Cardiovascular Health
By Way of the Gut



Cindy H. Carroll, RDN, LDN, RN

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Disclosures

- Nutrition and System Biology Continuing Education Coursework
- Prolon Fasting Mimicking Diet

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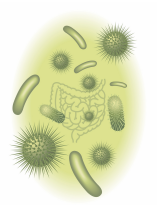
Learning Objectives

- Describe the relationship between gut permeability, the gut microbiome, inflammation and CVD.
- Describe endotoxemia and its link to IR, Type 2 diabetes, MetS, NAFLD/NASH and CVD.
- State the significance of LPS as it relates to LDL cholesterol, inflammation and cardiovascular risk.
- Describe the relationship between the gut microbiome and HDL cholesterol.
- Describe the role of the gut microbiome with bile acid formation and how it may influence CVD.

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Systems Biology

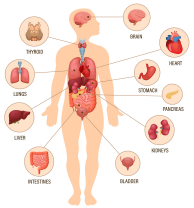
THE WHOLE IS GREATER THAN THE SUM OF ITS PARTS



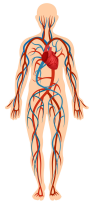
NOTHING OCCURS IN ISOLATION:

- Maintenance of health
- Acute or chronic disease





HUMAN INTERNAL ORGANS ANATOMY



HUMAN CIRCULATORY SYSTEM

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Structure Determines Function

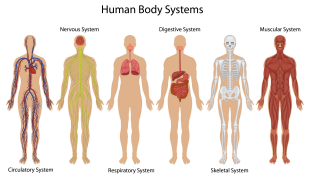
Anatomy

(structure or form—morphology)

& Physiology

(function or role)

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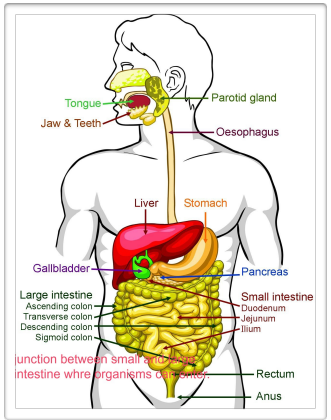
- Constipation/Diarrhea
- High Blood Pressure
- GERD
- Weight changes
- Elevated Blood Sugars
- Elevated Lipids
- SIBO



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Digestive System

Changing Structures With A Purpose



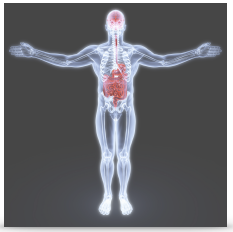
1. Mouth
2. Esophagus
3. Stomach
4. Small Intestine
5. Pancreas
6. Gal Bladder
7. Liver
8. Large intestine
9. Rectum/anus

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The Gut/Body Connection

Six Key Ingredients

Gut Organisms



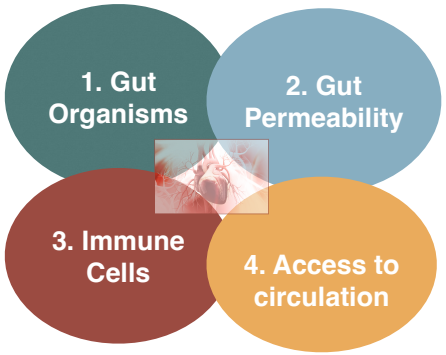
Enteric Nervous System

Immune Cells

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Gut To Organ (Heart) Axis

THE GUT/HEART CONNECTION:
FOUR KEY INGREDIENTS

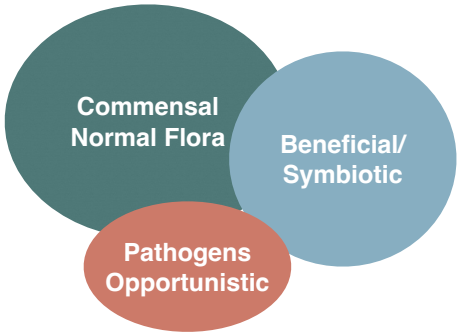


Singh, A. et al; Nutrients 2019, 11, 2216.
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1

The Gut Microbiota



Microbiota:
Bacteria
Virus
Fungi
Archaea

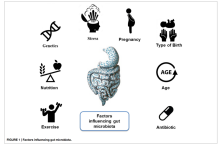


Dysbiosis- imbalance of commensal flora- usually indicating more pathogenic organisms.

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Each Organ Has its Own Ecosystem

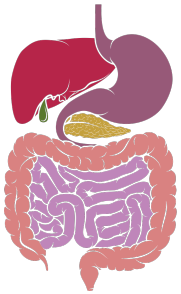




Esophagus ph < 4
Bacteroides, Pseudomonas, Prevotella, Streptococcus, Veillonella

Small Intestine ph 5-7.4
Bacteroides, Streptococcus, Clostridium, Lactobacillus, Enterococcus, Proteobacteria.

Terminal ilium- 7.4; Cecum ph 5.7
Roseburia, Butyrivbrio, Ruminococcus, Fecalibacterium, Fusobacteria



Stomach ph 2
Streptococcus, Prevotella, Enterococcus, Lactobacillus, Helicobacter pylori

Colon ph 5-5.7
Bacteroides, Clostridium, Prevotella, porphyromonas,Eubacterium, Streptococcus, Enterobacterium, Enterococcus, Lactobacillus, Fusobacteria.

Rectum ph 6.7

Tortora, G.J. et al; .H. (2021) Principles of Anatomy and Physiology, 16th Ed; John Wiley & Sons.

Cerdá, Begoña, et al. Frontiers in Physiology, vol. 7, 2016, doi:10.3389/fphys.2016.00051.
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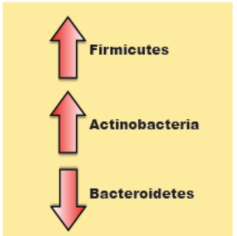
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Large Intestine



Location of most gut microbiota. Major phylums: 80-90 % Bacteroidetes and Firmicutes, 10 % Actinobacteria and less Verrucomicrobia.

