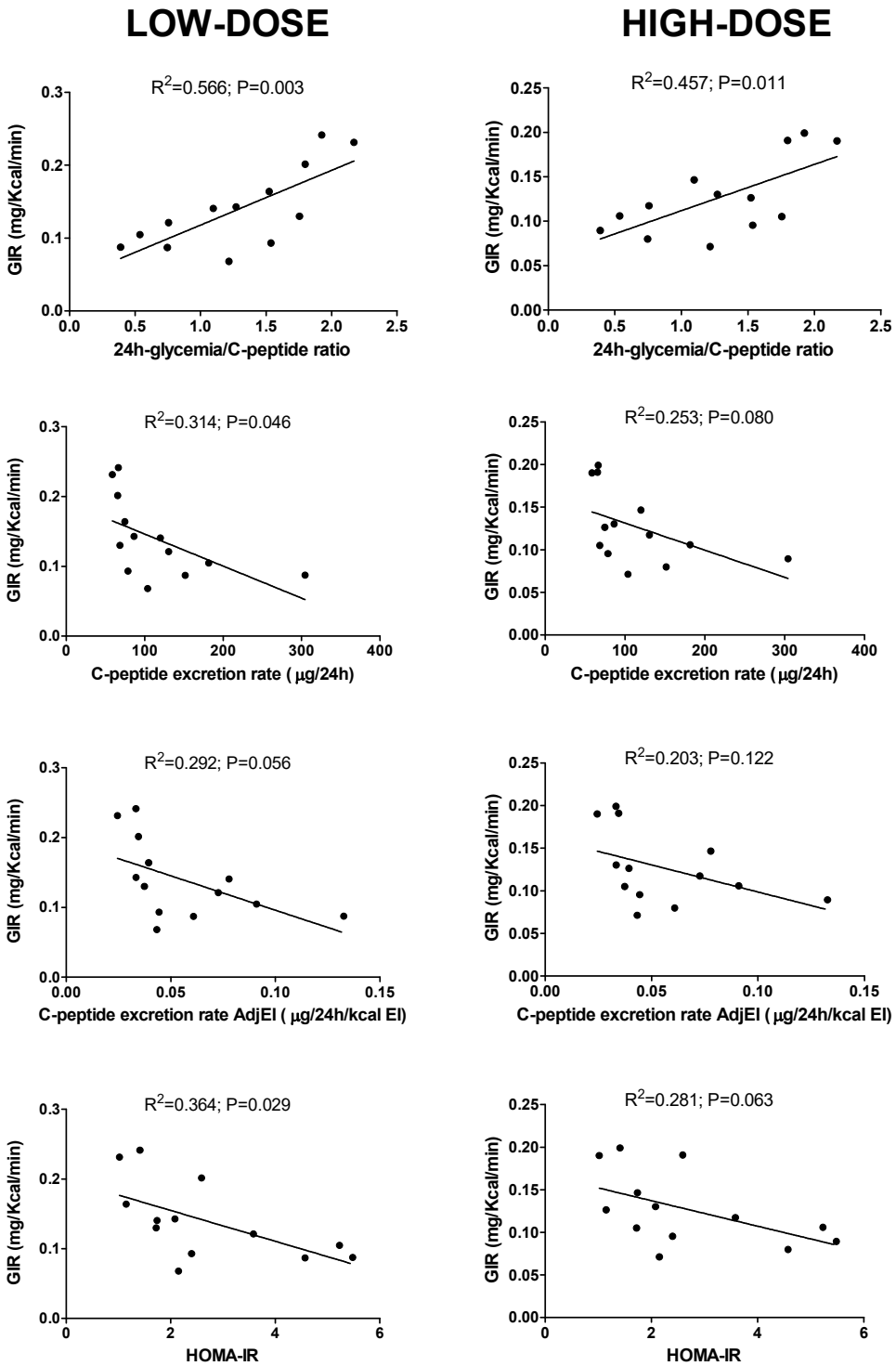

Figure 1. Associations between surrogate markers of insulin sensitivity and the glucose infusion rate (GIR) during low- and high-dose insulin infusion of a 2-step euglycemic-hyperinsulinemic clamp. EI: Energy intake; HOMA-IR: Homeostatic Model Assessment- Insulin Resistance.

P-084 Reproducibility of a Novel Approach for Assessing Metabolic Flexibility in a Respiratory Chamber.

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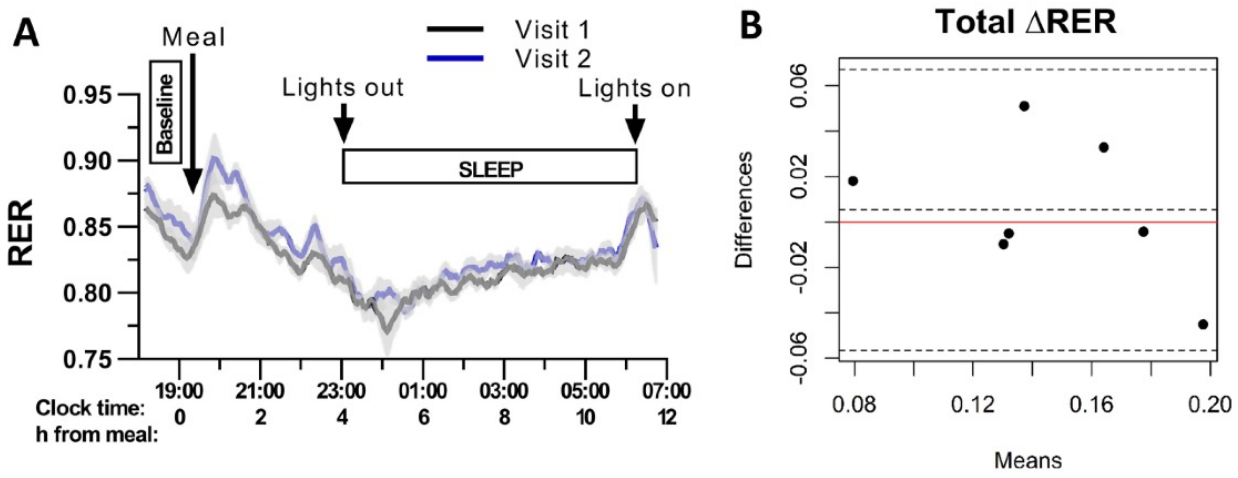
Background: Metabolic flexibility (MetFlex) is the body's ability to adapt fuel oxidation to fuel availability and energy demands. Impaired MetFlex is associated with poor metabolic health including ectopic lipid deposition, insulin resistance, weight gain, and potentially the development of type 2 diabetes. Recent evidence from our laboratory suggests that MetFlex can be determined in a respiratory chamber by quantifying overnight respiratory exchange ratio (RER) dynamics following a high-fat meal (McDougal et al. 2020). The aim of the current study was to determine the test-retest reliability of our MetFlex methodology.

Methods: Seven metabolically healthy subjects (6 men/1 women, 28.1 ± 7.8 years old, 26.4 ± 3.4 kg/m^2 BMI; 24.0 + 9.3 % body fat) completed two identical overnight chamber visits (17.30 – 7.00) separated by 5-7 days, being fed a high-fat (60% fat, 20% carbohydrate, and 20% protein; 40% of energy requirement) dinner at 19.00. The following overnight RER parameters were calculated: meal-stimulated rise in RER (ΔRER peak); fall in RER during the night (ΔRER nadir) from baseline RER; difference between the higher and the lower RER (total ΔRER); time to peak RER; time to nadir RER and; slope between the peak and nadir of RER . Intraclass correlation coefficients (ICCs) were calculated for each parameter to assess test-retest reliability.

Results: Total ΔRER showed the highest test-retest reliability, ICC = 0.74 (p = 0.018), followed by slope to RER nadir and time to nadir RER (ICC = 0.67, p = 0.033 and ICC = 0.57, p = 0.057, respectively). ΔRER peak, ΔRER nadir, and time to peak RER all had had ICCs < 0.50. The average RER time series for each visit and the Bland–Altman plot of Total ΔRER are shown in Figure 1A and B, respectively.

Figure 1



Conclusions: This study demonstrates that total ΔRER has a high test-retest reliability, while both slope to RER nadir and time to nadir RER have moderate test-retest reliability. These findings build upon ours and others previous work on the reproducibility of RER data and will inform future studies investigating the utility of using MetFlx as a novel biomarker for the incidence of metabolic dysfunction.

P-086 Respiratory gas exchange measurements under hypoxic conditions

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[1]Indiana University Bloomington, [2]MEI Research, Ltd

Short-term, overnight exposure to moderate hypoxia (15% O_2) can improve sensitivity to insulin. However, as hypoxia increases energy expenditure and suppresses appetite, it remains unclear whether effects relate to hypoxia or energy imbalance. To measure 24 h energy balance at hypoxic conditions, Indiana University Bloomington (IUB) and MEI Research constructed a room calorimeter (RC) to operate at hypoxic conditions (21-15% O_2). An air compressor (Powerex, LSQ05A4), nitrogen (N_2) generator (Nano, GEN2 I 4.0), and mass flow controller (Alicat, MC Series) send N_2 into the RC to lower O_2 concentration. Modules were added to CalRQ calorimeter software to set the target O_2 concentration manually, or control to an O_2 concentration profile.

Participant safety is essential in hypoxia studies. CalRQ includes O_2 and CO_2 concentration alarms coupled to automatic fresh air purge control. An independent O_2 depletion monitor (PureAire, TX-1100-DRA) delivers local and remote alerts at 14.5% O_2. An additional O_2 depletion monitor is just outside the calorimeters for staff safety.

N_2 added to the chamber is accounted for in both the oxygen uptake ($\dot{V}O_2$) and carbon dioxide elimination ($\dot{V}CO2$) calculations. N_2 and CO_2 may be infused to simulate a participant consuming O_2 and exhaling CO_2. Four, 500 min infusions of N_2 and O_2 were performed at 15% chamber O_2 concentrations with target VO_2 and VCO_2 of 0.332 and 0.287 l/min. Average VO_2 error ranged from -5 to 4% and average VCO_2 error was 2.5%.

These preliminary data show respiratory measurements can be made during hypoxic exposure in RC. N_2 added to achieve hypoxic conditions increased short-term noise in the $\dot{V}O_2$. Further work is needed on how inflow air is sampled and how the data are processed to help mitigate this noise. The O_2 concentration control loop requires tuning over varied conditions, including participant habitation and optimal pre-conditions. RC capable of respiratory measurements during hypoxia will prove crucial to inform appropriate participant feeding protocols to maintain energy balance.

P-087 Acute effects of ryanodine receptor antagonist dantrolene on muscle activity and cold-induced thermogenesis in lean, young men

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Background: Pathways that regulate cold-induced thermogenesis, the increase in metabolic rate above basal during cold exposure, represent potential pharmaceutical targets to increase daily energy expenditure and promote weight loss. However, the contribution of various pathways to cold-induced thermogenesis is still unclear. The ryanodine receptor regulates intracellular calcium release in skeletal muscle and is thought to play a role in both shivering and non-shivering cold-induced thermogenesis.

