Navigating Weight Management: Exploring Root Cause Pathophysiology and Holistic Strategies

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OPA Annual Conference & Trade Show
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Disclosures

- Paid speaker:
  - NovoNordisk Diabetes
  - Abbott Diabetes
  - Medtronic Diabetes
- Owner of PharmToTable, LLC

Learning Objectives

At the completion of this activity, the participant will be able to:

- Explain the root cause pathophysiology driving weight loss resistance and obesity
- Identify nutrition strategies beyond caloric restriction
- Discuss integrative and functional medicine approaches to a holistic weight management plan

The Obesity Epidemic

41.9% of U.S. adults

1 in 6 youth

$260.6 billion/year medical costs

4 million deaths/year

Worldwide prevalence nearly tripled between 1975 and 2016

State of Obesity 2022: Better Policies for a Healthier America. Trust for America's Health. Accessed September 24, 2023.
Obesity. World Health Organization. Accessed September 24, 2023.

Obesity

- A state of chronic or low-grade systemic inflammation
- Metaflammation: obesity-related chronic low-grade inflammation and subsequent altered metabolism

BMI (kg/m^2)	Classification
18.5-24.9	Normal weight
25-29.9	Overweight
30-34.9	Class 1 Obesity
35-39.9	Class 2 Obesity
≥ 40	Class 3 Obesity

- "BMI vastly underestimates true obesity"
  - New policy by the American Medical Association advises that BMI be used in conjunction with other valid measures of risk such as, but not limited to, measurements of visceral fat, body adiposity index, body composition, relative fat mass, waist circumference, and genetic/metabolic factors

Versini M, et al. *Autoimmun Rev*. 2014;13(9):981-1000.
Kawai T, et al. *Am J Physiol Cell Physiol*. 2021;320(3):C375-C391.

Obesity is associated with:

- Type 2 diabetes
- High blood pressure
- Cardiovascular disease
- Stroke
- Arthritis
- Sleep apnea
- Cancer (endometrial, breast, ovarian, prostate, liver, gallbladder, kidney, colon)
- Fatty liver (MAFLD)
- Asthma
- Gout
- Kidney disease
- Fertility problems
- Sexual function problems
- Mental health problems

Standard of Care

- Measurement of BMI and clinical assessment of weight-related complications are recommended to diagnose
- Goal of 5% to 10% weight loss within 6 months
- Lifestyle changes
  - “Eat less, exercise more”
    - Reduced-calorie healthy meal plan, physical activity, behavioral interventions
- Anti-obesity medications
- Bariatric surgery

Am J Manag Care. 2022;28(suppl 15):S288-S296. doi:10.37765/ajmc.2022.89292

The Problem with Restrictive Dieting

- Meta-analysis by Anderson, et al.
  - More than half of lost weight is regained within 2 years
  - More than 80% of lost weight is regained by 5 years

- 1/3- 2/3 of dieters regain **more weight** than they lost on their diets

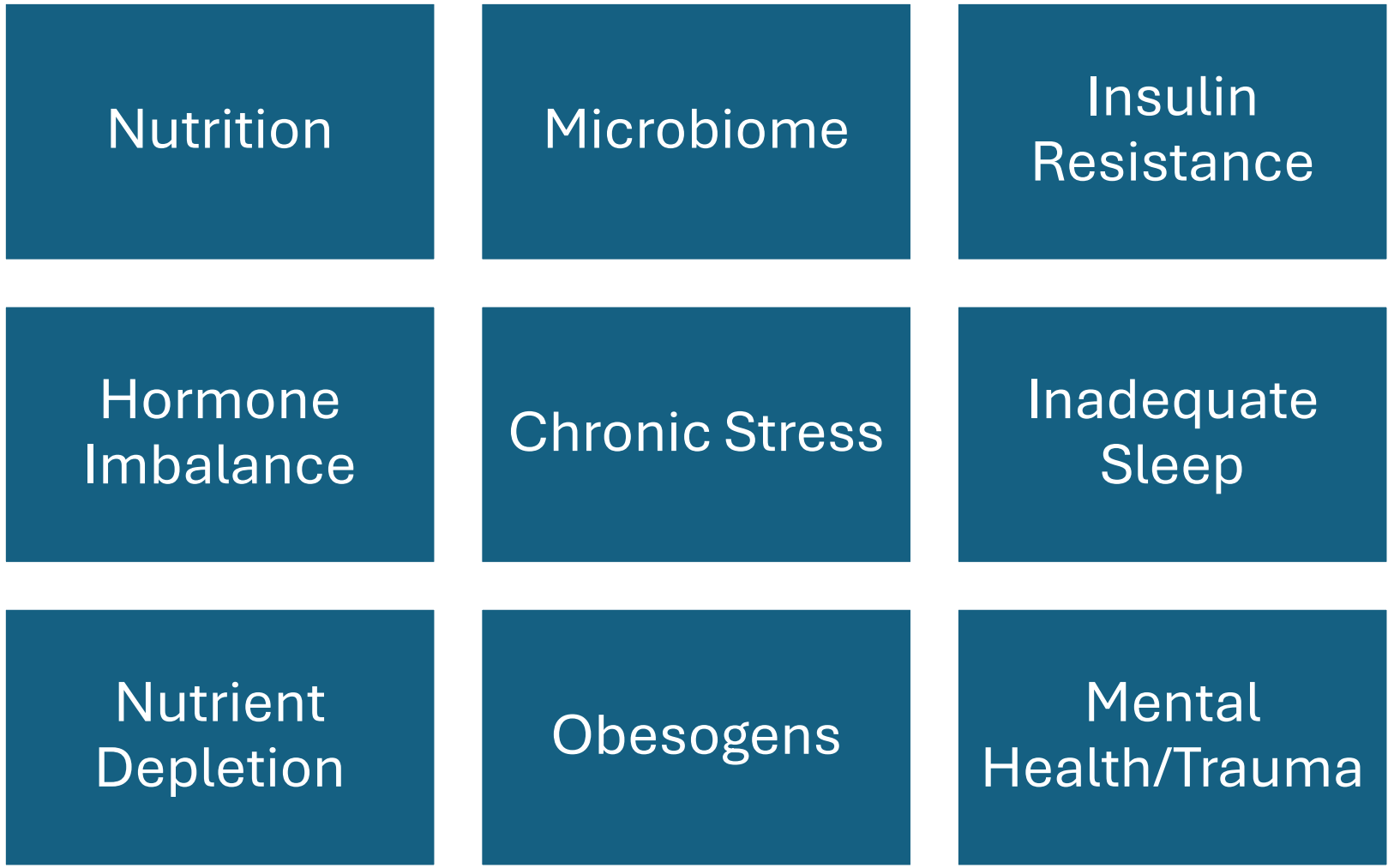
Anderson JW, et al. Am J Clin Nutr. 2001 Nov;74(5):579-84.
Mann T, et al. Am Psychol. 2007 Apr;62(3):220-33.

Exercise Alone isn’t Enough

- 150 minutes/week of moderate-intensity aerobic exercise typically produces little to no weight loss by itself
- Exercise shouldn’t be the sole focus for weight loss
- Physical activity has a plethora of beneficial health effects and should always be recommended 😉

Swift DL, et al. Prog Cardiovasc Dis. 2018 Jul-Aug;61(2):206-213.

What’s Missing?


Nutrition
Microbiome
Insulin Resistance
Hormone Imbalance
Chronic Stress
Inadequate Sleep
Nutrient Depletion
Obesogens
Mental Health/Trauma

Nutrition

- Overconsumption of ultra-processed foods
  - Ultra-processed foods: “formulations mostly of cheap industrial sources of dietary energy and nutrients plus additives, using a series of processes” and containing minimal whole foods
  - Ultra-processed foods represent >1/2 of all calories in the US diet and contribute nearly 90% of all added sugars
  - “Ultra-processed food products are usually packaged attractively and marketed intensively”
- Fewer people prepare meals at home
- Unhealthy food is often cheaper
- Nutrient decline in fruits, vegetables, and grains

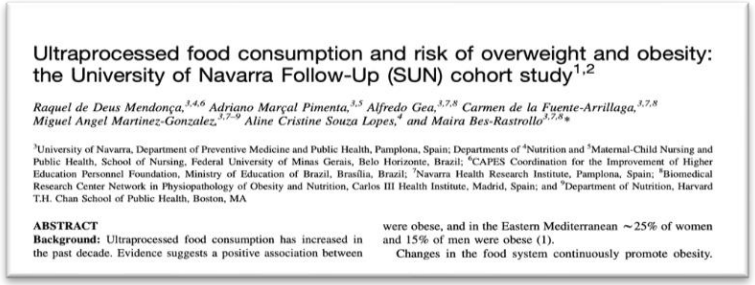
Martínez Steele E, et al. BMJ Open. 2016 Mar 9;6(3):e009892.
Monteiro CA, et al. Public Health Nutr. 2018 Jan;21(1):5-17.
Davis DR, et al. J Am Coll Nutr. 2004 Dec;23(6):669-82.

