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Longevity and Biological Ageing: Enhancing Health into Advanced Age



SESSION 9

Professor Kostas Tsintzas

Intermittent Fasting and Fasting-Mimicking Diets:
Physiological Effects, Cardiometabolic Health and Autophagy

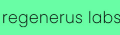
11:15 -12:00pm

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Intermittent Fasting and Fasting-Mimicking Diets: Physiological Effects, Cardiometabolic Health & Autophagy



Prof. Kostas Tsintzas
*The David Greenfield Human Physiology Unit
Division of Physiology, Pharmacology and Neuroscience
School of Life Sciences
University of Nottingham Medical School
Queen's Medical Centre
Nottingham, United Kingdom*

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Outline of the talk

Physiological & metabolic responses to fasting

Intermittent Fasting (IF): definitions, responses & health benefits

Unanswered research questions

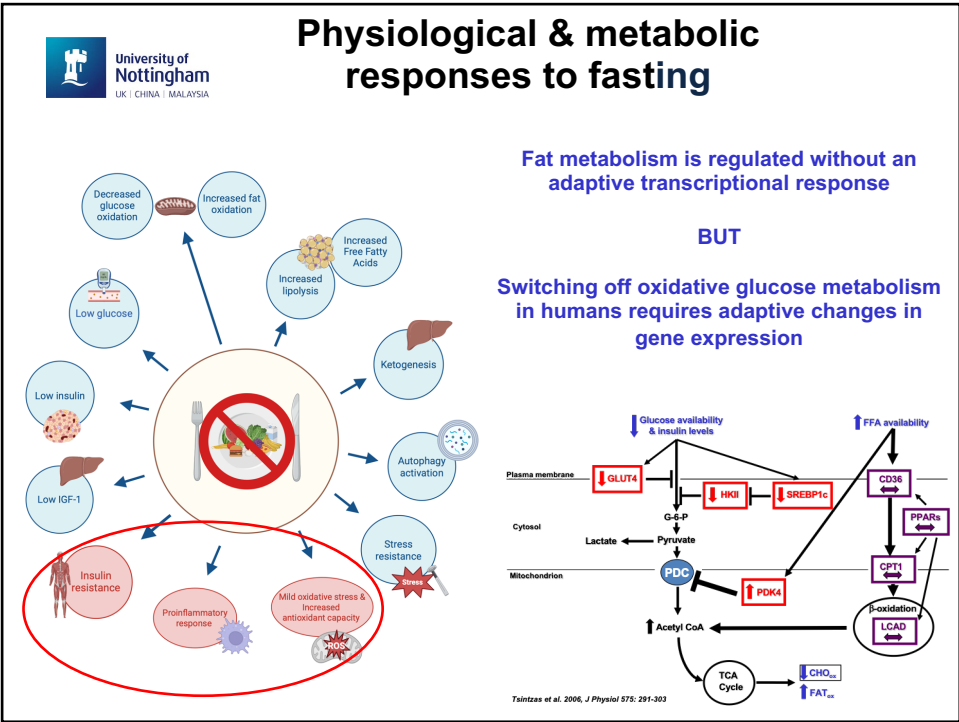
Fasting-Mimicking Diets (FMD): definition & health benefits

Research question: does FMD protein content affect cardiometabolic health & autophagy?

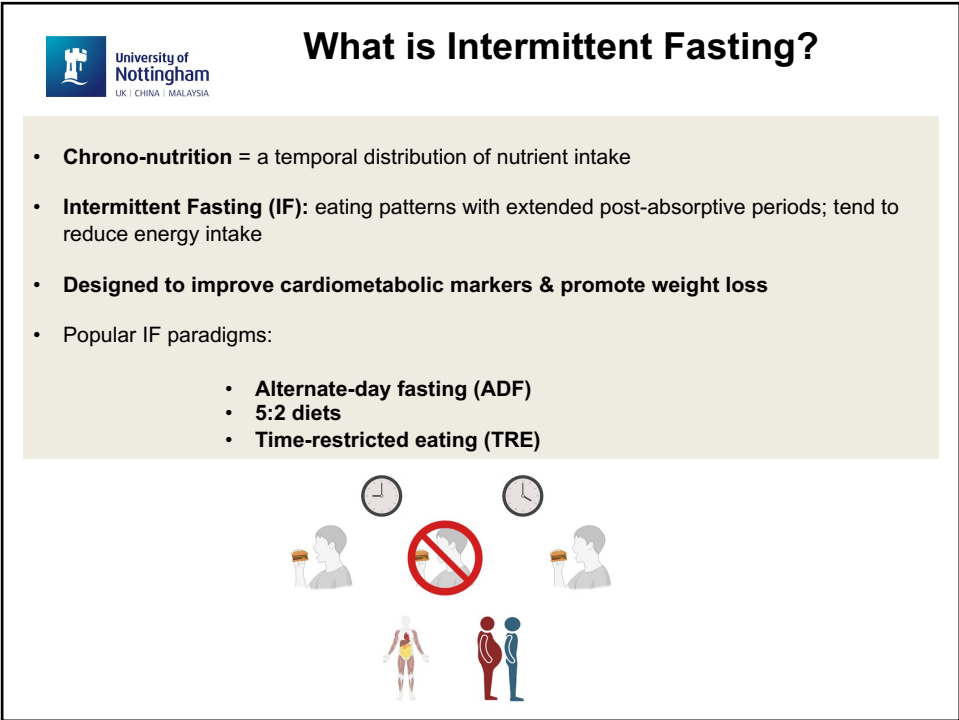
New findings: low vs. high protein FMD in healthy humans