Aim: We tested whether a single 100 mg dose of the ryanodine receptor antagonist dantrolene would reduce the contribution of skeletal muscle to cold-induced thermogenesis acutely in healthy, lean, young men.

Methods: In a metabolic chamber, we measured resting metabolic rate, muscle activity via surface electromyography (EMG), and thermo-physiological parameters such as skin and core temperature in 16 lightly clothed, fasted men (body mass index=21.9±1.8 kg/m^2; age 26.1±4.5 years) post-administration of placebo or 100 mg dantrolene during four hours of constant exposure to either a warm temperature (27.0±0.7^{o}C) or their coldest tolerated temperature before overt shivering (21.0±1.1^{o}C). Grip strength served as the positive control. Differences were evaluated with two-way analysis of variance controlled for multiple comparisons.

Results: Dantrolene reduced the peak grip strength similarly in both warm (-7.8±10.7%, p<0.01) and cold (-8.0±9.2%, p<0.01) conditions compared to placebo. In warm conditions, metabolic rate after placebo was 1.15±0.10 kcal/min and was not changed by dantrolene (1.14±0.10 kcal/min) as expected. In the 27°C ambient temperature, the weighted-mean skin temperature (33.4±0.6°C) was slightly reduced with dantrolene (33.2±0.7°C, p<0.01), but core temperature (36.6±0.3) was unchanged. Cold exposure reduced skin temperature to 30.8±0.9°C with placebo (p<0.001 vs. warm placebo condition) and this was further reduced to 30.6±1.0°C by dantrolene (p=0.01 vs. cold placebo condition). Cold exposure also increased metabolic rate (1.28±0.15 kcal/min, 10.9±11.7%, p<0.001) and muscle EMG activity (66.9±86.7%, p=0.03) and slightly reduced core temperature (36.2±0.3, p=0.001) with placebo. However, in the cold with dantrolene, the increase in metabolic rate (1.30±0.12 kcal/min, 14.9±9.1%) and muscle activity (89.2±111.4%) and reduction in core temperature (36.1±0.4) were no different than with placebo.

Conclusions: Despite evidence of antagonism at the ryanodine receptor, as indicated by a reduction in the positive control measure grip strength, a single 100 mg dose of dantrolene did not change muscle activity or metabolic rate in the cold. These results suggest that the acute suppression of the ryanodine receptor was not sufficient to alter cold-induced thermogenesis during mild cold exposure in healthy, lean, young men.

P-088 Ketone metabolism - Validation of 3-[11C]-OHB as a new PET tracer

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Introduction: Ketone bodies are produced in the liver as fuel when blood sugar levels are low as seen in ketogenic diets or prolonged fasting. In previous studies, we have observed that ketone bodies act as a kind of "super fuel" for the heart by improving its contractile efficiency. Therefore, methods that are able to quantify cardiac ketone body uptake will be an important tool. This study has the following purposes: 1) Investigate whether the endogenously found D-3-[^{11}C]-OHB enantiomer is absorbed and metabolized by the heart and if the same is true for the L-3-[^{11}C]-OHB enantiomer. 2) Whole-body biodistribution and cardiac kinetics of D-3-[^{11}C]-OHB. 3) Quantification of the metabolite ^{11}CO2.

Methods: Five pigs were examined under anesthesia in the following conditions: 1) Use of both enantiomers of 3-[^{11}C]-OHB, 2) low and elevated ketone bodies and 3) by comparison with the biodistribution of ^{11}C-acetate. PET scans were performed with a Siemens PET/CT system. The pigs were administered 76-410 MBq 3-[^{11}C]-OHB. Two different imaging protocols were used: 1) Dynamic imaging of the myocardium (60 minutes) and 2) D-whole-body imaging (16-20 passages over 70-90 minutes). Time activity curves were calculated using PMOD v4.1 and arterial samples were taken to measure blood and plasma activity. Tissue 3-[^{11}C]-OHB kinetics were analyzed in a 1-tissue model, where we assumed a rapid conversion of 3-[^{11}C]-OHB to ^{11}CO2. Circulation of ^{11}CO2 as a fraction of the total activity of ^{11}C was measured by purifying ^{11}CO2 from blood samples.

Results: Injection of D-3-[^{11}C]-OHB led to a rapid uptake with subsequent decrease in the ^{11}C activity of the myocardium. Injection of L-3-[^{11}C]-OHB resulted in a significantly lower myocardial uptake than the D-enantiomer. Uptake of D-3-[^{11}C]-OHB were similar in the myocardium regardless of the level of circulating ketone bodies, indicating unsaturated ketone kinetics. In the liver, ^{11}C activity increased rapidly after D-3-[^{11}C]-OHB administration and subsequently decreased slowly, which was markedly impaired during hyperketonemia. Circulating ^{11}CO2 reached 40% of the total ^{11}C activity in the blood after 20 minutes and remained constant throughout the duration of the studies.

Conclusion: The PET ketone tracer D-3-[^{11}C]-OHB shows kinetics and biodistribution compatible with the behavior of ketone bodies. The heart can absorb D-3-[^{11}C]-OHB without being affected by concomitant infusion of ketone bodies, whereas the liver exhibits saturation kinetics.

P-089 Gut microbiota and endocannabinoidome modulations in hypoabsorptive bariatric surgeries are associated with metabolic improvements

Paulette Mukorako[1]

[1]*CRIUCPQ*

Background Hypoabsorptive bariatric surgeries are recognized as the best treatment for achieving a long-term weight loss and metabolic improvements. Nevertheless, the mechanisms involved in the positive outcomes are still unknown.

Objective To evaluate how changes in the gut microbiota and endocannabinoidome (eCBome) are associated with the metabolic benefits of the most effective surgeries, biliopancreatic diversion with duodenal switch (BPD-DS) and single anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S).

Methods Male Wistar rats fed a high-fat diet were subjected to either BPD-DS or SADI-S. In addition, two SHAM control groups were added, a sham high-fat (SHAM HF) and a sham high-fat pair-weighed to the BPD-DS group (SHAM HF-PW). A combination of 16S rRNA gene sequencing and liquid chromatography LC-MS/MS were used to study respectively the gut microbiota composition and eCBome lipid mediators in intestinal segments of BPD-DS, SADI-S and SHAM rats. Body weight, fat mass, fecal energy loss, HOMA-IR and gastro-intestinal hormones were measured.

Results BPD-DS and SADI-S induced striking changes in gut eCBome and microbiota. In particular, jejunal and ileal increases in *N*-acylethanolamines such as oleoylethanolamine (OEA), linoleoylethanolamine (LEA), arachidonoylethanolamine (AEA) were positively correlated with PYY levels and fecal energy loss in both groups, while decreases in arachidonic acid (AA) and PGD_2 were associated with fat mass gain and HOMA-IR. These changes were associated with significant changes in intestinal abundances of *Clostridium* and *Enterobacteriaceae_g_2*.

Conclusions The present study shows that intestinal changes in the eCBome and microbiota may influence the beneficial metabolic outcomes of hypoabsorptive bariatric surgeries.

P-090 Measurement of energy expenditure of yellow mealworms in a mass rearing context

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During the last decade, insects have received increasing interest as sources of proteins for animal feed and human food. Yellow mealworm (*Tenebrio molitor*) is considered as one of the best options because of its protein content and its ease of breeding and feeding. This species of insect is commonly reared in crates containing agricultural by-products such as wheat bran. In a mass rearing context, an insect farm can harbor thousands of these crates with different insect life stages. Presently, only little data are available concerning the heat generation of yellow mealworms in rearing conditions, making it hard to scale livestock houses. In this context, the aim of this study was to measure the energy expenditure (EE) of insects at different life stages in optimal rearing conditions (temperature, hygrometry, insect density, water supply and food) during 24 hours using calorimetric cages. We measured feed consumption, body mass, O_2 consumption and CO_2 production for 10 different insect life stages (*i.e* eggs, 7mg larvae, 16mg larvae, 29mg larvae, 50mg larvae, 60mg larvae, 79mg larvae, 98mg larvae, pupas and adults). The results describe for the first time the profile of EE for each insect life stage in mass rearing conditions: EE was very low for eggs and quite low for pupas, higher with weight gain for larvae from 7 to 60mg (EE from 0.038 to 0.614 kcal/individual/h), stabilized beyond 60mg body weight (EE about 0.584 kcal/individual/h), and higher in adults (1.033kcal/individual/h). These observations suggest an interesting calorimetric potential for advanced larval stages and adults, in the context of thermal regulation of livestock buildings. Further studies are planned to analyze the complete life cycle of *Tenebrio molitor* including the impact of the photoperiod. Taken together, these data provide key knowledges for the scaling and sizing of new yellow mealworm farms.

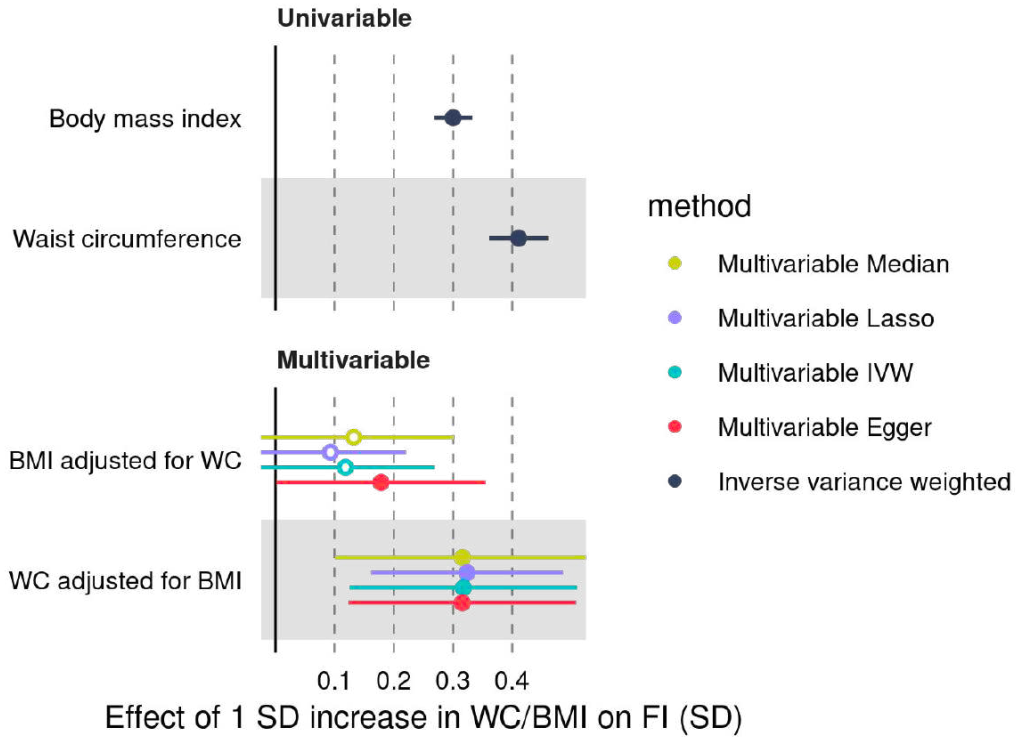
P-091 A bidirectional Mendelian randomization study disentangling the causal relations between body fat distribution, fasting insulin levels and insulin secretion