Addiction to Highly Processed Food

- University of Michigan National Poll on Healthy Aging
  - 13% met criteria for addiction to highly processed food in the past year
  - 44% indicated ≥1 symptoms of addiction to highly processed food
  - Most common symptoms:
    - intense cravings (24%)
    - inability to cut down intake despite a desire to do so (19%)
    - signs of withdrawal (17%)
  - Women > 2x as likely as men to meet criteria for addiction to highly processed food

This poll found that more than one in ten older adults met established criteria for an addiction to highly processed food. This is similar to, or may even surpass, the prevalence of addiction to other legal and easily accessible addictive substances, such as tobacco (10%) and alcohol (4%).

Gearhardt A, et al. Addiction to Highly Processed Food Among Older Adults. University of Michigan National Poll on Healthy Aging. January/February 2023.



Ultraprocessed food consumption and risk of overweight and obesity: the University of Navarra Follow-Up (SUN) cohort study[1,2]

*Raquel de Deus Mendonça,[3,4,6] Adriano Marçal Pimenta,[3,5] Alfredo Gea,[3,7,8] Carmen de la Fuente-Arrillaga,[3,7,8] Miguel Angel Martinez-Gonzalez,[3,7–9] Aline Cristine Souza Lopes,[4] and Maira Bes-Rastrollo[3,7,8]**

[3]University of Navarra, Department of Preventive Medicine and Public Health, Pamplona, Spain; Departments of [4]Nutrition and [5]Maternal-Child Nursing and Public Health, School of Nursing, Federal University of Minas Gerais, Belo Horizonte, Brazil; [6]CAPES Coordination for the Improvement of Higher Education Personnel Foundation, Ministry of Education of Brazil, Brasília, Brazil; [7]Navarra Health Research Institute, Pamplona, Spain; [8]Biomedical Research Center Network in Physiopathology of Obesity and Nutrition, Carlos III Health Institute, Madrid, Spain; and [9]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA

ABSTRACT

Background: Ultraprocessed food consumption has increased in the past decade. Evidence suggests a positive association between

were obese, and in the Eastern Mediterranean ~25% of women and 15% of men were obese (1).

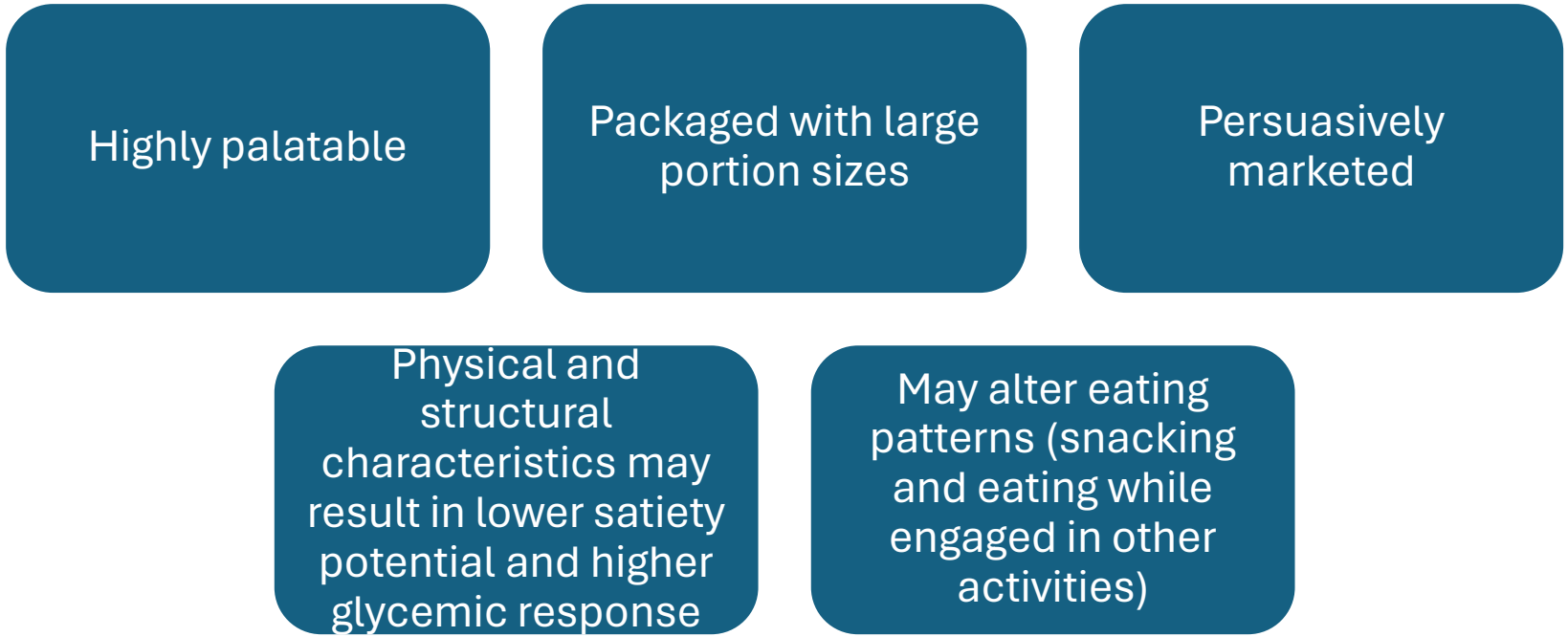
Changes in the food system continuously promote obesity.

- 8451 middle-aged Spanish university graduates
- Evaluated the association between ultra-processed food consumption and the risk of overweight and obesity
- Participants were initially not overweight or obese
- 8.9 years median follow-up
- Adults in the highest quartile of ultra-processed food consumption had a significantly higher risk of developing overweight/obesity than those in the lowest quartile

The results suggest that increased ultraprocessed food consumption is associated with a greater risk of overweight and obesity. Strategies for reducing the consumption of this group of foods, such as the maintenance of a traditional food culture and strengthening of the Mediterranean diet, should be encouraged as preventive approaches for obesity.

Mendonça RD, et al. Am J Clin Nutr. 2016 Nov;104(5):1433-1440.

Other potential mechanistic links between obesity and ultra-processed foods

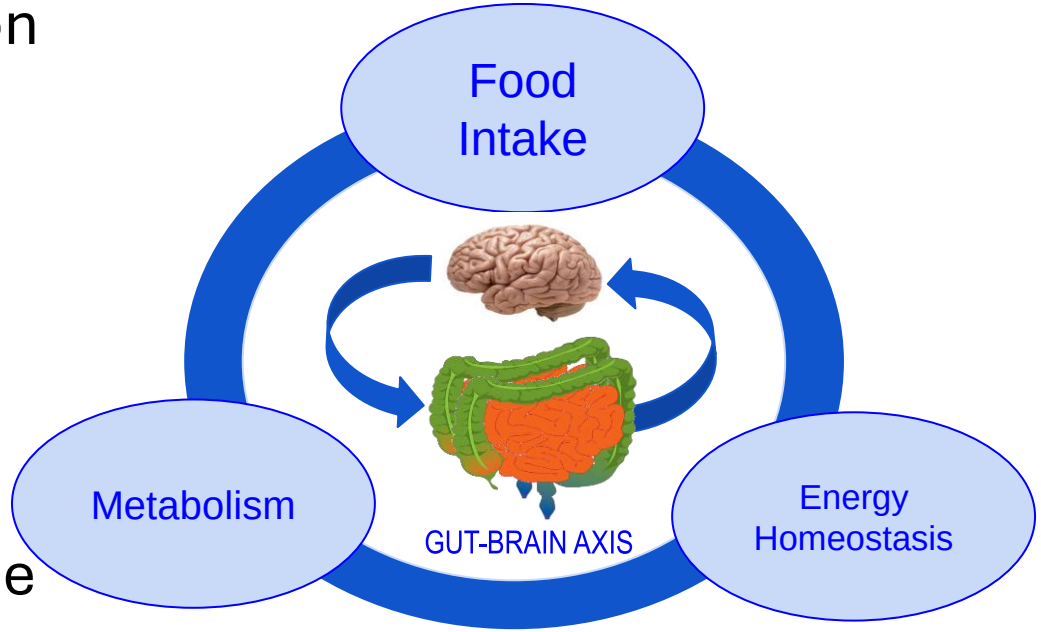


Poti JM, et al. Curr Obes Rep. 2017 Dec;6(4):420-431.

GIT Microbiome… an endocrine organ?

Roles:

- Carbohydrate digestion
- Hormone synthesis
- Neurotransmitter production
- Vitamin synthesis
- Immune response modulation
- Inflammatory response modulation



Galland L. *J Med Food*. 2014;17(12):1261-1272
Brown JM, et al. *Annu Rev Med*. 2015;66:343–359.