Obesity



Diabetes

- **Lower bifidobacterium and faecalibacterium prausnitizii (cross-feeding).**
- **Overall low diversity (low gene count).**

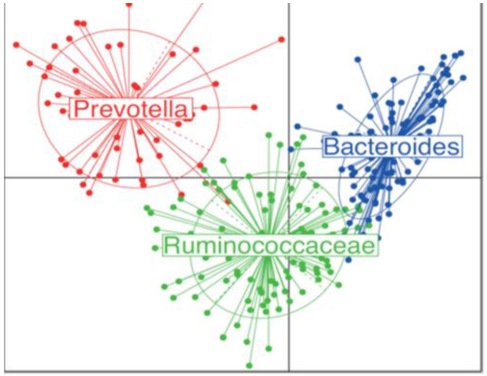
Lloyd-Price et al. Genome Medicine (2016

2 FEMS Microbiology Letters, 2015, Vol. 362, No. 21

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Enterotype May Drive the Dietary-Associated Cardiometabolic Risk Factors

*Ana C. F. de Moraes[1], Gabriel R. Fernandes[2], Isis T. da Silva[1], Bianca Almeida-Pititto[3], Everton P. Gomes[4], Alexandre da Costa Pereira[4] and Sandra R. G. Ferreira[1]**



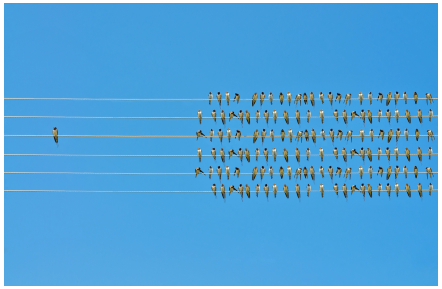
Moraes, Ana C. et al. Frontiers in Cellular and Infection Microbiology, vol. 7, 2017, http://creativecommons.org/licenses/by/4.0/)

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N = 1



- Individuals genetically, biochemically and microbially different.
- Risk factors applied to populations can't be applied to individuals.



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A Selective Intestinal Barrier

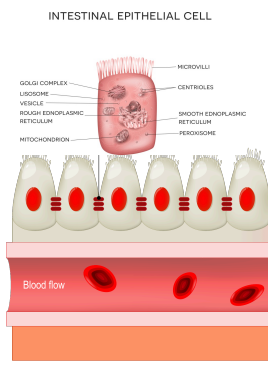
2

REVIEW **Open Access**

Intestinal permeability – a new target for disease prevention and therapy

Bischoff *BMC Medicine* 2011, **9**:24
http://www.biomedcentral.com/1741-7015/9/24

INTERFACE WITH BLOOD AND LYMPH



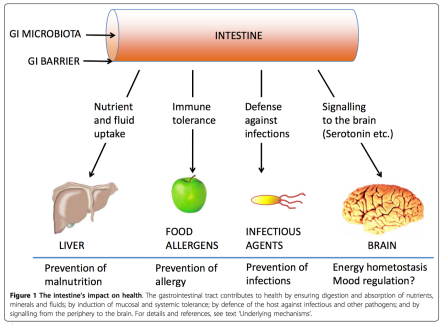


Figure 1 The intestine's impact on health. The gastrointestinal tract contributes to health by ensuring digestion and absorption of nutrients, minerals and fluids; by induction of mucosal and systemic tolerance; by defence of the host against infectious and other pathogens; and by signalling from the periphery to the brain. For details and references, see text 'Underlying mechanisms'.

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Bischoff SC, BMC Gastroenterol. 2014 Nov 18;14:189. doi: 10.1186/s12876-014-0189-7.

3 Gut Associated Lymph Tissue (GALT) Includes Appendix

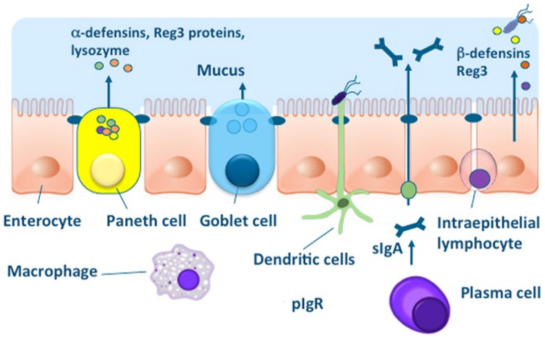


Figure 2 Chemical and physical barriers in the intestine. For explanations see text.

~ 70 % OF ALL IMMUNE CELLS

FRIEND VS. FOE

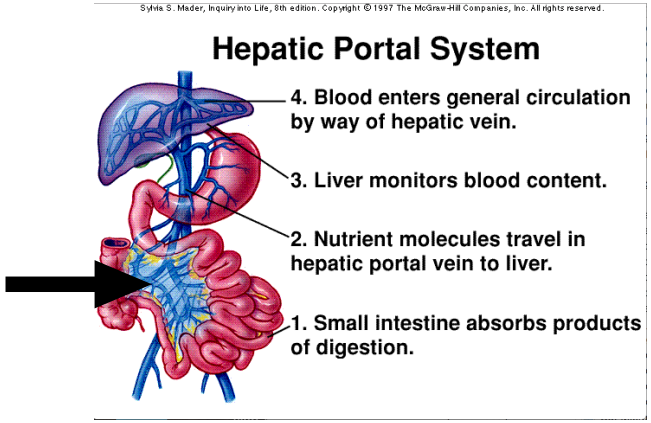
Bischoff, Stephan C, et al.." BMC Gastroenterology, vol. 14, no. 1, 2014, http://creativecommons.org/licenses/by/4.0/)

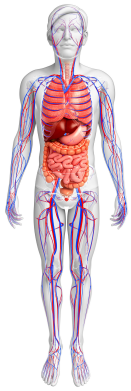
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4

Direct Access to Portal and Splanchinc Circulations

Sylvia S. Mader, Inquiry into Life, 8th edition. Copyright © 1997 The McGraw-Hill Companies, Inc. All rights reserved.



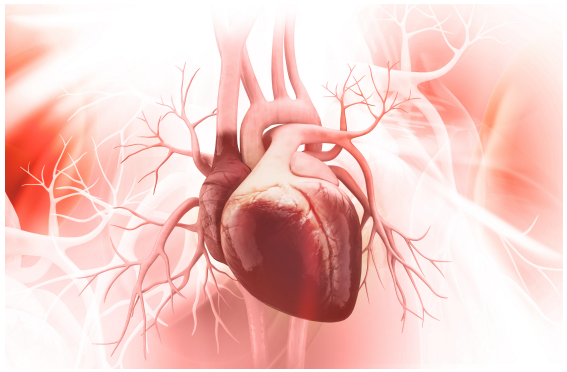


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Cardiovascular System

Cardiometabolic Disease/Heatlh



- Heart
- Vessels
- Blood

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The Silent System

The ongoing systemic effects and damage to the cardiovascular system are often "silent", as compared to GI, nervous system. Until they aren't, and a heart attack or stroke occurs.