Eloi Gagnon[1], Patricia Mitchell[1], Benoit Arsenault[1, 2]

[1]Quebec Heart and Lung Institute, [2]Laval University, Faculty of Medicine

Aims/hypothesis. Hyperinsulinemia and adiposity are both rising in prevalence and are associated with one another, but the directionality of this relation is debated. While insulin might directly cause fat mass accumulation, hyperinsulinemia can also be a direct consequence of an elevated body weight and abdominal adiposity. Here, we tested the direction of the causal effects of fasting insulin levels, body mass index and body fat distribution indices using a two-sample bidirectional Mendelian randomization framework. Methods. Mendelian randomization uses genetic variants to address causal questions. Because genetic variants cannot be modified by a subsequent disease, Mendelian randomization can readily assess direction of causality between two variables. We included summary statistics from large-scale genome-wide association studies for body mass index (n=806,834), waist-to-hip ratio adjusted for body mass index (n=694,649), abdominal subcutaneous and visceral adipose tissue (n=32,860), fasting insulin levels (n=98,210), pancreatic islets gene expression (n=420) and hypothalamus gene expression (n=155). We assessed the association using inverse variance-weighted and robust Mendelian randomization methods that relied on both statistically and biologically informed genetic instruments. Results. Both genetically predicted body mass index and waist-to-hip ratio adjusted for body mass index were positively associated with fasting insulin. Results were consistent across all robust Mendelian randomization methods and when variants mapped to the hypothalamus (presumably associated with food behaviour) were included. In multivariable Mendelian randomization analyses, when waist circumference and body mass index were mutually adjusted, the direct effect of genetically predicted waist circumference on fasting insulin was 2.69 times larger than the effect of genetically predicted body mass index on fasting insulin. Genetically predicted fasting insulin was not associated with adiposity indices. By contrast, using genetic instruments influencing pancreatic islets gene expression and fasting insulin (presumably more specific to insulin secretion), genetically predicted insulin was positively associated with body mass index and abdominal subcutaneous adipose tissue, but not with visceral adipose tissue. Conclusions/interpretation: Intra-abdominal fat accumulation was identified as a key contributor to fasting insulin levels. While insulin levels were not associated with adiposity indices, a selection of instruments linked with insulin secretion highlighted a positive effect of insulin secretion on subcutaneous abdominal adipose accumulation. Altogether, these results suggest a possible role of insulin secretion on subcutaneous

adipose tissue accumulation, saturation and dysfunction, leading to intra-abdominal/ectopic lipid deposition, which in turn, might promote insulin resistance and type 2 diabetes.



P-092 Usefulness of calorimetric chambers for measuring changes of energy expenditure in Parkinson disease patients

Christophe MONTAURIER[1], Yves BOIRIE[1, 2], Dominique MORAND[2], Céline LAMBERT[2], Bruno PEIRERA[2], Isabelle RIEU[2], Ruddy RICHARD[1, 2], Martine DUCLOS[1, 2], Franck DURIF[2]

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Background: The most important clinical disorders in patients with Parkinson disease (PD) are akinesia which seriously deprive patients from motor skills. The implantation of subthalamic stimulation electrodes is an interesting therapeutical option to reduce these symptoms. PD patients have a frequent and significant weight gain after surgery. A first study highlighted energy expenditure (EE) alterations confirmed in a recent study, both based on our 2 calorimetric chambers (CC). We used jointly data from CC and from wearable device like Actiheart (AH). AH records heart rate and physical activity, and calculates EE from these parameters added with gender, age and weight. The objective was to compare the EE results obtained by the 2 measurement systems (CC and AH).

Methods: The total duration of the measurements was 24 hours during the exact same observation periods for simultaneous recording data from the CC and from the AH. The periods included 1) sleep for sleeping metabolic rate (SMR) during the quietest 197.55 (± 62.07) consecutive minutes of the night, 2) the quiet period of wakefulness excluding activity and meals. For this quiet awake period, we compared the EE from CC and AH when the patients were in 2 distinct states: EE in patients with medications and no blockade (EEon), and EE in patients off medications with akinesia (EEoff). 19 PD patients were observed before surgery, and 11 of them after surgery.

Results: Both measurement methods (CC and AH) showed an increase in SMR after surgery (6.80% ± 12.88%, P=0.036 and 4.17% ± 4.24%, P=0.001, respectively). After surgery, weight gain (5.14% ± 6.21%, P=0.004) led to an increase in the BMR (3.12% ± 3.45%, P=0.002) calculated with Schofield equations which are used by AH for

the calculation of the EE when the patients were inactive. For the EEon and EEoff periods, the CC made it possible to highlight an EEoff greater than the EEon at equal posture of the volunteers (7.89% ± 10.85%, P=0.002), whereas the AH did not detect any modification (1.61 ± 9.93, P=NS).

Conclusion: If AH make it possible to perform estimates of EE on an outpatient basis at home, there are situations for which CC represent an indispensable tool. This is the case to obtain a real value of SMR or to highlight a difference in metabolism with patients having different states of motor disorders (ON vs OFF) and no change in physical activity.

P-093 Chronobiotic potential of pro-anthocyanidins in relation to different zeitgeber

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[1]Centre de Recherche de l'Institut universitaire de cardiologie et de pneumologie de Québec (CRIUCPQ), [2]Faculté de pharmacie, Université Laval, [3]Nutrigenomics Research Group, Universitat Rovira i Virgili, [4]Centre de recherche du CHU de Québec, [5]Faculté des sciences de l'agriculture et de l'alimentation, Université Laval, [6]Institut sur la nutrition et les aliments fonctionnels (INAF), [7]Faculté de médecine, Université Laval

INTRODUCTION: The environment influences internal biological clocks producing circadian rhythms. These rhythms are regulated by a central clock, but also intrinsically by clocks expressed in each organ. The synchronization of these clocks is achieved in response to zeitgebers (time givers). In addition to light, other zeitgebers, including diet and temperature, influence energy homeostasis. Consumption of a high fat diet (HFD) is well known to damage normal biological rhythms, leading to circadian disruptions and metabolic dysfunctions. As such, substances with chronobiotic properties may have the potential to resynchronize altered rhythms and improve metabolism.

OBJECTIVES: 1) To determine the synergistic impact of different zeitgebers on the intrinsic clocks of metabolic organs. 2) To evaluate the chronobiotic potential of pro-anthocyanidins (PACs) from berries in a HFD-induced obesity model.

METHODOLOGY: We evaluated the interaction between diet, temperature and PACs. Male C3H/HeJ mice were fed a HFD for 12 weeks. During the last 4 weeks, they were exposed to either 10˚C (cold) or 30˚C (warm) and received a daily gavage of PACs (0.2 mg/g) at ZT2. A multi-organ analysis of the molecular circadian clocks was then performed following sampling at different zeitgeber times. The faecal content of bile acids was also evaluated.

RESULTS: Regardless of the temperature, PACs improved glycemia without significantly affecting food intake and body weight and had a significant impact on the molecular circadian clock of brown adipose tissue. PACs also enhanced UCP1 protein expression in inguinal white adipose tissue. Cold exposure had profound impacts on bile acids and PACs influenced different bile acid metabolites depending on the temperature.

CONCLUSION: PACs could improve glucose metabolism through their chronobiotic properties. A more in-depth circadian analysis will allow a better understanding of the chronobiotic potential of PACs in relation to different zeitgebers.

P-096 Mechanical efficiency, adiposity, cardiometabolic fitness, and resting energy expenditure in healthy adults

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BACKGROUND: Energy efficiency has been studied for its potential association with the risk of overweight over time. It has also been a topic of interest for exercise physiologists who generally measure mechanical efficiency (ME) as a proxy variable to evaluate the amount of biological work being performed for a given oxygen consumption. OBJECTIVE: The aim of this study was to assess the impact of ME on body composition, cardiometabolic profile, and resting metabolic rate (RMR) in middle-aged (38.3 ± 14.3 years) participants from the Quebec Family Study (QFS). METHODS: Analyses were performed on a sample of 606 participants (272 males and 334 females). Participants performed a progressive ergocycle submaximal exercise test which included three consecutive 6-min workloads. Gross ME was calculated as the average workload / VO2 ratio measured during the last three minutes of the first workload. Correlations between gross ME and dependent variables were computed separately in males and females and differences in body composition and cardiometabolic variables between sex-specific tertiles of gross ME were assessed by ANOVA after adjustment for age. RESULTS: Significant correlations were observed between gross ME and body composition (20% <R2 < 48%) and cardiometabolic variables (3% <R2 < 20%) in both males and females. A significantly lower body fatness, a better cardiometabolic profile and a higher RMR (kcal/kg) were observed in individuals with a higher versus a lower gross ME. Interestingly, these differences remained significant after further adjustment for aerobic fitness or participation in moderate to vigorous physical activity. CONCLUSION: These results show that a better ME favorably influences adiposity, cardiometabolic fitness, and resting energy expenditure.

P-097 Characterization of a new hypothalamic neuronal population using RNAscope® in situ hybridization

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BACKGROUND The discovery of leptin in 1994 was an “eureka moment” in the field of neurometabolism. Rapidly, a neurobiological model emerged to explain leptin’s effects on energy homeostasis. According to this prevalent model, pro-opiomelanocortin (POMC) and agouti-related peptide (AgRP)-expressing neurons of the arcuate nucleus of the hypothalamus (ARC) are key in mediating leptin’s anorexigenic effects. While this model inspired many important discoveries on the central control of energy balance, a growing body of literature indicates that this model is overly simplistic. We now know that POMC neurons are highly heterogeneous and recent work suggests that yet unidentified GABAergic neuronal populations of the ARC may play a critical role in the integration of peripheral metabolic signals and the regulation of food intake. OBJECTIVE To characterize the molecular signature and study the heterogeneity of a new neuronal population of the ARC potentially involved in the control of energy homeostasis. METHODS We used RNAscope®, a cutting-edge *in situ* hybridization technology enabling simultaneous signal amplification on coronal brain slices from male mice. RESULTS We identified a new population of GABAergic neurons highly enriched in the ARC. This new population is distinct from POMC and AgRP neurons and robustly express the *New arcuate transcript* (*Nat*) mRNA. A sub-population of these ARC *Nat* neurons expresses the leptin receptor (*Lepr*). *Nat*-expressing neurons were also found to co-express the glucagon-like peptide 1 receptor (*Glp1r*). CONCLUSION The RNAscope® *in situ* hybridization technique allowed us to identify, locate and precisely characterize a new hypothalamic neuronal population potentially involved in the regulation of energy homeostasis. The RNAscope® technique thus seems suitable for the identification and localization of distinct cellular subpopulations among highly heterogenous cells.