Dysbiosis

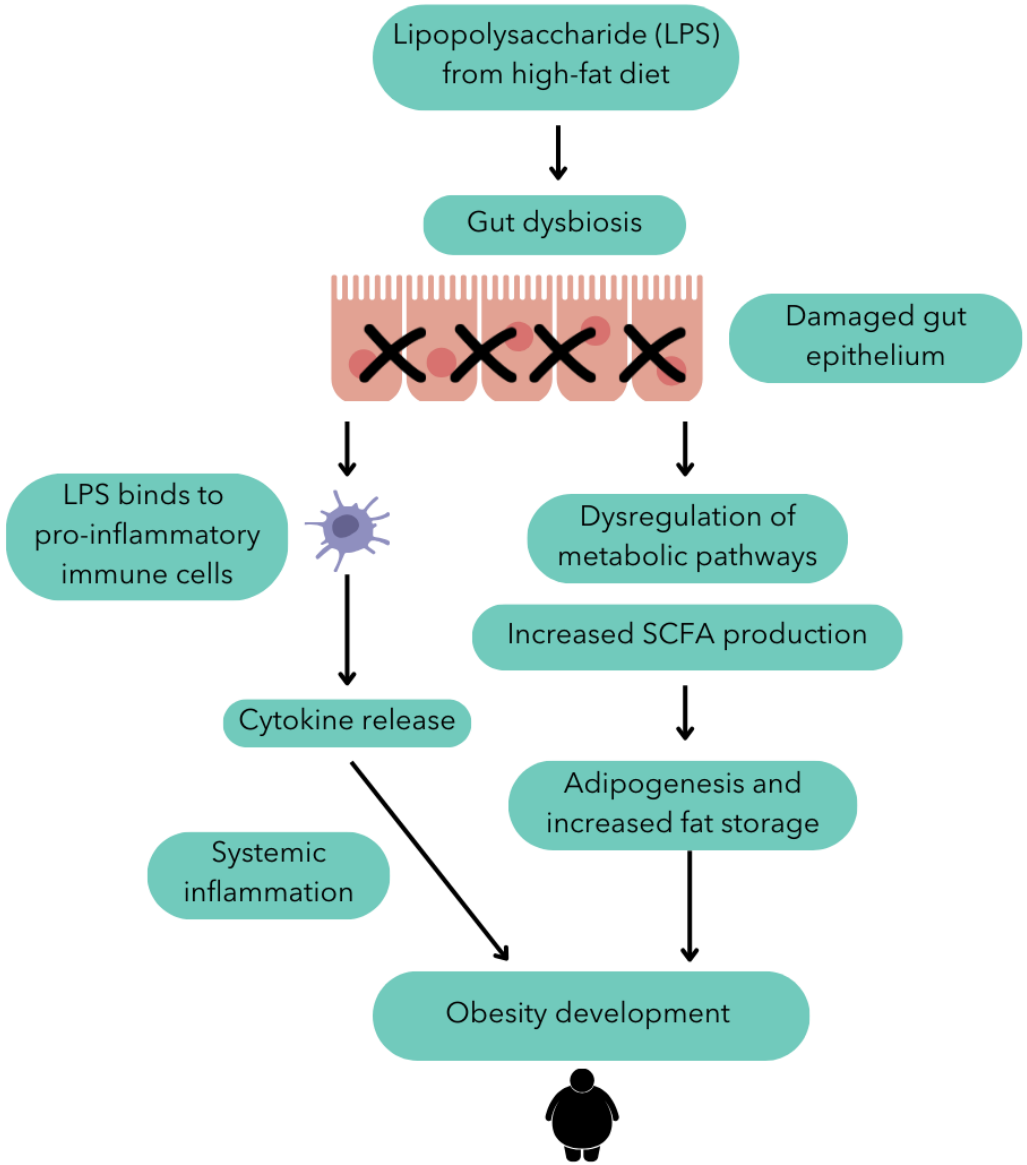
- Lipopolysaccharide (LPS)
  - Highly studied component of gram-negative bacteria
  - Stimulates production of numerous inflammatory mediators
  - Leads to intestinal permeability & chronic inflammation
  - Linked to depression
- Dysbiosis
  - Increases intestinal permeability (IP)

Creely SJ, et al. Am J Physiol Endrocrinol Metab.2007 Mar; 292(3):E740-7.
Dagci, H et al. Acta Tropica. doi:10.1016/S0001-706X(01)00191-7.
Maes M, et al. *Journal of Affective Disorders*. doi:10.1016/j.jad.2006.08.021.

Obese v Lean Microbiome

- Significantly elevated Firmicutes:Bacteroidetes (F:B) ratio in obesity compared to lean people
- Subjects with low microbial gene richness (MGR) often exhibit chronic inflammation, poor insulin sensitivity and higher BMIs
- Bariatric surgery improves MGR

Amabebe E, et al. Br J Nutr. 2020 May 28;123(10):1127-1137.
Napolitano M, et al. Front Microbiol. 2020 Nov 12;11:590370.
Lahtinen P, et al. JAMA Netw Open. 2022 Dec 1;5(12):e2247226.



Adapted from Napolitano M, et al. Front Microbiol. 2020 Nov 12;11:590370.

FMT for Obesity Treatment?

- Fecal microbiota transplantation (FMT) being studied for weight loss

- Studies have shown slight improvements in insulin sensitivity, abdominal adiposity, and lipid metabolism but less effect on weight reduction

Lahtinen P, et al. JAMA Netw Open. 2022 Dec 1;5(12):e2247226.

Article | Published: 05 July 2021

Fecal microbial transplantation and fiber supplementation in patients with severe obesity and metabolic syndrome: a randomized double-blind, placebo-controlled phase 2 trial

Valentin Mocanu, Zhengxiao Zhang, Edward C. Deehan, Dina H. Kao, Naomi Hotte, Shahzeer Karmali, Daniel W. Birch, Kalutota K. Samarasinghe, Jens Walter & Karen L. Madsen

Nature Medicine **27**, 1272–1279 (2021) | Cite this article

9381 Accesses | **94** Citations | **189** Altmetric | Metrics

Abstract

Fecal microbial transplantation (FMT) from lean donors to patients with obesity has been associated with metabolic benefits, yet results so far have been inconsistent. In this study, we tested the application of daily fiber supplementation as an adjunct to FMT therapy to

We provide proof of concept for the use of a single-dose oral FMT combined with daily low-fermentable fiber supplementation to improve insulin sensitivity in patients with severe obesity and metabolic syndrome.

Mocanu V, et al. Nat Med. 2021 Jul;27(7):1272-1279.

Effects of Fecal Microbiome Transfer in Adolescents With Obesity: The Gut Bugs Randomized Controlled Trial

Karen S W Leong [1 2], Thilini N Jayasinghe [1], Brooke C Wilson [1], José G B Derraik [1 2 3 4], Benjamin B Albert [1 2], Valentina Chiavaroli [1 5], Darren M Svirskis [6], Kathryn L Beck [7], Cathryn A Conlon [7], Yannan Jiang [8], William Schierding [1], Tommi Vatanen [1 9], David J Holland [10], Justin M O'Sullivan [1 2 11 12], Wayne S Cutfield [1 2 3]

Affiliations + expand

PMID: 33346848 PMCID: PMC7753902 DOI: 10.1001/jamanetworkopen.2020.30415

Free PMC article

Abstract

Importance: Treatment of pediatric obesity is challenging. Preclinical studies in mice indicated that weight and metabolism can be altered by gut microbiome manipulation.

Conclusion: In this randomized clinical trial of adolescents with obesity, there was no effect of FMT on weight loss in adolescents with obesity, although a reduction in abdominal adiposity was observed. Post-hoc analyses indicated a resolution of undiagnosed metabolic syndrome with FMT among those with this condition.

Leong KSW, et al. JAMA Netw Open. 2020 Dec 1;3(12):e2030415.

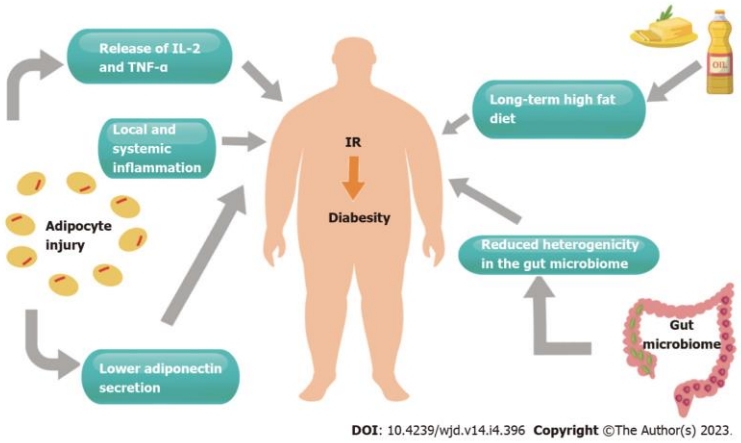
Insulin Resistance (IR)

- IR: decrease in the metabolic response of insulin-response cells to insulin.
- Skeletal Muscle: mutations that reduce the expression of insulin receptor or GLUT4, or any defect in either upstream or downstream signaling pathway would reduce glucose intake into the muscle resulting in a hyperglycemic state
- Adipose Tissue: Insulin acts on adipose tissue in two different ways: (1) stimulating glucose uptake and triglyceride synthesis; and (2) suppressing triglyceride hydrolysis and inducing the uptake of FFA and glycerol from circulation
  - When this tissue become resistant we see increase in FFA

Galicia-Garcia U,et al Int J Mol Sci. 2020;21(17):6275.