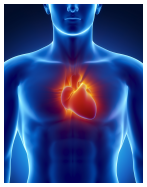
- Leading cause of death in men and women; ~655,000/yr deaths, 1 in every 4 deaths, CHD related.
- Every 34 seconds a death from cardiovascular disease, every 40 seconds an MI.
- More than half of deaths are men.
- Heart disease costs the U.S. >$200 B/year
- One in 5 heart attacks is silent- (damage done, but person not aware).

https://www.cdc.gov/heart-disease/data-research/facts-stats/index.html

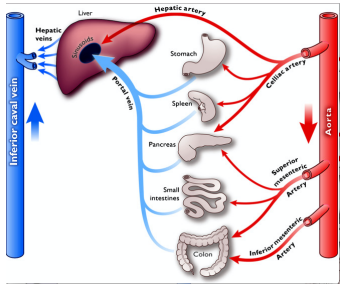
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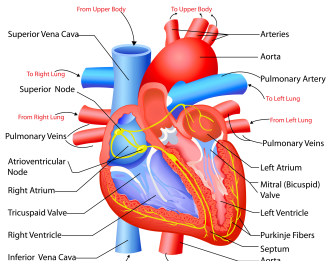
Heart

ACCESS TO THE GI TRACT



- Pumps ~ 2000 gallons of blood/day
- ~100,000 beats/day
- Blood is a medium for transfer of health and disease; how cells receive oxygen and nutrients.
- **Splanchnic circulation receives over 25% of the cardiac output.**





Tortora et al. Principles of Anatomy and Physiology 16 ed.

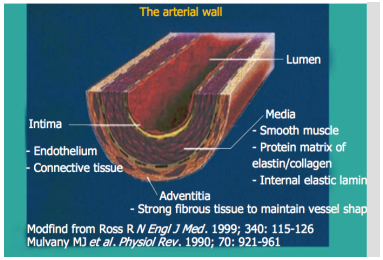
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Endothelial Lining- One Cell

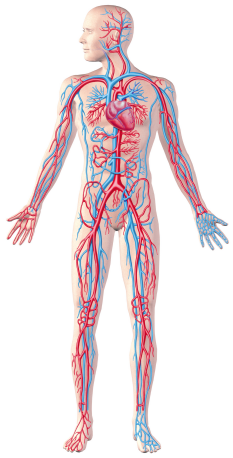
ALL VESSELS AND LYMPH

"Vascular disease is a balance between vascular injury and vascular repair"

Mark Houston, MD, Hypertension Institute







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ARTICLE

Received 24 Sep 2012 | Accepted 7 Nov 2012 | Published 4 Dec 2012

DOI: 10.1038/ncomms2266 OPEN

Symptomatic atherosclerosis is associated with an altered gut metagenome

Fredrik H. Karlsson[1], Frida Fåk[2,3,*], Intawat Nookaew[1,*], Valentina Tremaroli[2,3], Björn Fagerberg[2,3], Dina Petranovic[1], Fredrik Bäckhed[2,3] & Jens Nielsen[1]

"It is almost a certainty that microbiome-based clinical diagnostics and treatments will be available in the near future to identify patients who are at risk for developing CVD."

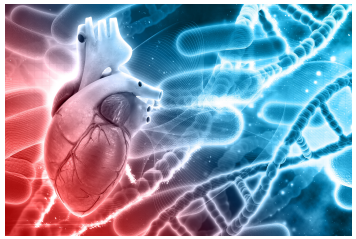
Alex J. Rai Director Columbia University Medical Center

Karlsson, Fredrik H., et al. Nature Communications, vol. 3, no. 1, 2012.

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Does The Gut Microbiome Predict CVD?

SIBO



DYSBIOSIS

CELIAC DISEASE

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Celiac Disease FOUNDATION

celiac.org

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This information should only be used with the advice of your physician or healthcare professional

Celiac Disease Linked To Almost Double Risk of Coronary Artery Disease

- Review of 22 m patients; CVD was significantly higher in all 24K + w/ celiac, regardless of age or gender vs controls. (9.5 % compared to 5.6 %) respectively.
- Linked to a 1.4 fold increase in risk of stroke—even in the absence of traditional CVD risk.
- Recent studies indicate that individuals with CD are at a higher risk of developing overall CVD, including an increased risk of myocardial infarction and atrial fibrillation.

Gajulapalli RD, et al. American College of Cardiology 2014 Scientific Sessions ; 2014.

Wang, Y.; et al; Celiac Disease and the Risk of Cardiovascular Diseases. *Int. J. Mol. Sci.* **2023**, *24*, 9974.

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SIBO and CVD risk

- > 1059 patients with MetS.
- 148 left heart catheterization and glucose breath test.
- SIBO positive- ~46 % NAFLD vs 40 % without SIBO.
- SIBO positive- Overwhelming higher frequency arteries affected by CVD and diabetes. **~ 80 % vs ~ 39 %** and with diabetes **~40 % vs 23%.**

- **One-vessel disease, 67.2 %.vs. 32.8%.**
- **Two-vessel disease, 85.7 % vs. 14.3 %.**
- **Three-vessel disease, 82.4 % vs. 17.6 %.**

https://consultqd.clevelandclinic.org/researchers-discover-gut-heart-connection-in-coronary-artery-disease/

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Li *et al. Microbiome* (2017) 5:14
DOI 10.1186/s40168-016-0222-x

Microbiome

RESEARCH Open Access

Gut microbiota dysbiosis contributes to the development of hypertension

- Decreased diversity (overgrowth of Prevotella and Klebsiella) in patients with pre-HTN and HTN.
- Fecal transplant of these gut microbiota from HTN humans to germ free mice; mice developed hypertension.

Li, Jing, et al. Microbiome, vol. 5, no. 1, 2017,

O'Donnell, J.A., *et al.* The gut microbiome and hypertension. *Nat Rev Nephrol* **19**, 153–167 (2023).

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Cardiometabolic Health



Gut-Cardiometabolic Axis

Gut 6-key Ingredients



- **Heart**
- **Vessels**
- **Blood**

- Cellular health- mitochondrial health
- Blood pressure regulation
- Lipid metabolism
- Glucose metabolism
- Energy production + fuel utilization

3 H's of Metabolic Dysfunction

- Hyperglycemia
- Hypertension
- Hyperlipidemia

- Insulin Resistance/pre-diabetes,T2.
- Obesity/Metabolic Syndrome
- NAFLD/NASH

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Microbial Pathways and CVD



Key Effects of the Gut Microbiome on Cardiovascular risk



Energy Balance

Inflammation Endotoxemia

Oxidative Stress

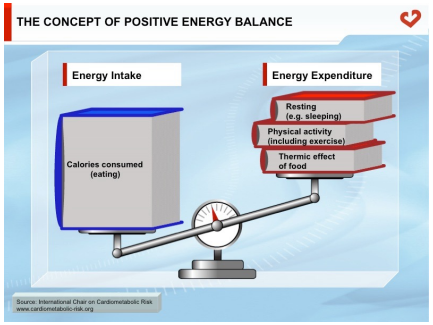
LPS

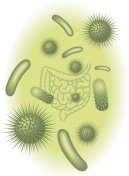
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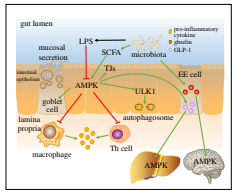
Whose Energy's Balance?