Conclusions & future directions

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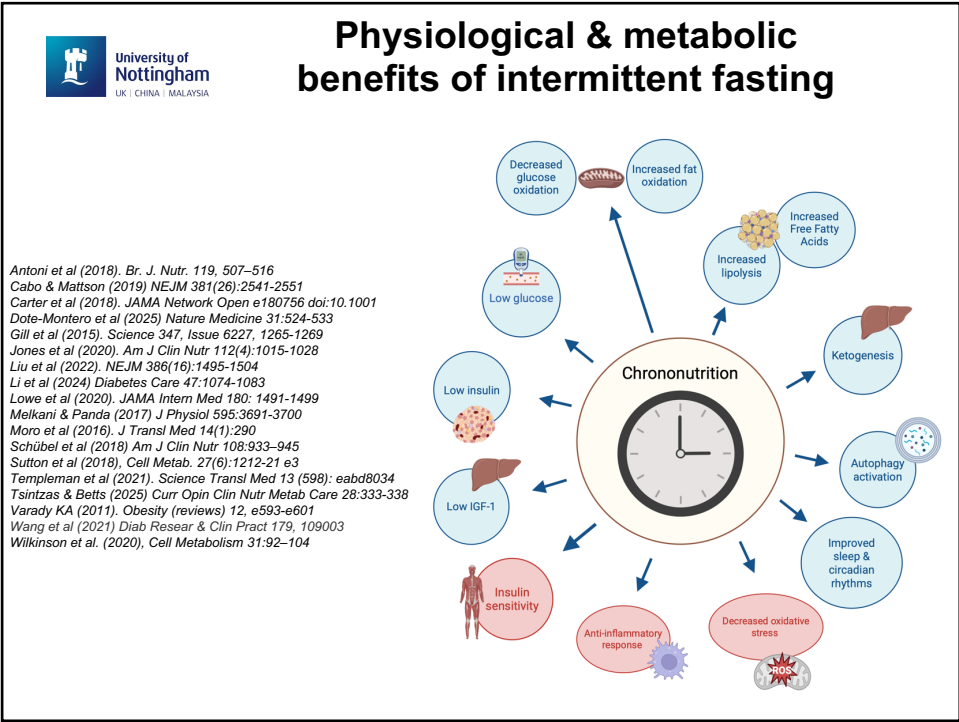


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Key Features of Intermittent Fasting paradigms

Type	Fasting Frequency	Restriction duration	Common protocols
Alternate-Day Fasting (ADF)	Every alternate day (3-4 days /week)	24 hr	Fast days: 0 – 25% estimated energy requirements Feed days: <i>ad libitum</i> consumption or 125% energy requirements Mean weekly energy reduction ~30-50%
5:2 diet	2 days/week typically non-consecutive	24 hr	2 days: very low-calorie diet (400-600 kcal) or 25% energy requirements 5 days: <i>ad libitum</i> or 100% energy requirements Mean weekly energy reduction ~25%
Time-Restricted Eating (TRE)	Daily	6-10 hr	Daily: pre-specified 'eating window' with <i>ad libitum</i> consumption Mean daily energy restriction ~300-400 Kcal (~20% weekly reduction)

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Unanswered research questions

- *Does IF lead to greater weight loss?*
- *Could IF cause greater lean mass loss?*
- *Are IF health benefits independent of weight loss?*
- *How much is due to fasting vs. energy restriction?*

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Calorie counting vs. minute counting; does nutrient timing matter for weight-loss?

Kostas Tsintzas^a, James A. Betts^b[Authors and Affiliations >](#)

Current Opinion in Clinical Nutrition & Metabolic Care 28(4):p 333-338, July 2025. | DOI: 10.1097/MCO.0000000000001135

KEY POINTS

- Meal timing is linked to metabolic health but it is unclear whether chrono-nutrition strategies promote weight-loss more effectively than other means of eliciting negative energy balance.
- Several recent studies have concluded that time-restricted eating may be superior to standard energy restriction for weight-loss but the data presented do not consistently support that inference.
- Further randomized controlled trials are needed, with validated, objective and mechanistic outcome measures and with direct contrasts between chrono-nutrition and relevant comparator conditions.

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Advances in Nutrition 15 (2024) 100130



Advances in Nutrition

AN INTERNATIONAL REVIEW JOURNAL

journal homepage: <https://advances.nutrition.org/>

Review

Effects of Intermittent Energy Restriction Compared with Those of Continuous Energy Restriction on Body Composition and Cardiometabolic Risk Markers – A Systematic Review and Meta-Analysis of Randomized Controlled Trials in Adults

Maite M. Schroot*, Peter J. Joris, Jogchum Plat, Ronald P. Mensink

Systematic Review & Meta- Analysis:

ADF, 5:2 diet and TRE either separately or combined showed limited differences for weight loss & cardiometabolic risk markers compared with **continuous energy restriction**.