“Diabesity”

- The strong pathophysiological link between obesity and diabetes
- Visceral adiposity → IR → diabetes



DOI: 10.4239/wjd.v14.i4.396

Figure 1 Pathophysiology of diabesity as evidenced by recent literature. IL-2: Interleukin-2; TNF-α: Tumor necrosis alpha; IR: Insulin resistance.

Michaelidou M, et al. World J Diabetes. 2023 Apr 15;14(4):396-411.

Hormone Imbalance

- Hypothyroidism
- PCOS
- Postpartum weight retention
- Menopause

Dabas J, et al. J Health Popul Nutr. 2024 Mar 2;43(1):37.

Chronic Stress

- Cortisol:
  - causes a redistribution of white adipose tissue to the abdominal region
  - increases appetite (“comfort food”)
- Factors that enhance cortisol production
  - Chronic stress
  - Intake of high glycemic foods
  - Lack of sleep
- Obese individuals on average have higher hair cortisol levels
- Hair cortisol concentration (HCC) correlated to a more persistent obesity over time

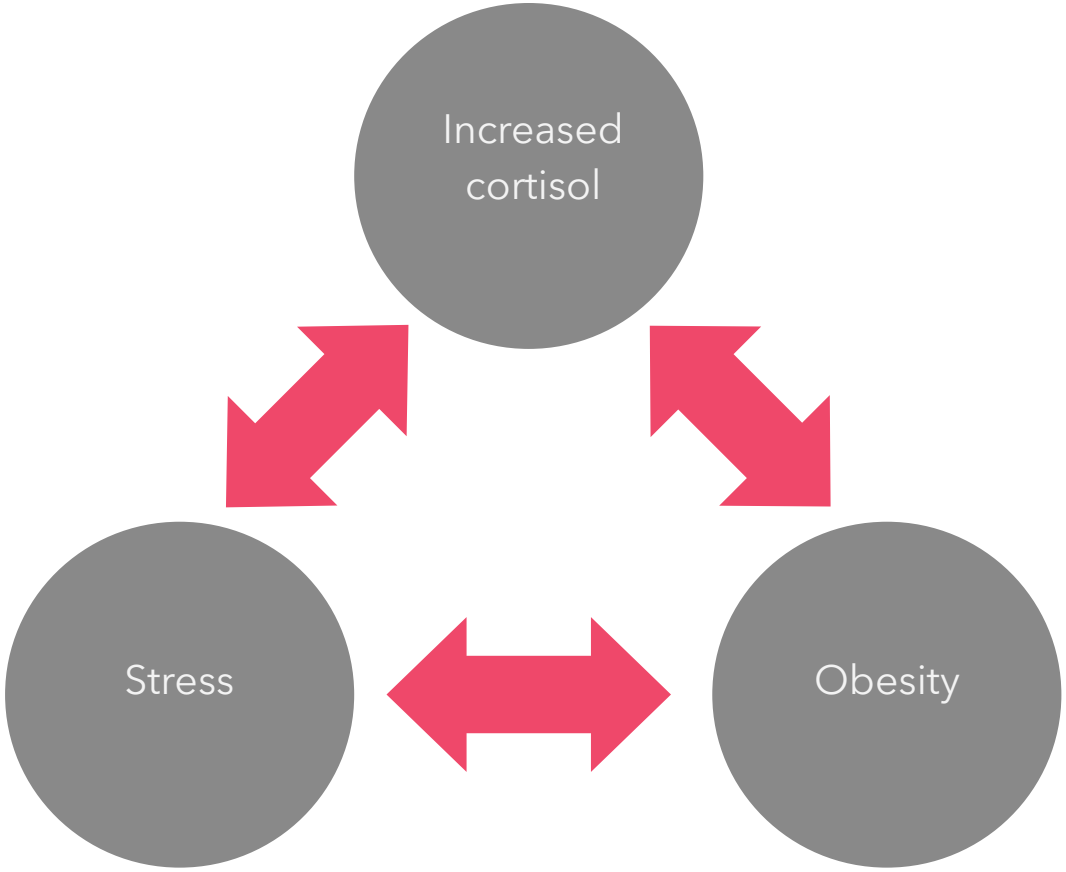
van der Valk ES, et al. Curr Obes Rep. 2018 Jun;7(2):193-203.

Possible Mechanisms

- Overactivity of the HPA axis
- Inflammatory markers
- Individual variation in enzymes that are involved in cortisol metabolism

van der Valk ES, et al. Curr Obes Rep. 2018 Jun;7(2):193-203.

Vicious Cycle



adapted from van der Valk ES, et al. Curr Obes Rep. 2018 Jun;7(2):193-203.

Interesting…

- Cross-sectional cohort study
- Sample of more than 140,000 adults from the general population of northern Netherlands

Associations Between Systemic and Local Corticosteroid Use With Metabolic Syndrome and Body Mass Index

Mesut Savas,[1,2] Taulant Muka,[3]* Vincent L. Wester,[1,2]* Erica L. T. van den Akker,[2] Jenny A. Visser,[1,2] Gert-Jan Braunstahl,[5,6] Sandra N. Slagter,[7] Bruce H. R. Wolffenbuttel,[7] Oscar H. Franco,[3] and Elisabeth F. C. van Rossum[1,

[1]Internal Medicine, Division of Endocrinology, Erasmus MC, University Medical Center Rotterdam, 3000 CA Rotterdam, Netherlands; [2]Obesity Center CGG (Centrum Gezond Gewicht), Erasmus MC, University Medica Center Rotterdam, 3000 CA Rotterdam, Netherland; [3]Epidemiology, Erasmus MC, University Medical Center Rotterdam, 3000 CA Rotterdam, Netherlands; [4]Pediatrics, Erasmus MC, University Medical Cente Rotterdam, 3000 CA Rotterdam, Netherlands; [5]Pulmonology, Erasmus MC, University Medical Center Rotterdam, 3000 CA Rotterdam, Netherlands; [6]Pulmonology, Sint Franciscus Gasthuis, 3045 PM Rotterdam, Netherlands; and [7]Endocrinology, University of Groningen, University Medical Center Groningen, 9700 RB Groningen, Netherlands

Context: Use of systemic corticosteroids (CSs) may induce adverse cardiometabolic alteration potentially leading to obesity and metabolic syndrome (MetS). Although evidence is accumulatin that local CSs have considerable systemic effects, their effects on cardiometabolic factors in th general population remain unclear

Conclusions: Use of local CSs, particularly inhaled types, as well as systemic CSs, was associated with higher likelihood of having MetS, higher BMI, and other adverse cardiometabolic traits, especially among women. Because the inhaled agents are the main group of prescribed CSs, this might be a substantial risk to public health in case of a yet-to-be-proven causal relationship.

Savas M, et al. J Clin Endocrinol Metab. 2017 Oct 1;102(10):3765-3774.

Sleep

- One-third or more adults sleep less than 7 hours per night
- Short sleep duration (>5 or 6 h/day) is associated with a 38% absolute increase in the incidence of obesity compared with normal sleep duration
- Every hour a person must shift their internal clock to match the wakefulness period between weekends and weekdays resulted in an increased odds ratio of 1.3 of having metabolic syndrome in the general population
- Circadian disruption associated with obesity
  - High snacking frequency
  - Reduction in total daily sleep
  - Increased exposure to bright light during the night
- Ghrelin increases with sleep restriction; leptin decreases

Garaulet M, et al. Int J Obes (Lond). 2010 Dec;34(12):1667-83.
Chaput JP, et al. Nat Rev Endocrinol. 2023 Feb;19(2):82-97.

Malnutrition in Obesity

- Despite excessive energy consumption, obesity is associated with a shortage of individual microelements
- May be due to:
  - overconsumption of foods high in calories with low-nutrient densities
  - insufficient access to nutrient-rich foods
  - changes in the absorption, distribution, or excretion of nutrients
  - altered micronutrient metabolism resulting from systemic inflammation

Kobylińska M, et al. Obes Facts. 2022;15(1):19-25.

Prevalence of Deficiencies

Micronutrient	Obesity	Type 2 Diabetes
Thiamine (B1)	15-29%	17-79%* includes type 1 data
Pyridoxine (B6)	0-11%	-------
Cobalamin (B12)	3-8%	22%
Folic acid	3-4%	-------
Asorbic acid (C)	35-45%	Decreased levels reported
Vitamin A	17%	-------
Vitamin D	80-90%	85-90%
Vitamin E	0%	0%
Zinc	14-30%	-------
Chromium	-------	20-40%
Selenium	58%	-------

Via M. ISRN Endocrinol. 2012;2012:103472.