P-098 Metabolic profiling of bile acids in mice conditioned to a modified Amylin liver NASH (AMLN) diet

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BACKGROUND: Metabolic associated fatty liver disease (MAFLD) is an umbrella term that includes a spectrum of disease severity from simple hepatic steatosis to a more aggressive inflammatory form (NASH), that may progress to liver fibrosis, cirrhosis and hepatocarcinoma. Despite the negative impact of this disease on morbidity and mortality, there are no approved drugs for its treatment. As such, there is an urgent need to understand the pathophysiology of MAFLD in order to develop appropriate care at an early stage of the disease, prevent disease progression, and reduce the cardiometabolic risk. Recent investigations revealed that bile acid (BA) sequestration reverses liver injury and prevents MAFLD in mice. This is in support to twin studies indicating that serum BA concentrations are perturbed progressively as liver fibrosis increases.

OBJECTIVE: Our goal is to take advantage of a diet-induced NASH model to understand the pathophysiology of MAFLD and characterize bile acids profile in this disease.

METHODS: C57BL/6 mice were fed a diet rich in palm oil (42%), fructose (20%) and cholesterol (2%) in order to induce different degrees of severity of MAFLD: steatosis (12 weeks), inflammation (20 weeks), fibrosis (32 weeks). Liver function was assessed by measuring biomarkers. The expression of enzymes involved in bile acid metabolism was measured by qPCR while bile acid levels were evaluated using liquid chromatography – mass spectrometry (LC-MS).

RESULTS: We observed a progressive increase in plasma alanine aminotransferase (ALT), liver tumor necrosis factor-α (TNFα), plasma cholesterol levels. We found many BA metabolites affected, including liver 7 Alpha-hydroxy-4-cholesten-3-one (7aC4), a surrogate for BA synthesis. ALT levels correlated with liver 7aC4, suggesting that BA accumulation in the liver could contribute to liver damage.

CONCLUSION: Diet-induced NASH model represents a good model for studying the pathophysiology of MAFLD. The progression of MAFLD correlates with alterations in BA metabolism. Future studies will allow us to evaluate the potential of anti-cholestatic compounds in preventing the progression of MAFLD.

P-099 Comparison between ActiGraph GT3X+ and Active style Pro-750C for assessments of free-living physical activity

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Objective: In Japan, Active style Pro (Omron Healthcare Co. Ltd., Kyoto, Japan) is frequently used to evaluate total step counts, moderate- to vigorous-intensity physical activity (MVPA) and sedentary behaviour (SB) for children, with revised prediction equations available for each age group. This study compared the measurements of daily total step counts, MVPA and SB between ActiGraph GT3X+ (ActiGraph Inc., Florida, USA) (AG) and Active style Pro-750C (ASP) in young children.

Methods: The participants were 75 Japanese young children aged 5 to 6 years from three kindergartens in the Tokyo metropolitan area. Participants wore the AG and ASP on the waist continuously for 7 days. Time spent in SB, light-intensity physical activity (LPA) and MVPA were calculated using Pate et al.'s cutpoints (2006) for AG data and Tanaka et al.'s (2019) conversion equations for ASP data.

Results: Correlations between the AG and the ASP were strong for total steps (r= 0.946), SB (r= 0.849), LPA (r=0.828) and MVPA (r=0.875). However, ASP produced lower estimates for SB (-21.4%) and MVPA (-64.6%) but higher for total step counts (+15.8%) and LPA (+174.0%) compared to AG.

Conclusions: Values of total steps, SB, LPA and MVPA times are considerably different between AG and ASP. However, relative rankings of individuals seem quite similar between AG and ASP, because the correlations between devices are strong.

P-100 Liver adrenoceptor alpha-1b plays a key role in glucose homeostasis

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The brain has several ways of influencing glucose metabolism, including activation of hepatic glucose production. This process depends on many hormonal and neural factors controlling several pathways that have evolved to protect the organism against hypoglycemia. Unfortunately, this sophisticated homeostatic process can be impaired in metabolic diseases such as obesity and type 2 diabetes, where autonomic dysfunctions including neuropathies have been described. Hepatic glucose production is regulated by numerous hormones and by the sympathetic nervous system (SNS). In particular, norepinephrine rapidly mobilizes glucose from the liver by increasing hepatic glucose production. Therefore, understanding the mechanisms by which the SNS, through the release of norepinephrine, regulates hepatic glucose production offers important possibilities to better understand and treat alterations in glucose homeostasis observed in metabolic disorders. Confirming a previous anatomical profiling study of GPCR expression, we observed that the adrenoceptor alpha-1b (*Adra1b*) was the dominant subtype expressed in the liver. We found that *Adra1b* expression was increased in diet-induced of genetically obese mouse models. Using CRISPR-Cas9 technology, we developed a conditional mouse model for the *Adra1b* gene. These mice were bred with an *Albumin*-Cre mouse to generate mice lacking *Adra1b* specifically in hepatocytes. We found that selective deletion of *Adra1b* in mouse liver reduced the ability of norepinephrine to cause hyperglycemia. We also found that mice lacking *Adra1b* in the liver were not able to maintain their glycemia during metabolically challenging conditions. Our data suggest that ADRA1B is key in mediating the effects of the autonomic nervous system on hepatic glucose production. Mice lacking *Adra1b* fails to maintain glycemia in response to metabolic challenges. Conversely, increased expression of liver *Adra1b* in obese models suggests that it could contribute to the hyperglycemic state. We believe that a better understanding of the receptors and pathways involved in the sympathetic outflow of the liver will help developing a thoughtful perspective on how the autonomic control of peripheral organs is altered in metabolic diseases.

P-101 Associations between non-invasive skeletal muscle oxidative capacity, cardiorespiratory fitness, physical activity, adiposity, and insulin sensitivity in healthy adolescents

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Background

Techniques to assess skeletal muscle oxygen consumption using near-infrared spectroscopy (NIRS) have been developed over the past decade, providing an alternative method to assess mitochondrial oxidative capacity that is non-invasive (as opposed to muscle biopsy) and less costly compared to other techniques (magnetic resonance spectroscopy). While NIRS has been used in a variety of populations, little data has been collected in healthy adolescent boys and girls. The purpose of this analysis is to identify associations between physiological variables associated with metabolic health and skeletal muscle oxidative capacity via NIRS in an ongoing study involving adolescent participants.

Methods

Healthy adolescent males and females (N=11, 16.1 years) completed assessments of skeletal muscle oxidative capacity via NIRS, cardiorespiratory fitness via maximal treadmill test, and body composition via dual energy x-ray absorptiometry. On a separate day, participants completed a hyperinsulinemic euglycemic clamp

procedure to assess insulin sensitivity. Participants also wore an activity monitor (Actigraph GT9x) on their non-dominant wrist for seven days to assess free-living physical activity. Body mass index percentile and Z-score were calculated based on CDC growth charts. Muscle oxygen consumption of the vastus lateralis was measured with a frequency domain, multiple distance NIRS (Dual-Channel OxiplexTS, ISS Medical, Champaign IL, USA) following an isometric contraction and repeated arterial occlusions. The recovery rate of deoxyhemoglobin was fit to an exponential curve, with the recovery time constant, where lower time indicates greater oxidative capacity.

Results

Preliminary analyses indicate body mass index percentile and body fat percent were positively correlated with a higher muscle oxidative capacity recovery time constant (r=0.61, p=0.046 and r=0.62, p=0.042, respectively). Maximal cardiorespiratory fitness was not correlated with recovery time constant, either when expressed as mL/kg/min or mL/kg of fat-free-mass/min (r=-0.61, p=0.078, r=-0.55, and p=0.127, respectively). Physical activity (vector magnitude average counts) was also not associated with recovery time constant (r=-0.31, p=0.360). Glucose infusion rate during the final 30 minutes of the hyperinsulinemic euglycemic clamp was also not associated with recovery time constant (r=-0.21, p=0.569).

Conclusion

Initial analyses of an ongoing study involving healthy adolescent boys and girls suggest skeletal muscle oxidative capacity is negatively associated with adiposity (BMI percentile, body fat percent). Cardiorespiratory fitness and physical activity were not significantly correlated with skeletal muscle oxidative capacity possibly in this preliminary analysis.

P-102 Impact of body weight on atherosclerotic cardiovascular disease incidence in individuals with and without ideal cardiovascular health

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Introduction: Individuals with an elevated body mass index (BMI) are at higher atherosclerotic cardiovascular diseases (ASCVD) risk. While the impact of an elevated BMI on ASCVD risk in individuals who are "metabolically healthy" is still debated, the respective contributions of BMI and actionable lifestyle and cardiometabolic risk factors on ASCVD risk remains largely unknown.

Objectives: To investigate the respective contributions of lifestyle and cardiometabolic risk factors and BMI to ASCVD incidence in apparently healthy individuals.

Methods: The study sample included 321,259 UK Biobank participants free of ASCVD recruited between 2006 and 2010. We developed a cardiovascular health score (CVHS) based on three lifestyle (smoking status, fruits and vegetables consumption and physical activity levels) and six cardiometabolic (systolic and diastolic blood pressure, HbA1c, LDL-C, HDL-C, C-reactive protein and triglyceride levels) parameters. As of August 2021, 15,699 participants had incident ASCVD (fatal or nonfatal myocardial infarction, ischemic stroke or cardiac revascularization procedures obtained from electronic health records). The impact of the CVHS on incident ASCVD alone and in BMI categories was assessed using Cox proportional hazards adjusted for age, sex, ethnicity and deprivation.

Results: Compared to participants with a very high CVHS (meeting all nine CVHS parameters), those with a very low CVHS (0-1) had an almost 10-fold higher ASCVD risk (hazard ratio [HR]=9.81 (95% CI, 7.11-13.51, p<0.001). In participants with a high CVHS (7-9), those with a BMI≥35.0 kg/m^2) had a slightly higher ASCVD risk (HR=1.25 [95% CI, 0.98-1.60], p=0.072) compared to those with a lower BMI 18.5-24.9 kg/m^2. In participants with a BMI

18.5-24.9 kg/m^2, those with a lower CVHS (0-2) had a higher ASCVD risk (HR=3.65 [95% CI, 2.56-5.21], p<0.001) compared to those with a higher CVHS (7-9).