Microflora extract energy from host
Host becomes more energy efficient

Multiple pathways—AMPK, LPS, SCFA.







AMPK Promotes:

- Increased glucose uptake
- Fatty acid oxidation
- Autophagy
- Improved insulin sensivity

Reduced AMPK:

- Decrease insulin sensitivity
- Increase fat storage
- Mitochondria-dysfx

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Xiaofei, S et al; Open Biol 2017 Aug; 7(8): 170104.
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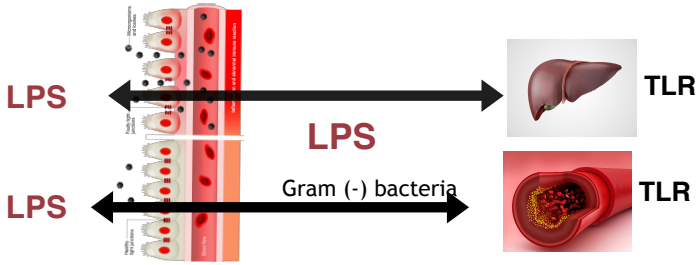
Inflammation
Lipopolysaccharide (LPS)

- Major cell wall component of gram-negative bacteria. Normally present in low concentrations.
- PAMPs—(Pathogen associated molecular patterns)- Bind with toll like receptors (TLRs).
- Commensal bacteria activate TLRs in key cells: Immune (macrophages), adipocytes, hepatic Kupffer and endothelial cells.
- LPS-endotoxin activates innate and adaptive immune response; macrophage influx into visceral fat cells leading to systemic inflammation.

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Chen, B., & Gautron, L. (2025). *Gut-derived lipopolysaccharides and metabolic endotoxemia: A critical review*. American Journal of Physiology-Endocrinology and Metabolism, 329(5).

Gut Dysbiosis



Increase gut permeability

LPS travels to circulation- TLR response

Altered fatty acid metabolism in liver

LPS binds to toll like receptors in endothelial cells, liver kupffer cells macrophages and adipocytes.

Impaired Insulin signaling

Chen, B., & Gautron, L. (2025). *Gut-derived lipopolysaccharides and metabolic endotoxemia: A critical review*. American Journal of Physiology-Endocrinology and Metabolism, 329(5).

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Caricilli, Andrea, et al. Nutrients, vol. 5, no. 3, 2013, pp. 829–851.

LDL Cholesterol+Endothelial Damage

- In circulation, 80-90% of LPS (endotoxin) is bound to lipoproteins—**LPS binding protein (LBP).** Protective to sequester LPS.
- LPS induces endothelial cell damage and LDL oxidation.
- Patients with highest LPS have increased carotid atherosclerosis.
- Inflammation key regulator of lipoprotein (LDL) metabolism.
- HDL (reverse cholesterol transport) helps lower LDL from circulation but also immune-modulate LPS.

Chen, B., & Gautron, L. (2025). *Gut-derived lipopolysaccharides and metabolic endotoxemia: A critical review*. American Journal of Physiology-Endocrinology and Metabolism, 329(5).

Vreugdenhil, Anita C.e., et al. Journal of Clinical Investigation, vol. 107, no. 2, 2001, pp. 225–234.,

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➡ **Older studies show septic patients have markedly elevated VLDL and LDL and lower HDL.**

LPS- 100s to 1000s pg/mL

- Provides host fuel to infection (old).
- Acute phase innate immune response—LBP/LPS binding protein (new)

LPS → LPS-binding protein (LBP) → CD14 → TLR4 → NF-κB activation → cytokines

Harris, Hobart W., et al. Journal of Endotoxin Research, vol. 6, no. 6, 2000.

Resl, M., *et al.* Storm of Cardiovascular Markers After LPS Administration in Human Volunteers. *J. of Cardiovasc. Trans. Res.* **14**, 941–947 (2021).

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Epidemiology/Health Services Research

ORIGINAL ARTICLE

Endotoxemia Is Associated With an Increased Risk of Incident Diabetes

- FINRISK97 cohort comprising 7,169 subjects aged 25–74 years and followed up for 10 years.
- (LPS) had a significant positive correlation with CRP, cholesterol, and triglyceride and negative correlation with HDL cholesterol.
- (Sub- septicemia) LPS levels of 0.3- up to 10s pg/ml)

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Pussinen, P. J., et al. Diabetes Care, vol. 34, no. 2, 2011, pp. 392–397.

Wang F et al. Postprandial LPS acts as a biomarker to stratify Cardiovascular disease risk and guide personalized nutrition The American Journal of Clinical Nutrition, 2026; 124

Available online at www.sciencedirect.com
ScienceDirect
Journal of Nutritional Biochemistry 63 (2019) 101–108
Journal of Nutritional Biochemistry

Gut microbiome and type 2 diabetes: where we are and where to go?

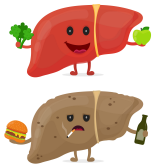
Sapna Sharma[a], Prabhanshu Tripathi[b,*]

"Several studies have reported gut microbiome dysbiosis as a factor in rapid progression of insulin resistance in T2D that accounts for about 90% of all diabetes cases worldwide. **The gut microbiome dysbiosis may reshape intestinal barrier functions and host metabolic and signaling pathways, which are directly or indirectly related to the insulin resistance in T2D.**"

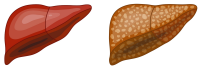
- Lower overall microbial diversity.
- Depletion of Askkermansia mucinophilia, mucin producing goblet cell and faecalibacterium prausnitizii.
- Depletion of butyrate (beneficial (SCFA)
- Gut derived endotoxemia (LPS), inflammation and insulin resistance.
- Chronically elevated insulin carries multiple risks and is common theme.