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JAMA Internal Medicine | Original Investigation

Effects of Time-Restricted Eating on Weight Loss and Other Metabolic Parameters in Women and Men With Overweight and Obesity The TREAT Randomized Clinical Trial

Dylan A. Lowe, PhD; Nancy Wu, MS; Linnea Rohdin-Bibby, BA; A. Holliston Moore, PhD; Nisa Kelly, MS; Yong En Liu, BS; Errol Philip, PhD; Eric Vittinghoff, PhD; Steven B. Heymsfield, MD; Jeffrey E. Olgin, MD; John A. Shepherd, PhD; Ethan J. Weiss, MD

12-week RCT: TRE (8 h, 12:00 – 20:00) vs. Control (3 regular meals/day)

No evidence that TRE improves weight loss vs. eating throughout the day (Δ between groups -0.26 kg; 95% CI -1.30 to 0.78)

Caution: greater appendicular lean mass loss with TRE; a concern for people at risk of sarcopenia

Lowe et al (2020). JAMA Intern Med 180: 1491-1499

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The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 21, 2022 VOL. 386 NO. 16

Calorie Restriction with or without Time-Restricted Eating
in Weight Loss

Deying Liu, M.D., Yan Huang, M.S., Chensihan Huang, M.D., Shunyu Yang, M.D., Xueyun Wei, M.D.,
Peizhen Zhang, M.D., Dan Guo, M.D., Jiayang Lin, M.D., Bingyan Xu, M.D., Changwei Li, Ph.D., Hua He, Ph.D.,
Jiang He, M.D., Ph.D., Shiqun Liu, M.D., Linna Shi, M.D., Yaoming Xue, M.D., and Huijie Zhang, M.D., Ph.D.

12-month RCT: TRE (8 h, 08:00 – 16:00) + daily calorie restriction vs. calorie
restriction alone

No evidence that TRE improves weight loss vs. Control
(Δ between groups -1.8 kg; 95% CI -4.0 to 0.4)

No difference in lean mass loss

Liu et al (2022). NEJM 386(16): 1495-1504

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Neither overnight fast nor 10 days of TRE lower
anabolic sensitivity & muscle protein synthesis



THE JOURNAL OF NUTRITION

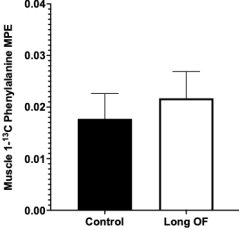
journal homepage: <https://jn.nutrition.org/>

Nutrient Physiology, Metabolism, and Nutrient-Nutrient Interactions

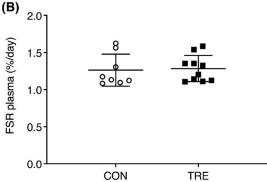
Effect of an Acute Prolonged Overnight Fast on Skeletal Muscle Insulin
and Anabolic Sensitivity in Healthy Men

Joanne E Mallinson¹, Mia Keeton¹, Aline Nixon¹, Abhishek Sheth¹, Robert Jones¹,
Pardeep Pabla¹, Joan MG Senden², Luc JC van Loon², Kostas Tsintzas^{1,2}

¹ School of Life Sciences, Division of Physiology, Pharmacology and Neuroscience, University of Nottingham Medical School, Queen's Medical
Centre, Nottingham, United Kingdom; ² Department of Human Biology, NUTRIM Institute for Nutrition and Translational Research in Metabolism,
Maastricht University, Maastricht, The Netherlands



Group	Muscle 1- ¹⁴ C Phenylalanine MPE
Control	~0.018
Long OF	~0.022



Group	FSR plasma (%/day)
CON	~1.2
TRE	~1.3

ORIGINAL ARTICLE
Time-Restricted Eating

Obesity | WILEY

Eight-hour time-restricted eating does not lower daily
myofibrillar protein synthesis rates: A randomized control trial

Evelyn B. Parr¹ | Imre W. K. Kouw¹ | Michael J. Wheeler¹ |
Bridget E. Radford¹ | Rebecca C. Hall¹ | Joan M. Senden² | Joy P. B. Goossens² |
Luc J. C. van Loon^{1,2} | John A. Hawley¹

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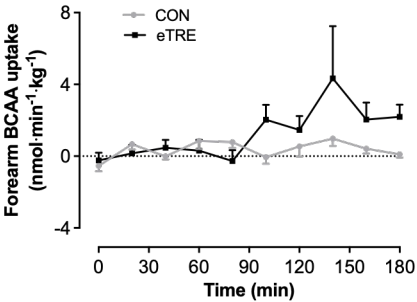
Two weeks of early time-restricted feeding (eTRF) improves skeletal muscle insulin and anabolic sensitivity in healthy men

Robert Jones,¹ Pardeep Pabla,¹ Joanne Mallinson,¹ Aline Nixon,¹ Tariq Taylor,¹ Andrew Bennett,² and Kostas Tsintzas¹

¹MRC Versus Arthritis Centre for Musculoskeletal Ageing Research, School of Life Sciences, University of Nottingham Medical School, Nottingham, United Kingdom; and ²School of Life Sciences, University of Nottingham Medical School, Nottingham, United Kingdom

However, 2 weeks of early TRE improves skeletal muscle branched-chain amino acid (BCAA) uptake after a mixed meal

An adaptive response to reduced energy & protein intake?



Time (min)	CON (nmol·min ⁻¹ ·kg ⁻¹)	eTRE (nmol·min ⁻¹ ·kg ⁻¹)
0	0	0
30	0.5	0.5
60	0.5	0.5
90	0.5	0.5
120	0.5	2.5
150	0.5	4.5
180	0.5	2.5

Jones et al (2020). Am J Clin Nutr 112(4):1015-1028

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Are the health benefits of IF independent of weight loss?