Bariatric Surgery Nutrient Deficiencies

- Procedures that bypass a portion of the small intestine, including Jejunoileal bypass (JIB), Biliopancreatic diversion (BPD), biliopancreatic diversion with duodenal switch (BPD-DS), and Roux- en-y gastric bypass (RYGB) carry the greatest risk of nutritional deficiencies.
  - JIB has been largely abandoned due to high risk of malabsorptive complications. BPD is also less commonly performed.
- Baseline, 6 month and annual screening after bariatric surgery
  - B1, B12, Folate, Iron, Vitamin D, Protein (albumin), Vitamin A, Vitamin E, Vitamin K, B6, Copper, Zinc
- Likely will need more than a multivitamin

Xanthakos SA. Pediatr Clin North Am. 2009 Oct;56(5):1105-21.

Obesogens

- Molecules with adverse effects on lipid metabolism and adipogenesis
- 1000+ chemicals reported to have endocrine effects
- Exposure from industrial and household products, pesticides, herbicides, plastics, detergents, flame retardants and personal care products
- 2002: Baillie-Hamilton proposed a link between the obesity epidemic and the increase in new industrial chemicals over the past four decades
- 2006: environmental obesogen hypothesis

Gupta R, et al. Current Research in Green and Sustainable Chemistry. 2020 Jun;3:100009.
Kelishadi R, et al. J Environ Public Health. 2013;2013:896789.

Common Obesogens

- Perfluoroalkyl compounds (PFCs)
- Phthalates
- Bisphenol A (BPA)
- Phytoestrogens (genistein and daidzein)
- Organophosphates
- Polychlorinated bi-phenyls (PCBs)
- Monosodium glutamate
- Heavy metals

Adverse Childhood Experiences (ACEs)

- ACEs: potentially traumatic events that occur in childhood (0-17 years)
- 46% increase in the odds of adult obesity following exposure to multiple ACEs
- ACEs associated with depression, anxiety, and eating disorders

Wiss DA, et al. Physiol Behav. 2020 Sep 1;223:112964.
Mares L.S. et al. Traumatology. 2023.

Mental Health

- Obesity and depression have a significant and bidirectional association

- Obesity associated with approximately 25% increased risk of developing mood and anxiety disorders

Rajan TM, et al. J Postgrad Med. 2017 Jul-Sep;63(3):182-190.
Simon GE, et al. Arch Gen Psychiatry. 2006 Jul;63(7):824-30.

Functional Approach

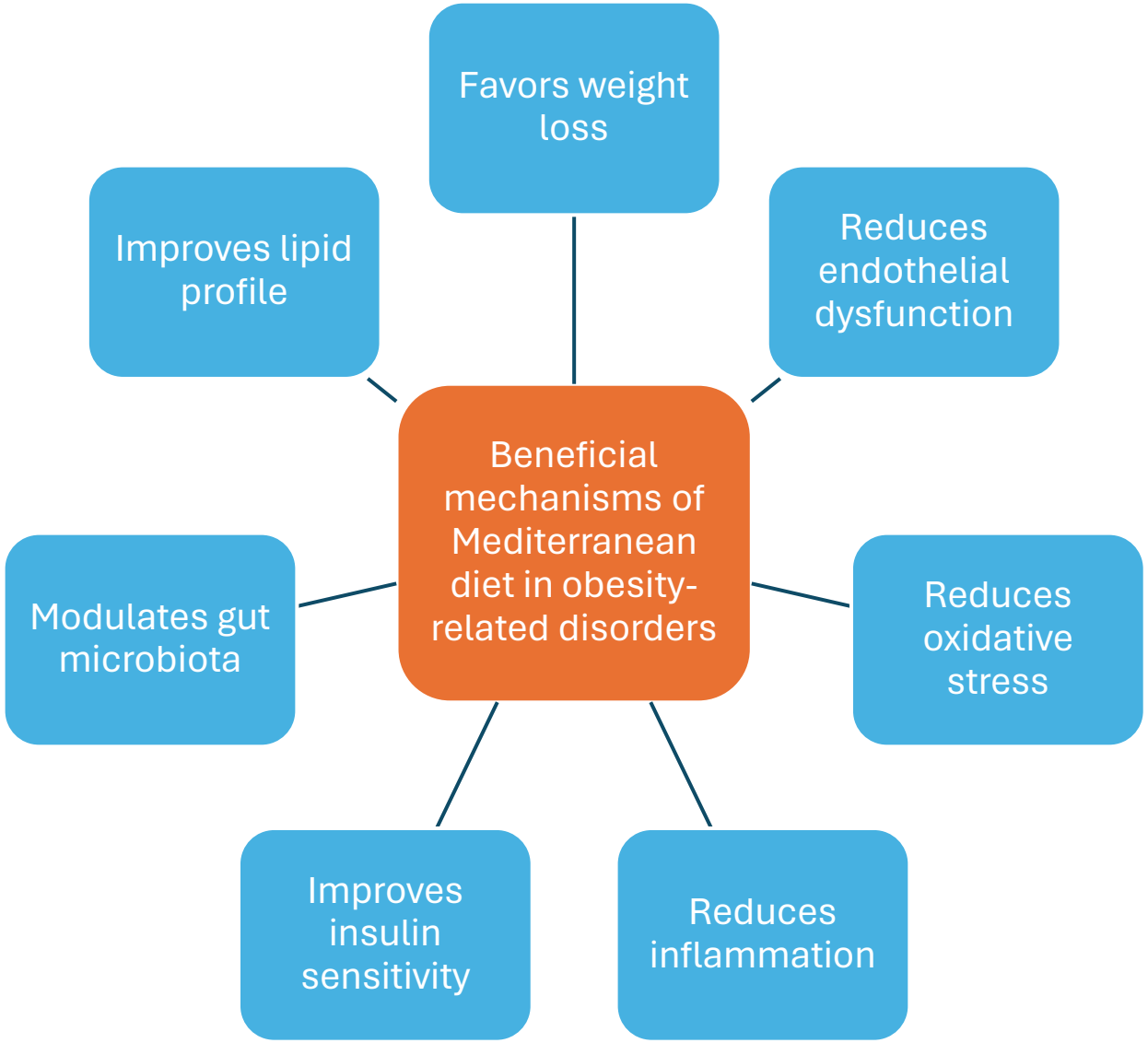
Labs To Consider

- CBC
- CMP
- Lipid profile
- Fasting insulin
- HbA1c
- Complete thyroid panel
- CRP
- Homocysteine
- Vitamin D
- Stool test
- Organic acids
- Omega-3 Fatty Acids

Mediterranean Diet (MD)

- Diet includes:
  - high intake of vegetables, fruits, nuts, cereals, whole grains, and extra-virgin olive oil
  - moderate consumption of fish and poultry
  - limited intake of sweets, red meat, and dairy products
- Higher adherence to MD is associated with increased likelihood of weight loss maintenance
- MD can reduce central adiposity and visceral fat
- MD pattern proved to be the most effective in prevention of obesity and obesity-related diseases compared to other diets

Muscogiuri G, et al. Curr Obes Rep. 2022 Dec;11(4):287-304.

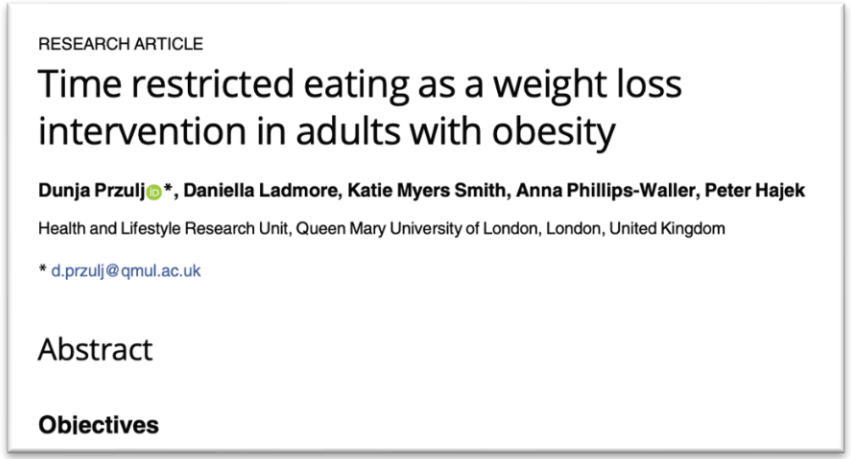


Adapted from Muscogiuri G, et al. Curr Obes Rep. 2022 Dec;11(4):287-304.

Fasting

- Intermittent fasting (IF): alternates feeding days with fasting days
  - protocols do not restrict feeding during the feasting days, where people are allowed to eat normally or *ad libitum* and then abstain from eating for one or 2 days
- Time- restricted eating (TRE): restricting the time when meals are consumed within 24 h
  - Most TRE studies range from 4–12 h of eating window without caloric restriction
  - Early TRE (eTRE): calories early in the day, fast remainder of the day (ex. 7am to 3 pm eating window)
  - Chrono-nutritional strategy
- Fasting-mimicking diets (FMD): periodic cycles of consecutive days consuming a reduced-calorie diet followed by eating *ad libitum*

Soliman GA. Front Public Health. 2022 Oct 28;10:1017254.