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NAFLD/NASH
Liver Metabolic Syndrome



- > 5% fat in liver w/out ETOH, or other liver disease. Up to 80% of diabetes have fat in liver
- Independent risk factor for CVD
- 75 %-100 % in populations with pre-existing metabolic conditions, (insulin resistance, metabolic syndrome, T2DB).
- NASH includes fibrosis- increases CVD mortality by 300 %, raising overall mortality by 70%.
- Preventable



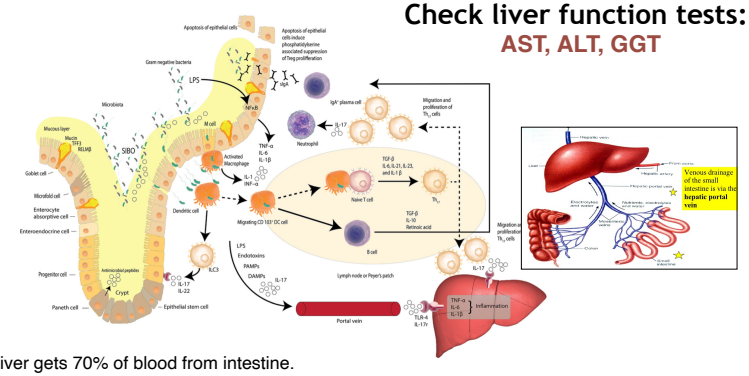
HEALTHY LIVER FATTY LIVER

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Athyros, Vasilios G, et al. World Journal of Gastroenterology, vol. 21, no. 22, 2015.

Liver Vulnerability and Gut Dysbiosis

Check liver function tests:
AST, ALT, GGT



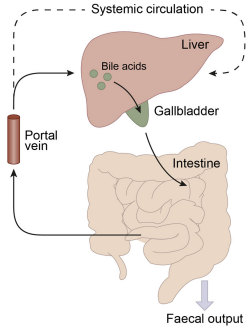
- Liver gets 70% of blood from intestine.
- Close anatomical and functional relationship between gut and liver via portal circulation.

Saltzman, Emma T., et al. Frontiers in Microbiology, vol. 9, 2018.
Pietro V, Giulia P, et. al. Pediatr Gastroenterol Nutr. 2013 May ; 56(5): 461–468.
http://creativecommons.org/licenses/by/4.0/)

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Enterohepatic Circulation

- **Bile acids not just about fat emulsification; also signaling molecules.**
- **Antibacterial roles; may change with SIBO or other dysbiosis.**
- Primary and secondary bile acid formation from cholesterol.
- Conjugates with glycine and taurine in the liver
- Gut microbes deconjugate and dehydroxylate primary bile acid—to secondary bile acid- enhancing diversity of acid pool in intestines.
- **Bile acids activate various receptors affecting cholesterol synthesis; HDL production, triglyceride metabolism.**
- **HDL is closely connected with bile acid metabolism.**
- **Bile acids indirect role in glucose management and appetite via GLP-1**
- Healthy colon has few bile salts, recirculates from terminal ileum.
- ~95 % of bile acid reabsorbed into intestinal enterocytes.
- Remaining ~ 5% excreted via feces-
- Recycled 4-12x/day.
- Gastric bile reflux and bile in colon—diarrhea.



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Wahlström A, Sayin SI, Marschall HU, Bäckhed F.
Intestinal Crosstalk between Bile Acids and Microbiota and Its Impact on Host Metabolism.
Cell Metabolism. 2016;24(1):41–50.

Primary & Secondary Bile Acids and Gut Diversity

Patients with C. scindens less likely to develop C. difficile infection

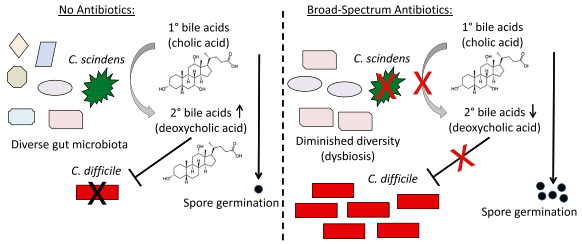


Figure 1. *S. scindens* and Secondary Bile Acids Inhibit *C. difficile* Growth
(Left) In the absence of antibiotics, the gut microbial community is diverse and includes bacteria such as *S. scindens* that convert primary bile acids into secondary bile acids, which, in turn, inhibits the growth of *C. difficile*. (Right) Broad-spectrum antibiotics diminish the diversity of the gut microbial community. Loss of certain bacteria such as *C. scindens* results in reduced production of secondary bile acids and increased growth of *C. difficile*. Additionally, accumulation of primary bile acids leads to increased spore germination of *C. difficile*.

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Buffie, CG, et al; Precision microbiome reconstitution restores bile acid mediated resistance to Clostridium difficile, nature. 2015 Jan



HDL and the Gut Microbiome
Quality (function) vs Quantity



- Binds bacterial toxins such as LPS
- Once bound, HDL helps transports toxins to liver for detox and elimination.
- In this way, HDL functions as part of **innate system,** not just a cholesterol transporter.

- Remove cholesterol from artery walls (reverse cholesterol transport)
- Lower oxidation
- Reduce inflammation
- Supports endothelial function

With Excessive Intestinal Permeability

- LPS enters circulation
- Chronic low grade inflammation
- HDL becomes oxidized or dysfunctional
- HDL less effective at removing cholesterol from artery walls

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Jiang Y, et al; The Gut Microbiome Affects Atherosclerosis by Regulating Reverse Cholesterol Transport. J Cardiovasc Transl Res. 2024 Jun;17(3):624-637. doi: 10.1007/s12265-024-10480-3. Epub 2024 Jan 17.

SCFAs and HDL Function

Greater microbial diversity and more beneficial bacteria are associated with better functioning HDL

Beneficial bacteria that produce SCFA



- Akkermansia mucinphilia
- Faecalbacterium prausnitzii
- Roseburia
- Bifidobacterium

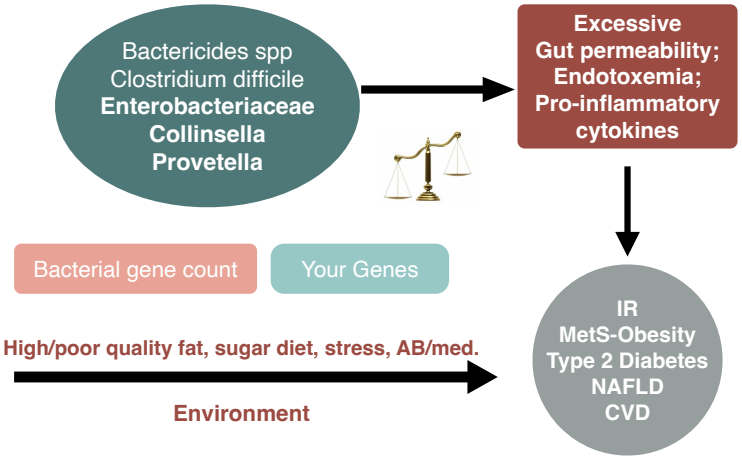


- SCFA-Butyrate strengthens intestinal barrier helping reduce inflammation.
- Enhances HDL's anti-inflammatory properties
- Less inflammation
- Improve insulin sensitivity
- Improve liver metabolism
- Supports cholesterol removal from tissues

Vrieze A, et al. *Microbiota and HDL metabolism*. Current Opinion in Lipidology. 2017