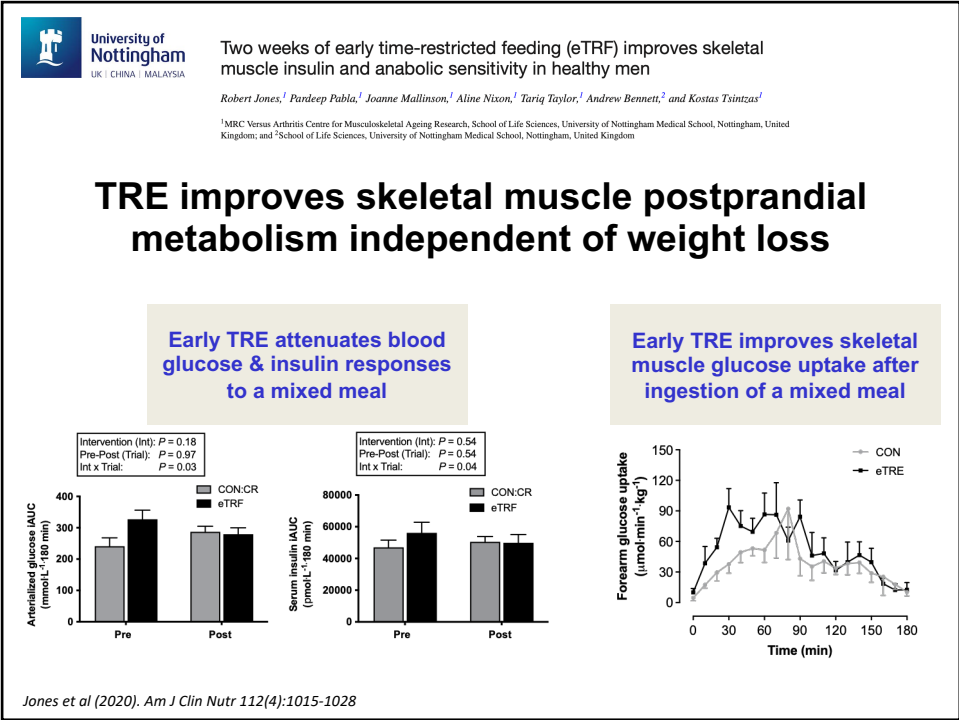
Some IF forms improve basal & post-prandial glucose metabolism independent of weight loss in healthy individuals (Jones et al 2020) and in obesity & impaired glucose tolerance (Sutton et al 2019)

However,

findings are inconsistent (Templeman et al 2019)

and may depend on IF type and/or fasting duration

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SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

METABOLISM

A randomized controlled trial to isolate the effects of fasting and energy restriction on weight loss and metabolic health in lean adults

Iain Templeman¹, Harry Alex Smith¹, Enhad Chowdhury¹, Yung-Chih Chen^{1,2}, Harriet Carroll^{1,3}, Drusus Johnson-Bonson¹, Aaron Hengist¹, Rowan Smith¹, Jade Creighton^{1,4}, David Clayton¹, Ian Varley¹, Leonidas Georgios Karagounis^{1,5}, Andrew Wilhelmsen¹, Kostas Tsintzas², Sue Reeves⁶, Jean-Philippe Walhin¹, Javier Thomas Gonzalez², Dylan Thompson¹, James Alexander Betts^{1*}

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What are the relative contributions of fasting versus energy restriction?

Daily energy restriction by 25% (75:75 group)

vs.

ADF with net energy restriction (150% on fed days) (0:150 group)

vs.

ADF without net energy restriction (200% on fed days) (0:200 group)

Not so fast

Intermittent fasting is increasingly popular, but whether fasting itself offers specific nutritional benefits in lean individuals compared to traditional daily calorie restriction is unknown. In a small clinical trial of healthy individuals, Templeman *et al.* found that alternate-day fasting without energy restriction was ineffective at reducing body mass. Even with net energy intake restricted to that of daily dieters, alternate-day fasting less effectively reduced body fat content and offered no additional short-term improvements in metabolic or cardiovascular health compared to daily energy restriction.

Templeman *et al.* (2021). *Science Transl Med* 13 (598): eabd8034

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SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

METABOLISM

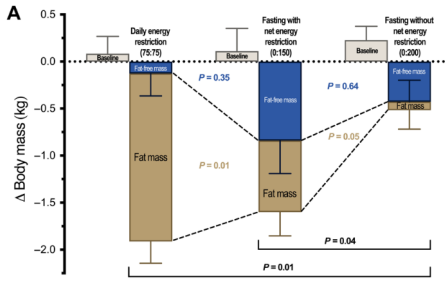
A randomized controlled trial to isolate the effects of fasting and energy restriction on weight loss and metabolic health in lean adults

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- Body mass (kg): Daily CR vs ADF with CR: **-1.91 (-1.29 to -2.54) kg** vs. **-1.60 (-0.93 to -2.28) kg**, P=0.46
- Fat mass (kg): Daily CR vs ADF with CR: **-1.75 (-1.25 to -2.25) kg** vs. **-0.74 (-0.02 to -1.24) kg**, P=0.01
- Lean mass (kg): Daily CR vs ADF with CR: **-0.03 (0.40 to -0.47) kg** vs. **-0.75 (0.09 to -1.59) kg**, P=0.35

A



Group	Δ Body mass (kg)	Δ Fat mass (kg)	Δ Lean mass (kg)
Daily energy restriction (75:75)	-1.91	-1.75	-0.03
Fasting with net energy restriction (0:150)	-1.60	-0.74	-0.75
Fasting without net energy restriction (0:200)	-0.03	-0.03	-0.03