	BMI (kg/m²)	Cases (n)	Total (n)	Event rate (%)	HR (95% CI)	P value
CVHS = 7-9 (Healthy)	18.5-24.9	1384	64179	2.16	1.00 (ref)	
	25.0-29.9	1867	53422	3.49	1.31 (1.23 - 1.41)	1.78e-14
	30.0-34.9	503	12378	4.06	1.56 (1.41 - 1.73)	1.69e-17
	≥35.0	67	2384	2.81	1.25 (0.98 - 1.60)	0.0722
CVHS = 5-6 (Moderately Healthy)	18.5-24.9	1653	38033	4.35	1.63 (1.52 - 1.76)	2.93e-41
	25.0-29.9	3847	67708	5.68	1.85 (1.74 - 1.97)	1.12e-84
	30.0-34.9	1920	30471	6.30	2.19 (2.04 - 2.35)	1.49e-108
	≥35.0	609	11325	5.38	2.28 (2.07 - 2.51)	6.34e-64
CVHS = 3-4 (Moderately Unhealthy)	18.5-24.9	431	4695	9.18	3.08 (2.76 - 3.43)	2.51e-91
	25.0-29.9	1389	14943	9.30	2.86 (2.65 - 3.08)	5.45e-164
	30.0-34.9	1036	11564	8.96	2.97 (2.74 - 3.22)	6.5e-152
	≥35.0	514	6648	7.73	3.06 (2.77 - 3.39)	2.65e-103
CVHS = 0-2 (Unhealthy)	18.5-24.9	31	254	12.20	3.65 (2.56 - 5.21)	1.08e-12
	25.0-29.9	171	1120	15.27	4.72 (4.02 - 5.54)	1.72e-80
	30.0-34.9	162	1094	14.81	4.67 (3.97 - 5.51)	7.21e-76
	≥35.0	109	958	11.38	4.29 (3.53 - 5.21)	3.02e-48

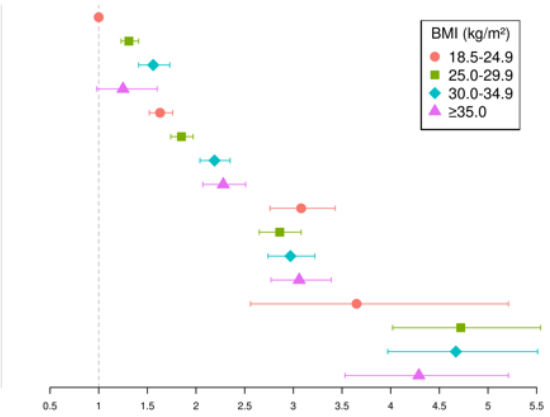

Figure 1. Impact of the body mass index on incident atherosclerotic cardiovascular disease in UK Biobank participants by cardiovascular health score categories.
Cox proportional hazards were adjusted for age, ethnicity, deprivation and sex. CVHS indicates cardiovascular health score.

Conclusions: In participants of the UK Biobank, the BMI was a poor predictor of ASCVD incidence in healthy individuals whereas cardiovascular risk factors strongly predicted ASCVD incidence in all BMI categories. Weight inclusive interventions targeting lifestyle-related and metabolic risk factors are likely to prevent cardiovascular outcomes, regardless of their impact on body weight.

P-103 The Effect of Acute Intermittent and Continuous Hypoxia on Plasma Circulating ßOHB Levels Under Different Feeding Statuses in Humans

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Introduction: Acute hypoxia is known to increase circulating nonesterified fatty acid (NEFA) levels. Adipose tissue lipolysis is a major source of NEFA into circulation and insulin suppresses this process when the tissue is insulin sensitive. NEFA can be esterified to triglycerides and/or completely/partially oxidized, the latter leading to ketogenesis in the liver. To our knowledge, the effect of hypoxia on ketogenesis, more specifically ßhydroxybutyrate (ßOHB) levels, remains unknown in humans. Therefore, the objective of this study was to determine the effect of acute intermittent and continuous hypoxia on circulating ßOHB levels under different feeding status.

Methods: Plasma samples from three different randomized crossover studies were assessed for ßOHB concentrations.

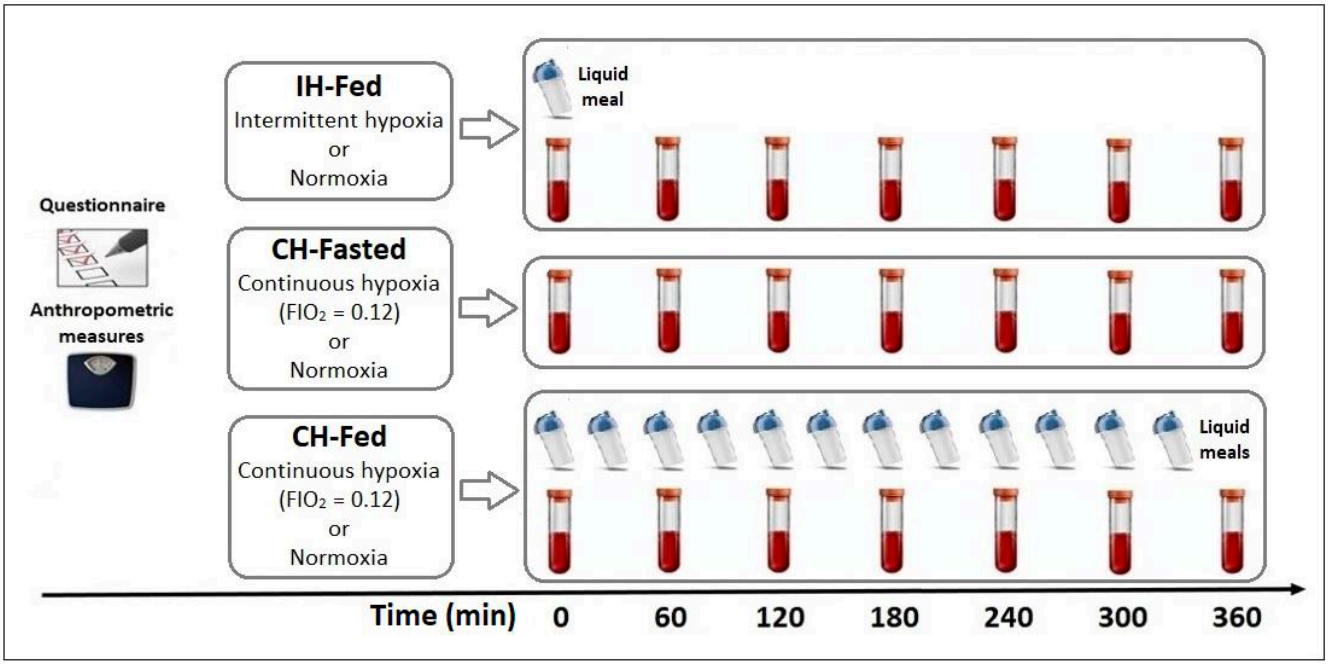

Figure 1. Schematic summary of the 3 randomized crossover studies in which ßOHB concentrations were assessed at the time indicated. In the IH-Fed study, 14 healthy men were exposed to 6 hours of normoxia or intermittent hypoxia (15 hypoxic events/ hour) following an isocaloric meal. In the CH-Fasted study, 10 healthy men were exposed to 6 hours of continuous normobaric hypoxia (FiO2= 0.12) or normoxia in the fasting state. In the CH-Fed study (CH-Fed), 9 healthy men were exposed to 6 hours of normoxia or CH in a constant prandial state.

In the first study, 14 healthy men (23 ± 3.5 years) were exposed to 6 h of normoxia or intermittent hypoxia (IH-Fed) (15 hypoxic events/hour) following an isocaloric meal. In the second study, 10 healthy men (26 ± 5.6 years) were exposed to 6 h of continuous normobaric hypoxia (CH-Fasted) (FiO2 = 0.12) or normoxia in the fasting state. In the third study (CH-Fed), 9 healthy men (24 ± 4.5 years) were exposed to 6 h of normoxia or CH in a constant prandial state. ßOHB, NEFA and insulin levels were measured during all sessions.

Results: In the IH-Fed study, ßOHB and NEFA levels tended to be greater over 6 h of IH (condition × time interaction, ßOHB p = 0.108 and NEFA p = 0.062) compared to normoxia. In the CH-Fasted study, ßOHB and NEFA levels increased over time in both experimental conditions, this effect being greater under CH (condition × time interaction, ßOHB p = 0.070; NEFA p = 0.046). In the CH-Fed study, ßOHB levels slightly increased up to 180 min before falling back to initial concentrations by the end of the protocol in both normoxia and CH (main effect of time, p = 0.062), while NEFA were significantly higher under CH (p = 0.006).

Conclusion: Acute normobaric hypoxia exposure tends to increase plasma ßOHB concentrations over time in healthy men. The stimulating effect of hypoxia on plasma ßOHB levels is however attenuated during postprandial and prandial states.

P-104 Impact of diet and lifestyle on obesity: a mendelian randomization study

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BACKGROUND- Obesity results form a complex interaction between a genetic predisposition to gain weight and unhealthy lifestyle. Despite evidence that poor diet and unhealthy lifestyle habits are associated with obesity, their role as putative causal factors in obesity has not been systematically investigated.

OBJECTIVE- Using Mendelian randomization (MR), we wanted to identify dietary and lifestyle factors causally involved in obesity using body mass index (BMI) as the outcome. MR is a statistical method that uses genetic variants as instruments to estimate the causal effects between risk factor and health outcomes.

METHODS- We selected summary statistics from 400 genome-wide association studies (GWAS) of dietary and lifestyle traits conducted in the UK Biobank (UKB, n > 500,000 individuals). For the outcome, we used BMI GWAS summary statistics from the GIANT Consortium studies (n = 339,224 individuals). MR analyses were performed using the TwoSampleMR package and only genome-wide significant polymorphisms (SNP) ($p < 5x10^{-8}$) were kept. We used inverse variance weighted (IVW) to assess the effect of the exposure on the outcome and MR-Egger to address the potential effect of pleiotropic variants on the outcome.

RESULTS – Preliminary MR analyses provided evidence of that some traits related to eating and physical activity habits were causally associated with BMI. For example, we observed that the type (skimmed) of milk ($\beta = 4,97$; $p = 5,49x10^{-18}$) or the bread ($\beta = -7,83$; $p = 3,25x10^{-11}$) were significantly associated to BMI. We also observed causal effects of the time spent watching television ($\beta = 2,01$; $p = 2,08x10^{-14}$) and usual walking pace ($\beta = -2,13$; $p = 8,04x10^{-28}$) on BMI.

CONCLUSIONS- Results of this study suggest that genetically predicted dietary and lifestyle factors are causally associated with BMI. The role of these factors as putative mediators of genetic susceptibility to obesity will be investigated using mediation analyses. This will allow the development of personalized nutritional interventions to better prevent and treat obesity.

P-105 Impact of ADRB3 an agonist on obesity and glucose metabolism in female mice

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INTRODUCTION: The Gs-coupled beta 3 adrenergic receptor (ADRB3) has emerged as a conceivable target for the treatment of obesity and type 2 diabetes. Although very efficient in rodents, the weight-loss properties of ADRB3 agonists in humans were however never proven with classic molecules primarily due to low affinity, low distribution, toxicity/off-target potentials, and species differences. This was until recently, when mirabegron, an FDA-approved drug for the treatment of overactive bladder, was evidenced as the first ADRB3 agonist capable of improving energy expenditure and glucose metabolism in humans. However, we still do not fully understand the systemic effects of ADRB3 agonists, particularly in organs such as the ovaries which express the highest levels of ADRB3 in humans. Given the critical role of ovaries in metabolism, the function of ADRB3 in these endocrine organs and the impact of mirabegron on sex hormones needs to be assessed.