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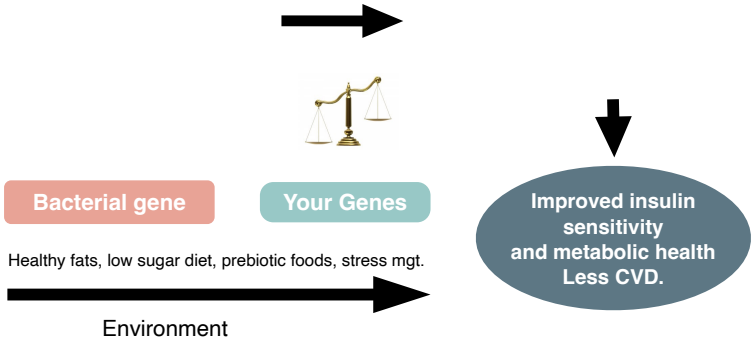
Dysbiotic Gut Microflora



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Boulangé et al. Genome Medicine (2016) 8:42

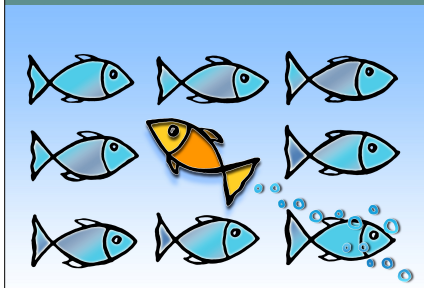
Healthy Gut Microflora



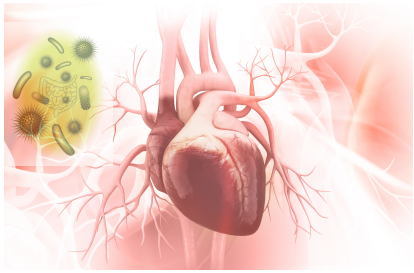
Boulangé et al. Genome Medicine (2016) 8:42

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Looking Both Ways At the Gut Microbiome and CVD



Biomarkers and Labs



Blood

- Hemoglobin A1C
- Fructosamine/glycated albumin
- Post-prandial + fasting glucose
- Insulin, fasting; c-peptide; HOMA-IR
- Leptin/Adiponectin ratio
- LFTs: GGT
- Advanced Lipid Panel: lipoprotein size, number and composition
- Triglycerides
- HDL
- Blood Pressure
- Inflammatory markers-hs-CRP; LpPLA2; MPO (myeloperoxidase)
- Fibrinogen
- Uric Acid
- Vitamin D
- Homocysteine

Other

- SIBO breath test
- Imaging/Echo/CT/MRI
- Liver Biopsy
- Urinary organic Acids- metabolites
- Gene SNPs
- Zonulin/Claudin antibodies
- LPS/LBP antibodies
- Waist circumference
- Waist to Hip ratio

Stool

- Calprotectin
- Secretary IgA
- EOS X

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Gut Microbiome Lab Analysis—DNA

Identifies what/who is there; Method/technology (broad or targeted) determines results; Q (PCR) is more targeted- if lab is looking for C difficile or Giardia or Salmonella the test searches for those organisms unique DNA sequences.

- Very sensitive
- Excellent for detecting infections
- Reproducible- relatively stable
- Well-established technology
- Quantifies targeted organism

Limitations

- Only detects organism the test designed for.
- Can't determine if alive, dormant, recently dead- DNA can remain after microbial death.

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Gut-Microbiome Lab Analysis—RNA

- Identifies the what/who but also its metabolic activity. Provides a snapshot of what the microbial community is doing at the time the sample was collected.
- Identifies microbial function
- Degrades quickly and reflects current activity, metabolic pathways and gene expression.

Detect increased activity related to:

- Beneficial SCFA production- butyrate and propionate
- Metabolism of bile acids
- Vitamin synthesis
- TMAO production

RNA limitations

- Results vary day to day because activity changes.
- mRNA degrades quickly so sample collection critical.
- Interpretation relies on proprietary algorithms. Reference databases still evolving.
- Limited evidence that RNA guided dietary recommendations improve long term health outcomes

Cardiovascular relevance- RNA theoretical advantage- heart disease appears to be influenced more by microbial metabolic activity than by mere presence or absence of individual species.

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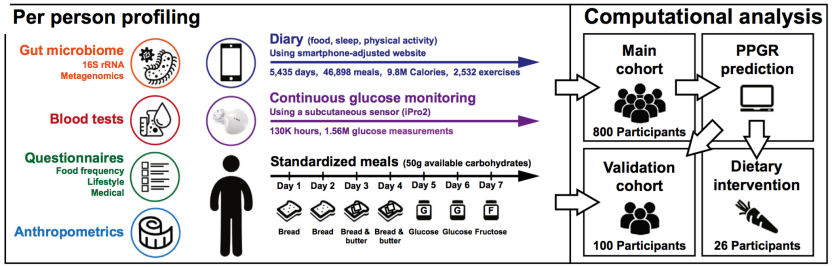
DayTwo

Article

Cell

Personalized Nutrition by Prediction of Glycemic Responses

Microbes → CHO → Blood glucose



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Zeevi D, Korem T, Zmora N, et al. Personalized Nutrition by Prediction of Glycemic Responses. *Cell*. 2015

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Diet—CVD + Gut Microbiome

- Carbohydrates: Quantity and quality
- Ketosis
- Choline, Carnitine, TMAO
- Polyphenols
- Fasting

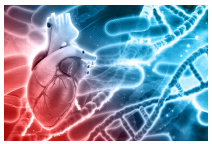


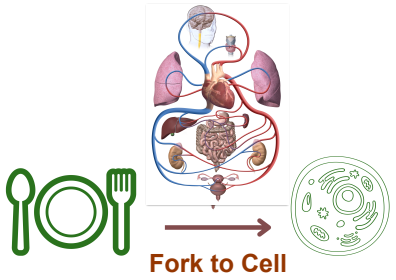
Nutrition is metabolic health and Metabolic health is nutrition!

Diet, Major Influencer Of Gut Microbiota

Signaling + Communicating To Cells, Genes and Microbes

- Cellular health- mitochondrial health
- Blood pressure regulation
- Lipid metabolism
- Glucose metabolism
- Energy production and fuel utilization







Carbohydrate





Become Metabolically Flexible

N=1

What is the quantity/quality of carbohydrates that will support a healthy gut microbiome and support glucose control and immunity.