Daily energy restriction: body mass loss almost entirely fat mass

ADF with energy restriction: body mass loss, but fat loss was attenuated

ADF without energy restriction: no change in body or fat mass

Templeman *et al.* (2021). *Science Transl Med* 13 (598): eabd8034

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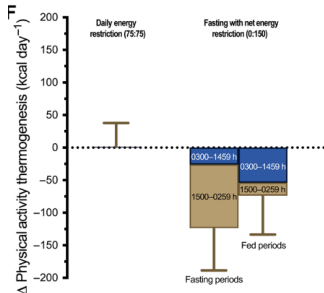
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ADF reduced daily physical activity energy expenditure; daily calorie restriction did not



The ~100 kcal/day reduction in physical activity thermogenesis equals 30 min walking per day

Templeman et al (2021). Science Transl Med 13 (598): eabd8034

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Conclusions & future directions

- IF paradigms do not produce greater weight loss than conventional energy restriction; extended fasting may partly reduce fat-free mass
- Some types (e.g. ADF) may attenuate fat loss and increase lean mass loss
- Some forms (e.g. early TRE) improve basal & post-prandial glucose metabolism independent of weight loss, in healthy individuals and those with obesity & impaired glucose tolerance
- These effects are inconsistent and may depend on IF type (TRE vs. ADF) and/or fasting duration (16h vs. 24h)
- Future research must isolate the effects of nutrient timing and fasting *per se* from energy restriction on weight loss in adults with obesity
- Is there an optimal fasting duration?
- Does IF reduce intake of essential nutrients (e.g. protein), impairing function and/or reducing lean mass vs. equal energy restriction without fasting?

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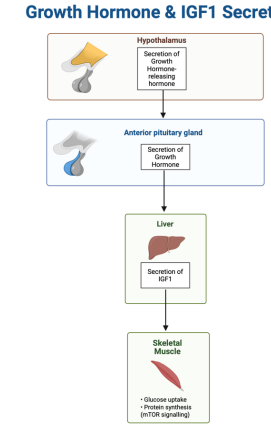


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What is FMD?

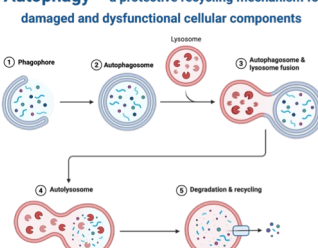
- Very-low-calorie diets (**VLCD**, ~600-800 kcal/day), e.g. Total Diet Replacements (TDR), are used for obesity & diabetes
- European Food Safety Authority (**EFSA**) recommends **≥75 g protein**
- Fasting Mimicking Diet (**FMD**): short-term (**4-7 days**) plant-based VLCD with **very low protein** (~10%E or ~15-20 g)
- **Designed to mimic fasting**
- Amino acid restriction is thought to:
 - *suppress circulating IGF-1*
 - *activate cellular autophagy*
- Both considered critical for health, ageing & lifespan

Growth Hormone & IGF1 Secretion



The diagram illustrates the hormonal axis for growth. It starts with the Hypothalamus secreting Growth Hormone-Releasing Hormone (GHRH), which stimulates the Anterior pituitary gland to secrete Growth Hormone (GH). GH then acts on the Liver to secrete IGF1. IGF1 then acts on Skeletal Muscle to promote Glucose uptake and Protein synthesis (via mTOR signaling).

Autophagy = a protective recycling mechanism for damaged and dysfunctional cellular components



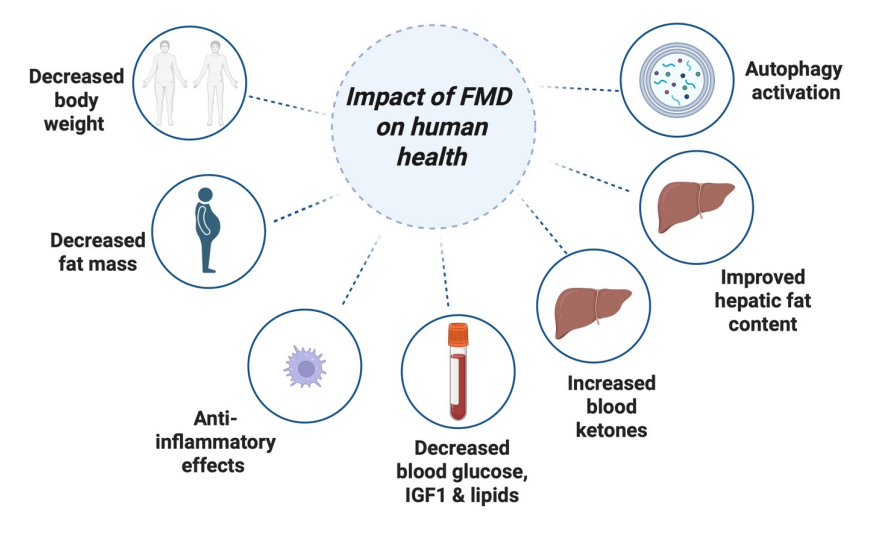
The diagram shows the five steps of autophagy: 1. Phagophore formation, 2. Autophagosome formation, 3. Autophagosome and lysosome fusion, 4. Autolysosome formation, and 5. Degradation and recycling of cellular components.

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Effect of FMD on Health outcomes



The infographic shows the central impact of FMD on human health, which includes: Decreased body weight, Decreased fat mass, Anti-inflammatory effects, Decreased blood glucose, IGF1 & lipids, Increased blood ketones, Improved hepatic fat content, and Autophagy activation.