METHODS: We developed an obesogenic diet supplemented in mirabegron. This diet was designed to allow a daily treatment of mice with ~1 mg/kg, which is 10 times less than the common dose used in mice (10 mg/kg) and representative of the lowest FDA-approved dose. Female C57BL6/J mice were either fed a low-fat diet (LFD, D12450H, 10%kcal from lipids), a high-fat diet (HFD, D12451, 45% kcal from lipids, paired to D12450 in terms of macronutrients content) or a HFD supplemented in mirabegron (HFD+M) for 12 weeks.

RESULTS: HFD+M prevented diet-induced obesity (DIO) in female mice. However, despite this resistance to DIO, mice treated with HFD+M were not protected from diet-induced glucose intolerance even though basal and glucose-induced insulin levels were comparable to mice fed LFD. They also tended to be more insulin resistant, despite no apparent liver steatosis. Expression of *Adrb3* mRNA was not altered in gonadal WAT, but was drastically decreased in ovaries with HFD. Progesterone levels were slightly (but not significantly) higher in females fed HFD+M.

CONCLUSION: These results suggest that obesity and mirabegron may synergically influence sex hormones in females. These data also highlight the need to better understand the sex differences in the pharmacology of

ADRB3 agonists, as negative metabolic effects may happen depending on the context in which these drugs are given.

P-106 Different effects of high-fat diet on two strains of mice

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[1]CRIUCPQ, [2]ULAVAL

Obesity and excess weigh represent a highly debilitating condition leading to associated disorders including cardiovascular disease as type 2 diabetes. Specialists consider obesity as an energy homeostasis system disorder. Accordingly, melatonin, which is well known as a modulator in sleep and circadian rhythm, takes part in energy metabolism in different ways. Recently, the interests towards study the gut microbiota influences in obesity and energy balance has raised. Obesity in human and rodents alter the gut microbiota. Studies show the interaction between melatonin and microbiota in relation to improvement obesity and excess weight disorders.

In this study, we investigated the effect of low-fat diet (LFD) and high-fat diet (HFD) on two different strains of mice which have drastically different level and rhythmicity of melatonin, C3H/HeJ that is melatonin-proficient and C57BL/6 melatonin-deficient mice. In addition, mice either received melatonin or placebo treatment in drinking water during the dark phase.

Our results showed significant increase in weight gain in HFD compared with LFD groups although C3H mice showed clear resistance to HFD in the last month of treatment. Accordingly, C57-HFD mice significantly higher food intake and metabolized energy compared with C3H-HFD mice. We observed strong effect of melatonin treatment on liver weight in C3H-HFD compared with C57-HFD mice consistence with less storage of triglyceride in liver and more in circulation. Interestingly melatonin administration lowered the level of TG in plasma of C3H-HFD mice. PIXImus results showed a dramatic HFD effect on increase visceral fat (rpWAT) in C57 mice while rpWAT in C3H-HFD mice was the same level as LFD mice. *In-situ* hybridization analysis of different regions of the brain showed melatonin treatment significantly increase NPY density in LFD mice while this effect was not enough to modulate NPY density in HFD mice.

Principal component analysis on our microbiota data indicated clear effect of HFD on C57 mince while this effect decreased in C3H mice after two months.

Our results suggest that C57 mice are more prone to obesity compared with C3H and at least part of it is due to different modulation of melatonin and microbiota in these two strains.

We aim to introduce new ways to prevent or treat obesity and based on modulatory effect of microbiota and melatonin, they could be new targets for prevention and treatment of obesity.

P-107 LATE BREAKING: Lipolysis drives expression of the constitutively active receptor GPR3 to induce adipose thermogenesis

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Thermogenic adipocytes possess a therapeutically appealing, energy-expending capacity, which is canonically cold-induced by ligand-dependent activation of β-adrenergic G protein-coupled receptors (GPCRs). Here, we uncover an alternate paradigm of GPCR-mediated adipose thermogenesis through the constitutively active receptor, GPR3. The N terminus of GPR3 confers intrinsic signaling activity, resulting in continuous Gs-coupling and cAMP production without an exogenous ligand. Thus, transcriptional induction of *Gpr3* represents the regulatory parallel to ligand-binding of conventional GPCRs. Consequently, increasing *Gpr3* expression in thermogenic adipocytes is alone sufficient to drive energy expenditure and counteract metabolic disease in mice. *Gpr3* transcription is cold-stimulated by a lipolytic signal, and dietary fat potentiates GPR3-dependent thermogenesis to amplify the response to caloric excess. Moreover, we find GPR3 to be an essential, adrenergic-independent regulator of human brown adipocytes. Taken together, our findings reveal a noncanonical mechanism of GPCR control and thermogenic activation through the lipolysis-induced expression of constitutively active GPR3.

P-109 LATE BREAKING: Impaired Postprandial Thermogenesis: A Feature of Dysglycaemia?

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A growing research focus has now emphasised the role of energy expenditure in the development of metabolic conditions such as prediabetes and type II diabetes (T2D). Prediabetes is defined by a modest elevation in blood glucose indicating an increased risk of developing T2D. Accounting for 5-15% of an individual's total daily energy expenditure, postprandial thermogenesis (PPT) refers to an acute increase in resting energy expenditure (REE) in the hours after eating. This is largely explained by the energy costs of processing the macronutrients of a meal. Most individuals spend the majority of the day in the postprandial state, often from breakfast time to bed time. Thus, over one's lifetime, it is feasible that even minor differences in PPT may possess true clinical significance. In contrast to REE, research indicates that PPT may actually be reduced in the development of both prediabetes and T2D. The present analysis of existing literature has found that this impairment may be exaggerated in hyperinsulinaemic-euglycaemic clamp studies compared to food and beverage consumption studies. Nonetheless, it is estimated that daily PPT following carbohydrate consumption alone is approximately 150 kJ lower among individuals with T2D. This estimate fails to consider protein intake which is notably more thermogenic than carbohydrate intake (20-30% vs 5-8% increase in postprandial energy expenditure, respectively). However, clinical trials investigating the role of protein intake on PPT have yet to be conducted among individuals in a dysglycaemic state. Regardless, studies investigating the thermogenic effect of glucose have attributed this impairment in PPT to the intricate workings of the insulin axis. Putatively, dysglycaemic individuals may lack the insulin sensitivity required to divert glucose towards storage – a more energy-taxing pathway. Accordingly, the majority of findings have associated an impaired PPT with a reduced "obligatory" energy output (i.e. the energy costs associated with nutrient processing). More recently, it has been reported that "facultative" thermogenesis (e.g. the energy costs associated with SNS stimulation) may also contribute to any impairment in PPT among individuals with prediabetes and T2D. Further research is required to ascertain whether meaningful changes in PPT, particularly in response to the food matrix, manifest in the prediabetic state, prior to the development of T2D. If this impairment is observed, it should be subsequently explored whether the measurement of PPT can be used to phenotype individuals at risk of developing future T2D, or if the enhancement of PPT represents a feasible target for nutritional intervention in prediabetes.

P-110 LATE BREAKING: Regional Difference in the Effect of the COVID-19 Epidemic on Domain Specific Physical Activity, Sedentary Behavior, and Sleeping Time in Japanese Adults

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Background: Physical activity (PA) and sedentary behavior (SB) have been affected by the COVID-19 pandemic and its restrictive environments, such as social distancing measures. Regional differences in the changes in domain-specific PA and SB in response to the COVID-19 pandemic are not clearly understood.

Objective: This study aimed to examine regional differences in domain-specific PA, SB, and sleeping time in response to the COVID-19 pandemic in Japan.

Methods: A total of 1,627 adults (aged 20–79 years; 1073 men and 855 women) responded to web-based surveillance. They retrospectively registered the PA data of their average day before and during the COVID-19 pandemic in a web-based PA record system. Residential areas were divided into urban (Greater Tokyo area), urban-rural (cities with a population >300,000), or rural (<50,000) areas. To confirm the current results, PA and step count data were obtained using a triaxial accelerometer on people living in urban and rural areas.

Results: Before the COVID-19 pandemic, there were no significant differences between these three regions in time spent sleeping, staying at home, working or studying, and exercising (*P*>.05). In contrast, people living in urban areas had a longer duration of SB and transportation, and a shorter duration of MVPA and lying or napping time compared to people living in rural areas (*P*<.05). During the COVID-19 pandemic, working or studying time significantly decreased, and staying home increased in all areas. A significant decrease was observed in transportation time (−7 min/day on average) and MVPA (−30 min/day) in urban and urban-rural areas, but not in rural areas. A significant increase was observed in time spent sleeping (+26 min/day) and lying or napping (+15 min/day) in urban and urban-rural areas, but not in rural areas. PA and step counts obtained using an accelerometer also significantly decreased in urban areas, but not in rural areas.

Conclusion: The effect of the COVID-19 pandemic on domain-specific PA and SB was significantly dependent on living area.

P-111 LATE BREAKING: Reproducibility of the resting metabolic rate and respiratory exchange ratio measurements provided by four commercially available metabolic carts and the Deltatrac II

Guillermo Sanchez-Delgado[1, 2, 3], Manuel Dote-Montero[1, 2], Isabella Reed[1], Eric Ravussin[1]

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Objective: In a previous study (poster by Dote-Montero et al.), we determined the accuracy and precision of four commercially available metabolic carts (Q-NRG [Cosmed; Rome, Italy], Omnical [Maastricht Instruments; Maastricht, The Netherlands], Vyntus CPX [Vyaire; Hochberg, Germany], and TrueOne 2400 [Parvo-Medics; Salt Lake City, USA]) as compared to our institutional “gold-standard” (Deltatrac II [Datex-Ohmeda; Helsinki, Finland]). We analyzed the reproducibility of resting metabolic rate (RMR) and respiratory exchange ratio (RER) measurements provided by these carts in 19 healthy adults.

Methods: Nineteen participants (8M/11F; 33.1±9.5 years old; 23.6±4.9 kg/m^2) had their RMR measured for 30 minutes with each of the five metabolic carts (in a randomized order) after an overnight fast. The same measurements were repeated within a week following an identical procedure. All the metabolic carts except the DeltaTrac II were new and used for the first time in this study. We calculated the day-to-day coefficient of variability (CV) for RMR and RER as standard deviation / mean x 100.

Results: The 5 metabolic carts did not provide comparable RMR and RER measures (all P<0.026). Moreover, the reproducibility of RMR and RER was also different across metabolic carts (all P<0.002). The Deltatrac II produced the most reproducible RMR measures (CV=1.6±1.2%), followed by the Omnical (CV=3.0±2.3%), the

Parvo (CV=4.9±4.6%) the Vyntus (CV=6.5±5.3%), and the Q-NRG (CV=10.7±10.7%). In contrast, the Omnical produced the most reproducible RER measures (CV=2.2±2.6%), followed by the Parvo (CV=2.3±2.9%), the Vyntus (CV=2.5±2.2%), the Deltatrac II (CV=3.5±3.6%), and the Q-NRG (CV=5.4±5.5%).