- Need based on physical activity and baseline level for essential organs. No established optimal amount of carbohydrate for any individual.
- Carbohydrate (glucose) metabolism represents anaerobic path (glycolysis) to ATP.
- When carbohydrates are reduced, dietary fat better able to do its job and lipolysis more easily initiated. Insulin inhibits lipolysis and beta oxidation.
- High glycemic index carbs cause large increase in insulin, favor carbohydrate oxidation, whereas low glycemic carbs reduce insulin response, which encourages lipolysis and fat oxidation.
- The insulin concentrations required to inhibit lipolysis are significantly lower than those needed to accelerate glucose metabolism **(BINGO).**
- Carbohydrates are the main source of fiber, prebiotics for gut microbiome.
- Quality matters- Carbs can help or hinder the gut microbiome, which can promote or prevent insulin resistance.
- Low carbohydrate and low fat—not sustainable.

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Luke Norton, Chris Shannon, Amalia Gastaldelli, Ralph A. DeFronzo, Insulin: The master regulator of glucose metabolism, Metabolism,Volume 129,2022,

Lean Mass Hyper Responders



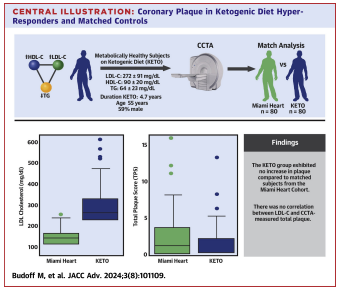
Ketogenic + Carnivore diet

Lipid Energy Model



Distinct Metabolic Phenotype- No evidence of CVD

- High LDL
- Lean body build (low body fat)
- Low BP
- Low inflammation
- High HDL and low triglycerides
- Excellent insulin sensitivity; Low fasting insulin
- Regular endurance or resistance exercise
- Few processed carbohydrates
- Often no obesity, diabetes, or metabolic syndrome



Budoff M, et al. JACC Adv. 2024;3(8):101109.

Mierzejewski, Jakub & Rafałowicz, Adam & Wojciechowska, Urszula. (2025). High LDL Cholesterol, Low Risk? Lean Mass Hyper-responder phenotype – A literature review. Quality in Sport. 43. 61260. 10.12775/QS.2025.43.61260.

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Dietary Ketosis Gut Microbiome-CVD



- Some high fat may increase bile-tolerant gram-neg bacteria and temporarily increase intestinal absorption of LPS from increase fat mobilization and LDL
- Dietary fiber, prebiotics, probiotics attenuate higher risk metabolites and promote protective SCFA and indole-3-P

N=1

Key Points and Counter Balances

- Elevated LDL without elevated inflammatory markers, IR or met dyfx does not increase cardiac risk
- LDL does more than transport cholesterol, it binds and neutralizes bacterial toxins, including LPS.
- HDL also plays a role in immune modulation to help clear LPS.
- Ketogenic diets may strengthen gut barrier- i.e. Increased Akkermansia m.
- Ketones reduce systemic inflammation i.e. beta hydroxybutyrate
- In the context of healthy carb matrix and lower carb, most recent meta-analyses find no beneficial effects of reducing SF intake on cardiovascular disease (CVD) and total mortality,
- Less visceral fat; Insulin sensitivity

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Beneficial Postbiotics

PREFERABLY FROM FOOD

(Fiber + 3 Ps: polyphenols, prebiotics, probiotics)

Butyrate-SCFA
- Reduces inflammation
- Protects intestinal barrier
- Less LPS into bloodstream
- Improves insulin sensitivity
- Reduces BP -modestly
- Regulate immune cells that limit chronic inflammation

Propionate SCFA
- May reduce cholesterol synthesis in liver
- Improves glucose metabolism
- Lowers inflammation
- May reduce BP

Acetate-SCFA
- Most abundant SCFA-some CVD protection
- Supports immune regulation
- Improves gut barrier
- Energy source
- Appetite regulation

Urolithin A
- Produced from ellagitannins: pomegranates, walnuts, raspberries.
- Gut bacteria dependent.
- CVD benefits-improved mito function
- Less inflammation
- Better endothelial function

Stool— Colon; microbial fermentation; not necessarily what SCFA the body absorbs.
Blood—SCFA enter bloodstream; systemic effects; low concentrations; research
Portal Vein—SCFA leaving intestine; best measure of absorption; research

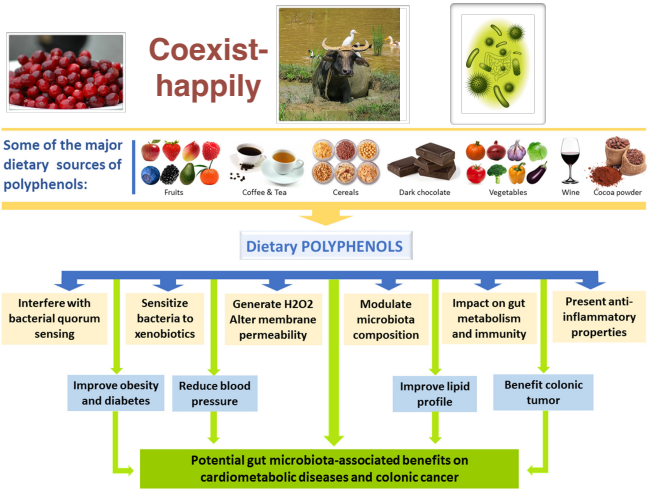
Indole-3-propionic acid (IPA)- made from dietary tryptophan by certain bacteria
- More IPA production generally associated with lower CVD risk
- Potent antioxidant
- Reduces inflammation
- Protects gut barrier
- Associated with less Type 2 risk.

- Tryptophan to **kynurenine production** → generally associated with higher CVD risk

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Rafique, N et alPromising Bioactivities of Postbiotics: A Comprehensive Review. *Journal of Agriculture and Food Research*. 2023

Polyphenol and CVD risk



Singh, *Nutrients* **2019**, *11*, 2216; doi:10.3390/nu11092216

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Carnitine, Choline and TMAO

ORIGINAL ARTICLE

MAYO CLINIC

L-Carnitine in the Secondary Prevention of Cardiovascular Disease: Systematic Review and Meta-analysis

- Carnitine— a fat-transporting compound, essential for normal heart function.
- 13 controlled trials- 3,629 patients. Carnitine supplementation associated with 27% reduction in all cause mortality.
- Decreased markers of vascular injury, oxidative stress and AGE values.

Choline Metabolism Provides Novel Insights into Non-alcoholic Fatty Liver Disease and its Progression

Karen D. Corbin and **Steven H. Zeisel**
University of North Carolina at Chapel Hill, Nutrition Research Institute, Kannapolis, North Carolina, USA

- Low choline diets may increase fatty liver and liver damage. Humans deprived of choline developed either fatty liver and liver cell death or skeletal muscle damage.
- **PEMT gene expression** induced by estrogen catalyzes production of liver phosphatidylcholine.
- Up to 40 % of women have PEMT polymorphism-increasing choline requirements similar to men.
- Choline supplementation promising therapeutic for NAFLD

Werida, R.H., Okda, S.M. Therapeutic potential of L-carnitine in coronary artery disease: a systematic review. *Inflammopharmacol* **34**, 1331–1342 (2026).