Brandhorst S, Cell Metab. 2015;22(1):86-99; Brandhorst S, Nat Commun. 2024;15(1):1309; Wei M, Sci Transl Med. 2017;9(377)

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Unanswered research question

Dietary intake of total, animal, and plant proteins and risk of all cause, cardiovascular, and cancer mortality: systematic review and dose-response meta-analysis of prospective cohort studies

Sina Naghshi,^{1,2} Omid Sadeghi,³ Walter C Willett,^{4,5} Ahmad Esmailzadeh^{6,7,8}

Given that intake of plant protein is associated with lower risk of all cause mortality (Naghshi, S et al 2020, BMJ 370:m2412)

Do the benefits of FMD require a low protein content?

How 'low' is low protein?

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Clinical Nutrition 52 (2025) 299–312

Randomized Control Trials

Effects of fasting-mimicking diets with low and high protein content on cardiometabolic health and autophagy: A randomized, parallel group study



Lucy Burns^a, Scott Cooper^a, Sarir Sarmad^a, Guido Funke^b, Antonio Di Mauro^c, George C. Gaitanos^c, Kostas Tsintzas^{a,*}

^aMRC Versus Arthritis Centre for Musculoskeletal Ageing Research, School of Life Sciences, University of Nottingham, Queen's Medical Centre, Nottingham, United Kingdom

^bLabor Tries w eg, 9403 Goldsch, Switzerland

^cHC International SA, 6353 Weggis, Switzerland

Aim of Research:

(a) to examine whether a 1-week low-protein VLCD (typical FMD) mimics fasting-induced benefits on glucose & lipid metabolism, inflammation & autophagy

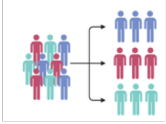
(b) to investigate how increasing dietary protein affects these outcomes

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Methods



Group A – Weight maintenance diet (Control)
Group B - Very low-calorie diet (850 Kcal) with low protein (10%)
Group C - Very low-calorie diet (850 Kcal) with high protein (30%)

Typical FMD

Protein 10%E

Fat 45%E

CHO 45%E

Novel FMD

Protein 30%E

Fat 25%E

CHO 45%E

Daily average energy intake and macronutrient composition of control and test diets for all participants

	CONTROL (n=16)	LP-FMD (n=15)	HP-FMD (n=15)
Energy (kJ)	6,703 ± 2,190	3,663 ± 132	3,621 ± 91
CHO (g)	159.9 ± 58.7	112.7 ± 4.4	101.1 ± 3.5
CHO (%E)	41.1 ± 9.8	51.4 ± 0.6	46.6 ± 0.8
Fat (g)	68.4 ± 24.6	41.1 ± 1.2	25.5 ± 0.9
Fat (%E)	36.9 ± 5.9	42.3 ± 0.7	26.5 ± 0.6
Protein (g)	78.3 ± 28.8	21.8 ± 1.3	65.6 ± 1.1
Protein (%E)	19.9 ± 4.6	10.1 ± 0.3	30.8 ± 0.4

Values are means ± SD. Low Protein/high fat Fasting Mimicking Diet (LP-FMD); High Protein/low fat Fasting Mimicking Diet (HP-FMD); Carbohydrate (CHO); Percent contribution to daily Energy intake (%E).

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Measurements

DEXA scan
(body composition)

Stool sample
(DNA analysis - microbiome)

Urine sample
(Urea & Creatinine)

Blood protein analysis

Blood gene analysis

Impact of Very Low Calorie Diets on Human Health



Cardiovascular function

Blood sample

Blood Glucose
Insulin
IGF1
Lipids
Ketones
Inflammatory markers

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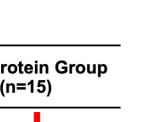
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Effects on Body composition

	Control Group (n=16)	Low Protein Group (n=15)	High Protein Group (n=15)
Body weight (kg)	↔	↓	↓
Lean mass (kg)	↔	↓	↓
BMC (kg)	↔	↔	↔
Fat mass (kg)	↔	↓	↓
Visceral fat mass (kg)	↔	↔	↓
Subcutaneous fat mass (kg)	↔	↓	↓



- Body weight (-2.7 kg), FM (-1.0 kg) & LM (-1.7 kg) decreased similarly in both groups
- **VAT decreased in high protein group only**
- SAT decreased similarly in both groups

Burns et al 2025, Clin Nutrition 52: 299-312

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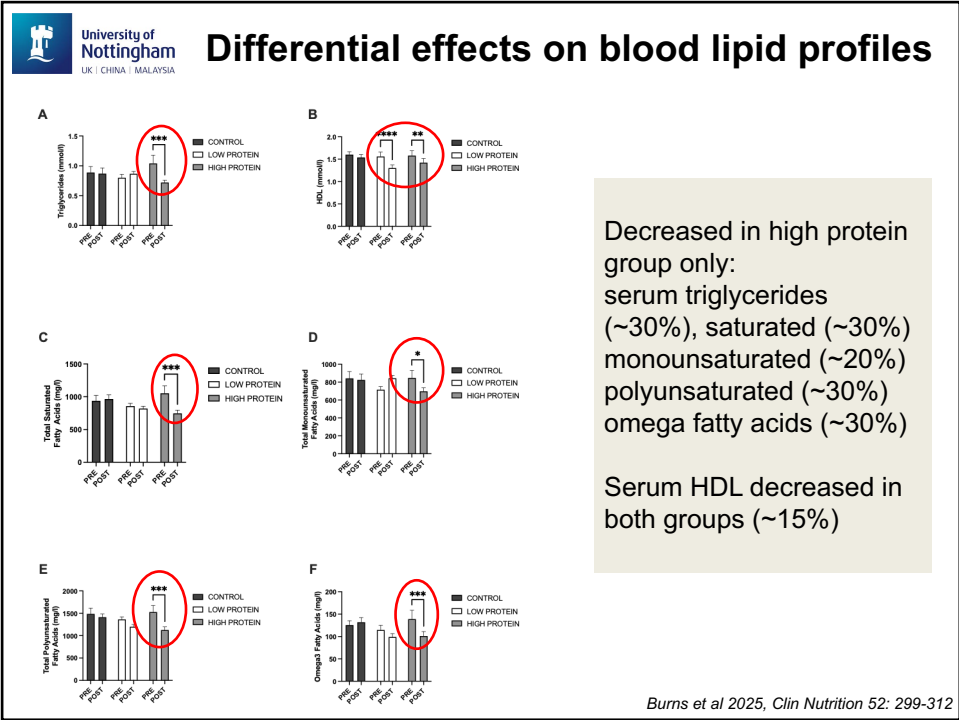
Blood metabolic markers