Conclusions: Those commercially available metabolic carts provide discrepant, non-comparable RMR and RER measures in repeated measures in 19 healthy study participants. Moreover, large differences were found in the reproducibility of RMR and RER measures, with some metabolic carts presenting poor reproducibility. The Deltatrac II metabolic cart provided more reproducible results for RMR than all of the tested metabolic carts.

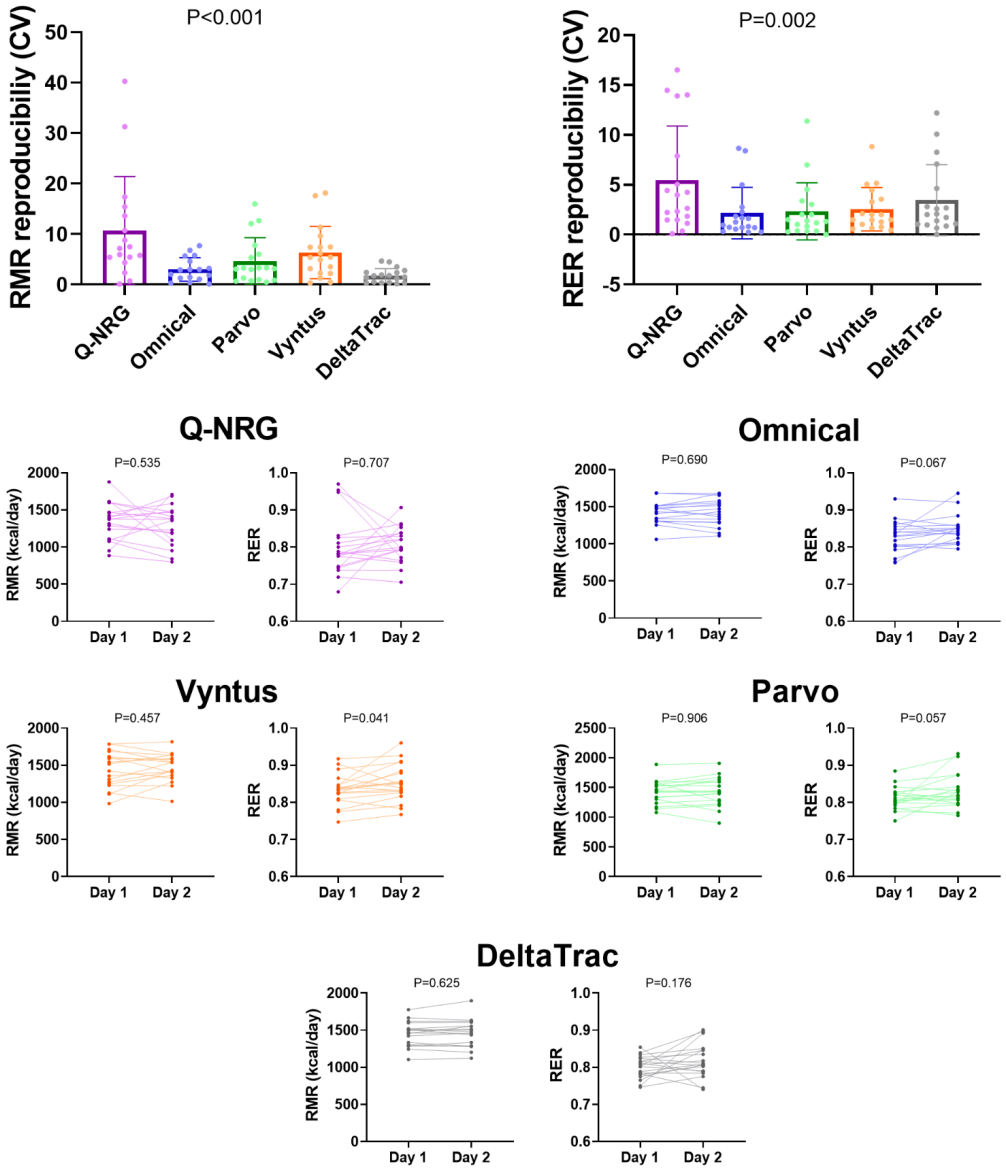

Figure 1. Reproducibility of the resting metabolic rate (RMR) and respiratory exchange ratio (RER) obtained with five metabolic carts. Data are presented as mean and standard deviation and/or individual data points The coefficients of variance were calculated as standard deviation / mean x 100. P-values from repeated measures analysis of variance (ANOVA).

P-112 LATE BREAKING: Cold acclimation in humans: responders and non-responders

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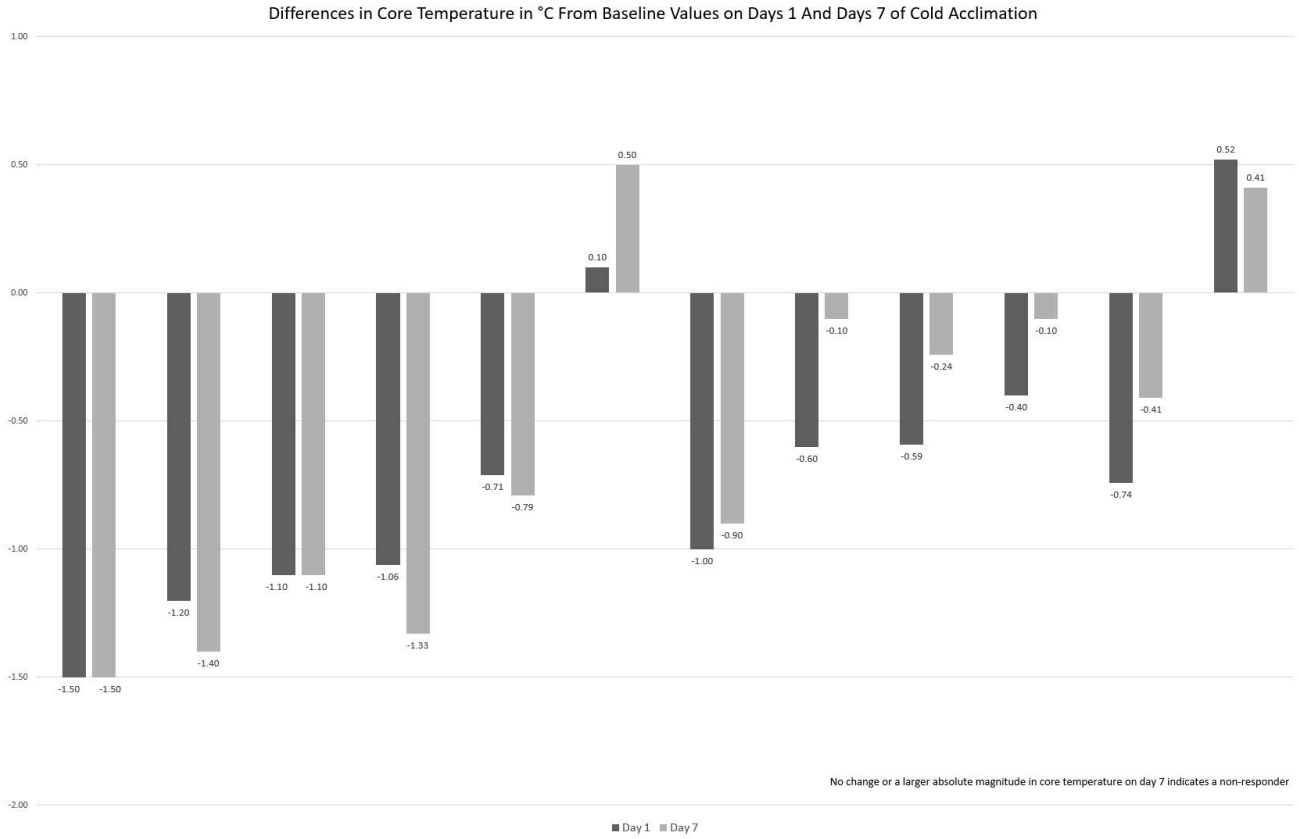
[1]University of Ottawa, [2]Universite De Sherbrooke

Humans are not only extremely vulnerable to cold environments, but cold responses are also extremely variable between individuals. Thus, establishing all-encompassing, cold-protective solutions is particularly difficult. A potential strategy is to repeatedly expose individuals to the cold or cold acclimation which has been shown to improve psychological (i.e., improved thermal sensation and comfort), insulative (i.e., cooling rate) and metabolic responses (i.e., increased brown adipose tissue mass and activity, reduced shivering). However, little is known on individual biological characteristics that may influence the level of cold acclimation between individuals to a given protocol. Consequently, the purpose of this study was to determine the variability in core temperature (Tcore) cooling rate during a cold acclimation protocol where men were exposed to 7 consecutive days of 14-16°C water immersion for 60 min or until core temperature reached 35.5°C. On average, there was no difference between cooling rate on day 1 and day 7, showing no insulative effect of cold acclimation ($p > 0.05$). On day 7, results showed that 6 participants had a decrease Tcore cooling rate (-0.25 ± 0.21 °C) and the other 6 participants had either no change or an increase in Tcore cooling rate (0.03 ± 0.23 °C).



This allowed us to divide the participant pool into 2 tentative cohorts: responders to cold acclimation (with a decrease in the magnitude of core temperature from baseline and non-responders with no change or an increase in magnitude of core temperature). Furthermore, there is no correlation between improvement in cooling rate for body weight ($r^2 = 0.019$, $p = 0.50$), for fat mass ($r^2 = 0.061$, $p = 0.97$), for lean body mass ($r^2 = 0.006$, $p = 0.28$), and for volume ($r^2 = 0.025$, $p = 0.56$). There is also a large range in the core temperature responses, from decreases in cooling of 0.50 °C to increases in cooling of 0.27 °C after 7 days.

This high interindividual variability in responses to the cold is thus currently unexplained, and further studies would be necessary to investigate the specific physical characteristics that would influence cold responses.

P-113 LATE BREAKING: GDF15 reduces non-alcoholic steatohepatitis independent of reductions in body mass in mice housed at thermoneutrality

Dongdong Wang[1], Gregory Steinberg[1], Sebastian Jørgensen[2]

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Growth differentiation factor 15 (GDF15) reduces food intake through binding to GFRAL in the hindbrain (reviewed in[1]), however, the body weight-independent roles of GDF15 in metabolic diseases such as NASH are poorly understood. In the current study we investigated the dose-dependent effects of recombinant GDF15 and matched caloric restriction in pair-fed controls on NASH in mice fed western diet and housed at thermoneutrality. We find that GDF15 reduces the NAFLD activity score, fibrosis score, liver TG, liver NEFA, serum ALT, liver fat percentage and liver α-SMA expression to a greater degree than pair-fed controls. Both GDF15 and pair-fed groups reduced immune cell infiltration in liver (CD45+ cells, CD45+CD11b+ cells, neutrophils, total liver macrophages, monocyte derived-Kupffer cells, non-macrophage WBCs, CD8+ T cells) to a similar degree before any changes in body weight suggesting this effect may be related to calorie restriction. In contrast, GDF15 but not pair feeding reduced markers of fibrosis (*Col1a1, Tgfb1, Timp1*). These data indicate that GDF15 exhibits body weight-independent effects on NASH. Further studies examining the mechanisms mediating these effects are in progress.