RESEARCH ARTICLE

Time restricted eating as a weight loss intervention in adults with obesity

Dunja Przulj*, Daniella Ladmore, Katie Myers Smith, Anna Phillips-Waller, Peter Hajek

Health and Lifestyle Research Unit, Queen Mary University of London, London, United Kingdom

* d.przulj@qmul.ac.uk

Abstract

Objectives

- n=50
- Mean weight loss:
  - 2.0 kg at 6 weeks
  - 2.6 kg at 12 weeks
- Among participants who provided follow-up data:
  - those who adhered to the intervention for ≤5 days/week recorded greater weight loss than those with lower adherence
- The intervention had no effect on blood pressure or lipid profile

Przulj D, et al. PLoS One. 2021 Jan 28;16(1):e0246186.

Twelve Months of Time-restricted Eating and Resistance Training Improves Inflammatory Markers and Cardiometabolic Risk Factors

TATIANA MORO[1], GRANT TINSLEY[2], FRANCESCO Q. PACELLI[1], GIUSEPPE MARCOLIN[1], ANTONINO BIANCO[3], and ANTONIO PAOLI[1]

[1]Department of Biomedical Sciences, University of Padova, Padova, ITALY; [2]Department of Kinesiology and Sport Management, Texas Tech University, Lubbock, TX; and [3]Department of Psychology, Educational Science and Human Movement, University of Palermo, Palermo, ITALY

- n=20
- 12 months of either a time-restricted eating (TRE) diet or a normal diet (ND) protocol, along with resistance training
- 12 months of TRE:
  - Body mass, fat mass, insulin-like growth factor 1, and testosterone were significantly lower
  - Inflammatory markers, insulin sensitivity, and lipid profile significantly improved

Moro T, et al. Med Sci Sports Exerc. 2021 Dec 1;53(12):2577-2585.

JAMA Intern Med. 2022 Sep; 182(9): 953–962.
Published online 2022 Aug 8. doi: 10.1001/jamainternmed.2022.3050
PMCID: PMC9361187
PMID: 35939311

Effectiveness of Early Time-Restricted Eating for Weight Loss, Fat Loss, and Cardiometabolic Health in Adults With Obesity

A Randomized Clinical Trial

Humaira Jamshed, PhD, [1,2] Felicia L. Steger, PhD, [1,3] David R. Bryan, MA, [1] Joshua S. Richman, MD, PhD, [4] Amy H. Warriner, MD, [5] Cody J. Hanick, MS, [1] Corby K. Martin, PhD, [6] Sarah-Jeanne Salvy, PhD, [7] and Courtney M. Peterson, PhD [1]

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- 90 participants with obesity
- 2 groups:
  - eTRE + ER (8-hour eating window from 7:00 to 15:00)
  - control eating (CON) + ER (≥12-hour window)
- eTRE + ER intervention:
  - more effective for weight loss (additional 2.3 kg loss relative to control group)
  - improved diastolic blood pressure
  - greater improvements in mood—including fatigue, vigor, and feelings of depression/dejection

Jamshed H, et al. JAMA Intern Med. 2022 Sep 1;182(9):953-962.

Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease

Min Wei[1,*], Sebastian Brandhorst[1,*], Mahshid Shelehchi[1], Hamed Mirzaei[1], Chia Wei Cheng[1], Julia Budniak[1], Susan Groshen[2], Wendy J. Mack[2], Esra Guen[1], Stefano Di Biase[1], Pinchas Cohen[1], Todd E. Morgan[1], Tanya Dorff[3], Kurt Hong[4], Andreas Michalsen[5], Alessandro Laviano[6], Valter D. Longo[1,7,†]

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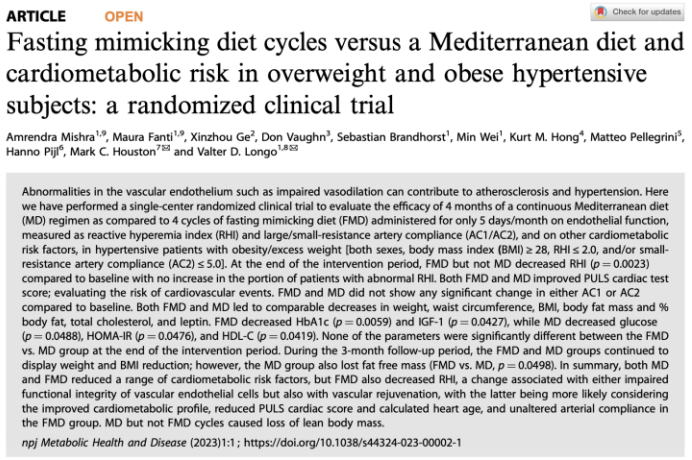
[2]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA.

- Randomized controlled trial of 100 subjects
  - 71 completed three cycles of FMD
    - randomized phase (n = 39)
    - crossed over from control diet to FMD (n = 32)
  - FMD group:
    - reduced body weight, trunk, and total body fat; lowered blood pressure; decreased insulin-like growth factor 1 (IGF-1)
  - Post hoc analysis (all 71 subjects from both arms who completed three FMD cycles)
    - confirmed effects of FMD on trunk and total body fat, blood pressure, and IGF-1

Wei M, et al. Sci Transl Med. 2017 Feb 15;9(377):eaai8700.

- Four cycles of a once a month 5-day long FMD compared to a continuous regimen of MD x 4 months
  - MD- 40 participants
  - FMD- 44 participants



ARTICLE OPEN

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Fasting mimicking diet cycles versus a Mediterranean diet and cardiometabolic risk in overweight and obese hypertensive subjects: a randomized clinical trial

Amrendra Mishra[1,9], Maura Fanti[1,9], Xinzhou Ge[2], Don Vaughn[3], Sebastian Brandhorst[1], Min Wei[1], Kurt M. Hong[4], Matteo Pellegrini[5], Hanno Pijl[6], Mark C. Houston[7]✉ and Valter D. Longo[1,8]✉

Abnormalities in the vascular endothelium such as impaired vasodilation can contribute to atherosclerosis and hypertension. Here we have performed a single-center randomized clinical trial to evaluate the efficacy of 4 months of a continuous Mediterranean diet (MD) regimen as compared to 4 cycles of fasting mimicking diet (FMD) administered for only 5 days/month on endothelial function, measured as reactive hyperemia index (RHI) and large/small-resistance artery compliance (AC1/AC2), and on other cardiometabolic risk factors, in hypertensive patients with obesity/excess weight [both sexes, body mass index (BMI) ≥ 28, RHI ≤ 2.0, and/or small-resistance artery compliance (AC2) ≤ 5.0]. At the end of the intervention period, FMD but not MD decreased RHI ($p = 0.0023$) compared to baseline with no increase in the portion of patients with abnormal RHI. Both FMD and MD improved PULS cardiac test score; evaluating the risk of cardiovascular events. FMD and MD did not show any significant change in either AC1 or AC2 compared to baseline. Both FMD and MD led to comparable decreases in weight, waist circumference, BMI, body fat mass and % body fat, total cholesterol, and leptin. FMD decreased HbA1c ($p = 0.0059$) and IGF-1 ($p = 0.0427$), while MD decreased glucose ($p = 0.0488$), HOMA-IR ($p = 0.0476$), and HDL-C ($p = 0.0419$). None of the parameters were significantly different between the FMD vs. MD group at the end of the intervention period. During the 3-month follow-up period, the FMD and MD groups continued to display weight and BMI reduction; however, the MD group also lost fat free mass (FMD vs. MD, $p = 0.0498$). In summary, both MD and FMD reduced a range of cardiometabolic risk factors, but FMD also decreased RHI, a change associated with either impaired functional integrity of vascular endothelial cells but also with vascular rejuvenation, with the latter being more likely considering the improved cardiometabolic profile, reduced PULS cardiac score and calculated heart age, and unaltered arterial compliance in the FMD group. MD but not FMD cycles caused loss of lean body mass.

npj Metabolic Health and Disease (2023)1:1 ; https://doi.org/10.1038/s44324-023-00002-1

- Primary outcome: endothelial function and arterial compliance
  - Both MD and FMD had similar effects on endothelial function during the 4-month intervention period
- Secondary outcome: cardiometabolic risk factors
  - After 3-month follow-up period, FMD showed a more sustained long-term effects with decreased Insulin, HbA1c, and HOMA-IR
  - MD group showed greater decrease in prevalence of diabetes*

- Only FMD group showed a significant decrease in trunk fat mass
- MD caused loss of lean body mass (FMD did not)

Mishra A, et al. *npj Metab Health Dis* **1**, 1 (2023).

Ketogenic diet (KD)

- Originally introduced in 1920
- Fat to carbohydrate ratio is 5:1
- Ketosis occurs as a result of the change in the body's fuel from carbohydrate to fat.
- A KD maintains the body in a state of ketosis, which is characterized by an elevation of D-b-hydroxybutyrate and acetoacetate.

Paoli A. Int J Environ Res Public Health. 2014 Feb 19;11(2):2092-107.