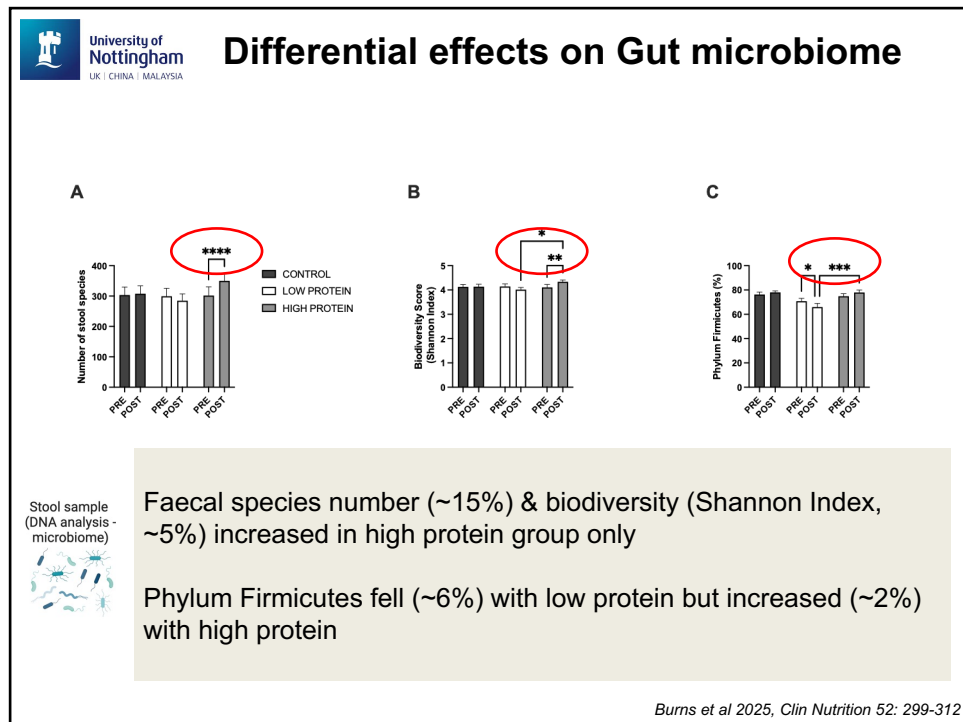
Similar reductions in
both groups in:
blood glucose (~10%)
IGF1 (~30%)
IGFBP3 (~10%)

Serum hydroxybutyrate
increased in both
groups, more with low
protein (~10-fold) than high
protein (~5-fold)