Sedhom SS, et al; The impact of choline supplementation on oxidative stress and clinical outcomes among patients with non-alcoholic fatty liver disease:Ther Adv Chronic Dis. 2025 Aug

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TMAO Not in Isolation

toxins

MDPI

Review

Trimethylamine *N*-Oxide: The Good, the Bad and the Unknown

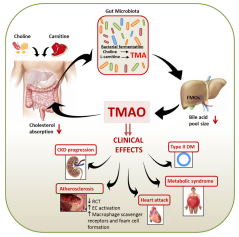
Manuel T. Velasquez, Ali Ramezani, Alotaibi Manal and Dominic S. Raj *

Division of Renal Diseases and Hypertension, The George Washington University School of Medicine, 2150 Pennsylvania Avenue NW, Washington, DC 20037, USA; mvelasquez@mfa.gwu.edu (M.T.V.); ramezani@gwu.edu (A.R.); malotaibi@email.gwu.edu (A.M.)

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Academic Editor: Raymond Vanholder

Received: 30 September 2016; Accepted: 3 November 2016; Published: 8 November 2016



- Microbiota metabolize dietary L-carnitine and choline.
- Liver converts TMA to TMAO. Potential link between TMAO end products and CVD —jury is out! TMAO itself induce damage or is it a marker of microbes?
- Fish contains TMAO
- Not everyone produces the same amount of TMAO-Diet, gut microbes, liver FMO enzymes and kidney function dependent.
- Bacteria capable of producing TMA include: Clostridium (certain species); Desulfovibrio; Anaerococcus; Escherichia coli (some strains)
- Dietary fiber, prebiotics, probiotics attenuate risk and and promote protective SCFA

Velasquez MT, et al. *Toxins.* 2016; 8(11):326. https://doi.org/10.3390/toxins8110326

Yarong Liu; et al; Mediators of Inflammation Volume 2020, Article ID 4634172, 15

Melasquez, M. et al Toxins 2016, 8, 326

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Intermittent Fasting, Autophagy Gut Microbiome + Metabolic Health

FASTING BIOLOGY-FAST WITH A PURPOSE



- Periodic fasting
- Upsignal of Autophagy
- Changes in Gut microbiome
- More beneficial microbial metabolites
- Improved gut barrier
- Less LPS entering bloodstream
- Lower systemic inflammation
- Improved insulin sensitivity
- Healthier blood vessels/endothelium
- More stable atherosclerotic plaques
- Lower CVD risk

- Against the design of the body to not fast- **metabolic dysychrony.**
- Most "Cleanses" especially juice/fruit cleanses, trigger insulin, don't as readily promote ketosis or autophagy.

SHOULD BE FIRST LINE OF DEFENSE FOR OBESITY AND METABOLIC DYSFUNCTION.

- Minimum of 12 hours recommended for most healthy people.
- Alternate-day fasting- 24-hours eating, 24-hrs fasting; one meal/day.
- Time-restricted feeding- 16/8 16-hour window of fasting and 8-hour window of feeding.
- 3-5 day water fast
- Fasting Mimicking Diet- macronutrient balance able to stimulate ketosis and autophagy.



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REVIEW ARTICLE

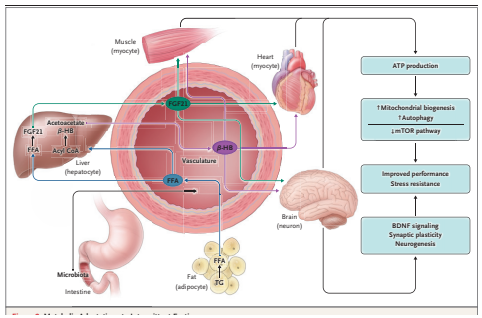
Dan L. Longo, M.D., *Editor*

Effects of Intermittent Fasting on Health, Aging, and Disease

Rafael de Cabo, Ph.D., and Mark P. Mattson, Ph.D.

- IF can significantly alter the gut microbiome, shifting balance, increasing beneficial bacteria like Lactobacillus and Bifidobacteria, and increasing bacterial diversity, potentially decreasing inflammation; longer term increase production of SCFA.
- Gut microflora adapts during fasting.
- **How you refeed after a fast can help populate beneficial bacteria- i.e. fiber; 3 Ps. (polyphenols, prebiotics, probiotics).**
- FMD (Prolon) positively affects gut microbiome.

EFFECTS OF INTERMITTENT FASTING ON HEALTH AND AGING



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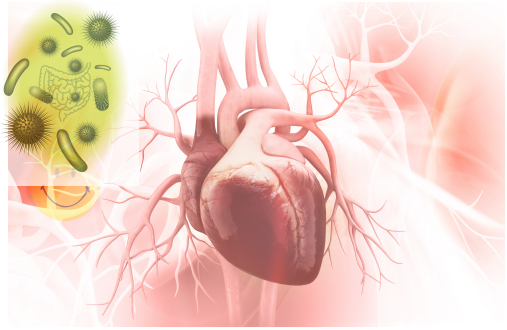


Key Take Aways



- Each organ in digestive system has its own ecosystem.
- Cardiovascular system-simpler design than GI: Heart, vessels and blood.
- Extensive vascular network in every system/organ. Endothelium with its immune properties is a functional component of all vessels. Blood is a medium for transfer of health and disease; how cells receive oxygen and nutrients.
- Gut microbes influence many pathways related to cardiometabolic health/disease. Assess digestive and CVD signs + sx.
- Intestinal permeability, translocation of gut microbes and LPS. LPS measured in blood and stool as marker of endotoxemia, can reflect LDL and HDL oxidation.
- IR many origins. Common theme related to many CVD risks.
- Hyperglycemia, hypertension and hyperlipidemia; 3 H's important risks to vessel health and beyond. Each play role in MetS.
- Key role of liver proximity and function to intestines; Enterhepatic and bile health; Monitor liver function—GGT, AST/AGT.
- Diet: Unique individual tolerance to carbs—quality and quantity depending on genes/snps and gut microbiome.
- Fiber and 3Ps- polyphenols, prebiotics, probiotics; promote SCFA, Indole-3-propionic acid (IPA) beneficial effects on CVD.
- Carnitine and choline Important nutrients to liver and heart health; TMAO potential cardiovascular risk; fiber and 3 Ps may attenuate cardiac risk.
- Ketosis; Intermittent Fasting and Autophagy-influence gut microbiome and can have positive cardiovascular effects.

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Thank You!



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