Hypothesized mechanisms of KD's weight loss effects

- Reduction in appetite due to higher satiety effect of proteins, effects on appetite control hormones and to a possible direct appetite suppressant action of the ketone bodies
- Reduction in lipogenesis and increased lipolysis
- Greater metabolic efficiency in consuming fats highlighted by the reduction in the resting respiratory quotient
- Increased metabolic costs of gluconeogenesis and the thermic effect of proteins

- Other beneficial effects:
  - Ketones may protect from cognitive impairment caused by weight gain and obesity
  - + effects on mood in overweight subjects
- "Attention should be paid to patient's renal function and to the transition phase from ketogenic diet to a normal diet that should be gradual and well controlled"

Paoli A. Int J Environ Res Public Health. 2014 Feb 19;11(2):2092-107.

Long-term effects of a ketogenic diet in obese patients

Hussein M Dashti MD PhD FICS FACS[1], Thazhumpal C Mathew MSc PhD FRCPath[4], Talib Hussein MB ChB[5], Sami K Asfar MB ChB MD FRCSEd FACS[1], Abdulla Behbahani MB ChB FRCS FACSI PhD FICS FACS[1], Mousa A Khoursheed MB ChB FRCS FICS[1], Hilal M Al-Sayer MD PhD FICS FACS[1], Yousef Y Bo-Abbas MD FRCPC[2], Naji S Al-Zaid BSc PhD[3]

HM Dashti, TC Mathew, T Hussein, et al. Long-term effects of a ketogenic diet in obese patients. Exp Clin Cardiol 2004;9(3):200-205.

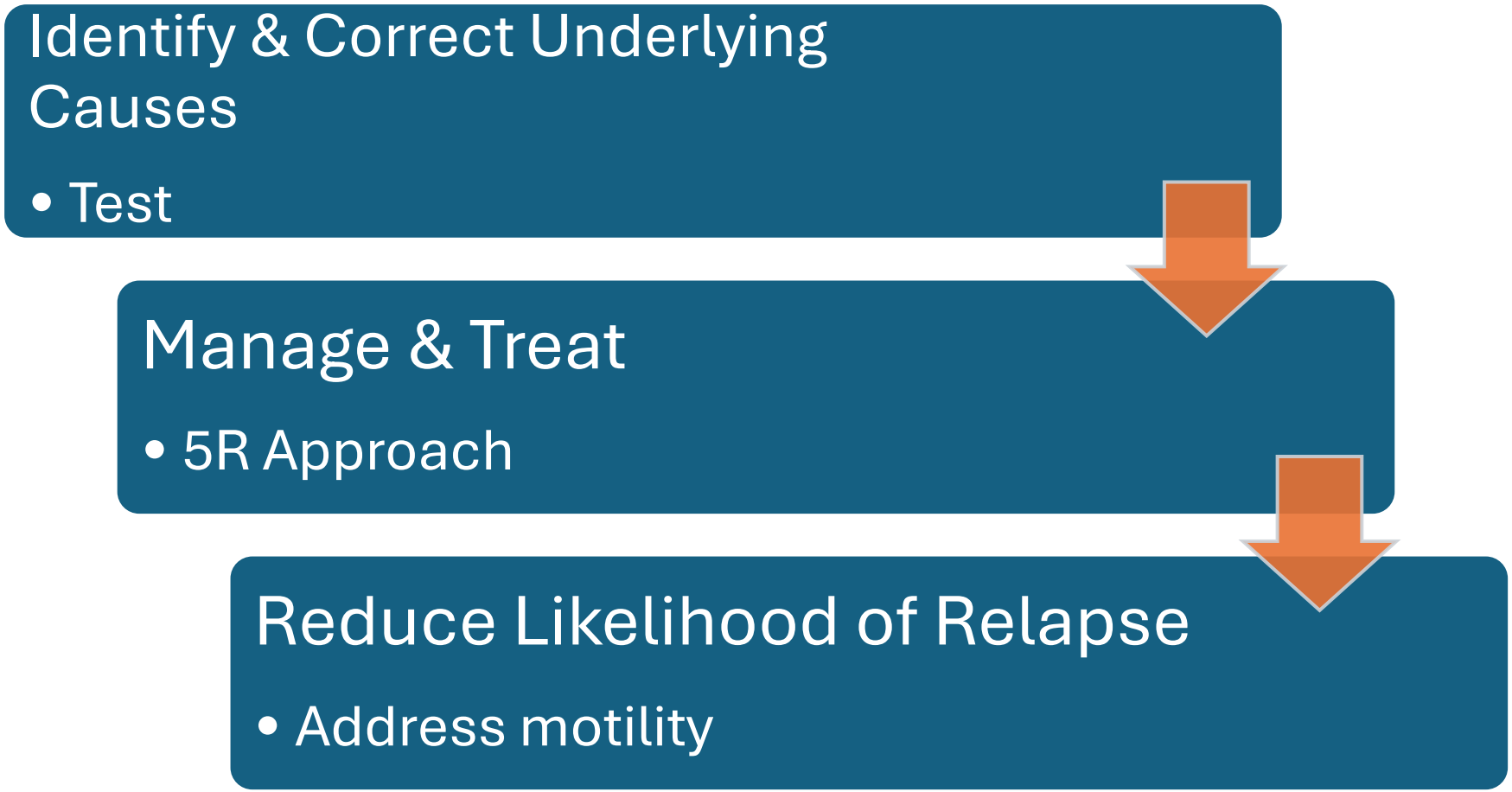
BACKGROUND: Although various studies have examined the short-term effects of a ketogenic diet in reducing weight in obese patients, its long-term effects on various physical and biochemical parameters are not known.
OBJECTIVE: To determine the effects of a 24-week ketogenic diet (consisting of 30 g carbohydrate, 1 g/kg body weight protein, 20% saturated fat, and 80% polyunsaturated and monounsaturated fat) in obese patients.
PATIENTS AND METHODS: In the present study, 83 obese patients (39 men and 44 women) with a body mass index greater than 35 kg/m^2, and high glucose and cholesterol levels were selected. The body weight, body mass index, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, fasting blood sugar, urea and creatinine levels were determined before and after the administration of the ketogenic diet. Changes in these parameters were monitored after eight, 16 and 24 weeks of treatment.
RESULTS: The weight and body mass index of the patients decreased significantly (P<0.0001). The level of total cholesterol decreased from week 1 to week 24. HDL cholesterol levels significantly increased, whereas LDL cholesterol levels significantly decreased after treatment. The level of triglycerides decreased significantly following 24 weeks of treatment. The level of blood glucose significantly decreased. The changes in the level of urea and creatinine were not statistically significant.
CONCLUSIONS: The present study shows the beneficial effects of a long-term ketogenic diet. It significantly reduced the body weight and body mass index of the patients. Furthermore, it decreased the level of triglycerides, LDL cholesterol and blood glucose, and increased the level of HDL cholesterol. Administering a ketogenic diet for a relatively longer period of time did not produce any significant side effects in the patients. Therefore, the present study confirms that it is safe to use a ketogenic diet for a longer period of time than previously demonstrated.

Key Words: *Diet; Ketosis; Obesity*

- 83 obese patients
- Objective: To determine the effects of a 24-week ketogenic diet (consisting of 30 g carbohydrate, 1 g/kg body weight protein, 20% saturated fat, and 80% polyunsaturated and monounsaturated fat) in obese patients
- Significant decrease in triglycerides, total cholesterol, LDL and glucose, and a significant increase in HDL cholesterol

Dashti HM, et al. Exp Clin Cardiol. 2004 Fall;9(3):200-5.

Address Gut Dysbiosis



5R Gut Protocol

Remove	• Food sensitivities, alcohol, aspirin, NSAIDS from the diet • Use antimicrobials for dysbiosis, infection, and/or parasites
Replace	• Digestive support to improve nutrient absorption and metabolism • May include digestive enzymes, or agents that promote improved motility and regular bowel movements
Reinoculate	• Provide an environment where good bacteria can thrive and where bad ones cannot • Use pre- and probiotics
Repair	• Support of the cellular repair process by providing specific nutritional support for the regeneration of the GI protective barrier • GI mucosa with healing nutrients and botanicals
Rebalance	• Lifestyle factors that influence the gut bacteria such as stress, sleep, exercise and relationships and assure ongoing gut health

Jones DS, et al. Textbook of Functional Medicine 2010.