1. Wang, D. *et al.* GDF15: emerging biology and therapeutic applications for obesity and cardiometabolic disease. *Nat Rev Endocrinol* 17, 592-607, doi:10.1038/s41574-021-00529-7 (2021).

P-114 LATE BREAKING: Electrophysiological Responses of Hypothalamic POMC Neurons to Leptin Are Dictated by Sex and Location

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[1]IUCPQ, [2]Laval University

Introduction: A prevalent model in the field of neurometabolism is that leptin directly activates pro-opiomelanocortin (POMC) neurons of the arcuate nucleus of the hypothalamus (ARC) to suppress feeding. However, this model has been recently challenged by evidence that POMC neurons are highly heterogenous. Furthermore, POMC neurons are also expressed in the retrochiasmatic area (RCA) and little is known about the effects of leptin on POMC neurons in females. Therefore, there is a need to better define the effects of leptin on hypothalamic POMC neurons in both males and females.

Objectives: 1) Determine the differences in leptin responsiveness of POMC neurons in the RCA and ARC 2) Determine if leptin responsiveness of these neurons differs by sex.

Methods: We used a mouse model allowing fluorescent labeling of adult POMC neurons (Pomc-CreERT2::tdTomato). Male and female mice (8-12 wk) were euthanized, and brains were rapidly removed and sectioned for whole-cell patch-clamp electrophysiology experiments. Current-clamp recordings were established from $POMC^{ARC}$ and $POMC^{RCA}$ neurons and slices were bath exposed to leptin (100nM). Changes in neuronal electrical excitability were assessed.

Results: In males, leptin excited 32% (*n*=34) of $POMC^{ARC}$ neurons and inhibited a smaller population of these cells (18%, *n*=34) which is consistent with previous electrophysiological studies. However, 26% (*n*=27) of $POMC^{RCA}$ neurons were inhibited by leptin with only a small proportion displaying leptin-induced excitatory effects (15%, *n*=27). These results suggest that leptin-responsive $POMC^{ARC}$ neurons are primarily excited by leptin, whereas $POMC^{RCA}$ neurons are primarily inhibited. In contrast, most POMC neurons were nonresponsive to leptin in females (73% $POMC^{ARC}$, *n*=44; 78% $POMC^{RCA}$, *n*=41). Of the female leptin-responsive POMC neurons, similar percentages of excitatory (23% $POMC^{ARC}$, *n*=44; 17% $POMC^{RCA}$, *n*=41) or inhibitory (4.5% $POMC^{ARC}$, *n*=44; 5% $POMC^{RCA}$, *n*=41) effects were observed between the regions examined.

Conclusion: Our data demonstrate that $POMC^{ARC}$ and $POMC^{RCA}$ respond differently to leptin in males; $POMC^{ARC}$ are mainly excited while $POMC^{RCA}$ are mainly inhibited. We also show that the majority of $POMC^{(ARC\ or\ RCA)}$ neurons are nonresponsive to leptin in females. Although leptin caused inhibitory effects in a proportion of POMC neurons in males, such leptin-induced inhibition of POMC neuron activity is virtually absent in females. This suggests that anatomical and sexual differences exist in the hypothalamic response to leptin.

P-115 LATE BREAKING: Implementation of a skeletal diagnosis-treatment system using localized BIA and EMS

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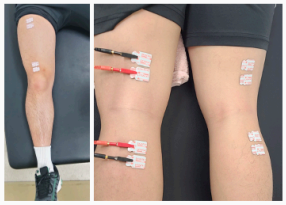
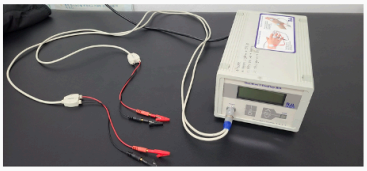
As an aging society continues, the global population with sarcopenia is increasing. Since such sarcopenia tends to increase with age and is highly likely to lead to secondary injuries such as fractures due to falls, appropriate examination and treating solutions are required. We aimed to develop implementation of a skeletal muscle diagnosis and treatment system using localized BIA and EMS (electrical muscle stimulation). As a pilot study, we measured BIA parameters and/or treat EMS for eight young healthy people during exercise or before and after exercise according to the healing stage of Anterior collateral ligament(ACL) rupture.



Electrode attach



BIA(Quantum II Desktop (RJL system))

Quadriceps; The electrode was attached at a point 5cm upper and lower the center of the quadriceps muscle, and at a point 3mm away from the center of the quadriceps muscle. ACL; The electrodes were attached at a distance of 5cm above and below the knee joint line at the rear, and the distance between the electrodes was set at 3mm.

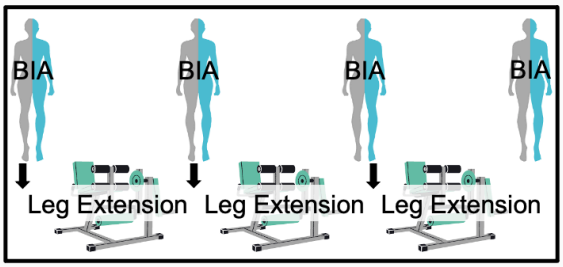


Fig. 1. Moderate Intensity exercise protocol

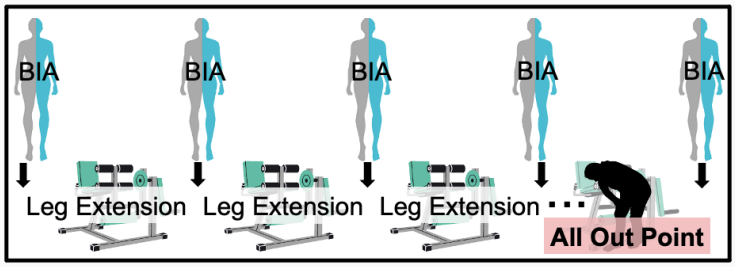


Fig. 2. All-Out exercise protocol

Fig. 1. 3 sets of 10 repetitions were performed at 50-69% intensity of 1RM, and BIA measurement was performed immediately after each set; Fig. 2. 10 repetitions at 50 to 69% intensity of 1 RM was performed to the point of failure that could no longer be performed, and BIA measurements were made immediately after each set.

As a result, there was no significant change in the subjects who exercised, and it was confirmed that the difference in parameters such as resistance (R), reactance (Xc), and phase angle right after exercise. After exercise with/without EMS, it has been implicated that the phase angle was lowered due to by-products such as lactic acid accumulated in the fascia, causing disturbing homeostasis and decreased *Xc* and PA, and that the changed parameters responded to the healing stage of the ACL injury. In future studies, it is necessary to measure subjects of various types of injury and ages, change in parameters in the post-exercise recovery period, and confirm changes in EMS and resistance exercise in the post-exercise recovery period.

P-116 LATE BREAKING: Shutting-down brown adipose tissue thermogenesis during cold deacclimation

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Brown adipose tissue (BAT) dissipates energy as heat enabling mammals to adapt to cold environments through non-shivering thermogenesis (NST). Mechanisms that control NST involve sympathetic activation, increased UCP1 activity and content, and mitochondrial biogenesis. However, the mechanisms that shut-down BAT NST when mammals move from a cold-acclimated state to a thermoneutral environment remain unclear.

We investigated adaptations in BAT mitochondrial energetics, content, and ultrastructure in C57BL6/J (WT) and *mitoQC* reporter mice at 3h, 12h, 24h and 48h following transfer from a cold-acclimated state (7d at 4oC) to a thermoneutral environment (30oC). *MitoQC* mice express a tandem-fusion protein (mCherry-GFP) targeted to the mitochondrial outer membrane. During mitophagy, GFP fluorescence is quenched due to its acid-labile properties, but mCherry fluorescence remains unaffected. We hypothesized coordinated adaptive mechanisms involving decreased uncoupled mitochondrial respiration, altered cristae structure and decreased surface area; decreased mitochondrial content; and increased mitophagy.

High-resolution respirometry of permeabilized BAT explants revealed a decrease in complex I driven leak respiration at 24h ($p<0.001$) and 48h ($p<0.01$). Complex I and II driven leak respiration decreased at 48h ($p<0.05$). Complex III driven (G3P) leak respiration was significantly decreased at 3h ($p<0.05$), 24h ($p<0.05$) and 48h ($p<0.001$). Non-mitochondrial respiration was decreased at 48h ($p<0.05$). Quantitative morphometry of transmission electron micrographs revealed decreased mitochondrial/cytoplasmic area by 48h ($p<0.001$), indicative of reduced mitochondrial content. Lipid droplet/cytoplasmic area increased ~50% by 48h ($p<0.01$), consistent with decreased lipolysis of stored lipid during adaptation to thermoneutrality. Mitochondrial protein/mg tissue decreased significantly with time ($p=0.03$). Mitochondrial number decreased significantly at 48h when compared to 3h ($p=0.017$). Mitochondrial cristae length and density are under investigation. Confocal microscopy analyses of *mitoQC* BAT using Imaris software shows a trend for an increase in mitophagic flux over time ($p=0.1$). Immunoblotting of key mitochondrial proteins and mitophagy marker proteins is underway. Taken together, adaptative mechanisms in BAT when mice move from a cold acclimated state to thermoneutrality involve decreases in uncoupled respiratory capacity, decreases in mitochondrial content, and increases in mitophagic flux.

P-117 LATE BREAKING: Hepatocyte-specific FBXW7 protects against NASH and regulates whole-body energy homeostasis via coordinating nutrient-sensing nuclear receptors

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Nonalcoholic steatohepatitis (NASH) is epidemiologically associated with obesity and diabetes, and can lead to liver cirrhosis and hepatocellular carcinoma if remains untreated. The intricate signaling pathways that

orchestrate hepatocyte energy metabolism and cellular stress, intrahepatic cell crosstalk, as well as peripheral tissue interplay remain elusive and are crucial for the development of anti-NASH therapies. Herein, we reveal the E3 ligase FBXW7 as a key factor regulating hepatic catabolism, stress responses, systemic energy homeostasis, and NASH pathogenesis, with attenuated FBXW7 expression as a feature of advanced NASH. Multiomics analysis and pharmacological intervention showed that loss of FBXW7 function in hepatocytes disrupts a metabolic transcriptional axis conjointly controlled by the nutrient-sensing nuclear receptors ERRα and PPARα, resulting in suppression of fatty acid oxidation, elevated ER stress, apoptosis, immune infiltration, fibrogenesis and ultimately NASH progression. These results provide the foundation for developing alternative strategies targeting nuclear receptors for the treatment of NASH.

This work was supported by a Foundation Grant from the Canadian Institutes of Health Research to V.G. (FDT-156254).