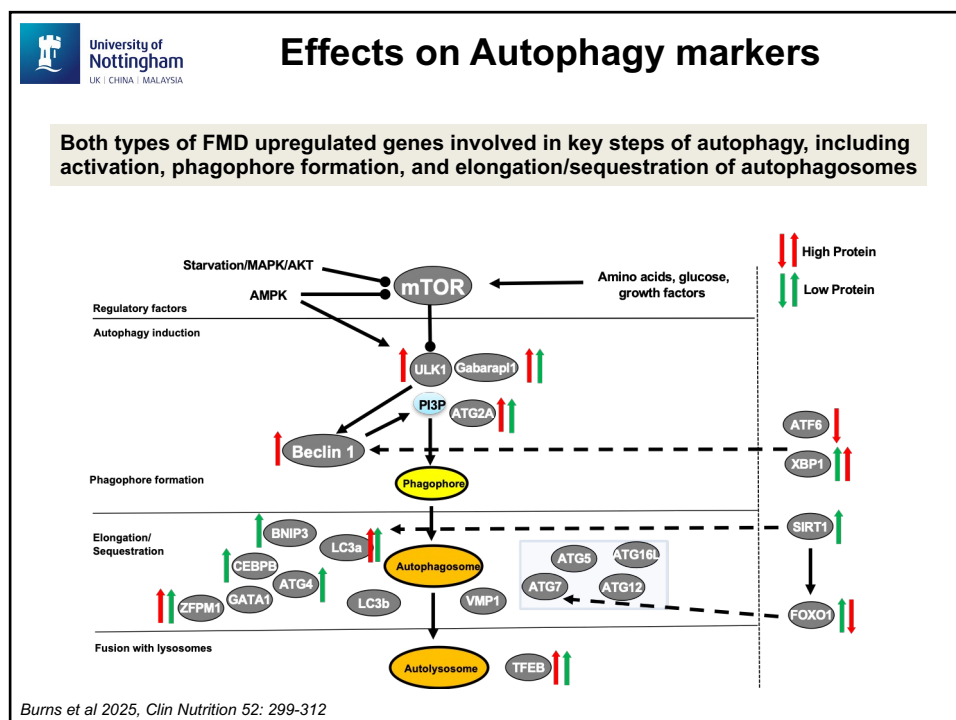
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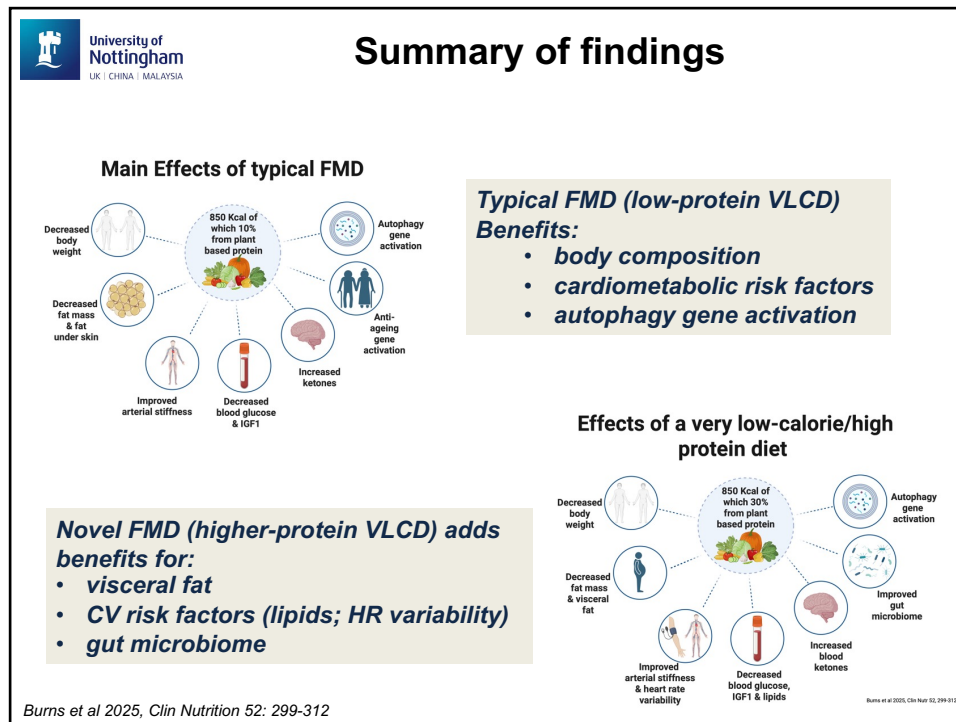




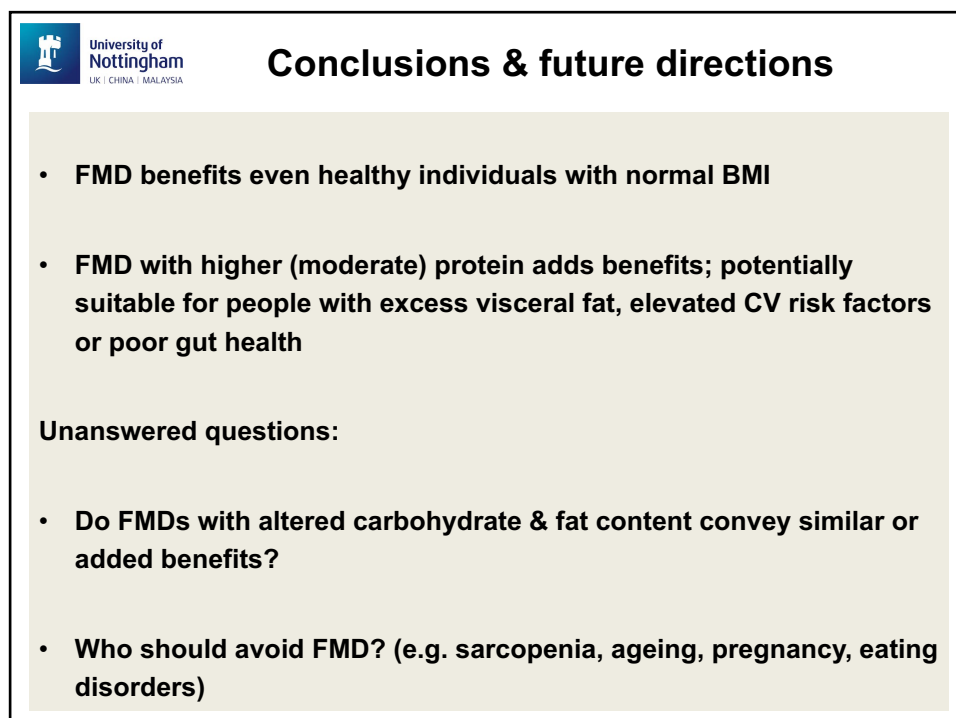
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Dr Robert Jones
Dr Pardeep Pabla
Dr Scott Cooper
Miss Lucy Burns

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Prof. Luc van Loon (Maastricht University)
Dr George Gaitanos (HC International SA)



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Longevity and Biological Ageing:
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Saturday 10th October

Featuring Dr. Felice Gersh, Professor Kostas Tsintzas,
Dr. Denise Furness, and Dr. Jeffrey Bland.



An event by:  Nutritional Medicine Institute

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