Probiotics

- Meta-analysis by Koutnikova et al.
  - Probiotics induced improvements in: body weight, BMI, waist circumference, body fat mass, & visceral adipose tissue mass in overweight but not obese individuals
- Meta-analysis by Tabrizi et al.
  - Probiotic supplementation significantly decreased weight, BMI, FPG, insulin, HOMA-IR, triglycerides, CRP in women with PCOS
- Meta-analysis by Lau et al.
  - Prevalence of obesity and hypertension was lower in the probiotic group

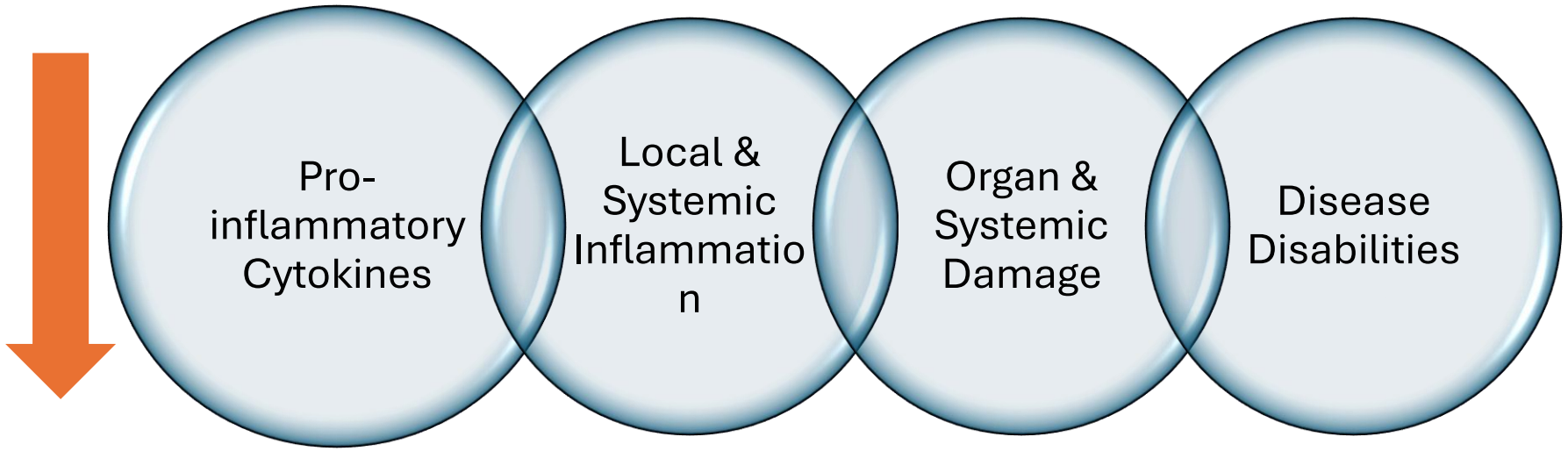
Koutnikova H, et al. BMJ Open. 2019 Mar 30;9(3):e017995.
Tabrizi R, et al. Probiotics Antimicrob Proteins. 2022 Feb;14(1):1-14.
Lau E, et al. Nutrients. 2019 Jun 28;11(7):1482.

Prebiotics

- Study of healthy, non-diabetic individuals that received supplementation with prebiotics (derived from chicory roots) for 2 weeks showed:
  - An increase in plasma GLP-1 and a decrease in postprandial glucose compared to individuals that received the control (dextrin maltose supplementation).
  - Prebiotic supplementation significantly lowered post-meal hunger scores and improved satiety scores.

Cani P, Lecourt E, Delzenne N, et al. *Am J Clin Nutr*. 2009;90(5):1236-1243. doi:10.1016/J.MAM.2012.11.001.

Exercise



Perandini LA. *Autoimmunity reviews*. 2012;12(2):218-224

Exercise

- Aerobic Exercise
  - Enhanced peripheral glucose uptake (PGU)[1]
  - Reduced glycemic variability and postprandial glucose (PPG)[2]

- Resistance Exercise
  - Increased serum adiponectin; reduced insulin resistance, and reduced levels of free fatty acid (FFA), and C-Reactive Protein (CRP)[3]

1. Winnick, JJ et al. *The Journal of Clinical Endocrinology & Metabolism*, 2008:*93*(3), 771-778.
2. Mikus, CR et al. Diabetologia, 2012:55(5), 1417-1423.
3. Brooks, NInt J Med Sci. 2006 Dec 18;4(1):19-27.

Stress Management

- Overweight and obese women who participated in an 8-week stress management program achieved a significantly larger reduction in BMI compared to control group (along with improved perceived stress and depression levels)
- Overweight and obese children and adolescents that underwent a stress-management intervention, had statistically significant weight loss and decrease in the levels of stress and depression, as well as in internalizing and externalizing problems

Christaki E, et al. J Hum Nutr Diet. 2013 Jul;26 Suppl 1:132-9.
Stavrou S, et al. J Mol Biochem. 2016;5(2):63-70.

Stress Management Techniques

- Meditation
- Yoga, tai chi, or qigong
- Journaling
- Physical activity
- Breath work
- Social connection
- Connect with nature
- Listen to relaxing music
- Spend time with a pet

Remove and/or Limit Environmental Toxins

- An important first step is to address the topic with patients (many people aren't aware of what they are or where they come from)
- Tips for reducing exposures:
  - Eat organic fruits & vegetables when possible
  - Minimize the use of cosmetics and personal care products (or switch to cleaner brands)
  - Remove artificial sweeteners, high fructose corn syrup, and preservatives from the diet
  - Swap plastic food/drink containers for glass or stainless steel
  - Drink filtered water
  - Get rid of air fresheners and candles in the home

Janesick AS, et al. Am J Obstet Gynecol. 2016 May;214(5):559-65.

Improve Sleep Quality & Quantity

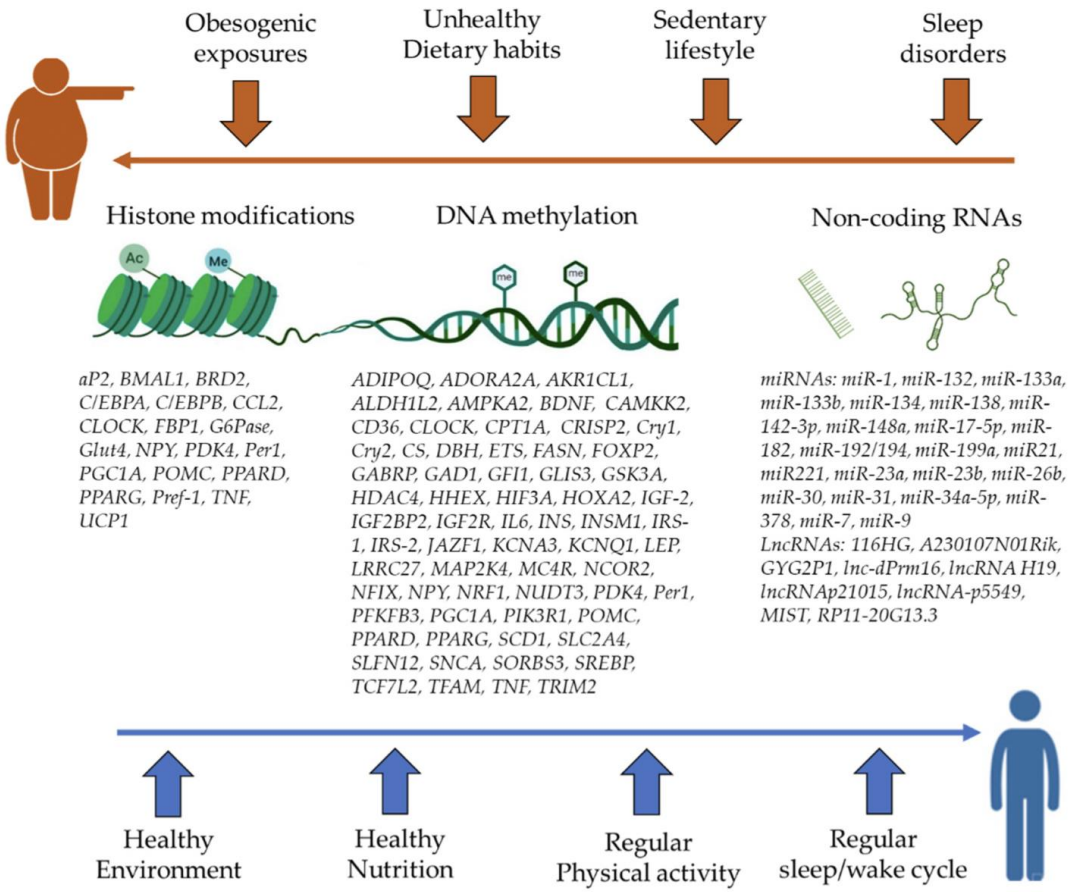
- Make sleep a priority!
- Go to sleep and wake up at the same time each day
- Avoid blue light in the evening (blue blocker glasses if needed)
- Limit caffeine intake
- Make sure sleep environment is dark and cool
- Get sunlight in the morning to help set circadian rhythm
- Physical activity
- Manage stress

Supplements

- Berberine
- Zinc
- Vitamin D
- Omega-3s
- Insulin sensitizers- lipoic acid, chromium, vanadium, cinnamon
- Hibiscus and lemon verbena polyphenols
- Green coffee bean extract

Boix-Castejón M, et al. *Food Funct*. 2018;9(6):3173-3184.
Roshan H, et al. *Br J Nutr*. 2018;119(3):250-258.

We Can Change the Course of Epigenetics



Mahmoud AM.. Int J Mol Sci. 2022 Jan 25;23(3):1341

Takeaways

- Obesity is a complex disorder that requires lifestyle modifications including nutrition, sleep, exercise.
- Patients with obesity should work with a provider to address underlying nutrient deficiencies and gut microbiome imbalances to achieve optimal results.

Need More Information?

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